

SLEEP AND HEALTH

SECOND EDITION



Edited by
Michael A. Grandner



Sleep and Health

This book belongs to sahil chopra
(sahilchopramd@empowersleep.com)

This page intentionally left blank

Sleep and Health

Second Edition

Edited by

Michael A. Grandner

Sleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine - Tucson, Tucson, AZ, United States



ACADEMIC PRESS

An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

Copyright © 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

For accessibility purposes, images in electronic versions of this book are accompanied by alt text descriptions provided by Elsevier. For more information, see <https://www.elsevier.com/about/accessibility>.

Books and Journals published by Elsevier comply with applicable product safety requirements. For any product safety concerns or queries, please contact our authorised representative, Elsevier B.V., at productsafety@elsevier.com.

Publisher's note: Elsevier takes a neutral position with respect to territorial disputes or jurisdictional claims in its published content, including in maps and institutional affiliations.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-443-13954-3

For information on all Academic Press publications visit our website
at <https://www.elsevier.com/books-and-journals>

Publisher: Stacy Masucci

Acquisitions Editor: Arindam Banerjee

Editorial Project Manager: Abdus Salam Mazumder

Production Project Manager: Omer Mukhtar

Cover Designer: Miles Hitchen

Typeset by TNQ Tech



Working together
to grow libraries in
developing countries

www.elsevier.com • www.bookaid.org

Dedication

For Nirav. I wish we could have done this together.

This page intentionally left blank

Contents

Contributors	xxi
Preface	xxvii
Acknowledgments	xxix

Part I General concepts in sleep health

1. The basics of sleep physiology and behavior

Andrew Scott Tubbs, Hannah K. Dollish, Fabian-Xosé Fernandez and Michael A. Grandner

Introduction	3
The definition of sleep	3
Conceptualizing sleep as a health behavior	3
Conceptualizing sleep as a physiological process	4
Sleep and circadian rhythms	6
Basic sleep physiology	8
Quantifying sleep	9
Conclusion	10
References	11

2. Epidemiology of sleep health

<i>Michael A. Grandner</i>	
Sleep at the population level	13
Defining insufficient sleep	13
Prevalence of insufficient sleep	14
Insufficient sleep in the population	14
Insufficient sleep by age	15
Insufficient sleep by sex	16
Insufficient sleep by race/ethnicity	16
Insufficient sleep by socioeconomic status	16
Insufficient sleep by geography	17
Key limitations to population estimates of insufficient sleep	18
Prevalence of poor sleep quality	18
Prevalence of sleep disorders	19
Prevalence of sleep complaints	19
Summary and conclusions	20
References	20

3. Sex differences in sleep health

Jessica Meers, Jacqueline Stout-Aguilar and Sara Nowakowski

Introduction	23
Sex differences in infant sleep	23
Sex differences in childhood sleep	24
Sex differences in adolescent sleep	24
Sex differences in young adult sleep	26
Sex differences in middle-aged sleep	26
Sex differences in older adult sleep	27
Conclusion	28
References	28

4. Sleep and health in older adults

Junxin Li and Nalaka S. Gooneratne

Introduction	35
Sleep changes in normal aging	35
Changes in sleep parameters	35
Changes in circadian rhythm	35
Changes in sleep homeostasis	35
Common sleep disturbances in older adults	36
Insomnia	36
Sleep-disordered breathing	36
Factors associated with sleep disturbances in older adults	37
Sleep and health in older adults	37
Cognitive function	37
Cardiovascular health	39
Psychiatric illness	40
Pain	41
Conclusion	42
References	44

5. Social-ecological model of sleep health

Michael A. Grandner

Introduction	51
The social ecological model	52
Sleep as a domain of health behavior	53
Conceptualizing sleep in a social-ecological model	54

Individual level	54	Sleep architecture and continuity across racial/ethnic groups	79
Social level	55	Sleep architecture and continuity across SES groups	81
Societal level	55		81
Combining upstream influences and downstream consequences	56		81
Applications of the model	57		81
References	58		81
6. Nocturnal Wakefulness and the Mind After Midnight			
<i>Andrew Scott Tubbs, Alisa Huskey, Fabian-Xosé Fernandez, Michael A. Grandner and Michael L. Perlis</i>			
Introduction	61	Insomnia complaints across racial/ethnic groups	83
Nocturnal wakefulness: Awake when your nervous system wants to sleep	61	Insomnia complaints across SES groups	84
Central neurophysiology	61	Restless leg syndrome (RLS) and periodic limb movements during sleep (PLMS)	87
Peripheral neurophysiology	62	Narcolepsy	88
Nocturnal wakefulness breeds the Mind After Midnight	62	Circadian rhythms	88
Impaired mood and affect	63		
Altered reward anticipation and receipt	63		
Executive dysfunction—The sleep of reason	63		
The Mind After Midnight begets behavioral dysregulation	64		
Suicide	64		
Homicide	64		
Substance use	64		
Food intake	65		
Conclusion	65		
Acknowledgments	66		
References	66		
Part II			
Contextual factors related to sleep			
7. Race, socioeconomic position and sleep			
<i>Girardin Jean-Louis, Judite Blanc and Douglas M. Wallace</i>			
Abbreviations	73	Neighborhoods and sleep health	95
Introduction	73	Theoretical justification for neighborhoods and sleep health	95
(Brief) history and definition of health disparities	74	Neighborhood factors associated with pediatric sleep	96
Sleep characteristics	74	Urbanicity and population density	96
Self-reported sleep duration across racial/ethnic groups	74	Neighborhood socioeconomic status (NSES)	96
Objective reported sleep duration across racial/ethnic groups	78	Neighborhood access to physical activity	96
Sleep duration within racial/ethnic groups	78	Neighborhood violence and safety concerns	96
Sleep duration across SES groups	79	Neighborhood factors associated with adult sleep	96
		Inadequate sleep duration and delayed sleep timing	97
		Insomnia	97
		Obstructive sleep apnea (OSA)	97
		Current limitations and future directions	98
		Studying long-term trajectories of neighborhood conditions and sleep	98

Evaluating evidence from natural experiments and other causal methods	98	Treatment for insomnia during the perinatal period	133
Using technological advances to studying neighborhoods and sleep at a larger scale	98	Conclusion	134
Are there interventions and policies to improve neighborhoods and sleep health?	99	References	134
Conclusions and public health significance	99		
Acknowledgments	99		
References	99		
9. Environmental exposures affected by long-term weather pattern changes in relation to sleep health			
<i>Rupsha Singh, Symielle A. Gaston and Chandra L. Jackson</i>			
Acronyms and abbreviations	105		
The physical environment and sleep	105		
The impact of light on sleep	106		
The impact of temperature on sleep	109		
The impact of noise on sleep	110		
The impact of vibrations on sleep	111		
The impact of air quality on sleep	112		
The impact of seasonality and latitude/longitude on sleep	113		
The social environment and sleep	114		
Psychosocial stress and sleep	114		
Social conditions, policies, and institutions:			
The impact of socioeconomic status and racism on sleep	114		
Community: The impact of neighborhood social and physical environments on sleep	115		
Community: Work environment and sleep	116		
Interpersonal relationships and sleep	116		
Glossary	118		
Acknowledgments	120		
References	120		
10. Sleep health during the perinatal period: From pregnancy to postpartum			
<i>Anna L. MacKinnon, Makayla Freeman, Jasleen Kaur, Katherine Silang, Dana Watts and Lianne Tomfohr-Madsen</i>			
Introduction	127	Interventions and strategies to improve sleep in families	147
Sleep changes during pregnancy	127	Behavioral interventions in families	147
Sleep changes during the postpartum	128	Environmental modifications for families	148
Partners' sleep in the perinatal period	129	Educational programs for families	148
Insomnia in pregnancy and postpartum	131	Medical treatments in a family context	148
Assessment of insomnia during the perinatal period	133	Conclusions and future directions	148
		Future directions and research agenda	148
		Clinical implications	149
		Conclusions	149
		References	149

Part III

Addressing sleep health at the community and population level

12. Obstacles to overcome when improving sleep health at a societal level

Michael A. Grandner

Introduction	157
Real-world barriers to sleep health	157
Lack of time	157
Social norms and beliefs	158
Physical environment	158
Health conditions and chronic pain	159
Substance use	160
Distractions and on-demand culture	160
Conceptualizing strategies for overcoming these barriers	160
The health belief model and application to sleep	160
The integrated behavioral model and application to sleep	161
The transtheoretical stages-of-change model	162
Other health behavior models	163
Implementing sleep health programs	163
Addressing perceived benefits	163
Addressing perceived barriers	163
Addressing social norms	164
Addressing self-efficacy and control	164
Addressing readiness	164
Conclusion	165
References	165

13. Screening for sleep disorders

Catherine A. McCall and Nathaniel F. Watson

Abbreviations	167
Introduction	167
Sleep-disordered breathing	168
STOP and STOP-BANG questionnaires	172
Berlin questionnaire	172
Hypersomnolence	172
Epworth Sleepiness Scale (ESS)	173
Functional outcomes of sleep questionnaire (FOSQ-30)	174
Stanford Sleepiness Scale (SSS)	174
Karolinska Sleepiness Scale (KSS)	174
Insomnia and sleep quality	174
Insomnia severity index (ISI)	175
Pittsburgh sleep quality index (PSQI)	175
Patient-reported outcomes measurement information system (PROMIS)	176

Circadian rhythm disorders	176
Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ)	176
Munich Chronotype Questionnaire (MCTQ)	179
Restless legs syndrome (RLS)	179
International Restless Legs Syndrome Scale (IRLS)	179
Consumer sleep technologies	179
Using screening data	180
References	181

14. Sleep hygiene and the prevention of chronic insomnia

Jason G. Ellis, Sarah F. Allen and Pamela Alfonso-Miller

Sleep hygiene	185
What is sleep hygiene?	185
Exercise	185
Caffeine	186
Alcohol	187
Food and liquid intake	187
Nicotine	187
Bedroom environment	187
Removal of electronics	188
Clockwatching	188
Measuring sleep hygiene	188
Do people with insomnia have poorer sleep hygiene than normal sleepers?	188
What is the role of sleep hygiene in the management of insomnia?	189
So, is there a role for sleep hygiene in sleep medicine and practice, beyond insomnia?	189
The prevention of chronic insomnia	190
Etiological models of insomnia	190
What we know about acute insomnia?	190
Can we prevent acute insomnia from becoming chronic?	190
Identifying those at risk	191
Conclusions	191
References	191

15. Actigraphic sleep tracking and wearables

Michael A. Grandner and Mary E. Rosenberger

Introduction	195
Scoring algorithms	195
Types of actigraph devices	197

Limitations of actigraphy and related considerations	198	Step 9: Prepare a draft instrument	231
Identifying sleep stages with actigraphy	199	Step 10: Test for readability	231
Other considerations	202	Step 11: Send to panel of experts	231
Scientific guidelines	202	Step 12: Conduct a pilot test	232
Evaluating commercially available sleep trackers	203	Step 13: Establish reliability and validity	232
Conclusions	204	Limitations of behavior change theories	232
References	204	Conclusion	233
References	204	References	233
16. Screen use, sleep, and circadian disruption		Part IV	
<i>David A. Reichenberger, Cynthia K. Snyder and Anne-Marie Chang</i>		Sleep and cardiometabolic health	
Acronyms/abbreviations	207	18. Insufficient sleep and obesity	
Importance of sleep for health	207	<i>Andrea M. Spaeth</i>	
Two-process model of sleep physiology	208	Sleep duration	237
Contextual factors influencing screen use and sleep behavior	208	Obesogenic behaviors	237
Emergence of modern screen use	209	Potential physiological mechanisms	239
Mechanisms through which screen use affects sleep	209	Group differences	240
The impact of screen use on sleep	211	Individual differences	241
Screen use may be an epiphenomenon of insomnia	212	Sleep timing	242
Conclusion	212	Sleep disorders	243
References	212	Sleep in individuals with obesity	244
17. Behavior change models and theories		The role of sleep in weight-loss interventions	244
<i>Adam Knowlden and Sarah Flora</i>		Conclusion	245
List of abbreviations	217	References	245
Foundation of theory for behavior change	217		
Utility of theory for changing health behaviors	218	19. Insufficient sleep and cardiovascular disease risk	
Causation in behavior change theories	218	<i>Sogol Javaheri, Omobomi Fashanu and Susan Redline</i>	
Types of theories	220	Abbreviations	253
Intrapersonal theories	221	Introduction	253
Interpersonal theories	226	Defining insufficient sleep	254
Community level theories	227	Pathophysiology	255
Measurement of models and theories for behavior change interventions	229	Insufficient sleep and blood pressure	255
Step 1: Define purpose of instrument	229	Insufficient sleep and coronary heart disease	257
Step 2: Identify objects of interest	229	Insufficient sleep and heart failure	259
Step 3: Constitutively define objects of interest	229	Insufficient sleep and stroke	259
Step 4: Operationally define objects of interest	230	Conclusions	260
Step 5: Review previously developed instruments	230	References	260
Step 6: Develop an original instrument	230		
Step 7: Select appropriate scales	230		
Step 8: Develop items	231		
20. Sleep health and diabetes: The role of sleep duration, quality, disorders, and circadian rhythm on diabetes		20. Sleep health and diabetes: The role of sleep duration, quality, disorders, and circadian rhythm on diabetes	
<i>Mary Carrasco, Carolina Scaramutti-Gladfelter, Sandra Wittleder, Rhoda Moise, Sujata Thawani, Sophia Tong, Debbie Chung, Girardin Jean-Louis and Azizi A. Seixas</i>		<i>Mary Carrasco, Carolina Scaramutti-Gladfelter, Sandra Wittleder, Rhoda Moise, Sujata Thawani, Sophia Tong, Debbie Chung, Girardin Jean-Louis and Azizi A. Seixas</i>	
Overview	265	Overview	265

Understanding physiological and mechanistic causes of diabetes	265	Autonomic nervous system	289	
Objective and subjective sleep health parameters and diabetes risk	267	Metabolically relevant hormones	290	
Sleep duration and diabetes	268	Conclusion and future directions	292	
Summary	273	References	292	
Qualitative sleep parameters (sleep quality, excessive daytime sleepiness, and social jet lag) and diabetes	273	Part V		
Sleep quality	273	Sleep and behavioral health		
Excessive daytime sleepiness and social jetlag	274	22. Sleep and food intake		
Physiological mechanisms	274	<i>Isaac Smith, Katherine Saed and Marie-Pierre St-Onge</i>		
Sleep disorders and diabetes	274	Abbreviations	303	
Obstructive sleep apnea (OSA)	274	Introduction	303	
Insomnia	275	Part 1: Sleep loss and food intake	304	
Insomnia and Painful Diabetic Neuropathy (PDN)	275	Part 2: Proposed mechanisms explaining the sleep–food intake relation	305	
Circadian rhythm and diabetes	276	Homeostatic mechanisms	305	
Independent and interactive associations between endogenous circadian and diabetes	277	Nonhomeostatic mechanisms	305	
Exogenous	277	Part 3: Influence of food intake on sleep duration and quality	307	
Endogenous and exogenous	278	Caloric consumption	307	
Circadian misalignment and diabetes	278	Protein	307	
The exacerbating role of sleep on well-being, quality of life, health, and mortality among diabetics	278	Carbohydrates	308	
Healthy sleep and reduced diabetes risk	278	Fat	309	
Summary	279	Vitamins and supplements	310	
References	279	Fruits	310	
21. Social jetlag, circadian disruption, and cardiometabolic disease risk	280	Alternative medicine	311	
<i>Susan Kohl Malone, Maria A. Mendoza and Freda Patterson</i>	280	Total dietary approaches	311	
Introduction	283	Conclusion	311	
Definitions and epidemiology	283	References	312	
Cardiometabolic syndrome	283			
Circadian rhythms	284			
Circadian disruption and social jetlag	285			
Circadian disruption and cardiometabolic health	285			
Circadian control of the cardiometabolic system	286			
Cardiovascular functioning	286			
Metabolism	286			
Environmental rhythms and cardiometabolic health	288			
Behavioral rhythms and cardiometabolic health	288			
Biological rhythms and cardiometabolic health	289			
Impact of exercise on sleep	319			
Observational research	319			
Experimental research	320			
Sedentary behavior	321			
Potential mechanisms of exercise	322			
Impact of exercise on sleep disorders	322			
Insomnia	322			
Sleep-disordered breathing	323			
Restless legs syndrome/periodic limb movements during sleep	323			
A bidirectional relationship: Impact of sleep on exercise	324			
Combined impact of exercise and sleep on health	324			
Conclusion	325			
References	326			

24. Sleep and alcohol use

Subhajit Chakravorty, Audrey Mills, Kimberly Hayes and Ryan Krouse

Introduction	333
Neurobiology of alcohol use	333
Insomnia and alcohol use	333
Introduction	333
Epidemiology of alcohol use or misuse and sleep-related problems	333
Childhood sleep problems and future alcohol use	333
Adult sleep problems and alcohol use	334
Do subjects with sleep problems gravitate toward alcohol consumption?	334
Overnight polysomnographic sleep studies	335
Genetic studies	335
Clinical findings	335
Insomnia in AUD	336
Treatments	337
Circadian rhythm abnormalities and alcohol use	337
Chronotype	337
Shiftwork and alcohol use	338
Chronopharmacokinetic studies	338
Individuals with AUD	338
Sleep duration abnormalities and alcohol use	338
Short and long sleep duration	338
Short sleep duration and alcohol consumption	339
Long sleep duration and alcohol	339
Clinical findings in adolescents and young adults	339
Breathing-related sleep disorders and alcohol use	339
Breathing-related sleep events	339
Breathing-related sleep disorders	339
Effect of alcohol use on breathing during sleep	340
Sleep-related movement disorders and alcohol use	340
Restless leg syndrome	340
Periodic limb movement disorder	340
Parasomnias and alcohol use	341
Other sleep-related issues associated with alcohol use	341
Discussion	341
References	342

25. Improved sleep as an adjunctive treatment for smoking cessation

Freda Patterson and Rebecca Ashare

Introduction	347
Epidemiology of cigarette smoking	347
Sleep continuity and architecture in smokers versus nonsmokers	348
Overview of sleep continuity and architecture	348
Sleep architecture in smokers versus nonsmokers	348
Sleep continuity in smokers versus nonsmokers	349
Sleep fragmentation in smokers versus nonsmokers	351
Daytime sleepiness in smokers versus nonsmokers	351
Summary	352
Smoking abstinence and sleep	352
Changes in sleep following abstinence	352
Relationship between sleep and cessation outcome	353
Effects of pharmacotherapy on sleep	356
Take home points: Relationship between sleep and cessation outcome	357
Possible mechanisms linking poor sleep to smoking cessation outcomes	357
Plausible adjunctive sleep therapies to promote smoking cessation	358
Overview	358
Behavioral treatments	359
Pharmacological treatments	359
Directions for future research	360
Acknowledgments	360
Conflicts of interest	361
References	361

26. Sleep and the impact of caffeine, energy supplements, and other stimulants

Ninad S. Chaudhary, Priyamvada M. Pitale and Favel L. Mondesir

Abbreviations	369
Introduction	369
Epidemiology	370
Epidemiology of sleep in caffeine	370

Epidemiology of sleep in energy drink supplements	372	Effects of sleep loss on vigilant attention	403
Epidemiology of sleep in other psychostimulants	373	The psychomotor vigilance test	404
Relationships in specific populations	373	PVT software and hardware	405
Physiology of caffeine in sleep-wake homeostasis	374	PVT duration	405
Role of adenosine and caffeine in sleep-wake cycle	375	PVT outcome metric	406
Genetic factors and response to caffeine	375	Research agenda	406
Environmental factors and response to caffeine	376	References	406
Health implications of caffeine (stimulant) use—Sleep disturbances model	377	29. Sleep loss, decision-making, and executive function	
Recommendations	379	<i>Sofia K. Fluke, Brieann C. Satterfield and William D. Scott Killgore</i>	
Conclusion	379	Abbreviations	411
References	380	Introduction	411
27. Sleep, stress, and immunity		Neurobiology of sleep and fatigue	412
<i>Aric A. Prather</i>		Alertness, sustained attention, and vigilance	412
Introduction	387	Psychomotor vigilance	412
Overview of the immune system	387	Wake state instability	414
Acquired immune system	387	Individual differences	416
Innate immune system	388	Executive functions	418
The aging immune system	388	Working memory	419
Sleep, acquired immunity, and infectious disease risk	388	Memoring encoding, consolidation, and retrieval	420
Sleep, innate immunity, and inflammatory disease risk	390	Inhibitory control	420
Sleep and immunological aging	391	Cognitive control	421
Beyond sleep: Does stress influence immunity?	392	Problem solving	423
Sleep and psychological stress: Reciprocal processes	393	Risk-taking, judgment, and decision-making	425
How does poor sleep and psychological stress affect immunity?	394	Self-rated risk propensity	425
Stress—sleep connection and immunity	395	Risky decision-making	425
Conclusion	395	Practical implications	429
References	396	Conclusions	429
Part VI		References	430
Sleep and brain health		30. Sleep and healthy decision-making	
28. Sleep loss and impaired vigilant attention		<i>Kelly Glazer Baron and Elizabeth Culnan</i>	
<i>Mathias Basner</i>		Abbreviations	437
Neurobehavioral consequences of acute and chronic sleep loss	403	Introduction	437
Differential vulnerability to sleep loss	403	Sleep as a health behavior	437
		Influences on sleep and health behaviors	437
		Short sleep duration is highly prevalent in the population	438
		What predicts the decision to sleep or not to sleep?	438
		Some individuals make time to sleep but cannot sleep	438
		Proposed pathways linking sleep to other health behaviors	439
		Exposure	439
		Neurocognitive factors	439

Linking sleep related changes in neurocognitive function to health behaviors	440	Introduction	473
Neuroimaging data	441	Definition, incidence, and prevalence	473
Affective response to sleep loss	441	Definition	473
Effort and motivation	442	Incidence and prevalence	474
Does changing sleep make it easier to make healthy decisions?	443	Theoretical perspectives on the etiology of insomnia	474
Summary	443	Stimulus control model	475
Glossary	444	Behavioral model (Spielman's 3P model)	476
References	444	Neurocognitive model	476
31. Sleep and mild traumatic brain injury		Cognitive model	476
<i>Jocelyn McCallum, Amanda Black, Charles H. Samuels and Jonathan Charest</i>		Psychobiological inhibition model	476
Introduction	449	Parallel process (transtheoretical) model	477
Defining sport-related concussion	449	Insomnia and psychiatric morbidity	477
Prevalence of concussion	450	Depressive disorders	477
Persistent symptoms and postconcussion	451	Suicide	478
Sleep	451	Bipolar disorder	479
Circadian rhythms	452	Anxiety disorders	479
Concussion: Impact on the physiology	453	Posttraumatic stress disorder	480
Sleep disturbances following a concussion	454	Attention-deficit/hyperactivity disorder	480
Sleep duration—concussion	455	Alcohol use disorder	481
Sleep and demographic differences	455	Autism spectrum disorder	481
Measuring sleep—concussion	455	Schizophrenia	481
Conclusion	456	Behavioral treatment of insomnia	482
References	456	What is CBT-I?	482
32. Sleep health and dementia risk		CBT-I in the context of psychiatric disorders	482
<i>Christopher N. Kaufmann, Chien-Yu Tseng, Brendan P. Lucey, Atul Malhotra and Adam P. Spira</i>		Conclusion	483
Introduction	461	References	483
Sleep and aging	461	34. Insomnia and cardiometabolic disease risk	483
Overview of dementia	462	<i>Julio Fernandez-Mendoza and Casandra C. Nyhuis</i>	
Sleep and dementia risk	462	Abbreviations	489
Impact of sleep interventions on dementia risk	464	Introduction	489
Conclusions and future directions	465	Insomnia: A symptom and a chronic disorder	489
Funding	465	Hypertension and blood pressure	491
Conflicts of interest	466	Type 2 diabetes and insulin resistance	497
References	466	Heart disease and stroke	499
		Stress, immunity, and health behaviors	500
		Public health and clinical implications	501
		Conclusion	503
		Glossary	503
		References	504
Part VII			
Public health implications of sleep disorders			
33. Insomnia and psychiatric disorders		35. Sleep apnea and cardiometabolic disease risk	
<i>Ivan Vargas, Sheila N. Garland, Jacqueline D. Kloss and Michael L. Perlis</i>		<i>Bernie Sunwoo and Atul Malhotra</i>	
Abbreviations	473	What is OSA?	509
		Who gets OSA?	510
		Does having OSA make you more likely to have cardiovascular disease?	511
		Hypertension	511
		Coronary artery disease	512
		Cerebrovascular disease	512

Heart failure	513	Dysfunctional thoughts about sleep and fatigue	538
Arrhythmias	513	Napping and extending time in bed	538
Why does OSA make you more likely to have cardiovascular disease?	514	Diet	538
What happens if we reduce apneic events?	514	Measurement of sleep–wake disturbance in cancer	539
Conclusion	515	Screening for cancer-related sleep disturbance and fatigue	539
References	515	Clinical interview	539
36. Comorbid insomnia and sleep apnea (COMISA)		Sleep only measures	540
<i>Alexander Sweetman</i>		Fatigue only measures	540
Abbreviations	521	Sleep and wake measures	540
Potential conflicts of interest	521	Treatment of sleep–wake disturbances and fatigue in cancer	541
History of COMISA	521	Exercise	541
Characteristics	522	Pharmacotherapy	541
Prevalence	523	Mindfulness-based interventions	542
Consequences	524	Cognitive behavioral therapy for insomnia (CBT-I)	543
Sleep	524	Mindful movement interventions	543
Daytime function	524	Bright light therapy	544
Mental health	524	Future research and clinical recommendations	544
Physical health	524	References	545
Quality of life	525		
Mortality	525		
Bi-directional associations	525		
Treatment	526		
OSA treatment	526		
Insomnia treatment	527		
Conclusion	530		
References	530		
Further readings	534		
37. Sleep–wake disturbances and the cancer care continuum			
<i>Alexandria Muench, Krista Greeley and Sheila N. Garland</i>			
Prevalence of sleep disturbance and fatigue in cancer	535	Part VIII	
Mechanisms of sleep disturbance and cancer-related fatigue	536	Sleep health in children and adolescents	
Predisposing factors	536		
Genetics	536	38. Sleep, obesity, and cardiometabolic disease in children and adolescents	
Biological sex	537	<i>Teresa Arora and Ian Grey</i>	
Precipitating factors	537	Introduction	555
Tumorigenesis	537	Defining overweight and obesity in children	555
Cytokine and HPA axis dysregulation	537	Causes and consequences of childhood obesity	556
Dysregulation of central 5-HT	537	Causes	556
Cancer treatment	537	Consequences	556
Lifestyle changes and financial stress	538	Attempts to reduce the obesity epidemic	557
Mood disturbances	538	The importance of sleep in relation to health	557
Pain	538	Evidence for a link between sleep duration and obesity in pediatric populations	557
Perpetuating factors	538	Other sleep parameters and childhood obesity	558
		Sleep and energy homeostasis	559
		Neurological responses and cognitive control to food and the role of sleep	560
		Future directions	561
		Metabolic disease	561
		Mechanisms of diabetes	562

Sleep and type 2 diabetes mellitus	563	Work factors impact nighttime sleep	595
Sleep and children	565	Sleep impacts work function and productivity	595
Sleep, diabetes, and children	565	What theories of work can tell us about modifiable work factors influencing sleep	596
Conclusion	567		596
References	567	Epidemiology of sleep and work	596
Further readings	571	The relationship between sleep and work in meta-analyses and representative surveys	597
39. Sleep and mental health in children and adolescents		Theories of work and work stress that influence sleep	598
<i>Michelle A. Short, Kate Bartel and Mary A. Carskadon</i>		Work stress	598
Introduction	573	Work demands and work-family conflict influence sleep	599
Sleep duration and mental health	574	Micro-longitudinal (daily level) effects of work stressors on sleep	599
Sleep quality and mental health	576	Sleep health and workers' future health risks	600
Improving sleep and mental health in children and adolescents	578	Workplace intervention effects on sleep	600
Families	578	Business case for sleep: Considering the evidence from the employer point of view	600
Schools	578	Worksite wellness, and the need for more attention to sleep	601
Clinicians	579	Worksite programs targeting sleep and sleep-related outcomes	602
Policymakers	580	Racial ethnic disparities in sleep health and sleep disorders	602
Conclusion	580	Future research topics and directions	605
Summary	580	References	606
Limitations and future research directions	581		
Concluding remarks	581		
References	581		
40. Delayed school start times and adolescent health		42. Sleep and health equity	611
<i>Aaron T. Berger, Rachel Widome and Wendy M. Troxel</i>		<i>Judite Blanc, Jao Nunes, Natasha Williams, Rebecca Robbins, Azizi A. Seixas and Girardin Jean-Louis</i>	
Delaying high school start time improves sleep	586	Introduction: Sleep and public health	611
Academic achievement, attention, and truancy	586	What is sleep health?	612
Mental health and risky behavior	588	Social determinants of sleep health dimensions and associated health outcomes	612
Unintentional injury	589	Health differences and the historical sleep gap between blacks and whites	612
Conclusions	590	Identifying determinants of health differences	612
References	590	History behind the black–white “sleep gap”	614
		Sleep health as a contributor to health disparities in modern days	614
Part IX		From sleep health disparities toward sleep health equity	615
Economic and public policy implications of sleep health		Conclusion	618
41. Sleep and health in the workplace		References	618
<i>Soomi Lee, Chandra L. Jackson, Claire E. Smith, Rebecca Robbins and Orfeu Marcello Buxton</i>			
Introduction	595		

43. Identifying and treating obstructive sleep apnea in commercial vehicle operators: A summary of guidance for clinicians	
<i>Indira Gurubhagavatula, Aesha M. Jobanputra and Miranda Tan</i>	
Prevalence	621
History of federally funded research and regulatory activity	622
Screening	622
Initial evaluation	624
Diagnosis	624
Treatment	624
Monitoring PAP therapy	625
Benefits of PAP therapy	625
Education	625
Conclusion	625
References	625
44. Value-based sleep and health: Health economic aspects of insomnia and obstructive sleep apnea	
<i>Emerson M. Wickwire</i>	
Overview of sleep health economics	629
Direct and indirect costs of sleep disorders	629
Health-related quality of life	630
Economic perspective: Perceived value of sleep disorder treatments	630
Economic benefit of sleep disorder treatments	631
Health economics of insomnia treatment	631
Health economics of OSA treatment	631
Transition to value-based care	633
Future research directions	633
Conclusions	635
Acknowledgments	635
References	635
45. Sleep and athletes	
<i>Michael A. Grandner and Amy Athey</i>	
Prevalence of sleep concerns in athletes	639
Importance of sleep health in athletes	639
Guideline documents and consensus statements	640
Identification and management of sleep disorders	641
Screening for sleep disorders	643
Developing a referral strategy for managing sleep disorders	643
Education and culture	643
Elements of an educational program	644
Optimization and competitive advantage	644
Improving healthy sleep	646
Ongoing monitoring programs	646
Managing travel and jetlag for performance	646
Evaluation of schedules	646
Utilizing circadian technology	646
Conclusion	646
References	647
46. Digital and telehealth sleep health interventions	
<i>Ruth K. Brombach and Jessica R. Dietrich</i>	
Introduction	649
Defining terms: Digital health, mHealth, eHealth, and telehealth	649
An exemplar digital sleep health intervention: dCBTI	650
Effectiveness of dCBTI	654
Advantages and benefits of dCBTI	654
Challenges and opportunities for dCBTI and other digital sleep health interventions	654
Personalization	654
Therapeutic relationship	655
Digital literacy	655
dCBTI and other digital sleep health interventions belong in a stepped care model	655
Conclusions and future directions	656
References	656
47. Sleep health in the primary care setting	
<i>Ivan Vargas, Jamie Walker, Mara Egeler, Abigail Vance, Julia T. Boyle and Alexandria Muench</i>	
Introduction	659
Prevalence and risk	659
Assessment	660
Treatment	661
Barriers and challenges	661
Future directions	662
References	662
48. Sleep health as an issue of public safety	
<i>Alexander P. Wolkow, Laura K. Barger and Matthew D. Weaver</i>	
Introduction	667

Demographics	667	49. The rise of patient advocacy in the sleep field	
Organizational structure	667		
Individuals	668		
Work hours and scheduling characteristics	668	<i>Julie Flygare</i>	
Shift duration	669	Introduction: The long road ahead	681
Weekly work hours	669	The power of patient advocacy	681
The association between work schedules and health and safety outcomes	669	Advancing patient-centered research	
Implementation of schedules based on sleep and circadian principles	670	and care in the sleep field	682
Physiological determinants of alertness	670	Sleep-related patient advocacy groups	682
Physiological determinants of fatigue in public safety	670	Increasing sleep awareness by elevating	
Sleep deficiency and health	672	patient voices	683
Sleep disorders	672	Partnership in research process	684
Fatigue risk management	674	Engaging PAGs and patient advocates	684
Conclusion	675	Patient inclusion at conferences	685
References	675	Patient inclusion on advisory boards	686
		Conclusion: Looking toward a brighter	
		future	686
		References	687
		Index	689

This page intentionally left blank

Contributors

Pamela Alfonso-Miller, Northumbria Sleep Research Laboratory, Northumbria University, Newcastle, United Kingdom

Sarah F. Allen, Northumbria Sleep Research Laboratory, Northumbria University, Newcastle, United Kingdom

Teresa Arora, Zayed University, College of Natural and Health Sciences, Department of Psychology, Abu Dhabi, United Arab Emirates

Rebecca Ashare, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States

Amy Athey, Athey Performance, Virginia Beach, VA, United States

Laura K. Barger, Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA, United States; Division of Sleep Medicine, Harvard Medical School, Boston, MA, United States

Kelly Glazer Baron, Division of Public Health, Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, United States; Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL, United States

Kate Bartel, School of Psychology, Flinders University, Adelaide, SA, Australia

Mathias Basner, Unit for Experimental Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States

Aaron T. Berger, Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, United States

Bharat Bhushan, Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

Martha E. Billings, Division of Pulmonary, Critical Care & Sleep Medicine, University of Washington, Seattle, WA, United States

Amanda Black, Department of Kinesiology, Faculty of Applied Health Sciences, Brock University, St. Catharines, ON, Canada

Judite Blanc, University of Miami Miller School of Medicine, Department of Psychiatry & Behavioral Sciences, Center for Translational Sleep and Circadian Sciences, Miami, FL, United States; University of Miami Miller, School of Medicine, Department of Psychiatry & Behavioral Sciences, Center for Translational Sleep and Circadian Sciences, Miami, FL, United States

Julia T. Boyle, Office of Research and Development, VA Boston Healthcare System, Boston, MA, United States; New England Geriatric Research Education and Clinical Center, VA Boston Healthcare System, Boston, MA, United States; Department of Psychiatry, Harvard Medical School, Boston, MA, United States

Ruth K. Brombach, Oregon State University, School of Psychological Science, Corvallis, OR, United States

Orfeu Marcello Buxton, Center for Healthy Aging, Pennsylvania State University, University Park, PA, United States; Department of Biobehavioral Health, Pennsylvania State University, University Park, PA, United States

Mary Carrasco, Department of Informatics and Health Data Science, University of Miami Miller School of Medicine, Miami, FL, United States; Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States

Mary A. Carskadon, E.P. Bradley Hospital, Brown University, Providence, RI, United States

Subhajit Chakravorty, Perelman School of Medicine, Philadelphia, PA, United States

Anne-Marie Chang, Department of Biobehavioral Health, Pennsylvania State University, University Park, MA, United States

Jonathan Charest, School of Psychology, Université Laval, Québec, QC, Canada

Ninad S. Chaudhary, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, United States; Department of Neurology, University of Alabama School of Medicine, Birmingham, AL, United States

Debbie Chung, Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States

Elizabeth Culnan, Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL, United States

Jessica R. Dietch, Oregon State University, School of Psychological Science, Corvallis, OR, United States

Hannah K. Dollish, Center for Adolescent Rewards, Rhythms, and Sleep, University of Pittsburgh, Pittsburgh, PA, United States

Mara Egeler, Department of Psychology, University of Notre Dame, Notre Dame, IN, United States

Jason G. Ellis, Northumbria Sleep Research Laboratory, Northumbria University, Newcastle, United Kingdom

Omobomi Fashanu, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Julio Fernandez-Mendoza, Penn State Health Sleep Research & Treatment Center, Behavioral Sleep Medicine Program, Hershey, PA, United States; Penn State College of Medicine, Hershey, PA, United States; Department of Psychiatry and Behavioral Health, Penn State College of Medicine, Hershey, PA, United States

Fabian-Xosé Fernandez, Evelyn F. McKnight Brain Institute, Department of Psychology, University of Arizona, Tucson, AZ, United States

Sarah Flora, University of Alabama, Tuscaloosa, AL, United States

Sofia K. Fluke, Sleep and Performance Research Center, Department of Translational Medicine and Physiology, Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, United States

Julie Flygare, Project Sleep, Los Angeles, CA, United States

Makayla Freeman, Department of Educational and Counselling Psychology, and Special Education, University of British Columbia, Vancouver, BC, Canada

Sheila N. Garland, Department of Psychology and Discipline of Oncology, Memorial University, St. John's, NL, Canada; Department of Psychology and Discipline of Oncology, Memorial University, St. John's, NL, Canada; Division of Oncology, Faculty of Medicine, Memorial University, St. John's, NL, Canada

Symielle A. Gaston, Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, United States

Nalaka S. Gooneratne, Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; Sleep Medicine Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

Suzanne Gorovoy, Department of Behavioral Sleep Medicine, University of Arizona College of Medicine, Tucson, AZ, United States

Michael A. Grandner, Sleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States

Krista Greeley, Department of Psychology, Memorial University, St. John's, NL, Canada

Ian Grey, United Arab Emirates University, Abu Dhabi, United Arab Emirates

Indira Gurubhagavatula, Department of Medicine, Division of Sleep Medicine, Perelman School of Medicine at the University Hospital of Pennsylvania Medical Center, Philadelphia, PA, United States; Sleep Disorders Clinic, Philadelphia VA Medical Center, Philadelphia, PA, United States

Lauren Hale, Program in Public Health, Department of Family, Population, and Preventive Medicine, Stony Brook University School of Medicine, Stony Brook, NY, United States

Kimberly Hayes, Cpl. Michael J. Crescenz VA Medical Center, Philadelphia, PA, United States

Alisa Huskey, Department of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States

Chandra L. Jackson, Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, United States; Division of Intramural Research, National Institute on Minority Health and Health Disparities, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, United States

Sarah James, Department of Sociology and Office of Population Research, Princeton University, Princeton, NJ, United States

Sogol Javaheri, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Girardin Jean-Louis, NYU Langone Health, Department of Population Health, New York, NY, United States; NYU Langone Health, Department of Psychiatry, New York, NY, United States; University of Miami Miller, School of Medicine, Department of Psychiatry & Behavioral Sciences, Center for Translational Sleep and Circadian Sciences, Miami, FL, United States; University of Miami Miller School of Medicine, Department of Psychiatry & Behavioral Sciences, Center for Translational Sleep and Circadian Sciences, Miami, FL, United States; Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States

Aesha M. Jobanputra, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, United States

Dayna A. Johnson, Division of Sleep and Circadian Disorders, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

Christopher N. Kaufmann, Department of Health Outcomes and Biomedical Informatics, University of Florida College of Medicine, Gainesville, FL, United States

Jasleen Kaur, Department of Psychology, University of Regina, Regina, SK, Canada

Christopher E. Kline, Physical Activity Research Center, Department of Health and Human Development, University of Pittsburgh, Pittsburgh, PA, United States

Jacqueline D. Kloss, Behavioral Sleep Medicine Program, University of Pennsylvania, Philadelphia, PA, United States

Adam Knowlden, The University of Alabama, Health Science, Tuscaloosa, AL, United States

Ryan Krouse, Coatesville VA Medical Center, Coatesville, PA, United States

Soomi Lee, Department of Human Development and Family Studies, Pennsylvania State University, University Park, PA, United States; Center for Healthy Aging, Pennsylvania State University, University Park, PA, United States

Junxin Li, Johns Hopkins University School of Nursing, Baltimore, MD, United States

Brendan P. Lucey, Department of Neurology, Washington University School of Medicine in St. Louis, St. Louis, MO, United States

Anna L. MacKinnon, Département de psychiatrie et d'addictologie, Université de Montréal, Montréal, QC, Canada; Centre de recherche Azrieli du CHU Sainte-Justine, Montréal, QC, Canada

Atul Malhotra, Department of Medicine, Division of Pulmonary, Critical Care, Sleep Medicine and Physiology, University of California San Diego, San Diego, CA, United States; UCSD, Medicine, La Jolla, CA, United States; Division of Pulmonary, Critical Care, Sleep Medicine, and Physiology, Department of Medicine, University of California San Diego, San Diego, CA, United States

Susan Kohl Malone, Rory Meyers College of Nursing, New York University, New York, NY, United States

Catherine A. McCall, Department of Pulmonary, Critical Care, and Sleep Medicine, VA Puget Sound Health Care System, Seattle, WA, United States; Department of Psychiatry, University of Washington Sleep Medicine Center, Seattle, WA, United States

Jocelyn McCallum, University of Calgary, Faculty of Kinesiology, Calgary, AB, Canada

Jessica Meers, Department of Medicine, Baylor College of Medicine, Houston, TX, United States

Maria A. Mendoza, Rory Meyers College of Nursing, New York University, New York, NY, United States

Audrey Mills, Drexel University College of Medicine, Philadelphia, PA, United States

Rhoda Moise, Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States

Favel L. Mondesir, Division of Cardiovascular Medicine, School of Medicine, University of Utah, Salt Lake City, UT, United States

Alexandria Muench, Department of Hematology Oncology, Penn Princeton, Princeton, NJ, United States; Behavioral Sleep Medicine Program, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, United States

Sara Nowakowski, Department of Medicine, Baylor College of Medicine, Houston, TX, United States

Jao Nunes, The City College of New York, New York, NY, United States

Cassandra C. Nyhuis, Penn State College of Medicine, Hershey, PA, United States

Freda Patterson, Department of Behavioral Health and Nutrition, College of Health Sciences, University of Delaware, Newark, DE, United States

Michael L. Perlis, Behavioral Sleep Medicine Program, University of Pennsylvania, Philadelphia, PA, United States; University of Pennsylvania Perelman School of Medicine, Department of Psychiatry, Philadelphia, PA, United States

- Priyamvada M. Pitale**, Department of Optometry and Vision Science, School of Optometry, University of Alabama at Birmingham, Birmingham, AL, United States
- Aric A. Prather**, Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA, United States
- Susan Redline**, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States
- David A. Reichenberger**, Oregon Institute of Occupational Health Sciences, Oregon Health & Science University, Portland, OR, United States
- Rebecca Robbins**, Division of Sleep Medicine, Harvard Medical School, Boston, MA, United States; Division of Sleep and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital, Boston, MA, United States; Harvard Medical School, Faculty of Arts & Sciences, Brigham and Women's Hospital, Harvard T.H. Chan School of Public Health, Boston, MA, United States
- Mary E. Rosenberger**, Stanford Center on Longevity and Psychology Department, Stanford University, Stanford, CA, United States
- Katherine Saed**, Institute of Human Nutrition, Columbia University Irving Medical Center, New York, NY, United States
- Charles H. Samuels**, Faculty of Medicine, Faculty of Kinesiology, University of Calgary, Calgary, AB, Canada
- Brieann C. Satterfield**, Sleep and Performance Research Center, Department of Translational Medicine and Physiology, Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, United States
- Carolina Scaramutti-Gladfelter**, Department of Informatics and Health Data Science, University of Miami Miller School of Medicine, Miami, FL, United States; Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States
- William D. Scott Killgore**, Social, Cognitive, and Affective Neuroscience (SCAN) Laboratory, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, United States
- Azizi A. Seixas**, Department of Informatics and Health Data Science, University of Miami Miller School of Medicine, Miami, FL, United States; Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States
- States; Harvard Medical School, Faculty of Arts & Sciences, Brigham and Women's Hospital, Harvard T. H. Chan School of Public Health, Boston, MA, United States; NYU Langone Health, Department of Population Health, New York, NY, United States
- Michelle A. Short**, School of Psychology, Flinders University, Adelaide, SA, Australia
- Katherine Silang**, Department of Psychology, University of Calgary, Calgary, AB, Canada
- Rupsha Singh**, Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, United States
- Isaac Smith**, Institute of Human Nutrition, Columbia University Irving Medical Center, New York, NY, United States
- Claire E. Smith**, Department of Psychology, University of South Florida, Tampa, FL, United States
- Cynthia K. Snyder**, School of Nursing and Allied Health, St. Joseph's University, Lancaster, PA, United States
- Andrea M. Spaeth**, Department of Kinesiology and Health, School of Arts and Sciences, Rutgers University, New Brunswick, NJ, United States
- Adam P. Spira**, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, United States; Johns Hopkins Center on Aging and Health, Baltimore, MD, United States
- Marie-Pierre St-Onge**, Institute of Human Nutrition, Columbia University Irving Medical Center, New York, NY, United States; Division of Endocrinology, Department of Medicine, Columbia University Irving Medical Center, New York, NY, United States; Sleep Center of Excellence, Department of Medicine, Columbia University Irving Medical Center, New York, NY, United States
- Jacqueline Stout-Aguilar**, School of Nursing, University of Texas Medical Branch, Galveston, TX, United States
- Bernie Sunwoo**, Department of Medicine, Division of Pulmonary, Critical Care, Sleep Medicine and Physiology, University of California San Diego, San Diego, CA, United States
- Alexander Sweetman**, School of Psychological Science, University of Western Australia, Perth, WA, Australia
- Miranda Tan**, Department of Psychiatry and Behavioral Services, Division of Sleep Medicine, Stanford

- University School of Medicine, Stanford, CA, United States
- Sujata Thawani**, Department of Neurology, NYU Langone Health, New York, NY, United States
- Lianne Tomfohr-Madsen**, Department of Educational and Counselling Psychology, and Special Education, University of British Columbia, Vancouver, BC, Canada
- Sophia Tong**, Macaulay Honors College, Hunter College, CUNY, New York, NY, United States
- Wendy M. Troxel**, RAND Corporation, Santa Monica, CA, United States
- Chien-Yu Tseng**, Department of Pharmaceutical Outcomes and Policy, University of Florida College of Pharmacy, Gainesville, FL, United States
- Andrew Scott Tubbs**, Washington University School of Medicine, Department of Psychiatry, St. Louis, MO, United States; Sleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States
- Abigail Vance**, Department of Psychology, University of Notre Dame, Notre Dame, IN, United States
- Ivan Vargas**, Behavioral Sleep Medicine Program, University of Pennsylvania, Philadelphia, PA, United States; Center for Sleep and Circadian Neurobiology, University of Pennsylvania, Philadelphia, PA, United States; Department of Psychology, University of Notre Dame, Notre Dame, IN, United States
- Jamie Walker**, Department of Psychological Science, University of Arkansas, Fayetteville, AR, United States
- Douglas M. Wallace**, Department of Neurology, Sleep Medicine Division, University of Miami Miller School of Medicine, Miami, FL, United States; Miami VA HealthCare System, Sleep Disorders Laboratory, Miami, FL, United States
- Nathaniel F. Watson**, Department of Neurology, University of Washington Sleep Medicine Center, Seattle, WA, United States
- Dana Watts**, Department of Psychology, University of Calgary, Calgary, AB, Canada
- Matthew D. Weaver**, Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA, United States; Division of Sleep Medicine, Harvard Medical School, Boston, MA, United States
- Emerson M. Wickwire**, Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, United States; Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, United States
- Rachel Widome**, Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, United States
- Natasha Williams**, NYU Langone Health, Division of Health and Behavior, Department of Population Health, Center for Healthful Behavior Change, New York, NY, United States
- Sandra Wittleder**, Department of Medicine, NYU Grossman School of Medicine, New York, NY, United States
- Alexander P. Wolkow**, School of Psychological Sciences, Monash University, Clayton, VIC, Australia
- Qian Xiao**, Department of Health and Human Physiology and Department of Epidemiology, University of Iowa, Iowa City, IA, United States

This page intentionally left blank

Preface

Over the past several years, there has been an increasing interest in the topic of “Sleep and Health,” which motivated the creation of this book. Although it has been known since the 1960s that population-level sleep variables were associated with health, daytime function, and even mortality—alongside diet, physical activity, smoking, alcohol use, etc.—the scientific landscape was quite sparse until more recently. In general, sleep research focused almost exclusively on basic sleep physiology and neuroscience or on clinical sleep disorders in terms of their etiology, pathophysiology, diagnosis, and treatment. The issue of sleep as a health issue in general was not widely pursued scientifically.

In the 1990s, research on sleep apnea demonstrated that not only did this condition represent a serious cardiovascular and metabolic risk factor, but also that it was much more prevalent than previously believed. This brought attention to sleep from those in the public health domain. This emerging focus on the public health impact of sleep disorders also coincided with the reemergence in the scientific literature of studies documenting the relationship between habitual sleep duration and mortality. The time was seemingly right, and this issue which had been somewhat dormant for decades was approached with renewed interest. Further, studies documenting potential mechanisms of this mortality relationship started to emerge, linking sleep duration with metabolism, brain function, obesity, cardiovascular disease, and other conditions.

In this period of time, the field of sleep research widened to address not only basic science and clinical conditions/treatments, but also issues related to sleep and health in general. Sleep duration items started to find their way into epidemiologic surveys and health surveillance efforts with increasing regularity. This led to hundreds of papers documenting relationships between habitual sleep variables at the population level and a wide range of outcomes. The emergence of this literature coincided with an increased recognition in the general public of the importance of sleep health. Popular press articles about sleep health started appearing with more frequency. Consumer technology began to address tracking and optimizing sleep. Athletes publicly bragged about how much sleep they got

in order to better prepare for competition. Political and business leaders publicly lamented the fact that their schedules disallowed sufficient sleep. The conversation was changing. This book will hopefully address this interest and provide useful information about ways that sleep is related to important aspects of health.

The purpose of this book is to serve as a sort of a handbook for individuals interested in the field of sleep and health. Members of the sleep research community more familiar with basic and/or clinical science may find this volume useful for better understanding the role of these basic and clinical processes in a public health context. Especially for those unfamiliar with the role of societal factors in health, this book may be useful for understanding these topics from a scientific perspective. This is important, as a wider translational view of the sleep field is necessary for understanding the mechanisms of these phenomena and their relationships to health. This volume should also be useful for public health professionals and others who study the role of health in society. These individuals may have experience in other domains of health but may need to better understand the importance of sleep in these contexts. Those who specialize in studying obesity, behavioral health, cardiovascular disease, or other areas may find this volume useful in relating those areas to sleep. There are also sections devoted to those who have a specific interest in policy, so that better policy decisions can be made in light of current research and data. Thus, this book has a wide range of applications, including helping those with sleep expertise gain a wider view on the role of sleep in society and helping those with expertise in social factors in health who wish to get a better understand of the importance of sleep.

To accomplish these goals, this book is divided into nine sections.

- The first section is “General Concepts in Sleep Health” and includes chapters on the basics of sleep physiology and measurement, basic epidemiology of sleep health factors, basic information about sleep across age and gender, and an introduction to the social-ecological model of sleep and health. This section will orient those new to the field of sleep to some of the basic concepts in sleep physiology and ontogeny.

- The second section is “Contextual Factors Related to Sleep” and focuses on the impact of where a person is and how that affects their sleep. This section includes chapters that address issues such as race/ethnicity, socio-economics, neighborhood factors, and other environmental exposures. These are often important elements that serve as determinants of health and have been shown to be linked to sleep in important ways.
- The third section is about “Addressing Sleep Health at the Community and Population Level.” It includes chapters on dealing with real-world obstacles in the way of healthy sleep, screening for and preventing sleep disorders, addressing sleep hygiene, understanding sleep tracking and technology, understanding the role of mobile technology and screen time in relation to sleep, and different ways of conceptualizing sleep in the context of other aspects of health. This section is somewhat broad but bridges basic understandings of sleep to real-world problems and constraints including schedule demands, technology, and access to healthcare.
- The fourth section is “Sleep Duration and Cardiometabolic Disease Risk” and includes chapters addressing connections between sleep/circadian issues and obesity, cardiovascular disease, and obesity. Since cardiometabolic diseases are still the leading causes of death in society, the many connections to sleep are especially relevant for those with an interest in public health.
- The fifth section is specifically focused on “Sleep and Behavioral Health,” since most of the underlying causes of chronic disease are driven by patterns in behavior. With this in mind, this section includes chapters that address many aspects of health behavior, including diet, physical activity, smoking, alcohol, caffeine and stimulants, and stress/immune function.
- The sixth section summarizes the literature on “Sleep Loss and Neurocognitive Function” and includes chapters that address vigilant attention, decision-making, learning and memory, and other brain functions. It also includes a chapter on how these effects on brain function impact not only safety and brain health but also chronic disease and healthy choices.
- The seventh section briefly discusses “Public Health Implications of Sleep Disorders” and includes chapters on the most common sleep disorders including insomnia and sleep apnea. Although many other books address sleep disorders specifically, this section focuses specifically on public health implications.
- The eighth section covers topics specifically relevant to “Sleep Health in Children and Adolescents” and includes chapters on cardiometabolic health risk, mental health, and impacts of delayed school start times. These issues have both health and policy implications.
- The final section is dedicated to “Economic and Public Policy Implications of Sleep Health” and lays out the science behind specific policy implications. These include issues such as health equity, sleep and health in the workplace, sleep and public safety, and sleep and transportation safety.

Hopefully, the next edition will address important topics that did not find their way into this one. For example, telehealth and telemedicine is a growing issue that is impacting both public health and public policy; and sleep medicine has been at the forefront of this movement. Also, even though there are chapters on insomnia and sleep apnea, these are not the only sleep disorders with public health implications—for example, restless legs syndrome and other sleep-related movement disorders have cardiometabolic implications, parasomnias have important forensic implications, narcolepsy is an important issue in the context of widespread immunization as a public health strategy, etc. And although there were chapters on race/ethnicity, this volume is still limited in its treatment of cultural beliefs and practices that play important roles in sleep. In terms of societal efforts to address sleep health, a future edition of this volume should probably address the rapidly growing interest in sleep among the athletics community. The next volume could also include chapters on the functions of sleep from an evolutionary biology perspective, empirically supported interventions for promoting sleep health at the community/population level, the public health issue of sleep and dementia risk, and economic impacts of sleep loss and untreated sleep disorders. There is still a lot of work to do!

The current volume brings together many of the leaders of the field to discuss a wide range of topics that encompass the field of sleep and health. This book provides useful information for a wide range of stakeholders and will hopefully contribute to the increasing interest in the field. At the end of the day, sleep is a foundational part of human biology and physiology. And sleep health can impact many systems in the body. This book is meant to start a conversation about all of these connections. It is hoped that this conversation leads to work that helps us to lead longer, healthier, more fulfilling lives.

Acknowledgments

This book represents the combined work of a lot of people over quite a long time. I would first like to thank all of the friends, colleagues, and experts I look up to (some individuals falling into multiple categories) who took the time to write thoughtful, informative, and helpful chapters on such a wide range of topics. It is truly amazing and actually quite humbling to see the incredible names on the list of contributing authors. So, thank you.

I also want to specifically thank a number of authors specifically who shaped the thinking around the content of the book, including Teresa Arora, Laura Barger, Kelly Baron, Mathias Basner, Orfeu Buxton, Mary Carskadon, Subhajit Chakravorty, Anne-Marie Chang, Ninad Chaudhary, Jay Ellis, Fabian Fernandez, Julio Fernandez-Mendoza, Sheila Garland, Nalaka Gooneratne, Indira Gurubhagavatula, Lauren Hale, Chandra Jackson, Girardin Jean-Louis, Dayna Johnson, Scott Killgore, Chris Kline, Adam Knowlden, Atul Malhotra, Sara Nowakowski, Freda Patterson, Michael Perlis, Aric Prather, Susan Redline, Mary Rosenberger, Azizi Seixas, Andrea Spaeth, Marie-Pierre St-Onge, Alex Sweetman, Lianne Tomfohr-Madsen, Wendy Troxel, Nate Watson, and Natasha Williams.

Managing a project like this takes a lot of effort and time, and I am really fortunate to have great staff at the Sleep and Health Research Program. Victor Chiquete managed the project, kept everything moving forward, and made sure that everybody was informed throughout the process. Denisse Armenta also deserves special mention for helping to make this book a reality. And the entire team

at Elsevier has been nothing short of amazing through this whole process from start to finish, especially Sara Pianavilla who stayed patient with me as we made it through this second edition!

I need to acknowledge my mentors, especially Michael Perlis, Allan Pack, Daniel Kripke, Sonia Ancoli-Israel, and Donna Giles. You will always be my role models for how to be a scholar, a teacher, a leader, and a communicator. I hope that this book can inspire people to work to improve others' lives as you have inspired me.

The concept of "sleep and health" is complicated and changing. Many individuals in addition to those already mentioned above have played important roles in shaping how I have approached this topic. These include Celyne Bastien, Janet Croft, David Dinges, Reuven Ferziger, Phil Gehrman, Kristen Knutson, Sanjay Patel, Megan Petrov, Dorothy Roberts, Michael Twery, Terri Weaver, Emerson Wickwire, Shawn Youngstedt, and others. I want to specifically acknowledge the influence of Nirav Patel, who coined the term "sleep disparity" and had the original idea for what became the Social-Ecological Model of Sleep and Health. He was a great friend and colleague, and I think he would be glad to see how far the field has come in such a short amount of time. This book is dedicated to his memory.

Most importantly, I want to thank my wife Ana Liza and our boys Benjy and Charlie, who give all my work meaning and inspire me to always ask questions, push boundaries, and make a difference. I hope that this book does all those things.

This page intentionally left blank

Part I

General concepts in sleep health

This page intentionally left blank

Chapter 1

The basics of sleep physiology and behavior

Andrew Scott Tubbs^{a,b}, Hannah K. Dollish^c, Fabian-Xosé Fernandez^d and Michael A. Grandner^a

^aSleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States;

^bWashington University School of Medicine, Department of Psychiatry, St. Louis, MO, United States; ^cCenter for Adolescent Rewards, Rhythms, and Sleep, University of Pittsburgh, Pittsburgh, PA, United States; ^dEvelyn F. McKnight Brain Institute, Department of Psychology, University of Arizona, Tucson, AZ, United States

Introduction

Sleep is an essential element of human health, supporting a wide range of systems including immune function, metabolism, cognition, and emotional regulation. To understand everything that sleep does, however, it is necessary to understand what sleep is. This chapter provides that foundation by discussing the conceptualization, physiology, and measurement of sleep.

The definition of sleep

Sleep is a naturally recurring and reversible biobehavioral state characterized by relative immobility, perceptual disengagement, and subdued consciousness. As a predictable and easily reversible phenomenon, sleep is distinct from states of anesthesia and coma, which typically involve the absence or suppression of neural activity. Additionally, proper sleep involves a dynamic interaction between *voluntary* decisions and *involuntary* biological activities. Turning off the lights, reducing noise, and lying down are voluntary behaviors, but the result is an involuntary increase in melatonin and a series of shifts in the activity patterns of the brain throughout the night. Sleep ultimately depends on this collaboration between behavior and biology, and a deficit in either will disrupt sleep.

Conceptualizing sleep as a health behavior

A health behavior is an action (or lack of action) by an individual that impacts their health. Conceptualizing sleep as a health behavior highlights how behavior and neurobiology interact, and how individuals can modify their health through sleep. Viewed in this way, sleep can be

divided into three processes: sleep need, sleep ability, and sleep opportunity. These processes are diagrammed in Fig. 1.1.

Sleep need is the biological requirement for sleep, or the minimal amount of rest the body requires to prepare for the next day. This need is defined by individual genetics and physiology and does not change after losing a night of sleep or oversleeping on the weekends. Unfortunately, there is no standard method for measuring sleep need. Although epidemiological studies suggest an average of 7–8 h for healthy adults, some individuals naturally need more sleep (e.g., children and adolescents) and some need less. Sleep need represents the core motivation for engaging in sleep and consistently failing to meet this need can promote cardiometabolic disease, impair cognitive functioning, and increase risk for psychiatric disorders.

The only way to satisfy sleep need is to sleep. The amount of sleep an individual can achieve is known as **sleep ability** and is approximated by total calculated sleep time. Unlike sleep need, sleep ability can change from one night to the next depending on life circumstances. Stress, a cold, or the death of a loved one can reduce sleep ability, while one night of sleep deprivation can increase sleep ability the following evening. Sleep ability cannot be directly controlled but it can be influenced by behavior.

Sleep opportunity is the time a person *makes available* for sleep. Sleep opportunity is measured by the amount of time the person stays in bed (although time spent in habitual “bedtime” activities like reading a book could theoretically be incorporated). Unlike the two previous processes, sleep opportunity is under conscious control and is the most vulnerable to environmental factors. This is illustrated by a trauma resident on a 24-h call:



FIGURE 1.1 A three process model of sleep. Sleep occurs as a function of the biological need for sleep, the behavioral opportunity for sleep, and an individual's present capacity for sleep.

accumulating fatigue slowly increases the resident's ability to sleep, but there is no sleep opportunity since the resident must be ready at a moment's notice to respond to a life-threatening crisis.

These three sleep processes work together to control sleep. Sleep need motivates the creation of sleep opportunity, which provides a context for sleep ability to produce sleep—thus satisfying sleep need and reinforcing the methods used to create sleep opportunity in the first place.

Conceptualizing sleep as a physiological process

Sleep involves a progression of neurophysiological changes in the brain. These changes are grouped (somewhat artificially) into stages based on scoring convention. To explore these changes, this section will briefly describe wakefulness and then proceed to give a description of each of the sleep stages.

Wakefulness

During wake, the brain is engaged in numerous, unrelated activities. For example, someone might be watching a TV show while listening for the sound of a car in the rain and thinking about whether there is enough food in the refrigerator for lunch tomorrow. The aggregated electrical activity produced by these processes can be observed using electroencephalography (EEG), as a high-frequency, low-amplitude signal traveling across the surface of the brain (Fig. 1.2). To understand what this means, imagine a crowd cheering in a sports stadium. Everyone is shouting at different times. This means that someone is always cheering (high frequency), but it is impossible to discern individual words because everyone's words are drowning each other out (low amplitude). Similarly, a high-frequency signal means many different processes are present in the circuitry of the brain, but the timing of these processes is scattered.

Because this activity is widespread, it is hard to resolve any one particular process, resulting in a low amplitude signal. The beta frequency is the classic frequency of active wake and ranges from 12 to 30 Hz (cycles per second). When subjects lie down and close their eyes, electrical activity generally slows to an alpha frequency (8.5–12 Hz), which indicates that the person is awake but not necessarily attending to their surroundings (Fig. 1.2). Along with electrical activity, wakefulness is characterized by high levels of arousal neurotransmitters, such as dopamine, noradrenaline, and serotonin. There is also increased autonomic activity; heart rate, respiratory rate, and blood pressure are constantly responding and adapting to changes in the body and the environment throughout the day.

NREM sleep: General overview

The first half of the sleep cycle can be divided into three distinct stages of non-rapid eye movement (NREM) sleep, aptly named stage 1, stage 2, and stage 3. Electrical activity throughout the brain decreases in frequency and increases in amplitude at each progressive stage. This reflects a reduction in overall neural activity but an increasing coordination among neurons (i.e., enhanced oscillation). Recalling the example from above, imagine if the crowd slowly coordinated their cheering. At first, the sound would still be noisy and unintelligible. However, once everyone followed along, a wave of quiet alternating with cheering would emerge. The number of cheers would decrease (lower frequency), but the volume and clarity of each cheer would steadily increase (higher amplitude). By the end of NREM the electrical activity of the brain is tightly synchronized, leading to lower frequency, higher amplitude oscillating waves known as “slow waves,” which cycle about once every second. The final stage of NREM is commonly referred to as slow wave sleep (SWS) because of the dominance of these waves.

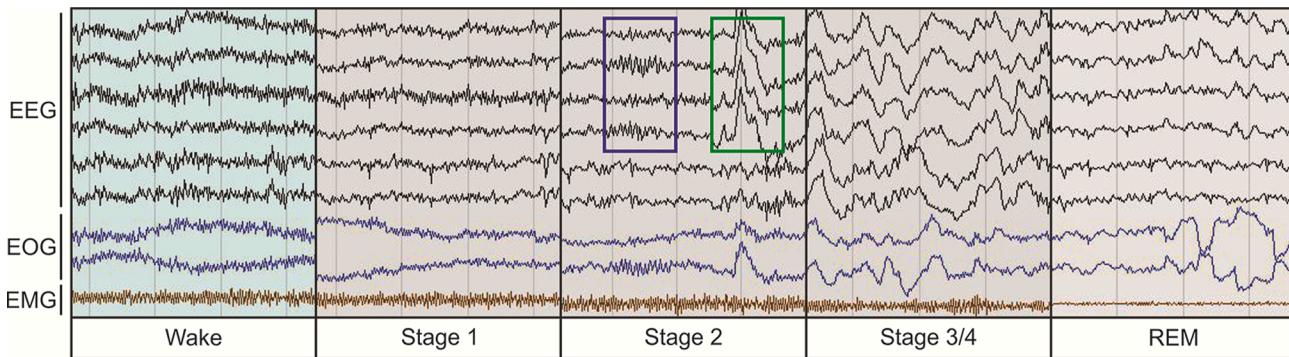


FIGURE 1.2 Example traces of the stages of sleep. This polysomnography data includes six channels of electroencephalography (EEG), two channels for electrooculography (EOG, eye movements), and one channel for electromyography (EMG, muscle tone). *Blue box* highlights a sleep spindle. *Green box* highlights a k-complex. Notice how in REM sleep the electrical activity is similar to wake or stage 1, but there is a complete lack of motor activity. *Images taken from an anonymous human recording.*

NREM sleep is also accompanied by a global decrease in wake-related neurotransmitters and impaired perception of external stimuli. In fact, most sensory inputs are specifically filtered out by the thalamus to protect sleep. Indices of autonomic activity such as heart rate, respiratory rate, temperature, and blood flow to the brain are reduced as one advances from one NREM stage to the next. Motor activity is markedly reduced but not completely absent.

NREM: Stage dissection

The Rechtschaffen and Kales scoring criteria divide NREM into four stages [1], while the more current American Academy of Sleep Medicine (AASM) criteria combine the last two NREM stages [2] since the distinction is not viewed as clinically relevant [3]. Here, in our stage dissection of NREM, we observe the AASM criteria.

Stage 1 is characterized by approximately 50% alpha frequency activity and the emergence of *theta* waves (4–7 Hz) in the EEG trace. Nonelectrophysiological markers can also include slow-rolling eye movements, unusual visual sensations that take the form of clouds or flares of light (phosphenes), and hypnagogic myoclonia, which are brief jerking movements. The arousal thresholds for waking during stage 1 are selective, as the brain determines if there is something worth attending to or whether it can commit to extended sleep. Here, for example, one's name spoken softly can awaken a person, whereas a similar sounding word spoken at the same intensity might not. Stage 1 accounts for 5% of total sleep time and, in healthy sleep, is the entry point for NREM stage 2.

Stage 2 is characterized by the absence of slow-rolling eye movements, mixed frequency neurophysiological activity, and the presence of two major transient electrical phenomena: k-complexes and sleep spindles. K-complexes are large-amplitude rapidly fluctuating bursts of brain activity, while spindles are 12–15 Hz oscillating signals

lasting 0.5–2 s (Fig. 1.2). These phenomena are theorized to support memory consolidation and/or filter sensory input. Stage 2 sleep comprises 45%–55% of total sleep time and is viewed as a bridge between light (stage 1) and deep (stage 3) NREM sleep.

Stage 3 sleep is often referred to as SWS owing to the prominence of high-amplitude, low-frequency *delta* oscillations recurring at ~1 Hz. The amount of time an individual spends in SWS positively correlates with lack of sleep, such that SWS is elevated during the first sleep cycle after a prolonged period of wakefulness. SWS is thought to discharge sleep pressure that has accumulated throughout the day because the amount of time spent in this stage decreases dramatically as the night progresses. SWS tends to coincide with the timing of peak growth hormone secretion, hinting at a role for this sleep stage in nightly maintenance and repair of the body. Additionally, oscillations that appear during SWS may function as a broad conduit for the repeated activation of memory centers of the brain to support memory-strengthening. The end of stage 3 NREM sleep is usually followed by entry into REM sleep.

Description of REM sleep

Rapid eye movement (REM) sleep represents a categorical shift in sleep-related brain activity and forms the latter half of the sleep cycle. While most neurotransmitters drop to low levels, acetylcholine levels match or exceed those produced during wake. The surge in acetylcholine creates patterns of electrical activity in the sleeping brain that approximate the high-frequency, low-amplitude patterns usually seen in alert individuals. Despite this increase in overall excitability, there is a paradoxical loss of muscle movement (i.e., sleep paralysis). The only exceptions are eye muscles, which show the rapid, jerking movements for which the stage is named, and the diaphragm, which remains functional but contracts erratically. The loss of

muscle tone leads to further narrowing of the upper airway, which can trigger snoring. Blood pressure and heart rate are also destabilized in REM sleep, in some cases leading to sympathetic “storms” of phasic arousal. At the same time, temperature regulation is impaired due to the loss of the ability to shiver.

Perhaps the most dramatic change associated with REM is in the content of dreams. In NREM, dreams are often more grounded, logical, and procedural, lacking any real visual or sensory detail. REM dreams, by contrast, are an absolute free-for-all of “sensory” experience, visual content, and emotions that can rapidly morph in content and affect with little reasoning. REM dreams may support memory consolidation processes, particularly by linking disparate concepts or connecting new ideas to old ones. They may also support emotional processing of difficult events (e.g., divorce, bereavement). This is based on functional imaging studies which show elevated activity in limbic regions during REM sleep and increases in emotional regulation inventories after subjects awake [4,5]. In recent years, connections between REM sleep and emotion regulation have been most manifest in individuals suffering from posttraumatic stress disorder.

Although the brain generates motor commands during dreams, the descending motor neurons are inhibited in the brainstem to prevent execution of these commands. When this process is disturbed (as in several neurological and psychiatric disorders), subjects will act out their dreams, often posing a danger to themselves or their bed partners. REM sleep accounts for approximately 25% of sleep and occurs in 4–6 episodes distributed across the night.

Moving through the sleep stages

Although the stages of sleep are presented in a particular order here, it should be noted that progression is not always linear. All subjects start in stage 1 but may proceed rapidly through stage 2–3, or they may backtrack to earlier stages before proceeding to REM. Conversely, while it is typical

to return from REM to NREM stage 1 or 2, it is possible to return to any NREM stage following an REM episode. An example diagram of sleep stages, known as a hypnogram, is presented in Fig. 1.3.

Sleep and circadian rhythms

Across cultures, geography, seasons, and age, humans tend to sleep at night and wake up in the morning. This phenomenon is so ubiquitous that it often escapes scrutiny, but consider if it were a different biological function. What if, for example, humans only used the restroom at certain times of day? It seems banal that sleep should occur at night, but it is actually a remarkable feat of biology that humans (and many other animals) consolidate this large set of biological processes to a particular stretch of the day.

Generally speaking, there are two factors that ensure sleep occurs at night. The first is sleep propensity or the drive for sleep. Physical and mental fatigue that accumulates during the day increases sleep propensity, and by nighttime, the elevated sleep propensity drives humans to engage in sleep. The other factor is the circadian system. The molecular machinery of the circadian system is found within each cell of the body, comprised of an interlocking set of signaling proteins that produce a ~24-h rhythm of cellular functions that can be further adjusted by cues in the environment. This machinery ensures that functions such as digestion and immune system maintenance are optimized at specific points in the 24-h solar day. For example, when the clock signals that it is biological night, the body responds by shifting neurobiological activities to favor sleep.

These two factors are formally referred to as the two process model of sleep (Fig. 1.4). In the morning, sleep propensity is low but increases over the course of wakefulness. Conversely, the circadian drive for wakefulness increases during the morning, peaks during the midday, and then drops at night. While there is a short, early

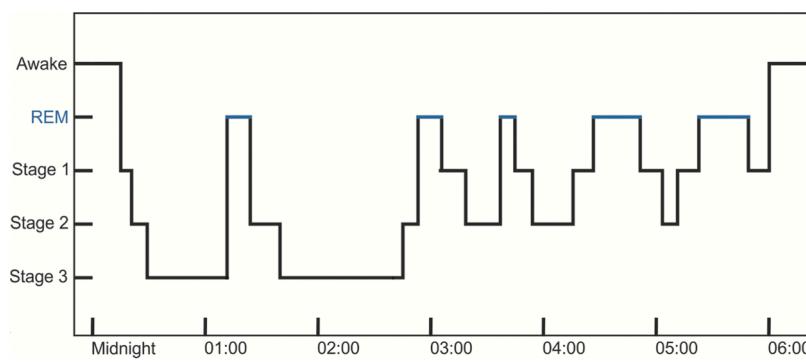


FIGURE 1.3 A hypnogram. This diagram displays the amount of time an individual spends in each sleep stage and when that stage occurs during the progression of a sleep period. Typical progression moves from awake to stage 1, then stage 2, then stage 3, then REM before returning to stage 1. However, an individual may go forward or backward between stages and may experience brief wakefulness between cycles.

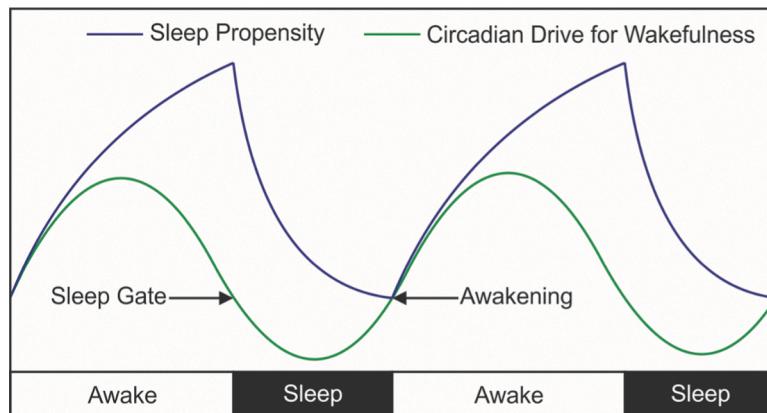


FIGURE 1.4 The two process model of sleep. Sleep propensity (blue line, sometimes called sleep pressure) mounts during wakefulness and increases an individual's ability to fall and stay asleep. Circadian rhythms of arousal (green line) enhance wakefulness and cognition during the biological day and decrease wakefulness and cognition during the biological night. The sleep gate marks the point at which sleep propensity is high enough and circadian arousal is diminished enough to allow for sleep onset.

evening peak that sustains wakefulness after sunset (referred to as the wake-maintenance zone), sleep propensity eventually exceeds circadian wakefulness, and sleep onset occurs. This point is referred to as the sleep gate. In humans, the peak of sleep propensity and the trough of wakefulness occur at night, which is why humans tend to sleep at that time.

So how exactly do these two forces work to generate the sleep gate? Sleep propensity is not well understood, but current theories focus on the buildup of certain substances (such as adenosine) that signal increasing levels of fatigue. This explains why caffeine, which opposes rising adenosine levels, is an effective stimulant.

The circadian system is largely underpinned by a part of the brain called the suprachiasmatic nucleus of the hypothalamus (SCN). Because of its circuit connections with the eye and ability to track sunrise and sunset, the

SCN can operate as the master pacemaker that synchronizes all the miniature cellular clocks of the body to the light schedule set by the Earth's rotation (like a conductor of a symphony orchestra). In the absence of external photic cues, the SCN can still produce an endogenous rhythm that approximates the lengths of day and night. However, this rhythm is imprecise and follows a schedule that—depending on the person—is slightly longer or shorter than 24 h. Without any means of correction, the endogenous rhythm set by the SCN would slowly drift away from the solar day's 24-h cycle (resulting in non-24-h circadian rhythm disorder; Fig. 1.5). Fortunately, the SCN can use the light information it receives from the eye on a daily basis to adjust for the difference in timing, a process known as entrainment.

Disruptions to the circadian system can manifest as difficulties with sleep. One example is jet lag. When an

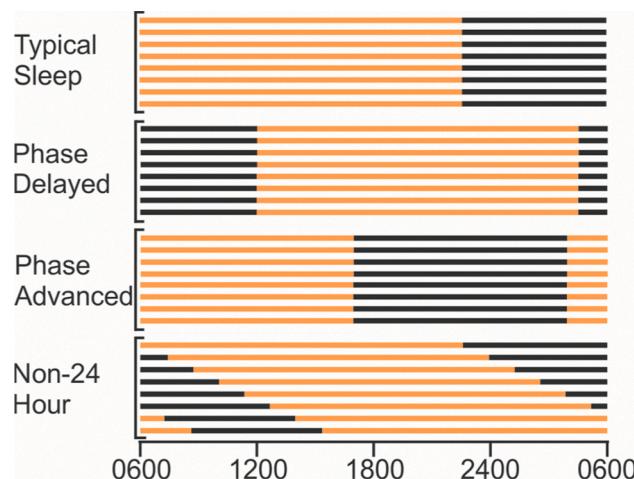


FIGURE 1.5 Circadian rhythms of wake and sleep. Each row represents a day. Wake is presented as yellow, while sleep is presented as black. Both typical and abnormal circadian rhythms are presented.

individual rapidly changes time-zones, the external light/dark cues of the new destination become misaligned with the endogenous rhythm of night and day, which is still operating on the previous light schedule. Depending on the direction of the shift, an individual may awaken hours before dawn in the new location (phase advance), or take hours to fall asleep after night has fallen (phase delay). Fortunately, after several sleep/wake intervals, the SCN will re-entrain the body to the new light/dark cues to normalize sleep. Examples of typical and atypical circadian rhythms are presented in Fig. 1.5.

Basic sleep physiology

Sleep and arousal emerge from coordinated interactions between multiple brain regions. This section will highlight brain regions, chemical signals, and physiological processes that coordinate sleep and wake.

The brainstem

The brainstem is the most evolutionarily conserved structure within brain and houses the autonomic nervous system, which regulates basic life-sustaining activities such as heart rate, blood pressure, and respiration. Regarding sleep and wake, the brainstem produces wake-promoting neuromodulators such as serotonin, norepinephrine, and dopamine that set the general volume of brain activity. The regions that produce these chemicals are collectively referred to as the ascending reticular activating system because they project to and activate higher order brain areas.

The hypothalamus

The hypothalamus supports three major processes associated with sleep. First, it houses the SCN and thus maintains circadian timekeeping. Second, the hypothalamus regulates the autonomic processes such as temperature. Third, it augments the wake-promoting neuromodulators of the brainstem with histamine and orexin (also known as hypocretin). Increased histamine and orexin drive wakefulness during the day, while low concentrations of histamine and orexin at night facilitate drowsiness and a tendency to sleep.

The thalamus

The thalamus serves as the gateway for information related to touch, taste, sight, and sound to travel to and between areas of the cerebral cortex. Although historically seen as a simple relay station, the thalamus is now understood to extensively filter ascending information. During sleep, the thalamus blocks most sensory information from reaching the cortex. Ambient noise, whispers, and low light are all

eliminated so that sleep can occur without having to consciously process what is going on in the environment.

Cerebrum

The cerebrum includes a variety of cortical and subcortical structures, such as the somatosensory and motor cortices, basal ganglia, and hippocampus. Sensory processing, motor commands, language, memory, and emotion all occur in or involve elements of the cerebrum, which exhibits the vast majority of neural activity in the brain. The cerebrum does not drive a specific element of sleep or wake, but the activity of billions of cortical neurons plays a large role in whether a person is awake or asleep.

Neuromodulators

As mentioned above, neuromodulators play a major role in sleep and wakefulness. Listed below are six major neuromodulators known to influence sleep.

- **Dopamine:** Produced by the substantia nigra and the ventral tegmental area of the brainstem, dopamine promotes wakefulness. Some other functions of dopamine include stimulation of the basal ganglia to promote voluntary movement, and stimulation of the nucleus accumbens as part of the pleasure and reward systems.
- **Histamine:** Produced by the tuberomammillary nucleus of the hypothalamus, histamine promotes wakefulness. This is why antihistamines such as diphenhydramine cause drowsiness; they are able to enter the brain and block the wakefulness promoting effect of histamine. Second-generation antihistamines, such as cetirizine, do not cause drowsiness because they do not cross the blood-brain barrier.
- **Norepinephrine:** The precursor to epinephrine (adrenalin), norepinephrine is produced by the locus coeruleus in the brainstem. Norepinephrine acts at the same receptors as epinephrine to stimulate wakefulness, although at a much reduced half-life.
- **Acetylcholine:** Although acetylcholine is often used as a neurotransmitter, it is also produced by the basal forebrain and multiple regions of the brainstem to act as a neuromodulator. Acetylcholine promotes wakefulness and supports REM sleep.
- **Serotonin:** Produced by the dorsal raphe nucleus of the brainstem, serotonin has more than 14 receptor subtypes, many of which differ in their activity. In general, increased serotonin promotes wakefulness and inhibits REM.
- **Orexin:** Produced by the lateral hypothalamus, orexin is a major wake-promoting agent in the brain. Its absence, most likely due to autoimmune destruction, is the chief cause of the sleep disorder narcolepsy. In addition, orexin enhances the activity of brainstem neuromodulators such as noradrenaline.

The autonomic nervous system

The autonomic nervous system is responsible for the subconscious regulation of heart rate, respiration, blood pressure, temperature, and other vital pieces of physiology. This system is divided into two opposing branches: the sympathetic (fight or flight) and parasympathetic (rest and digest) branches. During wakefulness, the sympathetic and parasympathetic branches are constantly adapting to environmental stimuli and emotional/mental processes. During NREM sleep, however, the sympathetic branch is largely quiescent, while the parasympathetic branch remains active. This results in a progressive decrease in heart rate, temperature, and blood pressure, which promotes and maintains NREM sleep moving through stages 1–3.

Quantifying sleep

Sleep incorporates a range of biological and behavioral activities, which cannot be captured by a single measurement. Instead, sleep is quantified within two broad domains: sleep continuity and sleep architecture.

Sleep continuity encapsulates the timeline of how a person sleeps. Total sleep time, sleep onset latency (amount of time it takes to fall asleep), and the number and duration of awakenings in the night are all measures of sleep continuity. Sleep continuity also includes sleep efficiency, which is defined as a ratio of sleep ability (total sleep time) to sleep opportunity (total time in bed). Sleep continuity variables are typically self-reported in a sleep diary or measured using an activity monitor (discussed below). This information can help identify sleep patterns over time or diagnose specific sleep disturbances, such as insomnia and circadian rhythm disorders. Sleep architecture quantifies each stage of sleep, and the progression through each stage, by changes in electroencephalographic activity. For example, measures of sleep architecture would capture if someone enters REM very quickly after sleep onset, a key symptom in the diagnosis of narcolepsy. The gold-standard for measuring sleep architecture is polysomnography (PSG).

Capturing both the psychological and physiological elements of sleep requires subjective and objective measurements. Subjective assessments, such as questionnaires or sleep diaries, rely on self-report data. Although subject perceptions may bias the results, these are the only measures that capture the subjective experience of sleep. Actigraphy and PSG are objective measures that replace subjective perceptions with independently observable data, such as changes in brain waves or body movement. Although researchers and clinicians tend to prefer objective data to self-reports, subjective data should be seen as complementary to objective data, not subordinate. In paradoxical insomnia, for instance, an objective method may

capture 8 h of sleep, while a patient may only report 30 min of sleep in between tossing and turning. It is tempting to think one of the measurements is wrong, but the reality is that something unusual is happening that neither measure adequately captures, and so only by comparing both measures does the paradoxical insomnia become evident.

Subjective measures

The simplest measure of sleep is a single question: "How much do you normally sleep?" This question varies in form, sometimes asking about weekday versus weekend sleep, sleeping alone or with a partner, and sleep before and after having a child. This basic question is widely used in epidemiological studies and large datasets, such as the National Health and Nutrition Examination Survey. However, this question offers the most limited insight into a person's sleep. First, it is subject to recall bias, in that subjects can recall things differently than what actually happened. The second problem is resolution, since asking about sleep in the last month or year will lead subjects to average across many nights based only on what they can remember. This reduces temporal precision and increases recall bias. However, this question may be the only way to acquire historical information about sleep, such as when a clinician is seeking to understand the course of a sleep disorder. When patients report decreasing sleep durations and increasing sleep onset latency over the course of a month, objective measures may not be necessary to initiate treatment for sleep-onset insomnia.

The next level of subjective measurements of sleep is validated questionnaires such as the Insomnia Severity Index. Questionnaires are subjective and retrospective but are usually standardized to capture specific data or screen for specific disorders. A wide variety of questionnaires exist, and a few are listed in Table 1.1.

The final subjective measurement, the sleep diary, has been used for decades in research and clinical settings. Subjects report on different sleep continuity variables shortly after waking up. A sleep diary is considered a prospective measurement of sleep, although recall bias may occur if too much time passes between the sleep episode and the recording date. Sleep diaries are easy to use (the subject can complete it on paper or electronically) and can be collected for any length of time, which is why they are an effective tool for longitudinal assessments of sleep and sleep/wake timing.

Objective measures

Objective measures replace subjective perceptions with measures of independent, observable phenomena. The most ubiquitous form of objective sleep measurement is actigraphy. An activity monitoring device, usually a wrist-

TABLE 1.1 Sleep questionnaires.

Questionnaire	Description
Insomnia Severity Index [6]	Self-report measure of symptoms of insomnia, such as difficulty falling asleep or waking up too early. Answers are scored as 0–4, added together, and compared to cutoffs to determine the likelihood of clinical insomnia.
Epworth Sleepiness Scale [7] Karolinska Sleepiness Scale [8]	Sleepiness scales measure a subject's propensity to fall asleep. The Epworth measures trait sleepiness, reflected in the ability to fall asleep in a variety of environments and contexts. The Karolinska measures state sleepiness, specifically the sleepiness experienced in the last 10 min on a 1–9 scale.
Pittsburgh Sleep Quality Index [9]	The PSQI measures the frequency of sleep difficulties, particularly subjective disturbances in sleep. Commonly used in research and as an outcome measure of sleep therapies.
Sleep Disorders Symptom Checklist-25 [10]	A 25 item questionnaire that assesses the most common symptoms of several sleep disorders, such as insomnia, circadian rhythm disorders, sleep apnea, bruxism, and narcolepsy.
STOP-BANG [11]	An 8 item questionnaire that generates a risk score for obstructive sleep apnea.
Morningness-Eveningness Questionnaire [12]	A 19 item questionnaire that measures an individual's circadian preference in wakefulness. Lower scores are associated with evening preference, while higher scores are associated with morning preference.

worn device, uses an accelerometer to detect and measure bodily motion. An activity threshold is set and any activity level below the threshold is classified as either “rest” or “sleep.” In addition to devices used by clinicians and researchers, there are consumer “smart” devices such as phones and watches that utilize actigraphy. However, the algorithms used to assess sleep efficiency and stages are proprietary and can vary between companies. It is important to choose a company and device that has been validated in many populations and against PSG data and other sleep metrics when conducting a study or for sleep assessment. An activity monitoring device can also include a light sensor, which allows the clinician to measure the natural and artificial light the patient is exposed to. This is useful for capturing an individual’s photoperiod (i.e., the period of light exposure), which can help determine if light exposure is related to the individual’s sleep. For example, blue light has a detrimental effect on sleep, and so identifying and limiting blue light late in the evening may improve sleep for some patients. Like sleep diaries, activity monitors provide day-to-day measures of sleep continuity. Multiple weeks of actigraphy data can be used to evaluate sleep/wake cycles and related circadian rhythms, and photopic data can show whether light exposure is affecting a person’s circadian rhythm. For example, repeated blue light exposure late at night may shift sleep onset to later in the evening, resulting in a delayed circadian phase. The coupling of actigraphy to light exposure allows the comparison of sleep/wake behavior with external photopic cues, which are helpful in assessing the synchronization of sleep/wake cycles with light/dark cycles.

The other objective measure of sleep is PSG, also known as a “sleep study.” During a sleep study, subjects spend 1–2 nights in the sleep laboratory wearing sensors that measure brain activity, eye movements, muscle movements, heart activity, respiratory activity, and blood oxygen levels. Additional sensors may be placed on the legs to measure periodic limb movements, which can occur naturally or as part of sleep movement disorders. PSG measures the electrical and physiological changes that occur during sleep and is currently the best way to determine sleep stages. The primary clinical utility of PSG, however, is for the diagnosis and treatment of sleep apnea. Sleep apnea is a condition where patients cease breathing during sleep, often due to upper airway collapse. The PSG captures these events as a decrease in both nasal airflow and blood oxygenation, and the number of events per hour is used as a measure of the severity of the sleep apnea. In some cases, physicians will order a “split-night” study, in which sleep apnea is measured in the first part of the night, and then positive airway pressure therapy is initiated to control the apnea in the second half.

Conclusion

Without sleep, a wide variety of systems such as cell division, metabolism, neurological functions, and mental and emotional health would all be greatly impaired. Diseases that affect sleep are life-altering and, if left untreated, can decrease quality of life and increase risk of death. It is also important to synchronize sleep to our external world, a job done exceedingly well by the biological clock. The

rhythmicity and predictability of sleep highlights where and how disruptions are occurring in various conditions and disorders. Understanding sleep at the fundamental level is critical in understanding the clinical significance sleep has on overall health.

References

- [1] Kales A, Rechtschaffen. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Neurolog Informat Network 1968;57:1968.
- [2] Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, Troester MT, Vaughn BV. AASM scoring manual updates for 2017 (version 2.4). J Clin Sleep Med 2017;13(5):665–6. <https://doi.org/10.5664/jcsm.6576>.
- [3] Moser D, Anderer P, Gruber G, Parapatics S, Loretz E, Boeck M, Kloesch G, Heller E, Schmidt A, Danker-Hopfe H, Saletu B, Zeithofer J, Dorffner G. Sleep classification according to AASM and Rechtschaffen & Kales: effects on sleep scoring parameters. Sleep 2009;32(2):139–49. <https://doi.org/10.1093/sleep/32.2.139>.
- [4] Rothbaum BO, Mellman TA. Dreams and exposure therapy in PTSD. J Trauma Stress 2001;14(3):481–90. <https://doi.org/10.1023/A:1011104521887>.
- [5] Desseilles M, Dang-Vu TT, Sterpenich V, Schwartz S. Cognitive and emotional processes during dreaming: a neuroimaging view. Conscious Cognit 2011;20(4):998–1008. <https://doi.org/10.1016/j.concog.2010.10.005>.
- [6] Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297–307. [https://doi.org/10.1016/S1389-9457\(00\)00065-4](https://doi.org/10.1016/S1389-9457(00)00065-4).
- [7] Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15(4):376–81. <https://doi.org/10.1093/sleep/15.4.376>.
- [8] Kaida K, Takahashi M, Åkerstedt T, Nakata A, Otsuka Y, Haratani T, Fukasawa K. Validation of the Karolinska sleepiness scale against performance and EEG variables. Clin Neurophysiol 2006;117(7):1574–81. <https://doi.org/10.1016/j.clinph.2006.03.011>.
- [9] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213. [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4).
- [10] Klingman KJ, Jungquist CR, Perlis ML. Questionnaires that screen for multiple sleep disorders. Sleep Med Rev 2017;32:37–44. <https://doi.org/10.1016/j.smrv.2016.02.004>.
- [11] Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008;108(5):812–21. <https://doi.org/10.1097/ALN.0b013e31816d83e4>.
- [12] Horne JA, Ostberg O. A self assessment questionnaire to determine Morningness Eveningness in human circadian rhythms. Int J Chronobiol 1976;4(2):97–110.

This page intentionally left blank

Chapter 2

Epidemiology of sleep health

Michael A. Grandner

Sleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States

Sleep at the population level

Sleep is a universal human phenomenon and impacts every person, every day (whether or not they actually get to sleep). For this reason, population-level estimates of sleep are important. However, they may be difficult to obtain. Since an individual is unconscious while they are sleeping (and for the time surrounding sleep onset and awakening), accurate assessment of the population burden of sleep disturbance may be difficult. Methods typically exist on a continuum whereby increased generalizability is compromised by reduced precision. For example, most population-level estimates are based on a retrospective self-report, which lacks precision. More precise measures, such as polysomnography and even actigraphy, have been thus far impractical for truly large and population-level assessments. Still, several tentative conclusions about the population can be drawn regarding sleep health.

Defining insufficient sleep

There has been a general lack of consensus on the definition of what constitutes “insufficient sleep” in the general population since at least 1964 [1], when Hammond published the finding that habitual short and long sleep duration were associated with increased mortality rates. Since that time, there has been considerable debate regarding how sleep insufficiency should be defined. Laboratory studies where sleep is manipulated in an experimental protocol are preferred by some (because of their precision) and population-based studies where individuals are observed relative to habitual sleep behaviors are preferred by others (because of their generalizability).

Regarding the former, information about the physiologic and health consequences of sleep duration often come from studies that employ *total sleep deprivation* (defined as an experimental manipulation where an individual is kept awake for at least an entire sleep period) and *partial sleep deprivation* (defined as an experimental manipulation

where an individual’s sleep period is restricted over a period of days). This is also sometimes called *sleep restriction*. Sometimes, partial sleep deprivation can be characterized as *chronic partial sleep deprivation* (defined as partial sleep deprivation over a period of weeks). All of these experimental manipulations can be useful to discern physiologic effects of changes in sleep duration, but they are generally poor approximations of real-world sleep. As such, *total sleep deprivation*, *partial sleep deprivation/sleep restriction*, and *chronic partial sleep deprivation* sacrifice generalizability for precision [2–4].

Other studies use population-based studies of sleep. These studies can characterize *habitual sleep duration* (defined as typical perceived sleep duration experienced in real-world settings), often categorized as *short sleep duration*, *normal/normative sleep duration*, and *long sleep duration* based on cutoffs that often vary by study. These studies may also model *sleep loss* (reduction in sleep duration over time). They may also capture aspects of sleep continuity, including *total sleep time* (calculated sleep duration based on time in bed, subtracting sleep latency and wake time after sleep onset). These parameters may be assessed retrospectively (e.g., through surveys and questionnaires) or prospectively; prospective assessments can be subjective (e.g., sleep diary) or objective (e.g., actigraphy). These studies often sacrifice precision for generalizability [2–4].

But what is “insufficient sleep?” Often, terms such as *sleep deprivation*, *sleep loss*, *short sleep*, and others are used interchangeably. Also, “insufficient sleep” is sometimes used interchangeably with concepts such as *sleep deficiency* (insufficient sleep duration or inadequate sleep quality), *poor sleep quality*, and even *insomnia* despite these concepts being misapplied to insufficient sleep [2–4].

With this in mind, defining insufficient sleep has been problematic, since all of these concepts have appropriated the label of “insufficient sleep.” For the purposes of this chapter, “insufficient sleep” will refer to sleep duration that

is likely too brief to meet physiologic needs. Also, this chapter focuses on habitual sleep duration in the population, and thus experimental terms such as *sleep deprivation* are not appropriate. Even at the population level, there is disagreement regarding how much sleep is “insufficient.” Various studies use cutoffs of 4, 5, 6, or 7 h as representing insufficient sleep.

Recently, a consensus panel was convened by the American Academy of Sleep Medicine and Sleep Research Society to determine the recommended amount of sleep for a healthy adult. This panel recommended that 7 or more hours were recommended [5]. In a follow-up manuscript, the panel members discussed in detail how this was reached, pointing out that the consensus was most clear that 6 h or less was likely insufficient and less clear for sleep durations between 6 and 7 h [5]. This finding was echoed in similar consensus statements issued by the National Sleep Foundation [6,7], the American Thoracic Society [8], and the American Heart Association [9]. Therefore, for the purposes of this chapter, “insufficient sleep” will generally refer to habitual sleep duration of 6 h or less.

Prevalence of insufficient sleep

In order to estimate the prevalence of insufficient sleep in the population, data sources that assess habitual sleep duration in large samples that are representative of the general population. Existing work in this area is limited, as most studies that investigate sleep in such samples do so without using well-validated assessments of sleep. It is important to note that most population estimates of habitual sleep duration are based on subjective,

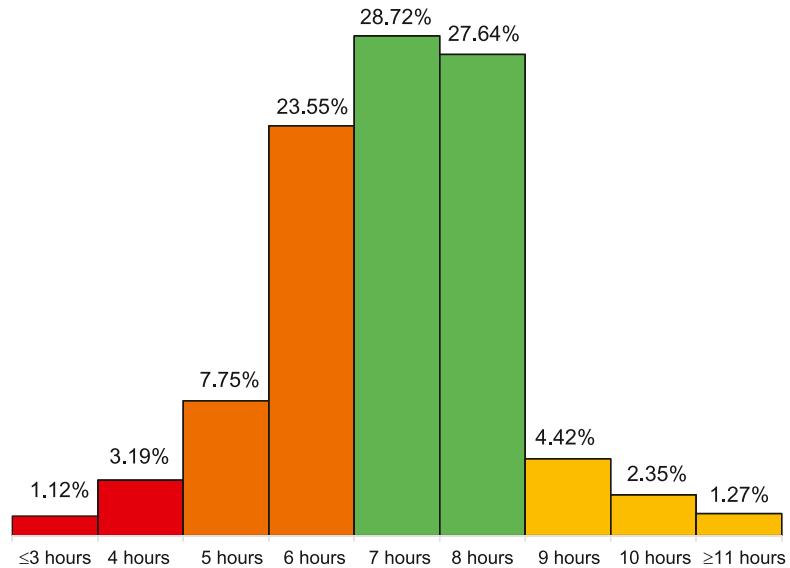
retrospective self-report, which presents biases in assessing sleep [10,11]. These estimates may better reflect time in bed than actual physiologic sleep and should be interpreted with appropriate caution.

Insufficient sleep in the population

Estimates of the prevalence of insufficient sleep have used the Behavioral Risk Factor Surveillance System (BRFSS) in the United States. The BRFSS is an annual telephone survey of hundreds of thousands of US adults, conducted by the Centers for Disease Control and Prevention (CDC) (<http://www.cdc.gov/brfss>). It is state-based, with population-weighted samples representing each strata of age, sex, race/ethnicity, and geographic region. Sleep duration in the BRFSS is assessed with the item, “on average, how many hours of sleep do you get in a 24-h period?” Responses are coded in whole numbers. Liu and colleagues reported population-weighted prevalence estimates for sleep duration around a cutoff of 7 h (based on the consensus statement [12] from the 2014 BRFSS ($N = 444,306$)). Overall, the age-adjusted estimated prevalence of insufficient sleep (≤ 6 h) was reported to be 35.1% of the US population. Grandner and colleagues [13] reported prevalence estimates also using the 2014 BRFSS. Estimated prevalence by hour was calculated, such that the estimated prevalence by hour of sleep duration was 1.12% for ≤ 3 h, 3.19% for 4 h, 7.75% for 5 h, 23.55% for 6 h, 28.72% for 7 h, 27.64% for 8 h, 4.42% for 9 h, 2.35% for 10 h, and 1.27% for ≥ 11 h. See Fig. 2.1 for a graphical representation of these data.

Other prevalence estimates have also been calculated using the National Health and Nutrition Examination

FIGURE 2.1 Distribution of sleep duration in the US population using 2014 BRFSS. Data from Grandner MA, Seixas A, Shetty S, Shenoy S. Sleep duration and diabetes risk: population trends and potential mechanisms. *Curr Diab Rep* 2016;16(11):106. PubMed PMID: 27664039.



Survey (NHANES). The NHANES is a survey that is also conducted by the CDC that includes a nationally representative sample (<http://www.cdc.gov/nchs/nhanes>). The sample size is much smaller than the BRFSS, though reliability of data may be improved since surveys were administered in person rather than over the phone. Similar to the BRFSS, NHANES assesses sleep duration by whole number hour (no partial hours). Unlike the BRFSS, though, NHANES assesses sleep duration with the item, "How much sleep do you usually get at night on weekdays or workdays?" Thus, this item may capture modal nighttime sleep, rather than 24-h sleep, which may include naps. Using the 2007–08 wave of NHANES, Grandner and colleagues calculated prevalence estimates for sleep duration by category, with 4.96% reporting ≤ 4 h, 32.16% reporting 5–6 h, 55.68% reporting 7–8 h, and 7.20% reporting ≥ 9 h [14]. Thus, insufficient sleep (≤ 6 h) was reported by 37.12% of the US population. The higher estimate relative to BRFSS may be explained by the wording of the item, which does not include naps or weekends. See Fig. 2.1 for an illustration of these values.

Lower estimates of short sleep duration are reported by Basner and colleagues using data from the American Time Use Survey (ATUS) [15]. The ATUS is conducted annually by the US Bureau of Labor Statistics and assigns activity codes to each 15-min increment of the 24-h day in a representative sample of US adults (<http://www.bls.gov/tus>). Because ATUS does not distinguish time in bed from time asleep, values will generally overestimate sleep and underestimate insufficient sleep [15]. Using ATUS from 2003 to 2011 ($N = 124,517$), the estimated prevalence of insufficient sleep (≤ 6 h) was 10.6%, compared to 78.4% for 6–11 h and 11.0% for ≥ 11 h.

Thus, estimates for insufficient sleep (≤ 6 h) from relatively recent, nationally representative surveys, are 10.6% from ATUS, 35.1% from BRFSS, and 37.12% from NHANES. These may vary as a result of the survey item asked, as well as other factors including the years included and sampling methodologies. Although other studies have examined large samples using more well-validated measures, none of these studies are nationally representative and thus cannot be used to develop population prevalence estimates.

Rather than assess insufficient sleep relative to a benchmark (sleep hours), an alternative approach would be to ask individuals how often they perceive their sleep to be insufficient. The 2008 BRFSS asked, "during the past 30 days, for about how many days have you felt that you did not get enough rest or sleep?" Based on this variable, McKnight-Eily and colleagues [16] reported prevalence estimates based on responses to this variable. They estimate that 30.7% of the population reports 0/30 days of insufficient sleep, with 1–13 days reported by 41.3% of the population, 14–29 days reported by 16.8% of the

population, and 30/30 days reported by 11.1% of the population. Based on these estimates, 27.9% of the US population reports perceived sleep insufficiency at least 2 weeks out of the month. Interestingly, this estimate is similar to the ~1/3 of the population who experience insufficient sleep based on sleep duration, though the overlap between these groups is only moderate [17].

Insufficient sleep by age

Based on BRFSS data, Liu and colleagues [18] provided age-based prevalence estimates for insufficient sleep (≤ 6 h). They reported estimates of 32.2% for those aged 18–24, 37.9% for 25–34, 38.3% for 35–44, 37.3% for 45%–64%, and 26.3% for those 65 or older (see Fig. 2.2). Of note, the lowest rate of insufficient sleep was seen among the oldest adults. This is consistent with other studies that showed that perceived insufficient sleep declines with age [19], as does self-reported sleep disturbance [20–22]. This is in contrast to more objective sleep disturbances, which are well-characterized to increase in older adults [23–25]. There are a number of potential reasons for this, including retirement offering greater sleep opportunity and differing expectations regarding sleep [26].

Similar prevalence estimates of sleep duration by age in NHANES were reported by Grandner and colleagues [14]. Among teenagers aged 16–17, prevalence of sleep duration was 0.63% for ≤ 4 h, 19.38% for 5–6 h, 62.47% for 7–8 h, and 17.52% for ≥ 9 h. For younger adults aged 18–30, prevalence was 4.83% for ≤ 4 h, 31.02% for 5–6 h, 54.44% for 7–8 h, and 9.81% for ≥ 9 h. For adults aged 30–50, prevalence was 5.86% for ≤ 4 h, 33.61% for 5–6 h, 55.49% for 7–8 h, and 5.03% for ≥ 9 h. For adults aged 50–65, prevalence was 4.95% for ≤ 4 h, 35.41% for 5–6 h, 56.04% for 7–8 h, and 3.61% for ≥ 9 h. For older adults 65 and older, prevalence was 4.17% for ≤ 4 h, 28.31% for 5–6 h, 55.58% for 7–8 h, and 11.94% for ≥ 9 h. Thus, prevalence of insufficient sleep (≤ 6 h) was reported to be 20.01% for those aged 16–17, 35.85% for those aged 18–30, 39.47% for adults 30–50, 40.36% for adults age 50%–65%, and

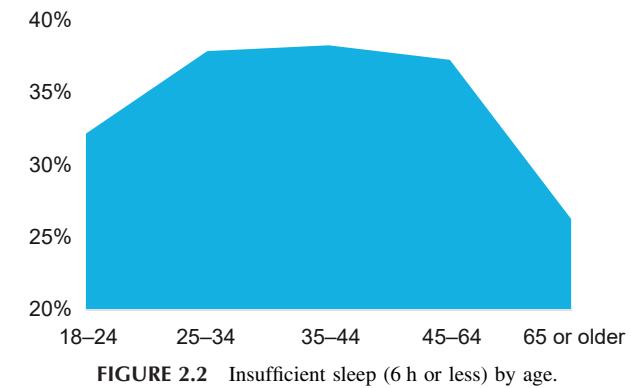


FIGURE 2.2 Insufficient sleep (6 h or less) by age.

32.48% for older adults over 65. Again, prevalence of insufficient sleep is highest in working age adults.

Using the ATUS data, Basner and colleagues [15] found that, compared to 15–24 year olds, increased likelihood of insufficient sleep (≤ 6 h) was seen in those aged 25–34 (OR = 1.38; 95% CI = 1.18; 1.61), 35–44 (OR = 1.40; 95% CI = 1.22; 1.62), 45–54 (OR = 1.68; 95% CI = 1.44; 1.94), and 55–64 (OR = 1.41; 95% CI = 1.18; 1.68) but not those 65 or older. Similarly, shortest sleep durations were seen in working age adults.

Using self-reported insufficiency from the BRFSS, McKnight-Eily and colleagues [16] report that the prevalence of self-reported insufficient sleep at least 14 of the past 30 days was reported by 31.3% of 18–24 year olds. Estimated prevalence was 34.2% for 35–34 year olds, 32.1% for 35–44 year olds, 27.2% for 45–64 year olds, and 15.0% for those 65 or older.

Insufficient sleep by sex

Several studies have examined sex relative to insufficient sleep. Liu and colleagues reports that based on the 2014 BRFSS data, insufficient sleep (≤ 6 h) is reported by 35.4% of men and 34.8% of women [18]. Using data from the 2007–08 NHANES, Whinnery and colleagues report no sex differences in likelihood of insufficient sleep (though they report that women are 35% less likely to report long sleep duration after adjusting for covariates) [27]. Using NHIS data, Krueger and Friedman report that men are 7% less likely to report ≤ 5 versus 7 h of sleep [28]. Basner and colleagues report that men are more likely to report insufficient sleep (OR = 1.27; 95% CI = 1.20; 1.35) [15]. McKnight-Eily reports that self-reported insufficient sleep at least 14 out of the past 30 days was reported by 25.5% of men and 30.4% of women [16]. Taken together, sex differences in insufficient sleep are likely small and difficult to observe. This is in contrast to self-reported sleep disturbances, which are much more prevalent in women [29–31].

Insufficient sleep by race/ethnicity

Many studies have documented differences in sleep duration by race/ethnicity. In general, racial/ethnic minorities are more likely to experience insufficient sleep duration. Actigraphic studies have shown that racial/ethnic minorities demonstrate a sleep duration between 40 and 60 min less than non-Hispanic white counterparts [32–34].

More data are available from survey studies that included larger numbers of people but lack the precision of objective measurements. For example, data from the NHIS have shown that sleep duration of 6 h or less was more prevalent among blacks/African-Americans, non-Mexican Hispanics/Latinos, and Asians/others, compared to non-

Hispanic whites [35,36]. Longitudinal analysis of NHIS data suggests that black–white differences in insufficient sleep have persisted, relatively unchanged since 1977 [37,38]. See Fig. 2.3 for an illustration of this.

Other population-level studies have found similar patterns. For example, Stamatakis showed in the Alameda County study that African-Americans were about twice as likely to report short sleep duration [39]. Using NHANES data, Whinnery and colleagues showed that blacks/African-Americans are about 2.5 times as likely to sleep <5 h and about twice as likely to sleep 5–6 h, compared to non-Hispanic whites. Non-Mexican Hispanics/Latinos were about 2.7 times as likely to sleep <5 h, and Asians/others were about four times as likely to sleep <5 h and about twice as likely to sleep 5–6 h. Mexican-Americans were the only minority group not more likely to report insufficient sleep [27].

Insufficient sleep by socioeconomic status

Perhaps due to environmental stressors, those of lower socioeconomic status are more likely to experience insufficient sleep. Kruger and Friedman used NHIS data to compute mean family income according to sleep duration [28]. They found that the highest mean income was reported among 7-h sleepers (\$48,065), with the lowest income levels in those sleeping 5 h or less (\$36,819) or 9 h or more (\$34,883). Stamatakis evaluated likelihood of insufficient sleep relative to income quintile [39]. This study reported that compared to the highest income quintile, short sleep duration (6 h or less) was increasingly reported in the fourth (3% more likely), third (11% more likely), second (29% more likely), and first quintile (54% more

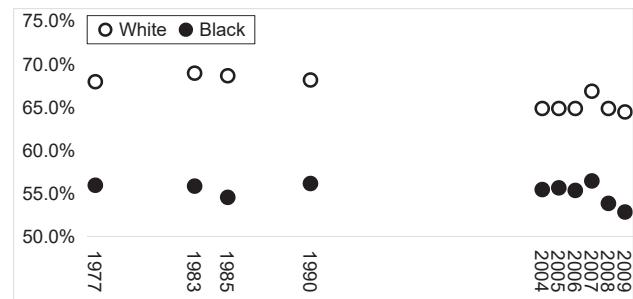


FIGURE 2.3 Black–white differences in 7–8 h sleep in the US population in NHIS. Data from Jean-Louis G, Grandner MA, Youngstedt SD, Williams NJ, Zizi F, Sarpong DF, Ogedegbe GG. Differential increase in prevalence estimates of inadequate sleep among black and white Americans. *BMC Public Health* 2015; 15:1185. PubMed PMID: 26611643; PMCID: PMC4661980; Jean-Louis G, Youngstedt S, Grandner M, Williams NJ, Sarpong D, Zizi F, Ogedegbe G. Unequal burden of sleep-related obesity among black and white Americans. *Sleep Health*. 2015;1(3):169–176. PubMed PMID: 26937487; PMCID: PMC4770938.

likely). Using BRFSS data, days of perceived insufficient sleep decreased at higher levels of household income [19].

Using NHANES data, Whinnery and colleagues examined several socioeconomic indices relative to sleep duration [27]. Compared to those with family income over \$75,000, increased likelihood of <5 h of sleep ($P < .05$) was observed for all categories, including <\$20,000 (OR = 5.5), \$20,000–\$25,000 (OR = 2.9), \$25,000–\$35,000 (OR = 4.1), \$35,000–\$45,000 (OR = 2.4), \$45,000–\$55,000 (OR = 2.8), \$55,000–\$65,000 (OR = 2.4), and even \$65,000–\$75,000 (OR = 3.8). Increased likelihood of 5–6 h sleep relative to those earning over \$75,000 was only seen in the lowest income group earning <\$20,000 (OR = 1.3). Education level was another socioeconomic indicator that was associated with sleep duration in this sample. Those with less than a high school education were approximately four times as likely to report <5 h of sleep, compared to college graduates. Similarly, those who completed some high school were more likely than college graduates to report <5 (OR = 5.3) and 5–6 (OR = 1.7) hours of sleep, those who completed high school were more likely than college graduates to report <5 (OR = 4.3) or 5–6 (OR = 1.6) hours, and those with some college were also more likely than college graduates to report <5 (OR = 3.6) or 5–6 (OR = 1.6) hours of sleep [27]. Another socioeconomic indicator evaluated in this study was lack of access to healthcare,

which was more common among those reporting <5 h of sleep. Food insecurity—a measure of inability to financially provide healthy access to enough food—was also more common among those reporting <5 and 5–6 h of sleep [27].

Insufficient sleep by geography

Insufficient sleep in the United States is differentially experienced across varying regions of the country. An analysis of self-reported perceived insufficient sleep using BRFSS data was reported [40]. Using a geospatial hotspot analysis, several key “hotspots” of insufficient sleep were identified in the United States, including parts of the southeast, parts of the Texas/Louisiana border, areas in the Midwest, and the largest hotspot in central Appalachia. “Coldspots” with abnormally low levels of insufficient sleep were seen in the northern Midwest (Wisconsin/Minnesota/Iowa), central Texas, central Virginia, and areas in along the West Coast. See Fig. 2.4 for a map of US counties relative to their proportion of insufficient sleep and Fig. 2.5 for a map of hotspots and coldspots.

Rather than examine statistical hotspots of perceived insufficient sleep, researchers at the CDC used BRFSS data to map prevalence of ≤6 h of sleep across the United States [18]. The US states with the highest prevalence were (in order) Hawaii (43.9%), Kentucky (39.7%), Maryland

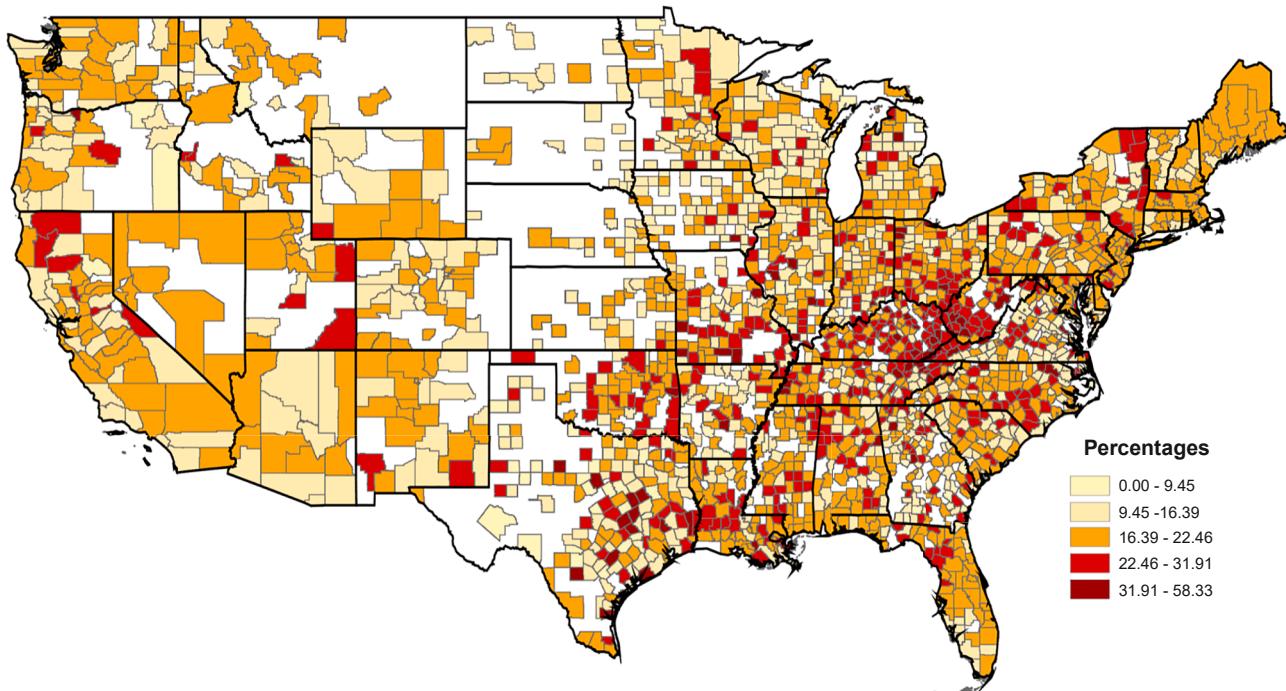


FIGURE 2.4 County-level insufficient sleep in the US. From Grandner MA, Smith TE, Jackson N, Jackson T, Burgard S, Branas C. Geographic distribution of insufficient sleep across the United States: a county-level hotspot analysis. *Sleep Health* 2015;1(3):158–165. PubMed PMID: 26989761; PMCID: 4790125. Map lines delineate study areas and do not necessarily depict accepted national boundaries.

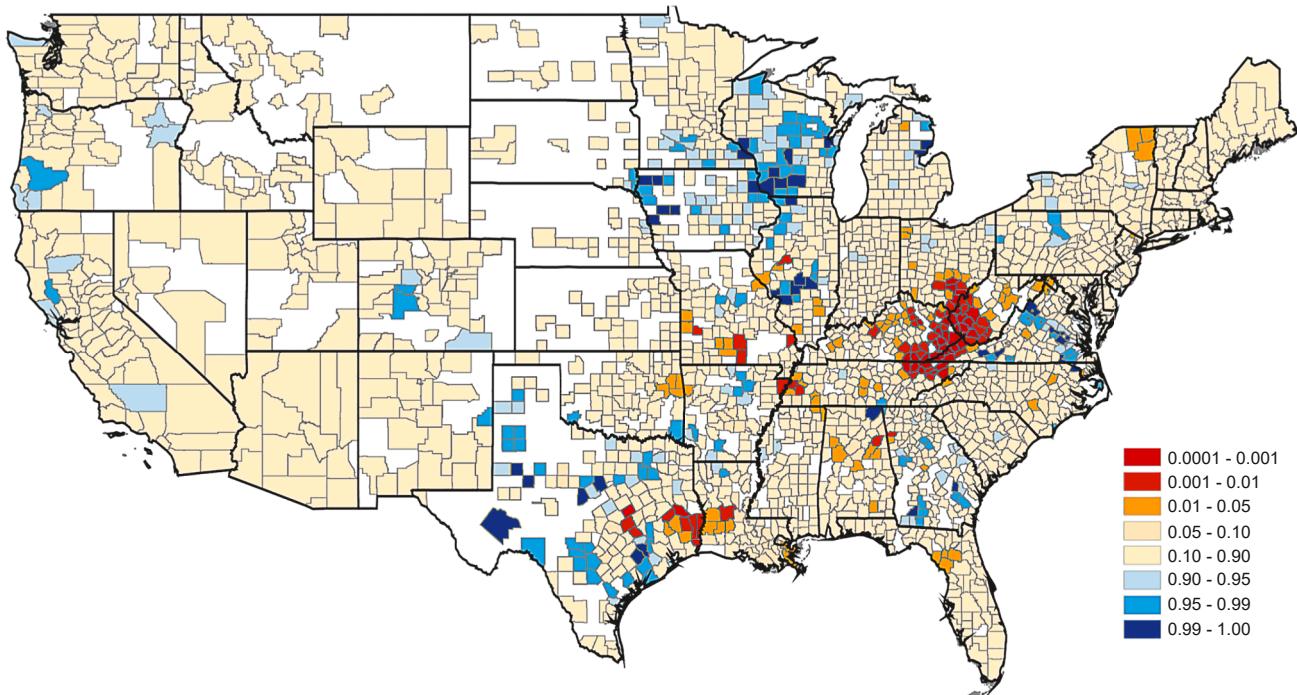


FIGURE 2.5 Hotspots and coldspots of insufficient sleep in the US. From Grandner MA, Smith TE, Jackson N, Jackson T, Burgard S, Branas C. Geographic distribution of insufficient sleep across the United States: a county-level hotspot analysis. *Sleep Health* 2015;1(3):158–165. PubMed PMID: 26989761; PMCID: 4790125. Map lines delineate study areas and do not necessarily depict accepted national boundaries.

(38.9%), Alabama (38.8%), Georgia (38.7%), and Michigan (38.7%). The US states with the lowest prevalence were (in order) South Dakota (28.4%), Colorado (28.5%), Minnesota (29.2%), Nebraska (30.4%), and Idaho (30.6%).

Key limitations to population estimates of insufficient sleep

There are several key limitations in the existing literature on insufficient sleep epidemiology. First, there is a lack of clarity of gold-standard methods for estimating population levels of sleep duration. Most of these studies used single-item self-report measures from surveys, which are fraught with psychometric problems [2,4,10]. Not only do self-report measures tend to overreport sleep relative to physiologic recordings and likely better approximate time in bed than physiologic sleep, they may be subject to a number of other biases, demand characteristics, and social desirability. There still exists no nationally representative dataset that estimates sleep duration based on gold-standard approaches, especially those that record physiologic sleep.

Second, the definition of insufficient sleep varies widely across studies, and most studies do not allow enough resolution to examine different cutoffs. Given recent consensus statements [5,6,8,9], a cutoff of 7 h seems reasonable, but there is yet no clear consensus on the range

between 6 and 7 h, where many Americans fall regarding their typical sleep habits. Also, it is not clear whether a determination of insufficient sleep should be made on the basis of physiologic sleep or perceived sleep.

Third, definitions of insufficient sleep are based on nomothetic, population-level recommendations which do not take into account individual differences in sleep need, sleep ability, and resilience to sleep loss. Also, these do not necessarily take into account sleep sufficiency relative to any particular outcome. Future work should consider these issues in order to take a more personalized/precision medicine view of sleep duration, as it relates to an individual and impacts on specific outcome measures, in a specific set of contexts.

Prevalence of poor sleep quality

Poor sleep quality, like insufficient sleep, has been variably defined. The National Sleep Foundation has recently attempted to develop a coherent conceptualization of sleep quality [41,42]. In a consensus document, elements of sleep quality included sleep latency (amount of time to fall asleep), wake time after sleep onset (amount of time awake at night), and sleep efficiency (proportion of the time in bed spent sleeping). Thus, sleep quality was generally defined as good sleep continuity. Recognizing the limitations of this, the National Sleep Foundation has begun

work on a tool to measure sleep satisfaction with is presented as another key element of overall sleep quality [43]. In addition to sleep-focused elements as indicators of sleep quality, perhaps daytime indicators can be useful as well. For example, daytime sleepiness is often an indicator of poor nighttime sleep [44,45] and may also serve as an indicator of poor sleep quality.

Prevalence of sleep disorders

Poor sleep quality can refer to a relatively wide range of problems, including sleep disorders as well as sleep symptoms. The most common types of sleep disorders in the population are insomnia and sleep apnea. Although other chapters in this volume focus specifically on these issues at the population level, it is important to note that the population prevalence of acute insomnia is high (about 4% per month) [46,47] and that although most of these resolve, approximately 10% of the population likely meets criteria for an insomnia disorder [48,49].

Regarding sleep apnea, prevalence estimates need to account for sex and body mass index. Relatively recent estimates of the prevalence of sleep apnea estimate that among men age 30–49, rates are 7.0%, 18.3%, 44.6%, and 79.5% for those with BMI of <25, 25–29.9, 30–39.9, and 40 or above, respectively. For men 50–70, the rates increase to 18.9%, 36.6%, 61.4%, and 82.8%, respectively. For women age 30–49, the rates of sleep apnea are lower, at 1.4%, 4.2%, 13.5%, and 43.0% for women with a BMI of <25, 25–29.9, 30–39.9, and 40 or higher, respectively. As with men, these numbers are higher in women age 50–70, with 9.3%, 20.2%, 41.1%, and 67.9% with sleep apnea among those with BMI of <25, 25–29.9, 30–39.9, and 40 or greater, respectively. This high prevalence of sleep apnea (Fig. 2.6) is particularly notable [50], especially since recent estimates suggest that approximately 85% of sleep apnea cases are never diagnosed, and up to half of diagnosed cases remain insufficiently treated [51].

Regarding circadian rhythm sleep disorders, the prevalence of delayed sleep phase disorder is estimated to be about 0.2% of the general population but 7%–16% of adolescents [52]. Prevalence of other circadian rhythm sleep disorders is largely unknown, though the prevalence of shift work disorder is estimated to be about 5%–10% of the population, based on prevalence estimates of night shift work and the prevalence of the disorder among shift workers [53].

Prevalence of sleep complaints

Several studies have examined prevalence of sleep complaints in the general population. For example, Grandner and colleagues [20] found that the rate of general sleep disturbance in the US population was about 16% in men

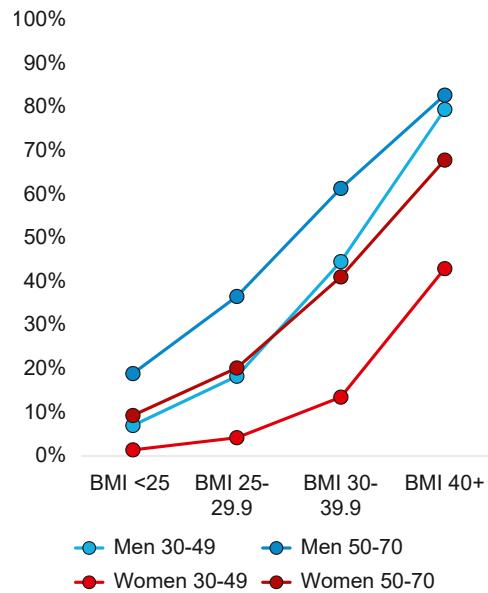


FIGURE 2.6 Estimated prevalence of sleep apnea by age group, sex, and BMI. From Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013. PubMed PMID: 23589584; PMCID: 3639722.

and 21% in women, and general daytime fatigue was 18% in men and 26% in women. However, this depended on age. Fig. 2.7 depicts the rates of these across age groups, illustrating a general decline in reports with age. Of note, in women, increased sleep duration and tiredness are evident around the age typical of menopause and in both men and women, fatigue increases starting at age 70. When odds ratios for these outcomes were computed after adjusting for covariates that included sociodemographics, health, and depression, the decrease in symptoms with age was even more pronounced. This has been replicated by several others, using other databases and addressing the issue of subjective sleep complaint in different ways [19,21]. In general, self-reported sleep complaints generally decrease with age. This is in contrast to objective sleep disturbances, which generally increase with age [23].

This general sleep complaint may be differentially experienced across demographic groups. Grandner and colleagues [54] showed that in addition to age and sex, general sleep disturbance was reported more frequently among non-Hispanic whites, compared to other groups. It was also more frequently reported by those with less education, less income, and lack of employment. In addition, it is reported more frequently among those in worse health overall and less healthcare access [20].

Regarding specific sleep complaints, Grandner and colleagues [55] examined data from the NHANES. In a nationally representative sample, the prevalence of self-reported sleep latency >30 min was 18.8%. Regarding other insomnia symptoms, the prevalence of difficulty at

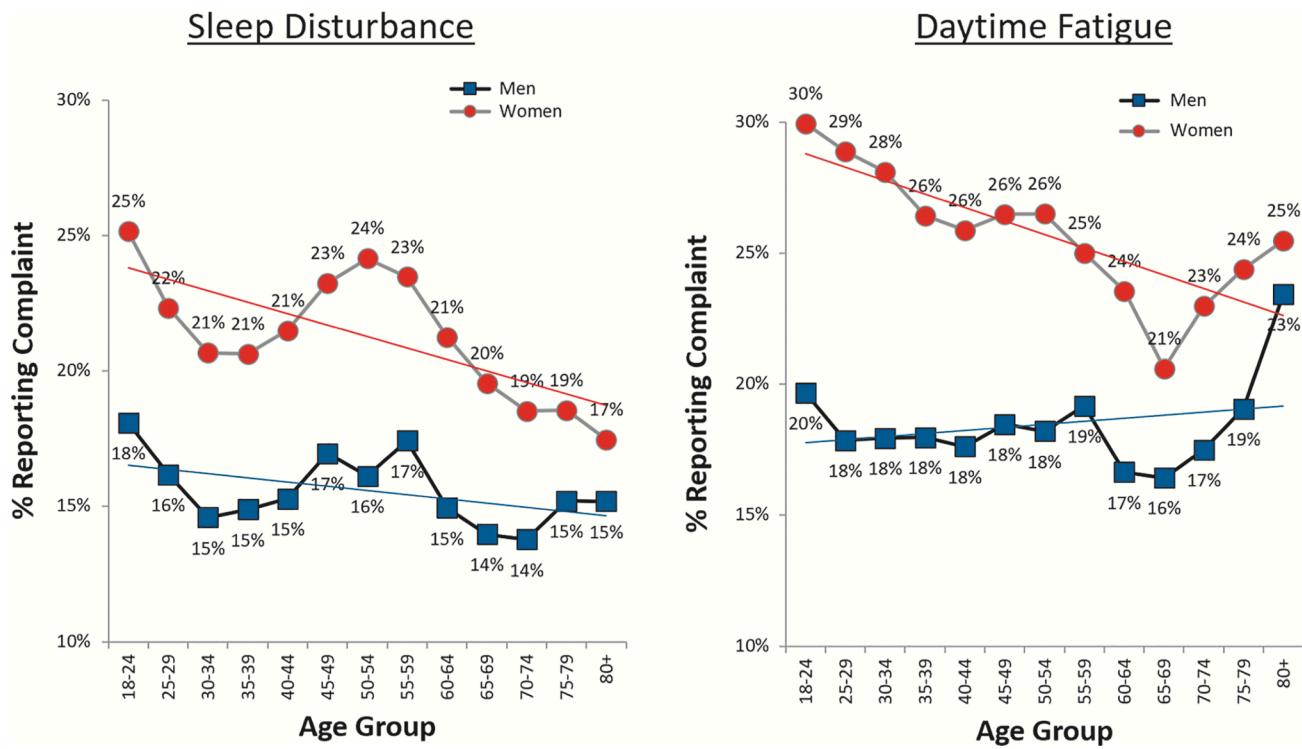


FIGURE 2.7 Prevalence of sleep disturbance and daytime fatigue by age and sex. Adapted from Grandner MA, Martin JL, Patel NP, Jackson NJ, Gehrman PR, Pien G, Perlis ML, Xie D, Sha D, Weaver T, Gooneratne NS. Age and sleep disturbances among American men and women: data from the U.S. Behavioral risk factor surveillance system. *Sleep*. 2012;35(3):395–406. Epub 2012/03/02. PubMed PMID: 22379246; PMCID: 3274341.

least once per week was 19.4% for falling asleep, 20.9% for resuming sleep during the night, and 16.5% for early morning awakenings; regarding problems at least three nights per week, these rates were reduced to 7.7%, 7.7%, and 5.8%, respectively. Regarding daytime symptoms, daytime sleepiness and nonrestorative sleep at least once per week were reported by 18.8% and 28.7% of the population, respectively; when the criterion was increased to three nights per week, this was reduced to 5.8% and 10.9%, respectively. In this sample, 70.6% of adults reported snoring at least once per week and 51% reported snoring at least three nights per week.

Summary and conclusions

Although accurately measuring sleeping individuals in large numbers is difficult, prevalence estimates for insufficient and poor quality sleep can be obtained from large-scale studies of health. Despite limitations of these estimates, it is clear that many adults are achieving insufficient sleep duration and/or inadequate sleep quality. This is concerning, since sleep is associated with so many important outcomes including health, daytime functioning, and mental well-being. Public health surveillance efforts should aim to improve measurement of sleep health at the population level across multiple domains. In addition,

public health intervention efforts should address healthy sleep as an important population health goal.

References

- [1] Hammond EC. Some preliminary findings on physical complaints from a prospective study of 1,064,004 men and women. *Am J Public Health Nation's Health* 1964;54:11–23. <https://doi.org/10.2105/AJPH.54.1.11>.
- [2] Grandner MA, Patel NP, Gehrman PR, Perlis ML, Pack AI. Problems associated with short sleep: bridging the gap between laboratory and epidemiological studies. *Sleep Med Rev* 2010;14(4):239–47. <https://doi.org/10.1016/j.smrv.2009.08.001>.
- [3] Grandner MA. Sleep medicine: a comprehensive guide to its development, clinical milestones, and advances in treatment. 2016. p. 495–509.
- [4] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M, Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL. Joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. *Sleep* 2015;38(8):1161–83. <https://doi.org/10.5665/sleep.4886>.
- [5] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M, Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL.

- Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep* 2015;38(6):843–4. <https://doi.org/10.5665/sleep.4716>.
- [6] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Adams Hillard PJ, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC. National Sleep Foundation's updated sleep duration recommendations: final report. *Sleep Health* 2015;1(4):233–43. <https://doi.org/10.1016/j.slehd.2015.10.004>.
- [7] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC, Adams Hillard PJ. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 2015;1(1):40–3. <https://doi.org/10.1016/j.slehd.2014.12.010>.
- [8] Mukherjee, Patel SR, Kales, Ayas, Strohl, Gozal, Malhotra A, American Thoracic Society ad hoc Committee on Healthy Sleep. An official American Thoracic Society statement: the importance of healthy sleep. Recommendations and future priorities. *Am J Respir Crit Care Med* 2015;191(12).
- [9] St-Onge, Grandner TA, Brown, Conroy NB, Louis GJ, Coons, Bhatt DL, American Heart Association Stroke Ccouncil. Sleep duration and quality: impact on lifestyle behaviors and cardiometabolic health: a scientific statement from the American Heart Association. *Am Heart Associat Coun Lifest Cardiometabol Health* 2016;134(18):367–86.
- [10] Kurina LM, McClintock MK, Chen JH, Waite LJ, Thisted RA, Lauderdale DS. Sleep duration and all-cause mortality: a critical review of measurement and associations. *Ann Epidemiol* 2013;23(6):361–70. <https://doi.org/10.1016/j.annepidem.2013.03.015>.
- [11] Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? *Epidemiology* 2008;19(6):838–45. <https://doi.org/10.1097/EDE.0b013e318187a7b0>.
- [12] Behavioral risk factor surveillance system 2014 codebook report. 2015.
- [13] Grandner MA, Seixas A, Shetty S, Shenoy S. Sleep duration and diabetes risk: population trends and potential mechanisms. *Curr Diabetes Rep* 2016;16(11). <https://doi.org/10.1007/s11892-016-0805-8>.
- [14] Grandner MA, Schopfer EA, Sands-Lincoln M, Jackson N, Malhotra A. Relationship between sleep duration and body mass index depends on age. *Obesity* 2015;23(12):2491–8. <https://doi.org/10.1002/oby.21247>.
- [15] Basner M, Spaeth AM, Dinges DF. Sociodemographic characteristics and waking activities and their role in the timing and duration of sleep. *Sleep* 2014;37(12):1889–906. <https://doi.org/10.5665/sleep.4238>.
- [16] McKnight-Eily LR, Presley-Cantrell LR, Strine TW, Chapman DP, Perry GS, Croft JB. Perceived insufficient rest or sleep - four states, 2006. *Morb Mortal Wkly Rep* 2008;57(8):200–3.
- [17] Altman NG, Izci-Balserak B, Schopfer E, Jackson N, Rattanaumpawan P, Gehrman PR, Patel NP, Grandner MA. Sleep duration versus sleep insufficiency as predictors of cardiometabolic health outcomes. *Sleep Med* 2012;13(10):1261–70. <https://doi.org/10.1016/j.sleep.2012.08.005>.
- [18] Liu Y, G Wheaton A, P Chapman D, J Cunningham T, Lu H, Croft JB. Prevalence of healthy sleep duration among adults—United States. *Morb Mortal Wkly Rep* 2014;65(6):137–41.
- [19] Grandner MA, Jackson NJ, Balserak BI, Gallagher RA, Bachmann RM, Williams NJ, Patel NP, Louis GJ. Social and behavioral determinants of perceived insufficient sleep. *Front Neurol* 2015;6(MAY). <https://doi.org/10.3389/fneur.2015.00112>.
- [20] Grandner MA, Martin JL, Patel NP, Jackson NJ, Gehrman PR, Pien G, Perlis ML, Xie D, Sha D, Weaver T, Gooneratne NS. Age and sleep disturbances among American men and women: data from the U.S. behavioral risk factor surveillance system. *Sleep* 2012;35(3):395–406. <https://doi.org/10.5665/sleep.1704UnitedStates>.
- [21] Soldatos CR, Allaert FA, Ohta T, Dikeos DG. How do individuals sleep around the world? Results from a single-day survey in ten countries. *Sleep Med* 2005;6(1):5–13. <https://doi.org/10.1016/j.sleep.2004.10.006>.
- [22] Zilli I, Ficca G, Salzarulo P. Factors involved in sleep satisfaction in the elderly. *Sleep Med* 2009;10(2):233–9. <https://doi.org/10.1016/j.sleep.2008.01.004>.
- [23] Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep* 2004;27(7):1255–73. <https://doi.org/10.1093/sleep/27.7.1255>.
- [24] Lindstrom V, Andersson K, Lintrup M, Holst G, Berglund J. Prevalence of sleep problems and pain among the elderly in Sweden. *J Nutr Health Aging* 2012;16(2):180–3. <https://doi.org/10.1007/s12603-011-0356-2>.
- [25] Cooke JR, Ancoli-Israel S. Normal and abnormal sleep in the elderly. *Handb Clin Neurol* 2011;98:653–65. <https://doi.org/10.1016/B978-0-444-52006-7.00041-1>.
- [26] Grandner MA, Patel NP, Gooneratne NS. Difficulties sleeping: a natural part of growing older? *Aging Health* 2012;8(3):219–21. <https://doi.org/10.2217/ahe.12.21>.
- [27] Whinnery J, Jackson N, Rattanaumpawan P, Grandner MA. Short and long sleep duration associated with race/ethnicity, sociodemographics, and socioeconomic position. *Sleep* 2014;37(3):601–11. <https://doi.org/10.5665/sleep.3508UnitedStates>.
- [28] Krueger PM, Friedman EM. Sleep duration in the United States: a cross-sectional population-based study. *Am J Epidemiol* 2009;169(9):1052–63. <https://doi.org/10.1093/aje/kwp023>.
- [29] Schredl M, Reinhard I. Gender differences in nightmare frequency: a meta-analysis. *Sleep Med Rev* 2011;15(2):115–21. <https://doi.org/10.1016/j.smrv.2010.06.002>.
- [30] Subramanian S, Gunupalli B, Murugan T, Bopparaju S, Chanamolu S, Casturi L, Surani S. Gender and ethnic differences in prevalence of self-reported insomnia among patients with obstructive sleep apnea. *Sleep Breath* 2011;15(4):711–5. <https://doi.org/10.1007/s11325-010-0426-4>.
- [31] Zhang B, Wing YK. Sex differences in insomnia: a meta-analysis. *Sleep* 2006;29(1):85–93. <https://doi.org/10.1093/sleep/29.1.85>.
- [32] Jean-Louis G, Kripke DF, Ancoli-Israel S, Klauber MR, Sepulveda RS. Sleep duration, illumination, and activity patterns in a population sample: effects of gender and ethnicity. *Biol Psychiat* 2000;47(10):921–7. [https://doi.org/10.1016/S0006-3223\(99\)00169-9](https://doi.org/10.1016/S0006-3223(99)00169-9).

- [33] Lauderdale DS, Knutson KL, Yan LL, Rathouz PJ, Hulley SB, Sidney S, Liu K. Objectively measured sleep characteristics among early-middle-aged adults: the CARDIA study. *Am J Epidemiol* 2006;164(1):5–16. <https://doi.org/10.1093/aje/kwj199>.
- [34] Ertel KA, Berkman LF, Buxton OM. Socioeconomic status, occupational characteristics, and sleep duration in African/Caribbean immigrants and US white health care workers. *Sleep* 2011;34(4):509–18. <https://doi.org/10.1093/sleep/34.4.509>.
- [35] Hale L, Do DP. Racial differences in self-reports of sleep duration in a population-based study. *Sleep* 2007;30(9):1096–103. <https://doi.org/10.1093/sleep/30.9.1096>.
- [36] Nunes J, Jean-Louis G, Zizi F, Casimir GJ, Von Gizecki H, Brown CD, McFarlane SI. Sleep duration among black and white Americans: results of the National Health Interview Survey. *J Natl Med Assoc* 2008;100(3):317–22. [https://doi.org/10.1016/S0027-9684\(15\)31244-X](https://doi.org/10.1016/S0027-9684(15)31244-X).
- [37] Jean-Louis G, Grandner MA, Youngstedt SD, Williams NJ, Zizi F, Sarpong DF, Ogedegbe GG. Differential increase in prevalence estimates of inadequate sleep among black and white Americans. *BMC Public Health* 2015;15(1). <https://doi.org/10.1186/s12889-015-2500-0>.
- [38] Jean-Louis G, Youngstedt S, Grandner M, Williams NJ, Sarpong D, Zizi F, Ogedegbe G. Unequal burden of sleep-related obesity among black and white Americans. *Sleep Health* 2015;1(3):169–76. <https://doi.org/10.1016/j.slehd.2015.07.003>.
- [39] Stamatakis KA, Kaplan GA, Roberts RE. Short sleep duration across income, education, and race/ethnic groups: population prevalence and growing disparities during 34 Years of follow-up. *Ann Epidemiol* 2007;17(12):948–55. <https://doi.org/10.1016/j.anepidem.2007.07.096>.
- [40] Grandner MA, Smith TE, Jackson N, Jackson T, Burgard S, Branas C. Geographic distribution of insufficient sleep across the United States: a county-level hotspot analysis. *Sleep Health* 2015;1(3):158–65. <https://doi.org/10.1016/j.slehd.2015.06.003>.
- [41] Knutson KL, Phelan J, Paskow MJ, Roach A, Whiton K, Langer G, Hillygus DS, Mokrzycki M, Broughton WA, Chokroverty S, Lichstein KL, Weaver TE, Hirshkowitz M. The National Sleep Foundation's sleep health index. *Sleep Health* 2017;3(4):234–40. <https://doi.org/10.1016/j.slehd.2017.05.011>.
- [42] Ohayon M, Wickwire EM, Hirshkowitz M, Albert SM, Avidan A, Daly FJ, Dauvilliers Y, Ferri R, Fung C, Gozal D, Hazen N, Krystal A, Lichstein K, Mallampalli M, Plazzi G, Rawding R, Scheer FA, Somers V, Vitiello MV. National Sleep Foundation's sleep quality recommendations: first report. *Sleep Health* 2017;3(1):6–19. <https://doi.org/10.1016/j.slehd.2016.11.006>.
- [43] Ohayon MM, Chen MC, Bixler E, Dauvilliers Y, Gozal D, Plazzi G, Vitiello MV, Paskow M, Roach A, Hirshkowitz M. A provisional tool for the measurement of sleep satisfaction. *Sleep Health* 2018;4(1):6–12. <https://doi.org/10.1016/j.slehd.2017.11.002>.
- [44] Ferini-Strambi L, Sforza M, Poletti M, Giarrusso F, Galbiati A. Daytime sleepiness: more than just Obstructive Sleep Apnea (OSA). *Med Lav* 2017;108(4):260–6. <https://doi.org/10.23749/ml.v108i4.6497>.
- [45] Malhotra RK. Sleepy or sleepless: clinical approach to the sleep patient. Springer International Publishing; 2015. <https://doi.org/10.1007/978-3-319-18054-0>.
- [46] Ellis JG, Gehrman P, Espie CA, Riemann D, Perlis ML. Acute insomnia: current conceptualizations and future directions. *Sleep Med Rev* 2012;16(1):5–14. <https://doi.org/10.1016/j.smrv.2011.02.002>.
- [47] Ellis JG, Perlis ML, Neale LF, Espie CA, Bastien CH. The natural history of insomnia: focus on prevalence and incidence of acute insomnia. *J Psychiatr Res* 2012;46(10):1278–85. <https://doi.org/10.1016/j.jpsychires.2012.07.001>.
- [48] Ohayon MM, Guilleminault C. Epidemiology of sleep disorders and sleep: a comprehensive handbook. United States: John Wiley and Sons; 2005. p. 73–82. <https://doi.org/10.1002/0471751723.ch10>.
- [49] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6(2):97–111. <https://doi.org/10.1053/smrv.2002.0186>.
- [50] Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177(9):1006–14. <https://doi.org/10.1093/aje/kws342>.
- [51] Underdiagnosing and undertreating obstructive sleep apnea draining healthcare system. American Academy of Sleep Medicine; 2016.
- [52] Zhu L, Zee PC. Circadian rhythm sleep disorders. *Neurol Clin* 2012;30(4):1167–91. <https://doi.org/10.1016/j.ncl.2012.08.011>.
- [53] International classification of sleep disorders. American Academy of Sleep Medicine; 2014.
- [54] Grandner MA, Patel NP, Gehrman PR, Xie D, Sha D, Weaver T, Gooneratne N. Who gets the best sleep? Ethnic and socioeconomic factors related to sleep complaints. *Sleep Med* 2010;11(5):470–8. <https://doi.org/10.1016/j.sleep.2009.10.006>.
- [55] Grandner MA, Ruiter Petrov ME, Rattanaumpawan P, Jackson N, Platt A, Patel NP. Sleep symptoms, race/ethnicity, and socioeconomic position. *J Clin Sleep Med* 2013;9(9):897–905. <https://doi.org/10.5664/jcsm.2990UnitedStates>.

Chapter 3

Sex differences in sleep health

Jessica Meers¹, Jacqueline Stout-Aguilar² and Sara Nowakowski¹

¹Department of Medicine, Baylor College of Medicine, Houston, TX, United States; ²School of Nursing, University of Texas Medical Branch, Galveston, TX, United States

Introduction

Biologically based sex differences contribute to sleep-related differences in men and women and may help explain the differential risk for sleep disorders [1–5]. Sex differences refer to biological and physiological differences between men and women, with the sex chromosomes and the gonadal hormones primarily contributing to these differences at the cellular, organ, and system levels. Emerging clinical evidence suggests that sleep dysregulation may have more severe health consequences for women than men. Several studies have demonstrated that women report more sleep difficulties [6,7] and are at greater risk for a diagnosis of insomnia compared to men [8,9]. In general, there is a higher prevalence of insomnia and dissatisfaction with sleep in women across a wide age range. In subjective studies, women report poorer sleep quality, difficulties falling asleep, frequent night awakenings and longer periods of time awake throughout the night [3]. In contrast, objective measures of sleep, measured by actigraphy and polysomnography, have demonstrated shorter sleep onset latency, increased sleep efficiency, and total sleep time in women compared to men [10–12], whereas a meta-analysis of sex differences of sleep behaviors in older adults (aged 58 +) revealed no sex differences in total sleep time [13]. In addition to sex differences found in complaint of sleep disturbances, sex differences also exist for treatment of sleep disorders. For example, in 2013 the US Food and Drug Administration required the manufacturers of Ambien to lower the recommended dose of zolpidem for women from 10 to 5 mg for immediate-release products and from 12.5 to 6.25 mg for extended-release products due to the risk of next-morning impairment and motor vehicle accidents. Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men. Zolpidem is the first drug in the United States to have different recommended doses for women versus men,

but it seems likely pharmacokinetic sex differences would lead to differences in rates of absorption, metabolism, and excretion of other medications as well. This review will focus on sex differences in sleep across the lifespan.

Sex differences in infant sleep

Newborns spend 60%–70% of the 24 h day in sleep, compared to just 20%–25% in adults [14,15]. The brain structures and systems that regulate sleep and the circadian process are still relatively immature in newborns, and neonates are not synchronized to the 24 h day. By the end of first month, though, infants begin to spend more time awake during the day and more time sleeping at night. Infants possess a very strong homeostatic drive for sleep, and, combined with the relative lack of a circadian rhythm, infants frequently cycle between sleep and wakefulness throughout the 24 h day, requiring frequent naps to dissipate the quickly building sleep pressure [14]. Sleep in early infancy has not yet developed the cyclic patterns found in later life and is more appropriately characterized as active sleep, quiet sleep, or indeterminate sleep [16]. It is not until roughly 3 months of age that infant sleep begins to consolidate to resemble the organization and rhythmicity that it will maintain throughout the lifespan [17].

The limited research into infant sleep has indicated small and inconsistent sex differences [18]. Even so, there are some important distinctions that could play a vital role in infant health. Males tend to lag behind females in the development of the central nervous system (CNS), leading females to have more mature respiration during the first 6 months [19] and more organized sleep patterns [20]. These immaturities have been linked with sudden infant death syndrome (SIDS), which affects males at rates about 1.5 times those of females [21]. Intuitively, the earlier development of the CNS system in infant girls suggests that circadian entrainment may happen at an earlier chronological age in girls compared to boys. In fact, there is some

evidence that suggests that girls do, in fact, demonstrate earlier rhythm development in terms of core body temperature [22]. Few studies, however, have examined sex differences of early circadian development, so conclusions cannot yet be drawn.

In terms of sleep continuity, although findings have been inconsistent, infant boys tend to have shorter sleep duration (by 5–10 min, on average) and wake earlier than girls [23–25]. Boys spend less time in motionless or quiet sleep compared to girls [25]. Thus, in the first year of life, boys are more active sleepers [26], wake more frequently, and tend to have lower sleep efficiency compared to girls [27]. By the end of the first 18 months, however, sex differences in nocturnal awakenings have been shown to diminish [18].

Sleep duration in infants has been linked to rates of physical growth and weight gain. For all infants, shorter sleep duration is correlated with a higher weight to length ratio. When examining the sleep duration—growth relationship by sex, poorer sleep quality (more fragmented sleep) is associated with a greater weight to length ratio in male infants at 6 months of age compared to female infants [28]. Thus, the link between poor sleep and weight gain likely begins in infancy and is particularly relevant for males.

Sex differences in childhood sleep

As development progresses into early childhood, homeostatic sleep drive remains higher compared to adolescents and adults [29]. Over the course of childhood, homeostatic sleep pressure trends toward a slower daytime build up, allowing for children to maintain longer periods of wakefulness during the day. By 12 months of age, children are napping on average twice daily for several hours [30]. By the third and fourth year, children begin to need shorter and less frequent naps as they move toward a more consolidated sleep–wake pattern [31]. In accordance with these changes, total sleep need decreases, and total sleep duration (including naps) moves from around 13 h at age two, 11 h at age six, to 10 h by age nine [32]. In childhood, daily sleep–wake patterns stay fairly consistent; wake typically occurs spontaneously and at consistent times, even on weekends [33].

Few studies have explored sex differences in childhood sleep, and the findings remain generally inconsistent and relatively small. Although some studies have found no sex differences at all [34], there is mounting evidence for general trends that mirror those found in infancy. Across the length of childhood, girls tend to sleep longer than boys [24,35,36], potentially attributed to later morning wake times in girls, as opposed to differing bed times [24]. It should be noted, however, that other studies have either found no such differences [37], or have found earlier wake

times in girls [38], and later bed times in boys [39]. Regardless, differences in sleep efficiency become more apparent during childhood, with girls showing higher sleep efficiency and smaller proportions of wakefulness compared to boys [36,40].

Despite the appearance of better sleep suggested by higher sleep efficiency and shorter awakenings, girls are more vulnerable to sleep complaints, even in childhood. These include problems with bedtime resistance, sleep anxiety, and daytime sleepiness [41]. In a study assessing insomnia across 5–12-year-olds, whereas rates in males remained steady, rates of insomnia for females reached their peak in late childhood (aged 11–12), at the cusp of pubertal onset [42].

Sleep problems such as these are correlated with emotional and affective problems throughout the lifespan. Sleep disturbance is both a risk factor for and a response to many emotional and behavioral problems [43–45]. In children, insomnia symptoms have been linked to behavioral problems, including both internalizing and externalizing behaviors, mood variability, and school problems [46]. Further, both prepubertal and pubertal girls with depression show a lower amplitude of circadian rest–activity cycles, indicating a lack of circadian entrainment to the 24 h clock, resulting in irregular sleep–wake schedules and sleep complaints [47]. Thus, early sleep problems may be one initiating factor related to emotional problems that may persist into adolescence, and girls may be especially vulnerable to the negative effects of poor sleep.

Health-related outcomes of poor sleep in childhood are highlighted by the associations that exist between short sleep duration and obesity in childhood through young adulthood. In children as young as 3 years of age, short sleep duration is associated with a greater body mass index (BMI) for boys but not for girls [39]. In a longitudinal study of 313 children/adolescents ages 8–19 years, Storfer-Isser et al. found sleep duration to have a negative linear association with BMI for boys but not girls, and the magnitude of the association decreased with age [48]. Thus, short sleep duration is associated with BMI and weight gain in boys during their middle childhood through young adulthood but less so through their middle-to-older adult years. Findings are contradictory, however, owing in part to differences in study design (cross-sectional vs. longitudinal), measurement (self-report vs. objective measures of sleep), race/ethnicity, and country of origin.

Sex differences in adolescent sleep

Puberty brings with it significant physical and psychological change and marks the emergence of most sex related differences in sleep health. Sleep itself is closely related to the regulation of endocrine functioning closely tied to

puberty initiation and reproductive functioning, including growth hormone, melatonin, and sex steroids, such as testosterone in males and estrogen and progestin in females [49,50].

Because girls typically begin puberty at an earlier chronological age, they begin to show circadian phase advancement before boys [51–54], and the sex differences found in infancy and childhood become more pronounced. Homeostatic sleep pressure slows significantly at the onset of puberty, allowing adolescents to be able to maintain wakefulness for even longer periods of time [31]. As adolescents mature, the circadian phase shifts later, causing more wakefulness in the evenings and later bedtimes [55,56]. Some studies have found as much as an hour difference in bedtimes once puberty is initiated [54]. The puberty-related changes in sleep and circadian timing can be attributed to the complex relationship between sleep and endocrine functioning. Melatonin is a hormone secreted by the pineal gland that is closely tied to the circadian rhythm. In humans, melatonin levels are lowest during the day and gradually increase in the hours just prior to sleep onset [57]. During childhood, melatonin peaks in the early evening; but during puberty, the timing of the melatonin peak begins to occur later [58].

Despite the biological shift toward a later bedtime, total amount of sleep need is not significantly lower than that of children. When this phase shift is combined with the increased demands that adolescents face in terms of school start times and other obligations, the result is often a sleep duration that does not meet recommendations [33,54,59]. As a result, daytime sleepiness increases dramatically during adolescence along with the physical, cognitive, and emotional consequences of inadequate sleep [60]. In boys, inadequate sleep is related to risk behaviors such as smoking, alcohol use, and excessive caffeine usage. For girls, however, poor sleep is associated with more emotional and relationship difficulties [61].

Adolescent girls continue exhibit a longer sleep period than boys [52,62,63], with later weekend wake times [54]. Sleep efficiency also remains higher for girls compared to boys [62]. Conversely, boys are, on average, more active sleepers and spend less time in motionless sleep compared to girls. In fact, as males mature and begin puberty, wake time after sleep onset increases [62,64]. Males also report later bedtimes and more weekday to weekend discrepancy in bed and wake times [65]. Conversely, girls tend to be more extreme sleepers, either sleeping much shorter (less than 6 h), or much longer (greater than 10 h) than average [66].

Prior to adolescence, no gender differences have been consistently detected in sleep architecture. Concurrent with the phase delay that occurs with puberty, slow wave sleep also begins to decline and is indicative of brain maturation. In prepubertal children, delta power remains the same

across both sexes. Girls, however, begin to experience this decline in slow wave activity before boys. By the age of 12, boys have greater delta power per minute comparatively, likely attributed to girls' earlier entry into puberty [67]. Sex differences remain to a degree, however, when pubertal status is controlled, suggesting that gender differences exist beyond pubertal timing [68].

Pubertal onset is a time when sex differences in sleep complaints tend to arise and are maintained into adulthood. Although the degree to which these hormonal changes are mechanistic of these differences remain unclear, adolescent girls report greater sleep difficulties than boys. Girls report longer sleep-onset latency and exhibit greater rates of insomnia compared to boys [65,69]. The increased insomnia risk in females persists across the lifespan [69,70]. Increased vulnerability to restless legs symptoms also co-occurs with pubertal onset and affects adolescent girls at higher rates than males contributing to poorer sleep quality and difficulty in sleep initiation [71,72]. Furthermore, because puberty is a time of increased vulnerability to affective disorders [73], the relationship between poor sleep and general emotional problems becomes more pronounced. Insufficient sleep is associated with higher ratings of anxiety, depression, and negative perceptions of health [74]. This is particularly problematic given that even when psychiatric disturbances are treated, sleep problems often persist [75].

Beyond emotional difficulties, insufficient sleep in adolescence continues to be linked with metabolic and cardiovascular consequences. In the National Longitudinal Study of Adolescent Health, Suglia et al. [76] found that short sleep duration was associated with obesity in adolescent males (mean age 16 years) but not females. However in longitudinal analyses of the same study, the investigators found short sleep in adolescents to be predictive of obesity in young adulthood (mean age 21 years) in both males and females. Also, during puberty, physiological changes that occur lead to differences in fat mass, body composition, and hormonal changes between adolescent boys and girls such that boys tend to decrease fat mass due to increases in growth hormone and testosterone and girls tend to increase fat mass due to estradiol. Thus, the relationship between sleep duration and metabolism, postpuberty into younger adulthood, may start favoring a greater obesogenic propensity among women compared to men. Further, sleep and obesity are both risk factors for hypertension, a particularly dangerous and growing health concern [77–79]. A study by Peach et al. found that sleep quality and daytime sleepiness directly serve as direct risk factors for greater BMI, which indirectly predicts hypertension. For males, however, shorter sleep duration was found to differentially drive these risks, whereas daytime sleepiness (a proxy for poor quality sleep) was more likely to be a risk factor for females. Therefore,

when considering the link between sleep and physiological health complaints, risk factors are differentially tied to biological sex, and thus findings of studies that do not take into sex into account may be misleading [80].

Sex differences in sleep disordered breathing also emerge during adolescence and are related to obesity. Whereas rates of obstructive sleep apnea are roughly equivalent in childhood, beginning in adolescence, males are affected in rates that exceed those of females [81]. These rates do not emerge until pubertal onset, indicating the potential role of sex steroids in muscle and fat distribution affecting airway structure, and further perpetuated by higher rates of obesity [82]. Poor sleep may therefore be both a risk factor for and a consequence of obesity, indicating that a focus on sleep should be at the center of the obesity crisis and that biologically based sex differences cannot be ignored.

Sex differences in young adult sleep

The sleep disturbances that initially emerge in adolescence frequently carry forward into adulthood. The multitude of biological, psychosocial, and environmental factors that contribute to insufficient sleep and sleep disturbance among adolescents similarly exist for young adults. This includes continued biological changes in the accumulation of homeostatic sleep pressure, increasing academic and vocational demands, and use of substances such as alcohol and caffeine [83,84]. Additionally, the form and function of sleep continues to change as we age [85]. General recommendations for sleep duration in young and midlife adults suggest 7–9 h of sleep per night [86]. Forty percent of American adults, however, report obtaining less than 7 h of sleep per night on weeknights [87]. Moreover, 38% of young and midlife adults report waking up feeling unrefreshed with 21% having difficulty falling asleep several nights per week. Among young adults ages 19–29, 67% reported not getting enough sleep to function properly [88]. In general, sleep duration decreases with age across the reproductive years. In a study, Campbell and Murphy evaluate the spontaneous sleep across the 24-h day among young, middle-aged, and older adults. Findings indicated that compared with young adults (10.5 h), middle-aged (9.1 h), and older adults (8.1 h) had significantly shorter average nighttime sleep duration [89]. Data from 160 healthy adults (without sleep complaints) aged between 20 and 90 years from the SIESTA database showed that sleep duration decreased about 8 min per decade in males and 10 min per decade in females. Further, they found an age-related increase in lighter sleep (NREM stage 1) associated with concomitant decreases in slow wave sleep for males and NREM stage 2 sleep for females [90]. Three separate meta-analyses found that age was linearly correlated with decreased sleep duration. It was further concluded that

there was an approximately 10–12 min reduction per decade of age in the adult population (with a stronger association in women and young adults when compared to men and middle-aged or older adults). Findings also indicated that sleep duration plateaued after the age of 60.

The sex differences in sleep that exist in adolescence through adulthood are attributed in part to the complex interaction of neuroendocrine changes associated with reproductive functioning [91]. In healthy males, this includes production of testosterone that remains fairly stable through most of young adulthood. In females, however, puberty initiates monthly cyclic changes in the production of various hormones, including follicle-stimulating hormone, luteinizing hormone, estrogen, and progesterone. During the first half of the cycle, estrogen predominates, whereas progesterone dominates the latter portion of the cycle prior to the sharp decline in both hormones if fertilization does not occur (the premenstrual period) [92]. At least one third of women report sleep disruptions related to their menstrual cycle [87]. Sleep quality decreases and sleep disturbances increase toward the end of each menstrual cycle [93,94]. These subjective sleep complaints mirror objective findings showing decreased sleep efficiency and total sleep time just prior to menses [95], although objective findings are mixed [95,96]. Regardless, these sleep disruptions have been linked to the increase in progesterone and a related rise in core body temperature [97].

It is well known that sleep plays a multitude of roles (including promoting growth, learning, and cognitive development), has a role in immunoprotective functionalities. In addition to obesity-related risk, studies have reported a significant association between poor sleep and heart disease in adults [98]. Furthermore, both short and long sleep durations have been associated with increased risk of coronary heart disease and type 2 diabetes as well as with daytime sleepiness and waking unrefreshed [99,100]. Short sleep in men in particular has been shown to decrease insulin sensitivity, increasing metabolic risk [101]. Similarly, short sleep duration has long been identified as a risk factor for hypertension, but this relationship is shown more consistently in females [102]. The precise mechanisms behind these findings, however, are poorly understood.

Sex differences in middle-aged sleep

The middle years of life are a significant time of change in sleep health. As much as 35% of the population aged 40–60 years old report sleep difficulties [103]. The sex differences in subjective sleep complaints found across adolescence and early adulthood tend to be amplified with aging, with women demonstrating increased risk of insomnia, poorer sleep quality, and more frequent awakenings, despite reporting earlier bedtimes and longer sleep

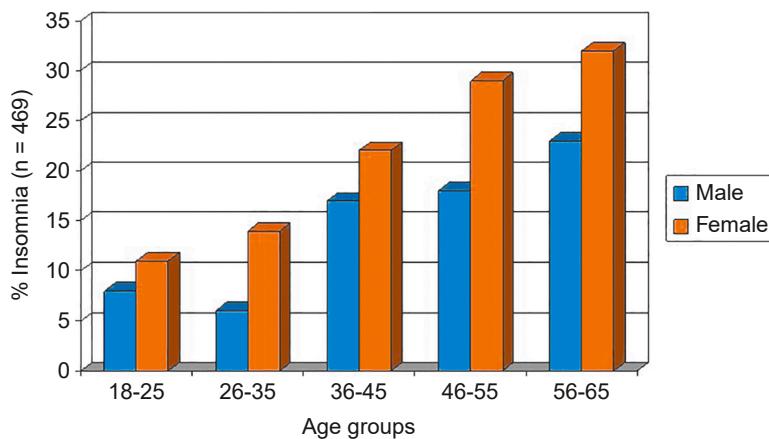


FIGURE 3.1 Age and sex distribution of insomnia. Adapted from Hohagen, *Eur Arch Psychiatry Clin Neurosci* 1993; with permission.

duration compared to men [3,104]. Conversely, the effects of aging on objectively measured sleep have been found to be more pronounced in men, including reductions in the deeper, more restorative sleep characterized by slow wave sleep and increases in lighter sleep stages, such as NREM stage 1 (Fig. 3.1) [105,106].

The modulating role of endocrine functioning on sleep continues to change through adulthood. The slowing of growth hormone secretion since adolescence is accompanied by age-related decreases of slow-wave sleep throughout the lifespan [50,107]. Rates of melatonin secretion decrease with age, as well. There is evidence that suggests that the typical nightly increase in nocturnal melatonin is reduced in older compared to younger adults [108]. The changes in gonadotropins and sex steroids that naturally occur with aging are arguably more strongly associated with sleep changes in midlife. In men, testosterone levels decrease progressively with age after year 30, and the diurnal patterning of testosterone may be reduced in older men [109]. Poorer sleep quality is associated with lower testosterone concentrations in men [110,111]. These naturally occurring decreases in testosterone may relate to the increased sleep fragmentation commonly seen in older adults [112]. In women, sleep may be even more sensitive to changes in the sex steroid milieu. Menopause, the permanent cessation of menstrual periods, occurs between 50 and 52 years of age for most women (although variations related to race/ethnicity, health, and lifestyle factors do exist) [113]. During and after menopause, estradiol levels decrease and follicle-stimulating hormone levels increase significantly. These changes in reproductive hormones have been linked to increased complaints of sleep disturbance. Insomnia prevalence rates increase from 33% to 36% in premenopausal women to 44%–61% in postmenopausal women [114–116]. Hot flashes occur in 60%–80% of women during the menopausal transition [117], and when they occur during the night, they are often associated

with subjectively reported arousals and sleep disturbance, although when objective measures are used, findings are mixed [118–125].

Rates of sleep apnea increase during the middle age, related to increased incidence of obesity and aging [126]. Rates of obstructive sleep apnea in men far exceed those of premenopausal women [127]. In men, the relationship between weight and sleep apnea is stronger than that of women [128,129]. Following the menopausal transition, however, risk for obstructive sleep apnea increases by 3.5 times for women [130]. Although the relationship between steroid hormones and sleep apnea are not yet clear, evidence suggests that estrogen and progesterone are protective factors, enhancing respiratory functioning in women [131,132]. Further, the changes in endocrine milieu associated with the menopause transition, that is, the decrease in estrogen has been found to be a prominent risk factor for weight gain [133], further contributing to postmenopausal sleep apnea risk in women. The increased risk for weight gain and sleep apnea further increases risk to cardiovascular and metabolic health in midlife. Poor sleep further compounds these risks for both men and women.

Sex differences in older adult sleep

Normative aging is often accompanied by greater difficulties in sleep initiation and maintenance. Older adults report longer sleep-onset latency, shorter sleep duration, and generally more fragmented sleep, as they spend more time awake during the night [134,135]. The timing of sleep changes as well, as older adults show a general advancing of circadian timing to an earlier nocturnal sleep period [136]. Napping frequency increases, with as many as 25% of adults aged 75–84 reporting daytime naps [137]. In fact, with the advancement of age, a greater vulnerability to circadian rhythm disorders such as advanced sleep phase and the deleterious effects of jet lag emerge [136].

Emerging evidence also suggests that sleep disruptions and complaints precede the emergence of dementia and related disorders and may increase risk [138].

Compared to women, men generally exhibit greater age-related changes objectively measured sleep. In a study of 2500 older adults, age was associated with continued decreases in slow wave sleep and increases in NREM stages 1 and 2, particularly for men. In fact, slow wave sleep (with a concomitant increase in NREM stages 1 and 2) was reduced by as much as 50% when comparing those over 70 to those aged 55—growing indeed, reductions in rates of slow-wave sleep have been consistently shown to increase across the lifespan in males relative to females [105,106,134]. Relatedly, following sleep deprivation, men experience reduced rebound effects on slow wave sleep compared to women [139]. It should be noted, however, that several studies have found no such sex difference in sleep architecture in older adults [10,140].

Unsurprisingly, subjective sleep quality appears to decrease in older adulthood. Interestingly, however, despite the greater objectively measured sleep disturbances found in men, older women exhibit greater subjective sleep complaints. Women have been shown to have greater self-reported sleep onset latency and report poorer sleep quality [3,104,106]. While the mechanisms behind these sex differences are unclear, it may be that variables impact women's perception of their sleep, such as health-related conditions like fibromyalgia, chronic pain, and overactive bladder.

Conclusion

There is an ever-growing body of work that demonstrates sex differences in sleep health across the lifespan. Research studies, in general, should be conscious of these differences and consider effects of sex when examining sleep. Further, investigators should take into account the timing of menstrual phase cycle when studying premenopausal women. The field has come a long way in recognizing and measuring sex differences in sleep health. Much work remains to be completed in examining sex differences related to the differential effects of subjective complaint versus objective measure of sleep and the varying impact of sleep duration and sleep disturbance as it relates to health outcomes for men versus women.

References

- [1] Manber R, Armitage R. Sex, steroids, and sleep: a review. *Sleep* 1999;22(5):540–55.
- [2] Sowers MF, Zheng H, Kravitz HM, Matthews K, Bromberger JT, Gold EB, Owens J, Consens F, Hall M. Sex steroid hormone profiles are related to sleep measures from polysomnography and the Pittsburgh sleep quality index. *Sleep* 2008;31(10):1339–49.
- [3] Zhang B, Wing YK. Sex differences in insomnia: a meta-analysis. *Sleep* 2006;29(1):85–93. <https://doi.org/10.1093/sleep/29.1.85>.
- [4] Krishnan V, Collop NA. Gender differences in sleep disorders. *Curr Opin Pulm Med* 2006;12(6):383–9. <https://doi.org/10.1097/01.mcp.0000245705.69440.6a>.
- [5] Mallampalli MP, Carter CL. Exploring sex and gender differences in sleep health: a society for women's health research report. *J Wom Health* 2014;23(7):553–62. <https://doi.org/10.1089/jwh.2014.4816>.
- [6] Åkerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Sleep disturbances, work stress and work hours: a cross-sectional study. *J Psychosom Res* 2002;53(3):741–8. [https://doi.org/10.1016/S0022-3999\(02\)00333-1](https://doi.org/10.1016/S0022-3999(02)00333-1).
- [7] Lindberg E, Janson C, Gislason T, Björnsson E, Hetta J, Boman G. Sleep disturbances in a young adult population: can gender differences be explained by differences in psychological status? *Sleep* 1997;20(6):381–7. <https://doi.org/10.1093/sleep/20.6.381>.
- [8] Jaussent I, Dauvilliers Y, Ancelin ML, Dartigues JF, Tavernier B, Touchon J, Ritchie K, Berset A. Insomnia symptoms in older adults: associated factors and gender differences. *Am J Geriatr Psychiatr* 2011;19(1):88–97. <https://doi.org/10.1097/JGP.0b013e3181e049b6>.
- [9] Singareddy R, Vgontzas AN, Fernandez-Mendoza J, Liao D, Calhoun S, Shaffer ML, Bixler EO. Risk factors for incident chronic insomnia: a general population prospective study. *Sleep Med* 2012;13(4):346–53. <https://doi.org/10.1016/j.sleep.2011.10.033>.
- [10] Carrier J, Land S, Buysse DJ, Kupfer DJ, Monk TH. The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20–60 years old). *Psychophysiology* 2001;38(2):232–42. <https://doi.org/10.1017/S0048577201991838>.
- [11] Bixler EO, Papaliaga MN, Vgontzas AN, Lin HM, Pejovic S, Karataraki M, Vela-Bueno A, Chrousos GP. Women sleep objectively better than men and the sleep of young women is more resilient to external stressors: effects of age and menopause. *J Sleep Res* 2009;18(2):221–8. <https://doi.org/10.1111/j.1365-2869.2008.00713.x>.
- [12] Jean-Louis G, Mendlowicz MV, Von Gizecki H, Zizi F, Nunes J. Assessment of physical activity and sleep by actigraphy: examination of gender differences. *J Wom Health Genit Base Med* 1999;8(8):1113–7. <https://doi.org/10.1089/jwh.1.1999.8.1113>.
- [13] Rediehs MH, Reis JS, Creason NS. Sleep in old age: focus on gender differences. *Sleep* 1990;13(5):410–24.
- [14] Hilliard T. Principles and practice of pediatric sleep medicine. *Arch Dis Child* 2006;91(6):546–7. <https://doi.org/10.1136/adc.2006.093955>.
- [15] Galland BC, Taylor BJ, Elder DE, Herbison P. Normal sleep patterns in infants and children: a systematic review of observational studies. *Sleep Med Rev* 2012;16(3):213–22. <https://doi.org/10.1016/j.smrv.2011.06.001>.
- [16] Peirano P, Algarin C, Uauy R. Sleep-wake states and their regulatory mechanisms throughout early human development. *J Pediatr* 2003;143(4):70–9. [https://doi.org/10.1067/s0022-3476\(03\)00404-9](https://doi.org/10.1067/s0022-3476(03)00404-9).
- [17] Lushington P, Martin J, Kennedy. The Oxford handbook of infant, child, and adolescent sleep and behavior. Oxford University Press; 2013. p. 2013.
- [18] Weinraub M, Friedman SL, Knoke B, Houts R, Bender RH, Susman EJ, Bradley R, Williams J. Patterns of developmental change in infants' nighttime sleep awakenings from 6 through 36 months of age. *Dev Psychol* 2012;48(6):1511–28. <https://doi.org/10.1037/a0027680>.

- [19] Hoppenbrouwers T, Hodgman JE, Harper RM, Sterman MB. Respiration during the first six months of life in normal infants: IV. Gender differences. *Early Hum Dev* 1980;4(2):167–77. [https://doi.org/10.1016/0378-3782\(80\)90020-1](https://doi.org/10.1016/0378-3782(80)90020-1).
- [20] Mirmiran M, Maas YGH, Ariagno RL. Development of fetal and neonatal sleep and circadian rhythms. *Sleep Med Rev* 2003;7(4):321–34. <https://doi.org/10.1053/smrv.2002.0243>.
- [21] Mage DT, Donner M. A unifying theory for SIDS. *Int J Pediatr* 2009;(2009):1–10. <https://doi.org/10.1155/2009/368270>.
- [22] Lodemore MR, Petersen SA, Wailoo MP. Factors affecting the development of night time temperature rhythms. *Arch Dis Child* 1992;67(10):1259–61. <https://doi.org/10.1136/adc.67.10.1259>.
- [23] McDonald L, Wardle J, Llewellyn CH, van Jaarsveld CHM, Fisher A. Predictors of shorter sleep in early childhood. *Sleep Med* 2014;15(5):536–40. <https://doi.org/10.1016/j.sleep.2014.01.005>.
- [24] Blair PS, Humphreys JS, Gringras P, Taheri S, Scott N, Emond A, Henderson J, Fleming PJ. Childhood sleep duration and associated demographic characteristics in an English cohort. *Sleep* 2012;35(3):353–60. <https://doi.org/10.5665/sleep.1694>.
- [25] Goodlin-Jones BL, Burnham MM, Gaylor EE, Anders TF. Night wakening, sleep-wake organization, and self-soothing in the first year of life. *J Dev Behav Pediatr* 2001;22(4):226–33. <https://doi.org/10.1097/00004703-200108000-00003>.
- [26] Robert Almli C, Ball RH, Wheeler ME. Human fetal and neonatal movement patterns: gender differences and fetal-to-neonatal continuity. *Dev Psychobiol* 2001;38(4):252–73. <https://doi.org/10.1002/dev.1019>.
- [27] Saenz J, Yaugher A, Alexander GM. Sleep in infancy predicts gender specific social-emotional problems in toddlers. *Front Pediatr* 2015;3. <https://doi.org/10.3389/fped.2015.00042>.
- [28] Tikotzky L, Marcus GDe, Har-Toov J, Dollberg S, Bar-Haim Y, Sadeh A. Sleep and physical growth in infants during the first 6 months. *J Sleep Res* 2010;19(1-Part-I):103–10. <https://doi.org/10.1111/j.1365-2869.2009.00772.x>.
- [29] Jenni OG, O' Connor BB. Children's sleep: an interplay between culture and biology. *Pediatrics* 2005;115:204–16.
- [30] Weissbluth M. Naps in children: 6 months–7 years. *Sleep* 1995;18(2):82–7. <https://doi.org/10.1093/sleep/18.2.82>.
- [31] Jenni OG, LeBourgeois MK. Understanding sleep-wake behavior and sleep disorders in children: the value of a model. *Curr Opin Psychiatr* 2006;19(3):282–7. <https://doi.org/10.1097/01.yco.0000218599.32969.03>.
- [32] Iglovstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics* 2003;111(2):302–7. <https://doi.org/10.1542/peds.111.2.302>.
- [33] Acebo C, Sadeh A, Seifer R, Tzischinsky O, Hafer A, Carskadon MA. Sleep/wake patterns derived from activity monitoring and maternal report for healthy 1- to 5-year-old children. *Sleep* 2005;28(12):1568–77. <https://doi.org/10.1093/sleep/28.12.1568>.
- [34] Wolfson AR. Sleeping patterns of children and adolescents: developmental trends, disruptions, and adaptations. *Child Adolesc Psychiatr Clin North Am* 1996;5(3):549–68. [https://doi.org/10.1016/s1056-4993\(18\)30348-1](https://doi.org/10.1016/s1056-4993(18)30348-1).
- [35] Meijer AM, Habekothé HT, Van Den Wittenboer GLH. Time in bed, quality of sleep and school functioning of children. *J Sleep Res* 2000;9(2):145–53. <https://doi.org/10.1046/j.1365-2869.2000.00198.x>.
- [36] Lemola S, Räikkönen K, Scheier MF, Matthews KA, Pesonen AK, Heinonen K, Lahti J, Komsi N, Paavonen JE, Kajantie E. Sleep quantity, quality and optimism in children. *J Sleep Res* 2011;20(1):12–20. <https://doi.org/10.1111/j.1365-2869.2010.00856.x>.
- [37] Seo WS, Sung HM, Lee JH, Koo BH, Kim MJ, Kim SY, Choi SJ, Shin IH. Sleep patterns and their age-related changes in elementary-school children. *Sleep Med* 2010;11(6):569–75. <https://doi.org/10.1016/j.sleep.2010.03.011>.
- [38] Iwata S, Iwata O, Iemura A, Iwasaki M, Matsuishi T. Determinants of sleep patterns in healthy Japanese 5-year-old children. *Int J Dev Neurosci* 2011;29(1):57–62. <https://doi.org/10.1016/j.ijdevneu.2010.09.004>.
- [39] Plancoulaine S, Lioret S, Regnault N, Heude B, Charles MA, Annesi-Maesano I, Bernard J, Botton J, Charles MA, Dargent-Molina P, de Lauzon-Guillain B, Ducimetière P, de Agostini M, Foliguet B, Forhan A, Fritel X, Germa A, Goua V, Hankard R, Heude B, Kaminski M, Larroque B, Lelong N, Lepeule J, Magnin G, Marchand L, Nabet C, Pierre F, Slama R, Saurel-Cubizolles MJ, Schweitzer M, Thiebaut Georges O, Kaminski M. Gender-specific factors associated with shorter sleep duration at age 3 years. *J Sleep Res* 2015;24(6):610–20. <https://doi.org/10.1111/jsr.12308>.
- [40] Montgomery-Downs HE, O'Brien LM, Gulliver TE, Gozal D. Polysomnographic characteristics in normal preschool and early school-aged children. *Pediatrics* 2006;117(3):741–53. <https://doi.org/10.1542/peds.2005-1067>.
- [41] Wang GH, Xu GX, Liu ZJ, Lu N, Ma R, Zhang ET. Sleep patterns and sleep disturbances among Chinese school-aged children: prevalence and associated factors. *Sleep Med* 2013;14(1):45–52. <https://doi.org/10.1016/j.sleep.2012.09.022>.
- [42] Calhoun SL, Fernandez-Mendoza J, Vgontzas AN, Liao D, Bixler EO. Prevalence of insomnia symptoms in a general population sample of young children and preadolescents: gender effects. *Sleep Med* 2014;15(1):91–5. <https://doi.org/10.1016/j.sleep.2013.08.787>.
- [43] Gregory AM, O'Connor TG. Sleep problems in childhood: a longitudinal study of developmental change and association with behavioral problems. *J Am Acad Child Adolesc Psychiatr* 2002;41(8):964–71. <https://doi.org/10.1097/00004583-200208000-00015>.
- [44] Gregory AM, Caspi A, Eley TC, Moffitt TE, O'Connor TG, Poulton R. Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *J Abnorm Child Psychol* 2005;33(2):157–63. <https://doi.org/10.1007/s10802-005-1824-0>.
- [45] Johnson EO, Chilcoat HD, Breslau N. Trouble sleeping and anxiety/depression in childhood. *Psychiatry Res* 2000;94(2):93–102. [https://doi.org/10.1016/S0165-1781\(00\)00145-1](https://doi.org/10.1016/S0165-1781(00)00145-1).
- [46] Calhoun SL, Fernandez-Mendoza J, Vgontzas AN, Mayes SD, Liao D, Bixler EO. Behavioral profiles associated with objective sleep duration in young children with insomnia symptoms. *J Abnorm Child Psychol* 2017;45(2):337–44. <https://doi.org/10.1007/s10802-016-0166-4>.
- [47] Armitage R, Hoffmann R, Emslie G, Rintelman J, Moore J, Kelly L. Rest-activity cycles in childhood and adolescent depression. *J Am Acad Child Adolesc Psychiatr* 2004;43(6):761–9. <https://doi.org/10.1097/01.chi.0000122731.72597.4e>.
- [48] Storfer-Ismer A, Patel SR, Babineau DC, Redline S. Relation between sleep duration and BMI varies by age and sex in youth age 8–19. *Pediatr Obes* 2012;7(1):53–64. <https://doi.org/10.1111/j.2047-6310.2011.00008.x>.

- [49] Lord C, Sekerovic Z, Carrier J. Sleep regulation and sex hormones exposure in men and women across adulthood. *Pathol Biol* 2014;62(5):302–10. <https://doi.org/10.1016/j.patbio.2014.07.005>.
- [50] Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA* 2000;284(7):861–8. <https://doi.org/10.1001/jama.284.7.861>.
- [51] Roenneberg T, Kuehnle T, Pramstaller PP, Ricken J, Havel M, Guth A, Merrow M. A marker for the end of adolescence. *Curr Biol* 2004;14(24):R1038. <https://doi.org/10.1016/j.cub.2004.11.039>.
- [52] Tonetti L, Fabbri M, Natale V. Sex difference in sleep-time preference and sleep need: a cross-sectional survey among Italian pre-adolescents, adolescents, and adults. *Chronobiol Int* 2008;25(5):745–59. <https://doi.org/10.1080/07420520802394191>.
- [53] Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: reliability, validity, and initial norms. *J Youth Adolesc* 1988;17(2):117–33. <https://doi.org/10.1007/bf01537962>.
- [54] Laberge L, Petit D, Simard C, Vitaro F, Tremblay RE, Montplaisir J. Development of sleep patterns in early adolescence. *J Sleep Res* 2001;10(1):59–67. <https://doi.org/10.1046/j.1365-2869.2001.00242.x>.
- [55] Carskadon MA, Acebo C, Richardson GS, Tate BA, Seifer R. An approach to studying circadian rhythms of adolescent humans. *J Biol Rhythm* 1997;12(3):278–89. <https://doi.org/10.1177/074873049701200309>.
- [56] Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. *Sleep* 1993;16(3):258–62. <https://doi.org/10.1093/sleep/16.3.258>.
- [57] Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. *Science* 1980;210(4475):1267–9. <https://doi.org/10.1126/science.7434030>.
- [58] Crowley SJ, Van Reen E, LeBourgeois MK, Acebo C, Tarokh L, Seifer R, Barker DH, Carskadon MA, Shea SA. A longitudinal assessment of sleep timing, circadian phase, and phase angle of entrainment across human adolescence. *PLoS One* 2014;9(11):e112199. <https://doi.org/10.1371/journal.pone.0112199>.
- [59] Anders TF, Carskadon MA, Dement WC, Harvey K. Sleep habits of children and the identification of pathologically sleepy children. *Child Psychiatr Hum Dev* 1978;9(1):56–63. <https://doi.org/10.1007/BF01463220>.
- [60] Carskadon MA, Acebo C. Regulation of sleepiness in adolescents: update, insights, and speculation. *Sleep* 2002;25(6):606–14. <https://doi.org/10.1093/sleep/25.6.606>.
- [61] Zhang J, Chan NY, Lam SP, Li SX, Liu Y, Chan JYW, Kong APS, Ma RCW, Chan KCC, Li AM, Wing YK. Emergence of sex differences in insomnia symptoms in adolescents: a large-scale school-based study. *Sleep* 2016;39(8):1563–70. <https://doi.org/10.5665/sleep.6022>.
- [62] Gaina A, Sekine M, Hamanishi S, Chen X, Kagamimori S. Gender and temporal differences in sleep-wake patterns in Japanese schoolchildren. *Sleep* 2005;28(3):337–42.
- [63] Olds T, Maher C, Blunden S, Matricciani L. Normative data on the sleep habits of Australian children and adolescents. *Sleep* 2010;33(10):1381–8. <https://doi.org/10.1093/sleep/33.10.1381>.
- [64] Short MA, Gradisar M, Lack LC, Wright H, Carskadon MA. The discrepancy between actigraphic and sleep diary measures of sleep in adolescents. *Sleep Med* 2012;13(4):378–84. <https://doi.org/10.1016/j.sleep.2011.11.005>.
- [65] Hysing M, Pallesen S, Stormark KM, Lundervold AJ, Sivertsen B. Sleep patterns and insomnia among adolescents: a population-based study. *J Sleep Res* 2013;22(5):549–56. <https://doi.org/10.1111/jsr.12055>.
- [66] Maslowsky J, Ozer EJ. Developmental trends in sleep duration in adolescence and young adulthood: evidence from a national United States sample. *J Adolesc Health* 2014;54(6):691–7. <https://doi.org/10.1016/j.jadohealth.2013.10.201>.
- [67] Campbell IG, Darchia N, Khaw WY, Higgins LM, Feinberg I. Sleep EEG evidence of sex differences in adolescent brain maturation. *Sleep* 2005;28(5):637–43. <https://doi.org/10.1093/sleep/28.5.637>.
- [68] Campbell IG, Grimm KJ, De Bie E, Feinberg I. Sex, puberty, and the timing of sleep EEG measured adolescent brain maturation. *Proc Natl Acad Sci U S A* 2012;109(15):5740–3. <https://doi.org/10.1073/pnas.1120860109>.
- [69] Knutson KL. The association between pubertal status and sleep duration and quality among a nationally representative sample of U. S. adolescents. *Am J Hum Biol* 2005;17(4):418–24. <https://doi.org/10.1002/ajhb.20405>.
- [70] Johnson EO, Roth T, Schultz L, Breslau N. Epidemiology of DSM-IV insomnia in adolescence: lifetime prevalence, chronicity, and an emergent gender difference. *Pediatrics* 2006;117(2):e247. <https://doi.org/10.1542/peds.2004-2629>.
- [71] Zhang J, Lam SP, Li SX, Li AM, Kong APS, Wing YK. Restless legs symptoms in adolescents: epidemiology, heritability, and pubertal effects. *J Psychosom Res* 2014;76(2):158–64. <https://doi.org/10.1016/j.jpsychores.2013.11.017>.
- [72] Silva GE, Goodwin JL, Vana KD, Vasquez MM, Wilcox PG, Quan SF. Restless legs syndrome, sleep, and quality of life among adolescents and young adults. *J Clin Sleep Med* 2014;10(7):779–86. <https://doi.org/10.5664/jcsm.3872>.
- [73] Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychol Med* 1998;28(1):51–61. <https://doi.org/10.1017/S003329179700593X>.
- [74] Moore M, Kirchner HL, Drotar D, Johnson N, Rosen C, Ancoli-Israel S, Redline S. Relationships among sleepiness, sleep time, and psychological functioning in adolescents. *J Pediatr Psychol* 2009;34(10):1175–83. <https://doi.org/10.1093/jpepsy/jsp039>.
- [75] Puig Antich J, Goetz R, Hanlon C, Tabrizi MA, Davies M, Weitzman ED. Sleep architecture and REM sleep measures in prepubertal major depressives: studies during recovery from the depressive episode in a drug-free state. *Arch Gen Psychiatry* 1983;40(2):187–92. <https://doi.org/10.1001/archpsyc.1983.01790020085008>.
- [76] Suglia SF, Kara S, Robinson WR. Sleep duration and obesity among adolescents transitioning to adulthood: do results differ by sex? *J Pediatr* 2014;165(4):750–4. <https://doi.org/10.1016/j.jpeds.2014.06.052>.
- [77] Babinska K, Kovacs L, Janko V, Dallos T, Feber J. Association between obesity and the severity of ambulatory hypertension in children and adolescents. *J Am Soc Hypertens* 2012;6(5):356–63. <https://doi.org/10.1016/j.jash.2012.08.002>.
- [78] Javaheri S, Storfer-Isser A, Rosen CL, Redline S. Sleep quality and elevated blood pressure in adolescents. *Circulation* 2008;118(10):1034–40. <https://doi.org/10.1161/CIRCULATIONAHA.108.766410>.

- [79] Assadi F. The growing epidemic of hypertension among children and adolescents: a challenging road ahead. *Pediatr Cardiol* 2012;33(7):1013–20. <https://doi.org/10.1007/s00246-012-0333-5>.
- [80] Peach H, Gaultney JF, Reeve CL. Sleep characteristics, body mass index, and risk for hypertension in young adolescents. *J Youth Adolesc* 2015;44(2):271–84. <https://doi.org/10.1007/s10964-014-0149-0>.
- [81] Spilsbury JC, Storfer-Isser A, Rosen CL, Redline S. Remission and incidence of obstructive sleep apnea from middle childhood to late adolescence. *Sleep* 2015;38(1):23–9. <https://doi.org/10.5665/sleep.4318>.
- [82] Fuentes-Pradera MA, Sánchez-Armengol Á, Capote-Gil F, Quintana-Gallego E, Carmona-Bernal C, Polo J, Delgado-Moreno F, Castillo-Gómez J. Effects of sex on sleep-disordered breathing in adolescents. *Eur Respir J* 2004;23(2):250–4. <https://doi.org/10.1183/09031936.03.00022003>.
- [83] Moore M, Meltzer LJ. The sleepy adolescent: causes and consequences of sleepiness in teens. *Paediatr Respir Rev* 2008;9(2):114–21. <https://doi.org/10.1016/j.prrv.2008.01.001>.
- [84] Hershner SD, Chervin RD. Causes and consequences of sleepiness among college students. *Nat Sci Sleep* 2014;6:73–84. <https://doi.org/10.2147/ISS.S62907>.
- [85] Espiritu JRD. Aging-related sleep changes. *Clin Geriatr Med* 2008;24(1):1–14. <https://doi.org/10.1016/j.cger.2007.08.007>.
- [86] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Adams Hillard PJ, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC. National Sleep Foundation's updated sleep duration recommendations: final report. *Sleep Health* 2015;1(4):233–43. <https://doi.org/10.1016/j.slehd.2015.10.004>.
- [87] Gillin JC. The sleep therapies of depression. *Prog Neuropsychopharmacol Biolog Psychiatr* 1983;7(2–3):351–64. [https://doi.org/10.1016/0278-5846\(83\)90123-9](https://doi.org/10.1016/0278-5846(83)90123-9).
- [88] Gradisar M, Wolfson AR, Harvey AG, Hale L, Rosenberg R, Czeisler CA. The sleep and technology use of Americans: findings from the National Sleep Foundation's 2011 sleep in America poll. *J Clin Sleep Med* 2013;9(12):1291–9. <https://doi.org/10.5664/jcsm.3272Australia>.
- [89] Campbell SS, Murphy PJ. The nature of spontaneous sleep across adulthood. *J Sleep Res* 2007;16(1):24–32. <https://doi.org/10.1111/j.1365-2869.2007.00567.x>.
- [90] Dorffner G, Vitr M, Anderer P. The effects of aging on sleep architecture in healthy subjects. *Adv Exp Med Biol* 2015;821:93–100. https://doi.org/10.1007/978-3-319-08939-3_13.
- [91] Conley CS, Rudolph KD, Bryant FB. Explaining the longitudinal association between puberty and depression: sex differences in the mediating effects of peer stress. *Dev Psychopathol* 2012;24(2):691–701. <https://doi.org/10.1017/S0954579412000259>.
- [92] Knudtson J, McLaughlin J. Menstrual cycle: Merck manuals. 2017. p. 2017.
- [93] Romans SE, Kreindler D, Einstein G, Laredo S, Petrovic MJ, Stanley J. Sleep quality and the menstrual cycle. *Sleep Med* 2015;16(4):489–95. <https://doi.org/10.1016/j.sleep.2014.12.001>.
- [94] Baker FC, Driver HS. Circadian rhythms, sleep, and the menstrual cycle. *Sleep Med* 2007;8(6):613–22. <https://doi.org/10.1016/j.sleep.2006.09.011>.
- [95] Zheng H, Harlow SD, Kravitz HM, Bromberger J, Buysse DJ, Matthews KA, Gold EB, Owens JF, Hall M. Actigraphy-defined measures of sleep and movement across the menstrual cycle in midlife menstruating women: study of Women's Health across the Nation Sleep Study. *Menopause* 2015;22(1):66–74. <https://doi.org/10.1097/GME.0000000000000249>.
- [96] Baker FC, Sassoon SA, Kahan T, Palaniappan L, Nicholas CL, Trinder J, Colrain IM. Perceived poor sleep quality in the absence of polysomnographic sleep disturbance in women with severe premenstrual syndrome. *J Sleep Res* 2012;21(5):535–45. <https://doi.org/10.1111/j.1365-2869.2012.01007.x>.
- [97] Sharkey KM, Crawford SL, Kim S, Joffe H. Objective sleep interruption and reproductive hormone dynamics in the menstrual cycle. *Sleep Med* 2014;15(6):688–93. <https://doi.org/10.1016/j.sleep.2014.02.003>.
- [98] Khan MS, Aouad R. The effects of insomnia and sleep loss on cardiovascular disease. *Sleep Med Clin* 2017;12(2):167–77. <https://doi.org/10.1016/j.jsmc.2017.01.005>.
- [99] Wang D, Li W, Cui X, Meng Y, Zhou M, Xiao L, Ma J, Yi G, Chen W. Sleep duration and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. *Int J Cardiol* 2016;219:231–9. <https://doi.org/10.1016/j.ijcard.2016.06.027>.
- [100] Shan Z, Ma H, Xie M, Yan P, Guo Y, Bao W, Rong Y, Jackson CL, Hu FB, Liu L. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diab Care* 2015;38(3):529–37. <https://doi.org/10.2337/dc14-2073>.
- [101] Wong PM, Manuck SB, Di Nardo MM, Korytkowski M, Muldoon MF. Shorter sleep duration is associated with decreased insulin sensitivity in healthy white men. *Sleep* 2015;38(2):223–31. <https://doi.org/10.5665/sleep.4402>.
- [102] Pepin JL, Borel AL, Tamisier R, Baguet JP, Levy P, Dauvilliers Y. Hypertension and sleep: overview of a tight relationship. *Med Rev* 2014;18(6):509–19. <https://doi.org/10.1016/j.smrv.2014.03.003>.
- [103] Phillips B, Mannino D. Correlates of sleep complaints in adults: the ARIC study. *J Clin Sleep Med: Off Pub Am Acad Sleep Med* 2005;1(3):277–83. <https://doi.org/10.5664/jcsm.26344>.
- [104] Reyner A, Horne JA. Gender- and age-related differences in sleep determined by home-recorded sleep logs and actimetry from 400 adults. *Sleep* 1995;18(2):127–34.
- [105] Hume KI, Van F, Watson A. A field study of age and gender differences in habitual adult sleep. *J Sleep Res* 1998;7(2):85–94. <https://doi.org/10.1046/j.1365-2869.1998.00103.x>.
- [106] Luca G, Rubio JH, Andries D, Tobbback N, Vollenweider P, Waeber G, Vidal PM, Preisig M, Heinzer R, Tafti M. Age and gender variations of sleep in subjects without sleep disorders. *Ann Med* 2015;47(6):482–91. <https://doi.org/10.3109/07853890.2015.1074271>.
- [107] Copinschi G, Caufriez A. Sleep and hormonal changes in aging. *Endocrinol Metab Clin N Am* 2013;42(2):371–89. <https://doi.org/10.1016/j.ecl.2013.02.009>.
- [108] Zeitzer JM, Duffy JF, Lockley SW, Dijk DJ, Czeisler CA. Plasma melatonin rhythms in young and older humans during sleep, sleep deprivation, and wake. *Sleep* 2007;30(11):1437–43. <https://doi.org/10.1093/sleep/30.11.1437>.
- [109] Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin*

- Endocrinol Metab 1983;56(6):1278–81. <https://doi.org/10.1210/jcem-56-6-1278>.
- [110] Penev PD. Association between sleep and morning testosterone levels in older men. Sleep 2007;30(4):427–32. <https://doi.org/10.1093/sleep/30.4.427>.
- [111] Schiavi R, White D, Mandeli J. Pituitary-gonadal function during sleep in healthy aging men. Psychoneuroendocrinology 1992;17 (6):599–609. [https://doi.org/10.1016/0306-4530\(92\)90018-3](https://doi.org/10.1016/0306-4530(92)90018-3).
- [112] Pandi-Perumal SR, Monti JM, Monjan AA. Principles and practice of geriatric sleep medicine: treatment of sleep disorders in the elderly. 2018. p. 2018.
- [113] Gold EB. The timing of the age at which natural menopause occurs. Obstet Gynecol Clin N Am 2011;38(3):425–40. <https://doi.org/10.1016/j.ogc.2011.05.002>.
- [114] Kravitz HM, Ganz PA, Bromberger J, Powell LHS-TK, Meyer PM. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. Menopause 2003;10 (1):19–28. <https://doi.org/10.1097/00042192-200310010-00005>.
- [115] Kravitz HM, Zhao X, Bromberger JT, Gold EB, Hall MH, Matthews KA, Sowers MFR. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. Sleep 2008;31(7):979–90.
- [116] National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. Ann Intern Med 2005;142(12):1003–13.
- [117] Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, Salamone L, Stellato R. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40–55 years of age. Am J Epidemiol 2000;152(5):463–73. <https://doi.org/10.1093/aje/152.5.463>.
- [118] Young T, Rabago D, Zgierska A, Austin D, Finn L. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. Sleep 2003;26(6):667–72. <https://doi.org/10.1093/sleep/26.6.667>.
- [119] Shaver J, Giblin E, Lentz M, Lee K. Sleep patterns and stability in perimenopausal women. Sleep 1988;11(6):556–61. <https://doi.org/10.1093/sleep/11.6.556>.
- [120] Ensrud KE, Stone KL, Blackwell TL, Sawaya GF, Tagliaferri M, Diem SJ, Grady D. Frequency and severity of hot flashes and sleep disturbance in postmenopausal women with hot flashes. Menopause 2009;16(2):286–92. <https://doi.org/10.1097/gme.0b013e31818c0485>.
- [121] Savard J, Davidson JR, Ivers H, Quesnel C, Rioux D, Dupré V, Lasnier M, Simard S, Morin CM. The association between nocturnal hot flashes and sleep in breast cancer survivors. J Pain Symptom Manag 2004;27(6):513–22. <https://doi.org/10.1016/j.jpainsympman.2003.10.013>.
- [122] Freedman RR, Roehrs TA. Lack of sleep disturbance from menopausal hot flashes. Fertil Steril 2004;82(1):138–44. <https://doi.org/10.1016/j.fertnstert.2003.12.029>.
- [123] Erlik Y, Tataryn IV, Meldrum DR, Judd HL, Lomax P, Bajorek JG. Association of waking episodes with menopausal hot flushes. J Am Med Assoc 1981;245(17):1741–4. <https://doi.org/10.1001/jama.1981.03310420031025>.
- [124] Freedman RR, Benton MD, Genik RJ, Graydon FX. Cortical activation during menopausal hot flashes. Fertil Steril 2006;85 (3):674–8. <https://doi.org/10.1016/j.fertnstert.2005.08.026>.
- [125] Woodward S, Freedman RR. The thermoregulatory effects of menopausal hot flashes on sleep. Sleep 1994;17(6):497–501. <https://doi.org/10.1093/sleep/17.6.497>.
- [126] Hall MH, Kline CE, Nowakowski S. Insomnia and sleep apnea in midlife women: prevalence and consequences to health and functioning. F1000Prime Rep 2015;7. <https://doi.org/10.12703/P7-63>.
- [127] Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001;163(3):608–13. <https://doi.org/10.1164/ajrccm.163.3.9911064>.
- [128] Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. Arch Intern Med 2005;165 (20):2408–13. <https://doi.org/10.1001/archinte.165.20.2408>.
- [129] Redline S, Schluchter MD, Larkin EK, Tishler PV. Predictors of longitudinal change in sleep-disordered breathing in a nonclinic population. Sleep 2003;26(6):703–9. <https://doi.org/10.1093/sleep/26.6.703>.
- [130] Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin sleep cohort study. Am J Respir Crit Care Med 2003;167(9):1181–5. <https://doi.org/10.1164/rccm.200209-1055OC>.
- [131] Driver HS, McLean H, Kumar DV, Farr N, Day AG, Fitzpatrick MF. The influence of the menstrual cycle on upper airway resistance and breathing during sleep. Sleep 2005;28 (4):449–56. <https://doi.org/10.1093/sleep/28.4.449>.
- [132] Popovic RM, White DP. Upper airway muscle activity in normal women: influence of hormonal status. J Appl Physiol 1998;84 (3):1055–62. <https://doi.org/10.1152/jappl.1998.84.3.1055>.
- [133] Davis SR, Castelo-Branco C, Chedraui P, Lumsden MA, Nappi RE, Shah D, Villaseca P. Understanding weight gain at menopause. Climacteric 2012;15(5):419–29. <https://doi.org/10.3109/13697137.2012.707385>.
- [134] Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 2004;27(7):1255–73. <https://doi.org/10.1093/sleep/27.7.1255>.
- [135] Kales A, Wilson T, Kales JD, Jacobson A, Paulson MJ, Kollar E, Walter RD. Measurements of all-night sleep in normal elderly persons: effects of aging. J Am Geriatr Soc 1967;15(5):405–14. <https://doi.org/10.1111/j.1532-5415.1967.tb02072.x>.
- [136] Duffy JF, Zitting KM, Chinoy ED. Aging and circadian rhythms. Sleep Med Clin 2015;10(4):423–34. <https://doi.org/10.1016/j.jsmc.2015.08.002>.
- [137] Foley DJ, Vitiello MV, Bliwise DL, Ancoli-Israel S, Monjan AA, Walsh JK. Frequent napping is associated with excessive daytime sleepiness, depression, pain, and nocturia in older adults: findings from the national sleep foundation 2003 sleep in America poll. Am J Geriatr Psychiatr 2007;15(4):344–50. <https://doi.org/10.1097/01.JGP.0000249385.50101.67>.

- [138] Pase MP, Himali JJ, Grima NA, Beiser AS, Satizabal CL, Aparicio HJ, Thomas RJ, Gottlieb DJ, Auerbach SH, Seshadri S. Sleep architecture and the risk of incident dementia in the community. *Neurology* 2017;89(12):1244–50. <https://doi.org/10.1212/WNL.0000000000004373>.
- [139] Reynolds CF, Kupfer DJ, Hoch CC, Stack JA, Houck PR, Berman SR. Sleep deprivation in healthy elderly men and women: effects on mood and on sleep during recovery. *Sleep* 1987;9(4):492–501. <https://doi.org/10.1093/sleep/9.4.492>.
- [140] Svetnik V, Snyder ES, Ma J, Tao P, Lines C, Herring WJ. EEG spectral analysis of NREM sleep in a large sample of patients with insomnia and good sleepers: effects of age, sex and part of the night. *J Sleep Res* 2017;26(1):92–104. <https://doi.org/10.1111/jsr.12448>.

This page intentionally left blank

Chapter 4

Sleep and health in older adults

Junxin Li^a and Nalaka S. Gooneratne^{b,c}

^a*Johns Hopkins University School of Nursing, Baltimore, MD, United States;* ^b*Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States;* ^c*Sleep Medicine Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States*

Introduction

The impact of sleep on health outcomes in older adults has become a topic of great interest in the geriatric research world. Current evidence supports a mostly bidirectional relationship between sleep and health. Characteristics of sleep often change with age; for example, sleep complaints and certain sleep disorders, such as sleep-disordered breathing (SDB) and insomnia, are more common in older adults than in young or middle-aged adults. Additionally, homeostatic sleep drive and circadian rhythm are less robust in older adults than in young adults [1]. Age-related changes in sleep make older adults more prone to develop sleep problems; however, disturbed sleep is not a part of normal aging. Disturbed sleep or sleep problems are largely due to existing comorbidities and polypharmacy use in older adults. At the same time, research suggests that disturbed sleep can result in a range of adverse health outcomes in older adults. In this chapter, we will review sleep changes in normal aging, primary sleep disorders in older adults, and the relationship between sleep and health outcomes concerning cognitive function, cardiovascular (CV) health, psychiatric illness, and pain in older adults.

Sleep changes in normal aging

Changes in sleep parameters

Sleep clearly changes with aging in multiple ways. For example, total sleep time (TST), the ability to maintain sleep, and the proportion of slow wave sleep decrease as people age from pediatric to older adulthood [2]. However, sleep does not change much in aging older adults with excellent health. For example, further age-associated decreases in these sleep parameters have not been observed after 60 years of age in relatively healthy older adults. Evidence suggests that older adults maintain their ability to

initiate sleep (i.e., sleep latency) and fall back to sleep after awakenings as rapidly as younger adults after the age of 60 years. In contrast, sleep efficiency continues to decline slowly with increasing age [1].

Changes in circadian rhythm

Circadian timing and circadian amplitudes change with increasing age [3]. Older adults commonly experience an age-related advance (1 h) in circadian phases and some degree of reduction in circadian amplitudes compared to young adults [1]. For instance, older adults often feel sleepy early in the evening and wake up early in the morning [1]. Body temperature, rhythm, and timing of secretion of melatonin and cortisol can also advance with aging [4]. These age-related changes in circadian systems may contribute to sleep disruption and daytime napping, which further decreases the circadian amplitude in older adults [3]. In addition, the ability to adjust to and recover from phase shifting (e.g., shift work or jet lag) decreases with aging, which may contribute to longer periods of sleep disruption and daytime dysfunction [1].

Changes in sleep homeostasis

Sleep homeostasis regulates wakefulness and sleep. Sleep pressure is generated by sleep homeostasis and builds up with the amount of time being awake. It increases during wakefulness and decreases during sleep [5]. Sleep homeostasis is reduced with aging [1,6], which may cause decreased TST and sleep efficiency as well as increased nocturnal awakenings, early morning awakening, and daytime sleepiness in older adults [7]. The age-related changes in sleep homeostasis cooccur with changes in circadian rhythm and contribute to earlier sleep times and less consolidated sleep in older adults [8].

Common sleep disturbances in older adults

Sleep disturbances such as difficulty initiating sleep, frequent nocturnal awakenings, early morning awakenings, nonrestorative sleep, and daytime sleepiness are prevalent in older adults. In addition, compared to young adults, the prevalence of primary sleep disorders (e.g., insomnia, SDB, periodic limb movements in sleep, restless legs syndrome, and REM sleep behavior disorder) is considerably higher in older adults. These primary sleep disorders contribute to poor sleep in older adults.

Insomnia

The incidence of insomnia increases continuously with age and is more frequent in women than in men [9]. Although up to 50% of older adults in epidemiological studies reported at least one insomnia symptom, such as difficulty falling asleep, maintaining asleep, or early morning awakenings [9], a smaller percentage of older adults (5%–20%) met clinical criteria for the diagnosis of insomnia depending on the definition [6]. In addition, since many older adults perceive these symptoms as expected sleep changes with normal aging rather than disturbed sleep, they do not seek help from healthcare professionals [1]. Furthermore, older adults are more likely to consider difficulty falling asleep as a sleep problem than difficulty staying asleep, even though the latter is more common [10]. These nocturnal sleep symptoms may cause impairments in daytime functioning, such as fatigue, daytime sleepiness, and mood/behavioral disturbances and lead to insomnia diagnosis.

According to the Diagnostic Criteria for Chronic Insomnia (ICSD-3), insomnia is defined as dissatisfaction with nocturnal sleep (i.e., difficulty falling, staying asleep, or early morning awakening) at least three nights per week for at least 3 months with clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning [9,11]. Insomnia may be primary or secondary to medical comorbidities and psychiatric illness, medication use, and lifestyle or environmental changes associated with aging [6].

Both pharmacological and nonpharmacological treatments are used to treat insomnia in older adults. The goal of treatment is to improve quantity and/or quality of sleep and reduce insomnia-related daytime impairments [9]. The treatment plan is usually selected based on the severity and duration of the insomnia symptoms, the patient's existing comorbid conditions, the patient's preference of treatment options, and vulnerability of patients to the adverse effects of medications [12]. Pharmacologic treatments, such as benzodiazepines, nonbenzodiazepine hypnotics, melatonin

receptor agonists, antidepressant, orexin-receptor agents, and antihistamine, should start with low doses and in most cases only be used for the short-term management of insomnia due to the side effects and long-term safety concerns [9]. In addition, the treatment effects usually do not sustain once the patient stops using the medications [13]. Behavioral treatments (e.g., cognitive behavioral therapy for insomnia (CBTi), physical activity, social engagement, and sleep hygiene), bright light therapy, and acupuncture are commonly used nonpharmacological treatments for insomnia. CBTi is a multicomponent cognitive and behavioral intervention which involves cognitive restructuring, sleep hygiene education, sleep restriction, relaxation, and stimulus control. Evidence suggests that CBTi is the most effective nonpharmacological treatment for insomnia and has more long-lasting effects than medications [13,14].

Sleep-disordered breathing

SDB is an umbrella term for chronic conditions in which repeated episodes of hypopnea or apnea (not breathing) during sleep occur throughout the night. SDB is a more prevalent condition in older adults than younger adults and in men than women. Obstructive sleep apnea (OSA) is the most common form of SDB. Several epidemiologic studies have shown that the prevalence of SDB ranged from 27% to 80% in people aged 60 years or older with one recent meta-analysis suggesting a prevalence of 35.9% [15,16]. Approximately 80% of older adults aged 71 and older had OSA (AHI >5), and the incidence increased 2.2 times for each 10-year increase of age [17].

Snoring and excessive daytime sleepiness (EDS) are main symptoms of SDB in older adults [16,18]. In an epidemiological study of older men, people with SDB were 50% more likely to have daytime sleepiness than those did not have sleep apnea [19]. In addition, studies also found that male gender, Asian race, advancing age, higher body mass index/obesity, neck girth, habitual snoring, hypertension, cardiovascular disease (CVD), and heart failure (HF) were independently associated with SDB in older adults, and the magnitude of some of these associations decreased with advancing age [15,19,20]. Older adults with SDB may also experience insomnia, and those with both sleep disorders have poorer sleep quality. In addition, the incidence of comorbid insomnia may be higher in women with SDB than in men with SDB [21].

The gold standard for diagnosing SDB in older adults is overnight polysomnography (PSG) [16]. Obtaining in-laboratory PSG recording from older adults, especially those with cognitive impairment can be challenging due to difficulties with transformation, understanding complicated instructions, and tolerance of equipment. Alternative diagnosing tests need to be explored in older adults. For

instance, using in-home unattended home sleep apnea testing that records airflow, symptoms of sleep apnea (e.g., snoring and sleepiness), BMI, neck circumference, age, and sex might be an effective and reliable way to diagnose OSA in older adults [22].

The first-line therapy for SDB is the continuous positive airway pressure therapy (CPAP). The compliance/noncompliance to CPAP treatment has been associated with gender, age, BMI, severity of OSA and symptoms, early experience of treatment, side effects, level of education and support received, marital status and behavioral (e.g., cigarette smoking) and cost factors [23,24]. Cognitive impairment may also be associated with poor CPAP adherence. Studies found that patients with Alzheimer's disease (AD) and depressive symptoms had worse adherence than people with mild to moderate AD and Parkinson's disease. People with mild cognitive impairment and Parkinson's disease could wear CPAP around 5 h per night [25,26]. One recent study noted that 73.6% of patients with MCI were adherent to CPAP at 3 month follow-up [27]. In addition, oral appliances are used to treat OSA, but its effectiveness in managing OSA varies by patient anatomy.

Factors associated with sleep disturbances in older adults

Sleep disturbances reported in older adults are usually multifactorial and cannot simply be explained by age alone. In addition to age and primary sleep disorders, medical conditions and changes in social engagement, lifestyle, and living environment associated with aging can contribute to sleep problems in older adults [16]. For example, older adults may be more sedentary and less engaged in daytime physical and social activities, which impacts sleep homeostasis and circadian regulation and leads to sleep disturbances [28]. In addition, life events such as loss of loved ones and transitioning to long-term care settings can create physical and emotional stressors that can cause acute sleep problems or worsen the sleep quality in older adults. These acute sleep problems can develop into long lasting chronic sleep disturbances if they are not treated properly. Additionally, environmental temperature, noise, and bright light exposure affect sleep quality in older adults [1].

Sleep and health in older adults

Approximately, 67%–75% of older adults aged 65 and over have two or more concurrent chronic medical conditions, the most common being osteoarthritis (OA), CVD disease, lung disease, cancer, diabetes, AD/dementia, anxiety, and depression [29,30]. The majority of these older adults take

prescription medications to treat these chronic conditions [31], which can impact their sleep. Epidemiological studies found that older adults with chronic medical conditions report more difficulty initiating sleep, difficulty maintaining sleep, daytime sleepiness, and fatigue than healthy older adults [30]. Growing evidence shows that sleep problems seen in older adults are more commonly related to comorbidities rather than normal aging [1]. On the other hand, in some cases, sleep disturbances can also trigger or worsen medical conditions in older adults. Older adults with sleep disturbance and comorbid medical conditions have increased risks of mortality and hospitalization and may also receive inappropriate polypharmacy [1,30]. Therefore, coexisting sleep disturbances and chronic medical conditions must be managed together to promote health and quality of life in older adults. We will review the relationship between sleep and multiple health outcomes in older adults, including cognitive function, CV health, mental health, and pain.

Cognitive function

Cognitive abilities change across the life span, generally declining with advancing age during midlife and older adulthood [32]. A number of health and behavioral modifiable factors contribute to cognitive decline in older adults. Growing evidence suggests a potential connection between sleep and cognitive function [33]. However, the mechanisms underlying the association are not fully understood, although there is an increasing awareness of the role of the glymphatic system, which facilitates clearance of neurotoxins during sleep, in this process [34]. In this section, we present evidence that examines the association between cognitive function/cognitive impairment and sleep disturbances in older adults, including studies of short/long sleep duration, poor sleep quality, self-reported sleep complaints, objectively measured sleep disturbances, daytime napping, EDS, insomnia, and SDB.

Sleep duration

Several large-scale epidemiologic studies have investigated the association between sleep duration and cognitive functioning in older adults and demonstrate inconsistent results. In general, current evidence suggests a potential U-shaped association between sleep duration and cognitive outcomes in older adults. Many studies showed that short- and long-sleep duration negatively impact older adults' cognitive function [35–37]. However, other studies have found no significant influence of sleep on cognitive function [38,39]. For instance, a systematic review and metaanalysis synthesized findings from 18 studies (11 cross-sectional and 7 prospective cohort studies; total $N = 97,264$) and found that self-reported short- and long-

sleep durations increased the likelihood for poor cognitive function by 1.40 and 1.58 times, respectively [40]. These associations were not moderated by gender or age. In terms of specific cognitive domains, the analysis of the cross-sectional studies revealed both short- and long-sleep durations were significantly associated with poor performance in multiple-domain tasks, executive function, verbal memory, and working memory capacity but not associated with processing speed. Short- and long-sleep durations were only associated with subsequent poor multiple-domain performance in the analysis of prospective studies. Another systematic review of 32 observational studies in older adults demonstrated similar findings: negative associations were found between short and long sleep durations and cognitive performance [41]. Additionally, this review found that greater changes in sleep duration from earlier life were associated with cognitive decline in later life [41]. Evidence from the prospective studies found that both long- and short-sleep durations were associated with an increased risk of cognitive impairment or dementia [42]. Most existing studies use self-reported sleep duration to examine the association between sleep duration and cognitive outcomes; however, there is an increasing need for prospective studies to use objective sleep measures (e.g., actigraphy).

Self-reported sleep complaints

Self-reported sleep complaints such as insomnia symptoms and poor sleep quality are more prevalent in older adults than young and middle-aged adults. Research has provided mixed findings but generally supports an association between these sleep complaints and worse cognitive performance or increased likelihood of cognitive decline/impairment [42,43]. A complicating factor is that many of these studies include healthy older adults populations with may attenuate some of the associations between poor sleep and cognitive decline [44]. Nevertheless, multiple prospective studies have shown that self-reported poor sleep quality or sleep complaints were independently associated with worse performance in global cognition and measures of specific cognitive domains or increased risk of cognitive impairment [45–50]. However, the association was nonsignificant in several cross-sectional studies [51,52] and another prospective study noted no link between sleep complaints and cognitive decline [53]. Schmutte et al. found that a longer sleep onset latency was cross-sectionally associated with worse performance in tests of verbal knowledge, long-term memory, and visuospatial ability in cognitive intact older adults [54]. The prospective studies suggest that sleep complaints were associated with an increased risk of developing cognitive impairment or dementia in older adults [42].

Objectively measured sleep disturbances

Actigraphy and PSG are the two most commonly used objective measures of sleep that provide more specific and detailed information on sleep than self-reported data. For example, actigraphy and PSG can reveal information about sleep fragmentation, sleep efficiency, night to night sleep variability, and sleep architecture, which are believed to be key sleep characteristics that impact changes in cognitive function in older adults [42,43]. A recent meta-analysis of 72 studies demonstrated that increased N2 and REM sleep were associated with improved cognitive outcomes [55]. While N3 was not, slow wave activity per se was marginally associated ($p=0.07$) [55]. Similarly, lower sleep onset latency, WASO, restlessness and higher sleep efficiency were associated with better cognition, however, total sleep time was not [55]. When evaluating specific cognitive domains, the main effects were seen in memory and executive function [55]. Findings were generally similar between actigraphy and PSG-derived measures. [55]. In addition, actigraphically measured sleep fragmentation was associated with higher severity of cognitive impairment [56] or increased risk of AD/cognitive decline [57]. Current evidence thus suggests a possible link between objectively measured poor sleep and cognitive outcomes in older adults [33].

Daytime napping

Napping is more prevalent in older adults than young and middle-aged adults across the world [58,59]. Older adults nap for numerous reasons such as to compensate for disturbed nighttime sleep, restore energy, reduce EDS or fatigue from comorbidities or medications, or simply as a habit [58]. The impact of daytime napping and cognitive function in older adults largely depends on features of the nap, the population, and napping measures used in the study. Current evidence yields mixed findings due to the heterogeneity of these aspects among studies. The association of long nap (e.g., ≥ 90 min or 2 h) with adverse cognitive outcomes is consistent in most epidemiological studies [37,60,61]. One recent epidemiological study among over 3000 Chinese older adults found that those who reported napping for <90 min at both baseline and follow up had better cognitive trajectories over 2 years than those who did not nap or napped longer [61]. In addition, positive cognitive effects were found in patients who engaged in nap intervention studies (nap intervention lasted from single session to 4-week); these patients demonstrated improvements in various domains of cognitive function, such as attention, alertness, and visual detection [62–64]. One study with 4-week nap intervention found that both 45 min and 2-h napping opportunities in the afternoon were associated with improved logical reasoning,

mathematical processing, and memory [62]. This evidence suggests that intentional naps within a certain duration may provide cognitive benefits in later life; however, this finding would benefit from future research to determine optimal nap duration.

Excessive daytime sleepiness

Approximately 20%–30% of older adults report EDS [1,42]. EDS can be a symptom of various disorders (e.g., SDB, CVD disease, and depression) or a result of sedative medications. These disorders and sedative medications have proven to increase the risk of cognitive impairment [42,65]. Both cross-sectional and prospective studies have found that EDS independently predicted cognitive impairment [45,66,67] and was associated with higher incidence of dementia [33,65,68]. EDS was measured subjectively in most of these studies. Future studies will need to explore the association between EDS and cognitive function using both subjective and objective measures of sleepiness to elucidate the relationship and underlying mechanisms.

Insomnia

Insomnia has been linked with worse daytime cognitive performance (e.g., working memory and episodic memory) in young and middle-aged adults [69]. Only a few studies have assessed this association in older adults, and the findings are inconsistent. Thus, no firm conclusion can be drawn based on the current state of the science. While some studies have shown a link between insomnia complaints and development of dementia [70], this has not been observed in other studies. For example, in a large-scale epidemiological study, self-reported insomnia was associated with increased risk of cognitive decline after 3 years in older men but not in older women [71]. The association was not significant in population-based samples of older Japanese-American men [66], French [65] and Italian older adults [68]. Some research examined the impact of insomnia intervention on cognitive outcomes and also yielded inconsistent findings. For example, one study showed that a multiple component insomnia intervention improved sleep (sleep onset latency and sleep efficiency) and performance on simple vigilance tasks [72]. However, another insomnia intervention that used brief behavioral therapy failed to achieve any cognitive benefits in community-dwelling older adults with insomnia [73].

Sleep disordered breathing

Numerous studies support a link between SDB and worse cognitive outcomes in older adults [33,74]. One systematic review and meta-analysis on the association between SDB and cognitive function and risk of cognitive impairment reviewed 14 population-based study (total $N = 4,288,419$)

[75]. Analysis of the cross-sectional studies suggested SDB was associated with worse executive function but revealed no significant association of SDB with memory or global cognition. Analyses of six prospective studies showed that people with SDB were more likely to develop cognitive impairment or were at risk of dementia. These findings suggest SDB is an essential modifiable risk factor of cognitive impairment in older adults and highlight the importance of early identification and treatment of SDB.

In addition, studies found that the severity of SDB may be associated with cognitive outcomes in older adults [76]. According to a recent narrative review, studies have found that higher apnea–hypopnea index (AHI) and respiratory disturbance index were associated with worse global cognition and domain specific cognitive outcomes, including vigilance, executive function, attention, and memory [76].

There are promising findings on positive airway pressure (PAP) treatments' improvements on cognitive function in older adults with SDB. Studies had shown both short-term and long-term PAP therapy could benefit cognitive functions in older adults [74,76]. Importantly, long-term PAP treatment may delay the onset of cognitive impairment in older adults with SDB and slow down the speed of cognitive decline in AD patients with SDB [74] [76,77]. Compliance with PAP therapy may be even more challenging in older adults with cognitive impairment than in the general population, although patients with mild cognitive impairment can have good adherence rates [78]. More research that aims to improve adherence of PAP therapy in older adults with cognitive impairment are needed to treat SDB and potentially promote cognitive outcomes in this population.

Both sleep disturbances and cognitive decline are prevalent in older adults. In general, current evidence suggests a link between disturbed sleep and adverse cognitive outcomes in later life, which directs us toward a potential approach to improve cognitive health through modifying sleep health. However, most of the reviewed research included observational studies, which do not lead to concrete conclusion based on causality. Future research investigating the effects of sleep promoting interventions on cognitive function in older adults is clearly warranted, especially given the growing number of older adults at risk for cognitive impairment.

Cardiovascular health

Cardiovascular diseases, including hypertension, coronary heart disease (CHD), peripheral arterial disease, HF, valvular heart disease, and strokes are prevalent in older adults. Heart disease is the leading cause of death in both men and women aged 65 and above [79]. Sleep characteristics and sleep disorders have been linked to CV health

in older adults. For example, epidemiological studies found that the prevalence of hypertension, arrhythmias, heart failure and coronary artery disease is higher in people with OSA than those without OSA [80].

Sleep duration

Literature suggests that both short- and long-sleep durations are predictors of poor CV outcomes in older adults, with a more prominent effect of long sleep (OR 1.37) relative to short sleep (OR 1.19) durations on cardiovascular mortality [81]. A large epidemiological study examined the association between sleep duration and strokes in over 150,000 US adults and found that only long-sleep duration (and not short sleep duration) was associated with higher prevalence of history of stroke [82]. One study that examined the association in both middle aged and older adults found that long-sleep duration (>9 h) is a risk factor for hypertension in older adults but not in middle aged adults [83]. A population-based study of Japanese older adults found that long-sleep duration was associated with higher risk of CV mortality among those with poor sleep quality [84]. In addition, findings from a systematic review with meta-analysis suggested long-sleep duration was associated 43% increased risk of CV mortality in older adults [85].

Sleep-disordered breathing

Adverse impacts of SDB on CV outcomes have been established in middle-aged adults but are not clear in older adults [16]. Research on whether SDB was associated with increased risk of hypertension is inconsistent in older adults. A study in 372 French older adults found that OSA was associated with an increased risk of new onset of hypertension. Severe OSA (AHI ≥ 30 per hour) was independently associated with 1.8-fold of increased risk of incident hypertension after 3 years [86]. However, this association was not found in the Sleep Heart Health Study [87] and the Osteoporotic Fractures in Men Study (MrOS) [88]. In addition, observational studies suggest that SDB independently increased the risk for stroke in older adults [89–91].

The association between SDB and HF might be bidirectional [80]. There is evidence that suggests that chronic HF (CHF) may contribute to the pathogenesis of SDB [30]. For instance, the nocturnal fluid that shifts from the legs to the neck in patient with CHF could increase the pharyngeal wall edema, which can contribute to SDB. In addition, sedentary lifestyle in CHF patients may lead to weight gain [92]. It is not clear whether higher prevalence of SDB increases the risk of HF in older adults. One analysis from an MrOS study found that central apnea and the Cheyne-Stokes respiration but not obstructive apnea, significantly

predicted incident HF over 7 years in older men [93]. Another prospective, longitudinal study found that older men with an AHI of 30 or greater had increased risk for HF compared to older men with an AHI <5 . However, no significant association was found in women [94]. The possible bidirectional association between HF and SDB suggests that treating either condition could potentially benefit both conditions in patients with both SDB and HF. Based on this body of evidence, the American Heart Association/American College of Cardiology 2022 HF guidelines identified CPAP as a Class IIa (moderate strength recommendation) to improve sleep quality and daytime sleepiness in patients with heart failure [95]. Future prospective, randomized, controlled trials are necessary to help further clarify if a benefit exists in specific CV outcomes and to what extent.

Insomnia and other sleep disturbances

Systematic reviews suggest that insomnia is significantly associated with increased risk of CV outcomes (e.g., myocardial infarction, stroke, and CHD) and mortality after adjusting for established CV risk factors in the general adult population [96–98]. This may remain true in the older adults since older adults were included in most of the reviewed studies and age was controlled for as a confounding factor. There are only a few studies that examine the association specifically in the older adult population, and the results support the association. For example, a cross-sectional study of approximate 3000 Chinese older adults who self-reported occasional insomnia and frequent insomnia were more likely to have CHD than those reported no insomnia [99]. A recent intervention study found that cognitive-behavioral therapy for insomnia led to reductions in fatigue and increased six-minute walk distance, along with improvements in sleep, in patients with heart failure [100].

The association between other sleep complaints and CVD has also been evaluated. Overall, there is a paucity of evidence to support the association between self-reported sleep quality and CV health in older adults. One population-based cohort study of Japanese older adults found no association between self-reported sleep quality and CV mortality [84]. In regards to daytime sleepiness, one prospective cohort study of around 6000 older adults found that daytime sleepiness at baseline predicted incident CHF, MI, and CV morbidity and mortality over 5 years [101].

Psychiatric illness

Psychiatric illnesses in older adults are common but less prevalent than in young adults. It has been estimated that

up to 15% and 13% of the population have anxiety and depression, respectively [102]. Anxiety and depression are serious concerns in older adults due to their association with poor health outcomes, including decreased functional status and an increased risk of morbidity [102]. Sleep disturbances, including daytime sleepiness, poor sleep quality, prolonged sleep latency, and long wake after sleep onset, are common in older adults with psychiatric illness, such as anxiety [103]. Epidemiological and meta-analytic studies have linked sleep disturbances with increased risks of developing depression and anxiety among older adults [104]. We will review current evidence on the relationship between sleep characteristics and psychiatric diseases, with a focus on depression and anxiety in older adults.

Sleep duration

A meta-analysis of seven prospective studies involving approximately 49,000 adults revealed that both short- and long-sleep durations were associated with increased risk of depression in the general adult population [105]. However, the association may not be significant in older adults. Two large prospective cohort studies found no significant association between sleep duration and later onset of depression in older men [106] and older women [107].

Insomnia

Evidence suggests that insomnia is a significant risk factor for both depression and anxiety in the general adult population. We did not find any studies on anxiety and diagnosis of insomnia specifically in older adults. Studies focused on older adults support this association between depression and insomnia [108,109]. Additionally, a cross-sectional study showed that depressive symptoms were more likely to be sustained in depressed older adults with insomnia than depressed older adults without insomnia [110]. Patients who had persistent insomnia had more residual depressive symptoms, suicidal ideation remission, and higher incidences of relapse than those who did not have insomnia [111,112].

When considering specific insomnia symptoms, as opposed to an insomnia diagnosis, certain insomnia symptoms may prospectively predict depression in older adults. A longitudinal study of approximately 5000 older men revealed a strong relationship between difficulty initiating sleep and incidence of depression after 3 years, whereas there was no association between early morning awakening or difficulty maintaining sleep and depression [109]. In addition, sleep disturbances may also be associated with anxiety symptoms. A study of 2759 older adults found that older adults with prolonged sleep latency (>30 min) were more likely to have diagnosis of anxiety or other mood disorders [113]. A cross-sectional study found

that after adjusting for depressive symptoms, medical conditions, and use of antianxiety medications, anxiety symptoms were independently associated with poor sleep efficiency and higher sleep fragmentation in older women [114].

Sleep-disordered breathing

One review of the literature noted that current evidence is not sufficient to illustrate the relationship between SDB and anxiety in the adult population [115]. A limited number of studies in the adult population yielded inconsistent findings, with 70% individuals with OSA having anxiety in some studies, to no association between the severity of apnea symptoms and anxiety symptoms in other studies [102]. One study showed that the PAP treatment may be effective in reducing anxiety symptoms among adult patients [116]. However, no study examined the relationship in older adults. Generally, current evidence suggests a relationship between OSA and depressive symptoms in the adult population [102].

Sleep quality and other sleep disturbances

A meta-analysis of nine studies explored the relationship between sleep quality and depression. The findings suggest that poor sleep quality is significantly associated with depression in older adults [117]. A population-based study of 2393 older adults found that short-sleep duration, daytime sleepiness, and sleep disturbance are independently associated with anxiety, and sleep medication is associated with depression [118].

The number of studies in older adults is limited compared to the body of research in the broader adult population. In general, sleep disturbances and sleep disorders are associated with increased risks of developing or maintaining depression and anxiety among the adult population. However, the strength of association in older adults may differ from that in young and middle-aged adults. Future prospective studies should further examine the association in older adults and explore whether adding strategies that address treatment for sleep problems can improve the efficacy of treatment for psychiatric disorders.

Pain

The prevalence of pain increases with advancing age. Over 50% of community-dwelling older adults and 80% of nursing home residents are affected by pain [30]. Pain makes older adults more prone to falls and is associated with decreased quality of life and increased risks of all-cause mortality. In older adults, pain is usually a symptom of one or more existing medical conditions [119]. The relationship between sleep and pain has been well examined in many epidemiological and experimental studies and

TABLE 4.1 Risk factors of poor sleep in older adults.

Risk factor	Description
Advancing age	<ul style="list-style-type: none"> Sleep changes from pediatric to older adulthood. Advancing age is associated with advanced sleep timing, shortened nocturnal sleep duration, increased frequency of daytime naps, increased nocturnal awakenings and time spent awake, and decreased slow wave sleep. Age related changes in sleep may reduce after 60 years of age among older adults with good health.
Chronic medical conditions	Cardiovascular diseases; pulmonary disease, cancer, Parkinson's disease, dementia, depression, anxiety and pain related illness, such as arthritis.
Medication	Diuretics, antidepressant, hypnotics, inappropriate use of OTC medications, etc.
Primary sleep disorders	Insomnia, sleep disordered breathing, REM behavior disorder, restless legs syndrome
Lifestyle factors	Sedentary lifestyle, lack of social engagement, irregular sleep schedules, caffeine use later in the day, excessive daytime napping.
Stressful events	Transition to live in a nursing home; death of loved ones
Environmental factors	Lack of daytime bright light exposure, excessive nighttime light exposure, too cold or hot room temperature, excessive noise, uncomfortable bedding, etc.

suggests a likely bidirectional association. Cross-sectional studies also found this/a relation between pain and insomnia or insomnia symptoms in older adults [30]. Older adults with chronic pain are more likely to report clinically significant insomnia symptoms than those without pain. Up to 80% older adults with pain reported at least one sleep compliant [119]. Acute or chronic pain contributes to sleep disturbances, and these changes in sleep can subsequently/cyclically impact pain perception and tolerance [30]. One study found day-to-day associations between objectively measured sleep and self-reported morning pain in community-dwelling older adults with insomnia [120]. In addition, some studies suggest that sleep disturbances are stronger predictors of pain than using pain to predict sleep disturbances [121], though this needs to be further explored through additional research.

Psychiatric conditions may play an important role in the relation between sleep disturbances and pain. A number of studies that explored this topic have suggested that psychiatric illnesses may mediate the relationship between sleep and pain. OA has been frequently associated with pain in older adults [30]. One study of 367 people with OA (mean age of 68 years) found that sleep was associated with pain and depression and depressive symptoms mediated the sleep–pain relationship in the cross-sectional analysis. However, baseline sleep disturbance pain was not associated with pain at follow-up [122]. Similarly, a longitudinal analysis of a sample of 1860 participants examined whether insomnia and sleep duration predict the onset of chronic multisite musculoskeletal pain over 6 years [121]. The findings suggest that insomnia and short

sleep duration are risk factors for developing chronic pain, and depressive symptoms partially mediate the effect for insomnia and short sleep with developing chronic pain. Another population-based prospective study found that insomnia symptoms were associated with an increased risk for new onset of pain after 2 years [119]. The relationship was not mediated by depression in this study. Anxiety symptoms accounted for 17% of the total effect of difficulty in initiating sleep and 15% of the total effect of difficulty in sleep maintenance on the new onset of pain, respectively.

There might be an association between OSA and pain in older adults. A randomized, double-blind crossover study found significant improvement in electrical pain tolerance when OSA patients were treated with CPAP [123]. In addition, improved sleep in older adults may benefit pain management. A recent study found that older adults with clinically significant improvements in insomnia symptoms within 2 months sustained the improvements in sleep measures over an 18 months period and showed improvements in measures of pain (Tables 4.1 and 4.2) [124].

Conclusion

Sleep patterns change with normal aging across the life-span from pediatric to middle age to older age but generally have minimal further progressive change in healthy older adulthood. Prevalent disturbed sleep or sleep problems in older adults are largely attributable to existing medical conditions and polypharmacy used to treat these

TABLE 4.2 Summary of reviewed evidence on sleep and reviewed health outcomes in older adults.

Health outcomes	Sleep duration		Insomnia symptoms/ sleep complaints	Poor sleep quality	Prolonged day- time napping	Excessive daytime sleepiness	Insomnia	Sleep disordered breathing
	Short	Long						
Cognitive function								
Global cognition	+	+	+	+	+	N/A	+/-	+
Cognitive decline/impair- ment/dementia	+	+	+	+	+	+	+/-	+
Cardiovascular health								
Hypertension	-	+	+	N/A	N/A	N/A	+	+/-
Stroke	-	+	N/A	N/A	N/A	N/A	+	N/A
Cardiovascular morbidity	+	+	N/A	+	N/A	N/A	+	N/A
Heart failure	N/A	N/A	+	N/A	N/A	+	+	+
Psychiatric illness								
Depression	-	-	+	+		+	+	N/A
Anxiety	+	-	+	N/A	N/A	+	N/A	+/-
Pain	+	-	+	+	N/A	N/A	+	+

-, denotes current evidence shows no clear association between the sleep character and the poor health outcome in general; +, denotes current evidence supports association between the sleep character and the poor health outcome in general; +/-, denotes current evidence yielded conflict findings; N/A, denotes the association either not reviewed or no related literature was found.

conditions, rather than aging. Older adults with chronic medical conditions commonly experience insomnia symptoms, daytime sleepiness, and fatigue. Those with sleep disturbance have an increased risk of multiple adverse health outcomes, such as impaired cognition, CV morbidity, depression, pain, etc. Likewise, these chronic conditions can contribute to sleep disturbances or sleep disorders in older adults, causing a cyclical effect. Sleep interventions need to be incorporated in the management of chronic conditions as they often occur concurrent with sleep problems and vice versa. Future studies, in addition to testing mechanistic pathways and associations, should also test whether treating sleep and chronic medical condition concurrently could add treatment effects to both conditions.

References

- [1] Li J, Vitiello MV, Gooneratne NS. Sleep in normal aging. *Sleep Med Clin* 2018;13(1):1–11. <https://doi.org/10.1016/j.jsmc.2017.09.001>.
- [2] Geisler P., Wehrle R., Yassouridis A., Ultsch A., Wetter TC., Schulz H. Sleep and Aging. A Polysomnographic Follow-Up Study, Some 40 Years Later. *J Sleep Res.* 2025. doi:10.1111/jsr.70039. PMID: 40098583.
- [3] Keihani A., Mayeli A., Ferrarelli F. Circadian Rhythm Changes in Healthy Aging and Mild Cognitive Impairment. *Adv Biol (Weinh).* 2023;7(11) :e2200237. doi:10.1002/adbi.202200237. PMID: 36403250
- [4] Duffy JF, Zitting KM, Chinoy ED. Aging and circadian rhythms. *Sleep Med Clin* 2015;10(4):423–34. <https://doi.org/10.1016/j.jsmc.2015.08.002>.
- [5] Ujma PP., Bódizs R. Sleep homeostasis occurs in a naturalistic setting. *Sleep Health.* 2025;11(3):335–343. doi: 10.1016/j.sleh.2025.01.007. Epub 2025 Mar 4. PMID: 40044473.
- [6] Wennberg AM, Canham SL, Smith MT, Spira AP. Optimizing sleep in older adults: treating insomnia. *Maturitas* 2013;76 (3):247–52. <https://doi.org/10.1016/j.maturitas.2013.05.007>.
- [7] Li Y, Tan Y, Zhao Z. Impacts of aging on circadian rhythm and related sleep disorders. *Biosystems* 2024;236:105111. <https://doi.org/10.1016/j.biosystems.2023.105111>.
- [8] Taillard J, Gronfier C, Bioulac S, Philip P, Sagaspe P. Sleep in Normal Aging, Homeostatic and Circadian Regulation and Vulnerability to Sleep Deprivation. *Brain Sci* 2021;11(8):1003. <https://doi.org/10.3390/brainsci11081003>.
- [9] Brewster GS, Riegel B, Gehrman PR. Insomnia in the older adult. *Sleep Med Clinics* 2018;13(1):13–9. <https://doi.org/10.1016/j.jsmc.2017.09.002>.
- [10] Cochen V, Arbus C, Soto ME, Villars H, Tiberge M, Montemayor T, Hein C, Veccherini MF, Onen SH, Ghorayeb I, Verny M, Fitten LJ, Savage J, Dauvilliers Y, Vellas B. Sleep disorders and their impacts on healthy, dependent, and frail older adults. *J Nutr Health Aging* 2009;13(4):322–9. <https://doi.org/10.1007/s12603-009-0030-0>.
- [11] Medicine AAoS. International classification of sleep disorders—third edition (ICSD-3). American Academy of Sleep Medicine; 2014. p. 2014.
- [12] Hassinger AB., Bletnicky N., Dudekula R., El-Solh AA. *Selecting a pharmacotherapy regimen for patients with chronic insomnia.* *Expert Opin Pharmacother.* 2020;21(9):1035–1043. PMID: 32202451; PMCID: PMC7432988.
- [13] Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Fam Pract* 2012;13. <https://doi.org/10.1186/1471-2296-13-40>.
- [14] Rossman J. *Cognitive-Behavioral Therapy for Insomnia: An Effective and Underutilized Treatment for Insomnia.* *Am J Lifestyle Med.* 2019;13(6):544–547. PMID: 31662718.
- [15] Ghavami T, Kazeminia M, Ahmadi N, Rajati F. Global Prevalence of Obstructive Sleep Apnea in the Elderly and Related Factors: A Systematic Review and Meta-Analysis Study. *J Perianesth Nurs* 2023;38(6):865–75. <https://doi.org/10.1016/j.jopan.2023.01.018>.
- [16] Chowdhuri S, Patel P, Badr MS. Apnea in older adults. *Sleep Med Clin* 2018;13(1):21–37. <https://doi.org/10.1016/j.jsmc.2017.09.003>.
- [17] Durán J, Esnaola S, Rubio R, Iztueta Á. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 year. *Am J Respir Crit Care Med* 2001;163(3):685–9. <https://doi.org/10.1164/ajrccm.163.3.2005065>.
- [18] Kleisiaris CF, Kritsotakis EI, Daniil Z, Tzanakis N, Papaioannou A, Gourgoulianis KI. The prevalence of obstructive sleep apnea-hypopnea syndrome-related symptoms and their relation to airflow limitation in an elderly population receiving home care. *Int J COPD* 2014;9:1111–7. <https://doi.org/10.2147/COPD.S67779>.
- [19] Mehra R, Stone KL, Blackwell T, Ancoli Israel S, Dam TTL, Stefanick ML, Redline S. Prevalence and correlates of sleep-disordered breathing in older men: osteoporotic fractures in men sleep study. *J Am Geriatr Soc* 2007;55(9):1356–64. <https://doi.org/10.1111/j.1532-5415.2007.01290.x>.
- [20] Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM. Predictors of sleep-disordered breathing in community-dwelling adults: the sleep heart health study. *Arch Intern Med* 2002;162 (8):893–900. <https://doi.org/10.1001/archinte.162.8.893>.
- [21] Bublitz M, Adra N, Hijazi L, Shaib F, Attarian H, Bourjeily G. A Narrative Review of Sex and Gender Differences in Sleep Disordered Breathing: Gaps and Opportunities. *Life (Basel)* 2022;12 (12). <https://doi.org/10.3390/life1212203>.
- [22] Morales CR, Hurley S, Wick LC, Staley B, Pack FM, Gooneratne NS, Maislin G, Pack A, Gurubhagavatula I. In-home, self-assembled sleep studies are useful in diagnosing sleep apnea in the elderly. *Sleep* 2012;35(11):1491–501. <https://doi.org/10.5665/sleep.2196>.
- [23] Mehrtash M, Bakker JP, Ayas N. Predictors of Continuous Positive Airway Pressure Adherence in Patients with Obstructive Sleep Apnea. *Lung* 2019;197(2):115–21. <https://doi.org/10.1007/s00408-018-00193-1>.
- [24] Russo-Magno P, O'Brien A, Panciera T, Rnp R, Rounds S. Compliance with CPAP therapy in older men with obstructive sleep apnea. *J Am Geriatr Soc* 2001;49(9):1205–11. <https://doi.org/10.1046/j.1532-5415.2001.49238.x>.
- [25] Ayalon L, Ancoli-Israel S, Stepnowsky C, Marler M, Palmer BW, Liu L, Loredo JS, Corey-Bloom J, Greenfield D, Cooke J.

- Adherence to continuous positive airway pressure treatment in patients with Alzheimer disease and obstructive sleep apnea. *Am J Geriatr Psychiatr* 2006;14(2):176–80. <https://doi.org/10.1097/01.JGP.0000192484.12684.cd>.
- [26] Chong MS, Ayalon L, Marler M, Loredo JS, Corey-Bloom J, Palmer BW, Liu L, Ancoli-Israel S. Continuous positive airway pressure reduces subjective daytime sleepiness in patients with mild to moderate Alzheimer's disease with sleep disordered breathing. *J Am Geriatr Soc* 2006;54(5):777–81. <https://doi.org/10.1111/j.1532-5415.2006.00694.x>.
- [27] Richards KC., Lozano AJ., Morris J., Moelter ST., Ji W., Vallabhaneni V., Wang Y., Chi L., Davis EM., Cheng C., Aguilar V., Khan S., Sankhavaram M., Hanlon AL., Wolk DA., Gooneratne N. Predictors of Adherence to Continuous Positive Airway Pressure in Older Adults With Apnea and Amnestic Mild Cognitive Impairment. *J Gerontol A Biol Sci Med Sci*. 2023;78(10):1861–1870. doi: 10.1093/gerona/glad099. PMID: 37021413; PMCID: PMC11007392.
- [28] Li J, Yang B, Varrasse M, Li K. Sleep among long-term care residents in China: a narrative review of literature. *Clin Nurs Res* 2018;27(1):35–60. <https://doi.org/10.1177/1054773816673175>.
- [29] Fillenbaum GG, Pieper CF, Cohen HJ, Cornoni-Huntley JC, Guralnik JM. Comorbidity of five chronic health conditions in elderly community residents: determinants and impact on mortality. *J Gerontol Series A Biolog Sci Med Sci* 2000;55(2):M84. <https://doi.org/10.1093/gerona/55.2.M84>.
- [30] Onen SH, Onen F. Chronic medical conditions and sleep in the older adult. *Sleep Med Clin* 2018;13(1):71–9. <https://doi.org/10.1016/j.jsmc.2017.09.007>.
- [31] Innes GK., Ogden CL., Crentsil V., Concato J., Fakhouri TH. Prescription Medication Use Among Older Adults in the US. *JAMA Intern Med*. 2024;184(9):1121–1123. doi: 10.1001/jamainternmed.2024.2781. PMID: 38949837; PMCID: PMC11217884.
- [32] Hughes ML, Agrigoroaei S, Jeon M, Bruzzese M, Lachman ME. Change in Cognitive Performance From Midlife Into Old Age: Findings from the Midlife in the United States (MIDUS) Study. *Journal of the International Neuropsychological Society* 2018;24(8):805–20. <https://doi.org/10.1017/S1355617718000425>.
- [33] Ferini-Strambi L., Liguori C., Lucey BP., Mander BA., Spira AP., Videnovic A., Baumann C., Franco O., Fernandes M., Gnarra O., Krack P., Manconi M., Noain D., Saxena S., Kallweit U., Randerath W., Trenkwalder C., Rosenzweig I., Iranzo A., Bradicich M., Bassetti C. Role of sleep in neurodegeneration: the consensus report of the 5th Think Tank World Sleep Forum. *Neurol Sci [Internet]*. 2024;45(2):749–767. doi:10.1007/s10072-023-07232-7. PMCID: 5219881
- [34] Zhao L., Tannenbaum A., Bakker ENTP., Benveniste H. Physiology of Glymphatic Solute Transport and Waste Clearance from the Brain. *Physiology (Bethesda)*. 2022; 37(6). doi: 10.1152/physiol.00015.2022. Epub 2022 Jul 26. PMID: 35881783; PMCID: PMC9550574.
- [35] Lo JC, Loh KK, Zheng H, Sim SKY, Chee MWL. Sleep duration and age-related changes in brain structure and cognitive performance. *Sleep* 2014;37(7):1171–8. <https://doi.org/10.5665/sleep.3832>.
- [36] Xu L, Jiang CQ, Lam TH, Liu B, Jin YL, Zhu T, Zhang WS, Cheng KK, Thomas GN. Short or long sleep duration is associated with memory impairment in older Chinese: the Guangzhou Biobank Cohort Study. *Sleep* 2011;34(5):575–80. <https://doi.org/10.1093/sleep/34.5.575>.
- [37] Blackwell T, Yaffe K, Laffan A, Ancoli-Israel S, Redline S, Ensrud KE, Song Y, Stone KL. Associations of objectively and subjectively measured sleep quality with subsequent cognitive decline in older community-dwelling men: the MrOS Sleep Study. *Sleep* 2014;37(4):655–63. <https://doi.org/10.5665/sleep.3562>.
- [38] Martin MS, Sforza E, Barthélémy JC, Thomas-Anterion C, Roche F. Does subjective sleep affect cognitive function in healthy elderly subjects? The Proof cohort. *Sleep Med* 2012;13(9):1146–52. <https://doi.org/10.1016/j.sleep.2012.06.021>.
- [39] Loerbroks A, Debling D, Amelang M, Stürmer T. Nocturnal sleep duration and cognitive impairment in a population-based study of older adults. *Int J Geriatr Psychiatr* 2010;25(1):100–9. <https://doi.org/10.1002/gps.2305Germany>.
- [40] Lo JC, Groeger JA, Cheng GH, Dijk DJ, Chee MWL. Self-reported sleep duration and cognitive performance in older adults: a systematic review and meta-analysis. *Sleep Med* 2016;17:87–98. <https://doi.org/10.1016/j.sleep.2015.08.021>.
- [41] Devore EE, Grodstein F, Schernhammer ES. Sleep duration in relation to cognitive function among older adults: a systematic review of observational studies. *Neuroepidemiology* 2016;46(1):57–78. <https://doi.org/10.1159/000442418>.
- [42] Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol* 2014;13(10):1017–28. [https://doi.org/10.1016/S1474-4422\(14\)70172-3](https://doi.org/10.1016/S1474-4422(14)70172-3).
- [43] Babu OM, Brannick M, Mortimer J, Sleep, et al. Cognitive impairment, and Alzheimer's disease: A Systematic Review and Meta-Analysis. *Sleep* 2017;40(1). <https://doi.org/10.1093/sleep/zsw032>.
- [44] Scullin MK, Blilwise DL. Sleep, cognition, and normal aging: integrating a half century of multidisciplinary research. *Perspect Psychol Sci* 2015;10(1):97–137. <https://doi.org/10.1177/1745691614556680>.
- [45] Elwood PC, Bayer AJ, Fish M, Pickering J, Mitchell C, Gallacher JEJ. Sleep disturbance and daytime sleepiness predict vascular dementia. *J Epidemiol Commun* 2011;65(9):820–4. <https://doi.org/10.1136/jech.2009.100503>.
- [46] Sterniczuk R, Theou O, Rusak B, Rockwood K. Sleep disturbance is associated with incident dementia and mortality. *Curr Alzheimer Res* 2013;10(7):767–75. <https://doi.org/10.2174/15672050113109990134>.
- [47] Ma Y, Liang L, Zheng F, Shi L, Zhong B, Xie W. Association Between Sleep Duration and Cognitive Decline. *JAMA Netw Open* 2020;3(9):e2013573. <https://doi.org/10.1001/jamanetworkopen.2020.13573>.
- [48] Johar H, Kawan R, Emeny RT, Ladwig KH. Impaired Sleep Predicts Cognitive Decline in Old People: Findings from the Prospective KORA Age Study. *Sleep*. 2016;39(1):217–226. Published 2016 Jan 1. doi:10.5665/sleep.5352
- [49] Keil SA, Schindler AG, Wang MX, et al. Longitudinal Sleep Patterns and Cognitive Impairment in Older Adults. *JAMA Netw Open* 2023;6(12):e2346006. <https://doi.org/10.1001/jamanetworkopen.2023.46006>.
- [50] Bernstein JPK, Calamia M, Keller JN. Multiple self-reported sleep measures are differentially associated with cognitive performance in community-dwelling nondemented elderly. *Neuropsychology* 2018;32(2):220–9. <https://doi.org/10.1037/neu0000407>.

- [51] Hsieh S, Li TH, Tsai LL. Impact of monetary incentives on cognitive performance and error monitoring following sleep deprivation. *Sleep* 2010;33(4):499–507. <https://doi.org/10.1093/sleep/33.4.499>.
- [52] Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Ensrud KE, Stefanick ML, Laffan A, Stone KL. Association of sleep characteristics and cognition in older community-dwelling men: the MrOS sleep study. *Sleep* 2011;34(10):1347–56. <https://doi.org/10.5665/SLEEP.1276>.
- [53] Jausset I, Bouyer J, Ancelin ML, Berr C, Foubert-Samier A, Ritchie K, Ohayon MM, Berset A, Dauvilliers Y. Excessive sleepiness is predictive of cognitive decline in the elderly. *Sleep* 2012;35(9):1201–7. <https://doi.org/10.5665/sleep.2070>.
- [54] Schmutte T, Harris S, Levin R, Zweig R, Katz M, Lipton R. The relation between cognitive functioning and self-reported sleep complaints in nondemented older adults: results from the Bronx Aging Study. *Behav Sleep Med* 2007;5(1):39–56. https://doi.org/10.1207/s15402010bsm0501_3.
- [55] Qin S., Leong RLF., Ong JL., Chee MWL. Associations between objectively measured sleep parameters and cognition in healthy older adults: A meta-analysis. *Sleep Medicine Reviews*. 2023;67:101734. doi:10.1016/j.smrv.2022.101734. PMID: 36577339.
- [56] Naismith SL, Rogers NL, Hickie IB, MacKenzie J, Norrie LM, Lewis SJG. Sleep well, think well: sleep-wake disturbance in mild cognitive impairment. *J Geriatr Psychiatr Neurol* 2010;23 (2):123–30. <https://doi.org/10.1177/0891988710363710>.
- [57] Lim ASP, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep* 2013;36(7):1027–32. <https://doi.org/10.5665/sleep.2802Canada>.
- [58] Zhang Z, Xiao X, Ma W, Li J. Napping in Older Adults: A Review of Current Literature. *Curr Sleep Med Rep* 2020;6(3):129–35. <https://doi.org/10.1007/s40675-020-00183-x>.
- [59] Furuhata R, Kaneita Y, Jike M, Ohida T, Uchiyama M. Napping and associated factors: a Japanese nationwide general population survey. *Sleep Med* 2016;20:72–9. <https://doi.org/10.1016/j.sleep.2015.12.006>.
- [60] Li J, Cacchione PZ, Hodgson N, Riegel B, Keenan BT, Scharf MT, Richards KC, Gooneratne NS. Afternoon napping and cognition in Chinese older adults: findings from the China health and retirement longitudinal study baseline assessment. *J Am Geriatr Soc* 2017;65 (2):373–80. <https://doi.org/10.1111/jgs.14368>.
- [61] Li J, Chang YP, Riegel B, Keenan BT, Varrasse M, Pack AI, Gooneratne NS. Intermediate, but not extended, afternoon naps may preserve cognition in Chinese older adults. *J Gerontol Ser A Biolog Sci Med Sci* 2018;73(3):360–6. <https://doi.org/10.1093/gerona/glx069>.
- [62] Campbell SS, Stanchina MD, Schlang JR, Murphy PJ. Effects of a month-long napping regimen in older individuals. *J Am Geriatr Soc* 2011;59(2):224–32. <https://doi.org/10.1111/j.1532-5415.2010.03264.x>.
- [63] Milner CE, Cote KA. A dose-response investigation of the benefits of napping in healthy young, middle-aged and older adults. *Sleep Biol Rhythms* 2008;6(1):2–15. <https://doi.org/10.1111/j.1479-8425.2007.00328.x>.
- [64] Korman M, Dagan Y, Karni A. Nap it or leave it in the elderly: a nap after practice relaxes age-related limitations in procedural memory consolidation. *Neurosci Lett* 2015;606:173–6. <https://doi.org/10.1016/j.neulet.2015.08.051>.
- [65] Clémence Cavaillès, Claudine Berr, Catherine Helmer, Audrey Gabelle, Isabelle Jaussent, Yves Dauvilliers in “Complaints of daytime sleepiness, insomnia, hypnotic use, and risk of dementia: a prospective cohort study in the elderly”; 2022; 14(1):12; PMID: 35057850
- [66] Foley D, Monjan A, Masaki K, Ross W, Havlik R, White L, Launer L. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. *J Am Geriatr Soc* 2001;49(12):1628–32. <https://doi.org/10.1046/j.1532-5415.2001.t01-1-49271.x>.
- [67] Ohayon MM, Vecchierini MF. Daytime sleepiness and cognitive impairment in the elderly population. *Arch Intern Med* 2002;162 (2):201–8. <https://doi.org/10.1001/archinte.162.2.201>.
- [68] Merlino G, Piani A, Gigli GL, Cancelli I, Rinaldi A, Baroselli A, Serafini A, Zanchettin B, Valente M. Daytime sleepiness is associated with dementia and cognitive decline in older Italian adults: a population-based study. *Sleep Med* 2010;11(4):372–7. <https://doi.org/10.1016/j.sleep.2009.07.018>.
- [69] Fortier-Brochu E, Beaulieu-Bonneau S, Ivers H, Morin CM. Insomnia and daytime cognitive performance: a meta-analysis. *Sleep Med Rev* 2012;16(1):83–94. <https://doi.org/10.1016/j.smrv.2011.03.008>.
- [70] Osorio RS., Pirraglia E, Agüera-Ortiz LF., During EH., Sacks H., Ayappa I., Walsleben J., Mooney A., Hussain A., Glodzik L., Frangione B., Martínez-Martín P., de Leon MJ. Greater risk of Alzheimer's disease in older adults with insomnia. *J Am Geriatr Soc*. 2011;59(3):559-62. doi: 10.1111/j.1532-5415.2010.03288.x. PMID: 21391952; PMCID: PMC3378676.
- [71] Cricco M, Simonsick EM, Foley DJ. The impact of insomnia on cognitive functioning in older adults. *J Am Geriatr Soc* 2001;49 (9):1185–9. <https://doi.org/10.1046/j.1532-5415.2001.49235.x>.
- [72] Altena E, Van Der Werf YD, Strijers RLM, Van Someren EJW. Sleep loss affects vigilance: effects of chronic insomnia and sleep therapy. *J Sleep Res* 2008;17(3):335–43. <https://doi.org/10.1111/j.1365-2869.2008.00671.x>.
- [73] Wilckens KA, Hall MH, Nebes RD, Monk TH, Buysse DJ. Changes in cognitive performance are associated with changes in sleep in older adults with insomnia. *Behav Sleep Med* 2016;14 (3):295–310. <https://doi.org/10.1080/15402002.2014.1002034>.
- [74] Bubu OM., Andrade AG., Umasabor-Bubu OQ., Hogan MM., Turner AD., de Leon MJ., Ogedegbe G., Ayappa I., Jean-Louis G G., Jackson ML., Varga AW., Osorio RS. Obstructive sleep apnea, cognition and Alzheimer's disease: A systematic review integrating three decades of multidisciplinary research. *Sleep Med Rev*. 2020;50:101250. doi: 10.1016/j.smrv.2019.101250. Epub 2019 Dec 12. PMID: 31881487; PMCID: PMC7593825.
- [75] Leng Y., McEvoy CT., Allen IE., Yaffe K. Association of Sleep-Disordered Breathing With Cognitive Function and Risk of Cognitive Impairment: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2017 Oct 1;74(10):1237-1245. doi: 10.1001/jamaneurol.2017.2180. Erratum in: *JAMA Neurol*. 2018;75 (1):133. doi: 10.1001/jamaneurol.2017.3677. PMID: 28846764; PMCID: PMC5710301.
- [76] Dzierzewski JM, Dautovich N, Ravits S. Sleep and cognition in older adults. *Sleep Med Clin* 2018;13(1):93–106. <https://doi.org/10.1016/j.jsmc.2017.09.009>.

- [77] Osorio RS, Gumb T, Pirraglia E, Varga AW, Lu SE, Lim J, Wohlleber ME, Ducca EL, Koushyk V, Glodzik L, Mosconi L, Ayappa I, Rapoport DM, De Leon MJ. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology* 2015;84(19):1964–71. <https://doi.org/10.1212/WNL.0000000000001566>.
- [78] Richards KC., Lozano AJ., Morris J., Moelter ST., Ji W., Vallabhaneni V., Wang Y., Chi L., Davis EM., Cheng C., Aguilar V., Khan S., Sankhavaram M., Hanlon AL., Wolk DA., Gooneratne N. Predictors of Adherence to Continuous Positive Airway Pressure in Older Adults With Apnea and Amnestic Mild Cognitive Impairment. *J Gerontol A Biol Sci Med Sci.* 2023;78(10):1861–1870. doi: 10.1093/gerona/glad099. PMID: 37021413; PMCID: PMC11007392.
- [79] Martin SS., Aday AW., Almarzooq ZI., Anderson CAM., Arora P., Avery CL., Baker-Smith CM., Barone Gibbs B., Beaton AZ., Boehme AK., Commodore-Mensah Y., Currie ME., Elkind MSV., Evenson KR., Generoso G., Heard DG., Hiremath S., Johansen MC., Kalani R., Kazi DS., Ko D., Liu J., Magnani JW., Michos ED., Mussolini ME., Navaneethan SD., Parikh NI., Perman SM., Poudel R., Rezk-Hanna M., Roth GA., Shah NS., St-Onge MP., Thacker EL., Tsao CW., Urbut SM., Van Spall HGC., Voeks JH., Wang NY., Wong ND., Wong SS., Yaffe K., Palaniappan LP. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. *Circulation.* 2024;149(8):e347–e913. doi: 10.1161/CIR.0000000000001209. Epub 2024 Jan 24. Erratum in: *Circulation.* 2024 May 7;149(19):e1164. doi: 10.1161/CIR.0000000000001247. Erratum in: *Circulation.* 2025 Jun 24;151(25):e1095. doi: 10.1161/CIR.0000000000001344. PMID: 38264914. PMCID: PMC12146881.
- [80] Yerem Y., Hani J., Jeremy R T., Susan R., Devin L B., Nabil El-Sherif., Reena M., Biykiem B., Chiadi Ericson N. Virend K Somers in “Obstructive Sleep Apnea and Cardiovascular Disease: A Scientific Statement From the American Heart Association”; 2021; 144(3):e56–e67; PMID: 34148375
- [81] Chayakrit K., Anusith T., Zhen W., HongJu Z., Ann M F., Sakkarin C., Tao S., Takeshi K., Edgar A. in “Association between short and long sleep durations and cardiovascular outcomes: a systematic review and meta-analysis”; 2019; 8(8):762–770; PMID: 29206050
- [82] Fang J, Wheaton AG, Ayala C. Sleep duration and history of stroke among adults from the USA. *J Sleep Res* 2014;23(5):531–7. <https://doi.org/10.1111/jsr.12160>.
- [83] Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK, Malaspina D. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* 2006;47(5):833–9. <https://doi.org/10.1161/01.HYP.0000217362.34748.e0>.
- [84] Suzuki E, Yorifuji T, Ueshima K, Takao S, Sugiyama M, Ohta T, Ishikawa-Takata K, Doi H. Sleep duration, sleep quality and cardiovascular disease mortality among the elderly: a population-based cohort study. *Prev Med* 2009;49(2–3):135–41. <https://doi.org/10.1016/j.ypmed.2009.06.016>.
- [85] Silva AAda, Mello RGBde, Schaan CW, Fuchs FD, Redline S, Fuchs SC. Sleep duration and mortality in the elderly: a systematic review with meta-analysis. *BMJ Open* 2016;6(2):e008119. <https://doi.org/10.1136/bmjopen-2015-008119>.
- [86] Guillot M, Sforza E, Achour-Crawford E, Maudoux D, Saint-Martin M, Barthélémy J-C, Roche F. Association between severe obstructive sleep apnea and incident arterial hypertension in the older people population. *Sleep Med* 2013;14(9):838–42. <https://doi.org/10.1016/j.sleep.2013.05.002>.
- [87] Haas DC, Foster GL, Nieto FJ, Redline S, Resnick HE, Robbins JA, Young T, Pickering TG. Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the sleep heart health study. *Circulation* 2005;111(5):614–21. <https://doi.org/10.1161/01.CIR.0000154540.62381.CF>.
- [88] Fung MM, Peters K, Redline S, Ziegler MG, Ancoli-Israel S, Barrett-Connor E, Stone KL. Decreased slow wave sleep increases risk of developing hypertension in elderly men. *Hypertension* 2011;58(4):596–603. <https://doi.org/10.1161/HYPERTENSIONAHA.111.174409>.
- [89] Stone KL, Blackwell TL, Ancoli-Israel S, Barrett-Connor E, Bauer DC, Cauley JA, Ensrud KE, Hoffman AR, Mehra R, Stefanick ML, Varosy PD, Yaffe K, Redline S. Sleep disordered breathing and risk of stroke in older community-dwelling men. *Sleep* 2016;39(3):531–40. <https://doi.org/10.5665/sleep.5520>.
- [90] Munoz R, Duran-Cantolla J, Martínez-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G. Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke* 2006;37(9):2317–21. <https://doi.org/10.1161/01.STR.0000236560.15735.0F>.
- [91] Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005;353(19):2034–41. <https://doi.org/10.1056/NEJMoa043104>.
- [92] Yumino D, Redolfi S, Ruttanaumpawan P, Su MC, Smith S, Newton GE, Mak S, Bradley TD. Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. *Circulation* 2010;121(14):1598–605. <https://doi.org/10.1161/CIRCULATIONAHA.109.902452>.
- [93] Javaheri S, Blackwell T, Ancoli-Israel S, Ensrud KE, Stone KL, Redline S. Sleep-disordered breathing and incident heart failure in older men. *Am J Respir Crit Care Med* 2016;193(5):561–8. <https://doi.org/10.1164/rccm.201503-0536OC>.
- [94] Gottlieb DJ, Yenokyan G, Newman AB, O’Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122(4):352–60. <https://doi.org/10.1161/CIRCULATIONAHA.109.901801>.
- [95] Heidenreich PA., Bozkurt B., Aguilar D., Allen LA., Byun JJ., Colvin MM., Deswal A., Drazner MH., Dunlay SM., Evers L.R., Fang J.C., Fedson S.E., Fonarow G.C., Hayek S.S., Hernandez A. F., Khazanie P., Kittleson M.M., Lee CS., Link MS., Milano CA., Nnacheta LC., Sandhu AT., Stevenson L.W., Vardeny O., Vest AR., Yancy CW.; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145(18):e895–e1032. doi: 10.1161/

- CIR.0000000000001063. Epub 2022 Apr 1. Erratum in: Circulation. 2022 May 3;145(18):e1033. doi: 10.1161/CIR.0000000000001073. Erratum in: Circulation. 2022 Sep 27;146(13):e185. doi: 10.1161/CIR.0000000000001097. Erratum in: Circulation. 2023 Apr 4;147(14):e674. doi: 10.1161/CIR.0000000000001142. PMID: 35363499.
- [96] Javaheri S., Redline S. Insomnia and Risk of Cardiovascular Disease. *Chest*. 2017;152(2):435-444. doi: 10.1016/j.chest.2017.01.026. PMID: 28153671; PMCID: PMC5577359.
- [97] Li M, Zhang XW, Hou WS, Tang ZY. Insomnia and risk of cardiovascular disease: a meta-analysis of cohort studies. *Int J Cardiol* 2014;176(3):1044–7. <https://doi.org/10.1016/j.ijcard.2014.07.284>.
- [98] Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur J Prev Cardiol* 2014;21(1):57–64. <https://doi.org/10.1177/2047487312460020>.
- [99] Zhuang J, Zhan Y, Zhang F, Tang Z, Wang J, Sun Y, Ding R, Hu D, Yu J. Self-reported insomnia and coronary heart disease in the elderly. *Clin Exp Hypertens* 2016;38(1):51–5. <https://doi.org/10.3109/10641963.2015.1060983>.
- [100] Redeker NS, Yaggi HK, Jacoby D, Hollenbeck CS, Breazeale S, Conley S, et al. Cognitive behavioral therapy for insomnia has sustained effects on insomnia, fatigue, and function among people with chronic heart failure and insomnia: the HeartSleep Study. *Sleep* 2022;45(1):zsab252. <https://doi.org/10.1093/sleep/zsab252>.
- [101] Newman AB, Spiekerman CF, Enright P, Lefkowitz D, Manolio T, Reynolds CF, Robbins J. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. *J Am Geriatr Soc* 2000;48(2):115–23. <https://doi.org/10.1111/j.1532-5415.2000.tb03901.x>.
- [102] Nadorff MR, Drapeau CW, Pigeon WR. Psychiatric illness and sleep in older adults: comorbidity and opportunities for intervention. *Sleep Med Clin* 2018;13(1):81–91. <https://doi.org/10.1016/j.jsmc.2017.09.008>.
- [103] Wetherell JL, Le Roux H, Gatz M. DSM-IV criteria for generalized anxiety disorder in older adults: distinguishing the worried from the well. *Psychol Aging* 2003;18(3):622–7. <https://doi.org/10.1037/0882-7974.18.3.622>.
- [104] Yan-Ping Bao, Ying Han, Jun Ma, Ru-Jia Wang, Le Shi, Tong-Yu Wang, Jia He, Jing-Li Yue, Jie Shi, Xiang-Dong Tang, Lin Lu in “Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: Meta-analysis and systematic review”; 2017; 75:257-273; PMID: 28179129
- [105] Zhai L, Zhang H, Zhang D. Sleep duration and depression among adults: a meta-analysis of prospective studies. *Depress Anxiety* 2015;32(9):664–70. <https://doi.org/10.1002/da.22386>.
- [106] Paudel M, Taylor BC, Ancoli-Israel S, Blackwell T, Maglione JE, Stone K, Redline S, Ensor KE. Sleep disturbances and risk of depression in older men. *Sleep* 2013;36(7):1033–40. <https://doi.org/10.5665/sleep.2804>.
- [107] Maglione JE, Ancoli-Israel S, Peters KW, Paudel ML, Yaffe K, Ensor KE, Stone KL. Subjective and objective sleep disturbance and longitudinal risk of depression in a cohort of older women. *Sleep* 2014;37(7):1179–87. <https://doi.org/10.5665/sleep.3834>.
- [108] Perlis ML, Smith LJ, Lyness JM, Matteson SR, Pigeon WR, Jungquist CR, Tu X. Insomnia as a risk factor for onset of depression in the elderly. *Behav Sleep Med* 2006;4(2):104–13. https://doi.org/10.1207/s15402010bsm0402_3.
- [109] Yokoyama E, Kaneita Y, Saito Y, Uchiyama M, Matsuzaki Y, Tamaki T, Munezawa T, Ohida T. Association between depression and insomnia subtypes: a Longitudinal Study on the Elderly in Japan. *Sleep* 2010;33(12):1693–702. <https://doi.org/10.1093/sleep/33.12.1693>.
- [110] Pigeon WR, Hegel M, Unützer J, Fan MY, Sateia MJ, Lyness JM, Phillips C, Perlis ML. Is insomnia a perpetuating factor for late-life depression in the IMPACT cohort? *Sleep* 2008;31(4):481–8. <https://doi.org/10.1093/sleep/31.4.481>.
- [111] Taylor DJ, Walters HM, Vittengl JR, Krebaum S, Jarrett RB. Which depressive symptoms remain after response to cognitive therapy of depression and predict relapse and recurrence? *J Affect Disord* 2010;123(1–3):181–7. <https://doi.org/10.1016/j.jad.2009.08.007>.
- [112] Nadorff MR, Ellis TE, Allen JG, Winer ES, Herrera S. Presence and persistence of sleep-related symptoms and suicidal ideation in psychiatric inpatients. *Crisis* 2014;35(6):398–405. <https://doi.org/10.1027/0227-5910/a000279>.
- [113] Desjardins S, Leblanc M-F, Desgagné A. Sleep problems in anxious and depressive older adults. *Psychol Res Behav Manag* 2015;8:161. <https://doi.org/10.2147/PRBM.S80642>.
- [114] Spira AP, Stone K, Beaudreau SA, Ancoli-Israel S, Yaffe K. Anxiety symptoms and objectively measured sleep quality in older women. *Am J Geriatr Psychiatr* 2009;17(2):136–43. <https://doi.org/10.1097/JGP.0b013e3181871345>.
- [115] Diaz SV, Brown LK. Relationships between obstructive sleep apnea and anxiety. *Curr Opin Pulm Med* 2016;22(6):563–9. <https://doi.org/10.1097/MCP.0000000000000326>.
- [116] Li YY, Mazarakis T, Shen YC, Yang MC, Chang ET, Wang HM. Anxiety and depression are improved by continuous positive airway pressure treatments in obstructive sleep apnea. *Int J Psychiatry Med.* 2016 Aug;51(6):554-562. doi: 10.1177/0091217417696737. Epub 2017 Mar 6. PMID: 28629298.
- [117] Becker NB, Jesus SN, João KADR, Viseu JN, Martins RIS. Depression and sleep quality in older adults: a meta-analysis. *Psychol Health Med* 2017;22(8):889–95. <https://doi.org/10.1080/13548506.2016.1274042>.
- [118] Potvin O, Lorrain D, Belleville G, Grenier S, Préville M. Subjective sleep characteristics associated with anxiety and depression in older adults: a population-based study. *Int J Geriatr Psychiatr* 2014;29(12):1262–70. <https://doi.org/10.1002/gps.4106>.
- [119] Dunietz GL, Swanson LM, Jansen EC, Chervin RD, O’Brien LM, Lisabeth LD, Braley TJ. Key insomnia symptoms and incident pain in older adults: direct and mediated pathways through depression and anxiety. *Sleep* 2018;41(9). <https://doi.org/10.1093/sleep/zsy125>.
- [120] Dzierzewski JM, Williams JM, Roditi D, Marsiske M, McCoy K, McNamara J, Dautovich N, Robinson ME, McCrae CS. Daily variations in objective nighttime sleep and subjective morning pain in older adults with insomnia: evidence of covariation over time. *J Am Geriatr Soc* 2010;58(5):925–30. <https://doi.org/10.1111/j.1532-5415.2010.02803.x>.
- [121] Generaal E, Vogelzangs N, Penninx BWJH, Dekker J. Insomnia, sleep duration, depressive symptoms, and the onset of chronic multisite musculoskeletal pain. *Sleep* 2017;40(1). <https://doi.org/10.1093/sleep/zsw030>.
- [122] Parmelee PA, Tighe CA, Dautovich ND. Sleep disturbance in osteoarthritis: linkages with pain, disability, and depressive

- symptoms. *Arthritis Care Res* 2015;67(3):358–65. <https://doi.org/10.1002/acr.22459>.
- [123] Onen SH, Onen F, Albrand G, Decullier E, Chapuis F, Dubray C. Pain tolerance and obstructive sleep apnea in the elderly. *J Am Med Dir Assoc* 2010;11(9):612–6. <https://doi.org/10.1016/j.jamda.2010.04.003>.
- [124] Vitiello MV, McCurry SM, Shortreed SM, Baker LD, Rybarczyk BD, Keefe FJ, Von Korff M. Short-term improvement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. *Pain* 2014;155(8):1547–54. <https://doi.org/10.1016/j.pain.2014.04.032>.

This page intentionally left blank

Chapter 5

Social-ecological model of sleep health

Michael A. Grandner

Sleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States

Introduction

Insufficient sleep duration and/or poor sleep quality represents a significant, unmet public health problem [1]. In epidemiological studies, spanning over 40 years and multiple continents, short and/or long sleep duration, as well as poor sleep quality, is associated with increased mortality risk [2,3]. Additionally, insufficient and/or poor quality sleep is associated with (and thought to play a causal role in) four of the seven leading causes of death, including heart disease, stroke, accidents, and diabetes, as well as other important health outcomes, such as weight gain and obesity, depression, and cognitive deficits. Current research is exploring mechanistic aspects of these relationships, such as isolating genetic vulnerabilities, identifying biomarkers for daytime sleepiness, and determining ways in which sleep plays a role in protective signaling pathways.

What these studies have in common is that they are exploring the “downstream” effects of sleep-related problems, clarifying how sleep plays a role in cardiometabolic disease, in addition to other adverse health outcomes, and how these pathways may explain the well-documented relationships with mortality. Increasingly, attention has focused on determinants of sleep—“upstream” influences that play a role in the development of the problematic sleep patterns that are predictive of worse health. A better understanding of the determinants of sleep will aid in the identification of modifiable factors and intervention targets that can be manipulated. For example, as poor diet is known to be associated with a number of negative health states, understanding the determinants of obesity (e.g., advertising, access to healthy food, socioeconomic status, sedentary lifestyle) has identified useful targets for change.

Accordingly, this chapter proposes a theoretical model for considering insufficient and/or poor quality

sleep in the context of its associated negative health outcomes (e.g., obesity, diabetes, cardiovascular disease, depression), as well as its likely determinants. Since there is sparse literature on determinants of sleep, we constructed our model with input from existing models for other health behaviors (e.g., diet, exercise). These models are typically based on a social-ecological framework, which conceives of a behavior of interest (e.g., a person’s diet) in the context of individual-level factors, which are embedded within social networks (e.g., family, work), which are themselves interrelated and embedded within larger networks (e.g., community, religion), which exist in a context of society that influences these networks in a number of ways (e.g., laws, technology, economics). Using a traditional social-ecological approach as a starting point, we constructed our model as a series of embedded systems (individual level, social level, and societal level), identifying key components of those systems believed to be determinants of sleep.

In summary, this model presents a conceptual framework for the “downstream” negative effects of insufficient and/or poor quality sleep, as well as the “upstream” determinants. The upper part of the model (determinants) is constructed based on existing theoretical models for other health behaviors, focusing on aspects thought to be particularly germane to sleep. The second part of the model (outcomes) is constructed as a synthesis of available data from epidemiological and experimental studies. Together, the model considers a global view of sleep and health, establishing a framework for future research to explore the determinants of sleep from a societal standpoint. Future studies will add clarity to the model, discerning unique and combined influences from the individual, community, and society levels. Finally, interventions developed based on this model can address problematic sleep at the individual (e.g., improving an individual’s sleep), social (e.g., promoting workplace

initiatives that minimize sleep-related impairments or increasing healthy sleep habits in families), and societal (e.g., public policy initiatives and educational campaigns) levels.

The social ecological model

The social-ecological model was originally proposed by Bronfenbrenner [4]. This model was intended to conceptualize the role of the individual in their environment. A key feature of this model is that the individual exists at the center of a nested set of constructs that describe levels of the environment in relation to the individual. The idea is that each level is nested within the next and so on. A schematic of the main components of the model is displayed in Fig. 5.1. First, the model starts with the individual. Each individual person is believed to exist within their own specific social-ecological framework of nested systems.

The first layer beyond the individual is the “microsystem.” This is the system in which the individual is embedded. According to this model, the microsystem refers to the set of interactions between the individual and elements of their environment at home, at school or work, etc. These are specific environments that the individual interacts with. In each of these environments, the individual takes on a specific role (e.g., mother or father, worker, son or daughter, teacher, friend) for specific periods of time. A key element of the microsystem is that this is where the individual specifically acts in relation to those around them.

The next layer around the microsystem is the “mesosystem.” Just as the individual is embedded within the microsystem of people, places, and roles, the microsystem is itself embedded within the mesosystem. This system describes the interrelations among elements of the

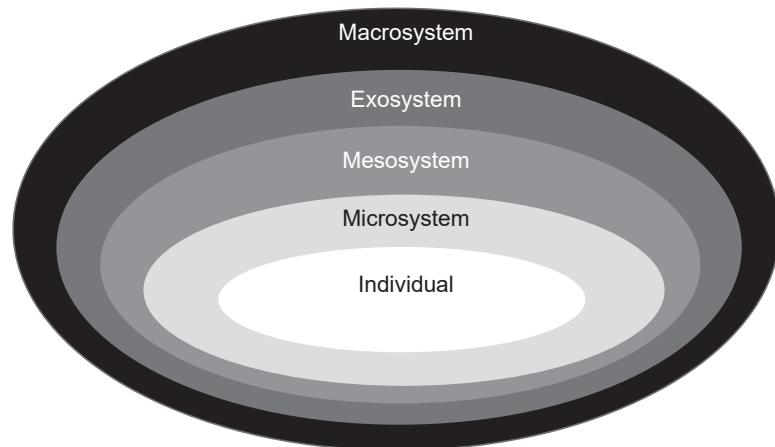
microsystem that are outside of the individual. For example, the interactions of a child at home with their parents and at school with their teachers exist within the microsystem, but the parent–teacher meeting would, for example, exist within the mesosystem. The mesosystem represents the collected microsystems of the other people that the individual interacts with in their own microsystem.

The next layer around the mesosystem is the “exosystem.” This system of interactions encompasses elements of the mesosystem that do not specifically interact with the microsystem of the individual. For example, the neighborhood, a person’s industry, the media, the consumer landscape, and the communication system of mobile phones represent discrete and conceptual members of the exosystem. The exosystem is the milieu within which the mesosystem exists. It represents the interactions and human processes that facilitate, hinder, control, or modify elements of the mesosystem (e.g., a company or a school) that then influences the microsystem (e.g., a workplace or a classroom), which influences the individual.

Beyond the exosystem, which exists outside of the mesosystem, is the “macrosystem.” The macrosystem includes the constructs within which the exosystem exists. The mesosystem rarely includes specific entities (as these would likely exist in the exosystem). Rather, the macrosystem reflects the common ideas, expectations, prototypes, and stereotypes that guide the exosystem. For example, there are sets of ideas in a culture about how a workplace should be, which influences the exosystem of an industry, which influences a specific company, which influences a specific workplace, which influences a specific individual. Thus, the macrosystem is the most abstract of the layers of the social-ecological model.

This concept of embedded systems reflecting layers of abstraction (the social-ecological framework) has remained a useful construct in understanding health behavior. For

FIGURE 5.1 Social-ecological model.



example, it has guided the development of interventions for diet [5], physical activity [6,7], substance abuse [8], stress management [9], vaccination [10], suicide prevention [11], environmental change [12], and other domains. It is possible that this model can also be applied to sleep, which itself is an important domain of health behavior.

Sleep as a domain of health behavior

The concept of a “health behavior” refers to a behavioral domain that can have broad impact on health, functioning, and longevity. This idea gained strength when it was found that behavioral factors were the leading “actual” causes of death in the United States in 2000 [13]. The leading “actual” causes of death were smoking, poor diet, lack of physical activity, and alcohol consumption, which accounted for >38% of all deaths combined. Insufficient and/or poor quality sleep was not considered in these analyses, but assessment of the mortality data for sleep duration and sleep apnea suggests that many deaths may be at least partially sleep-related. Further, insufficient and/or poor quality sleep has wide-ranging physiologic and psychological outcomes (described below). For these reasons, we propose that sleep represents a domain of health behavior.

Many studies have documented adverse physiologic, medical and psychological outcomes associated with habitual short sleep duration and experimental sleep deprivation (i.e., insufficient sleep duration), as well as poor sleep quality in general and sleep disorders such as insomnia, sleep apnea, and others (see other chapters in this volume). Accordingly, in building the model, we began with a proposed causal pathway linking sleep to adverse outcomes (Fig. 5.2). As depicted, the main

domains impacted by sleep include general health, cardiovascular health, metabolic health, immunologic health, behavioral health, emotional health, cognitive health, and physical health.

Several studies have shown that habitual short sleep duration is associated with increased risk of hypertension, heart attack, and stroke [14]. In addition, short sleep duration has been associated with elevated cholesterol and inflammatory markers [15]. Habitual poor quality sleep has also been associated with elevated risk of cardiovascular disease [16]. Insomnia—especially in the context of short sleep duration—has been shown to be associated with elevated cardiovascular disease risk [17]. Regarding sleep apnea, a large body of literature describes very strong relationships between sleep apnea and cardiovascular function [18]. Although the primary mechanism proposed for this link is through intermittent hypoxia, there is evidence that the sleep fragmentation that occurs as part of sleep apnea is independently associated with negative effects (see chapter in this volume).

Many studies have also found that short sleep duration is associated with increased body mass index and/or risk of obesity [19]. These findings are supported by a growing literature of epidemiologic studies that demonstrate prospective weight gain associated with short sleep duration [20–22] and laboratory studies that show that sleep deprivation is associated with increased calorie intake (despite no difference in energy use) [23]. Although fewer studies have explored sleep quality in this regard, a number of studies have shown that sleep disturbance is associated with increased risk of obesity (see chapter in this volume).

The role of sleep in mental health is also well-established. Poor sleep is a well-characterized risk factor for stress and is related to dysregulation of neuroendocrine

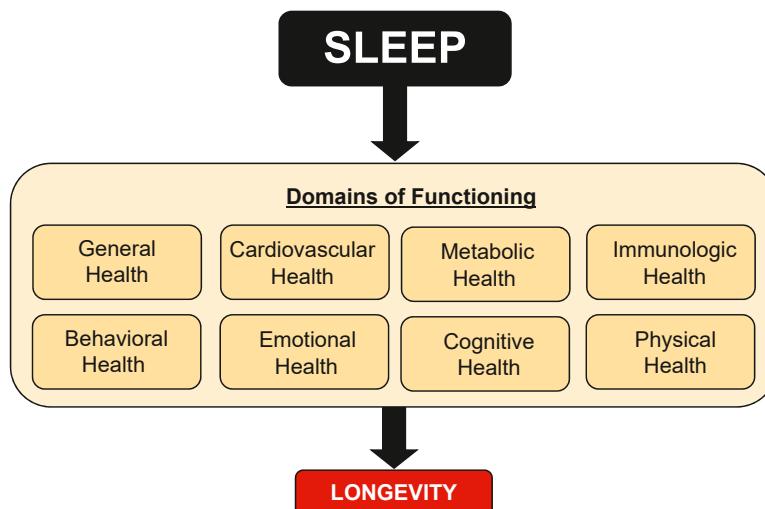


FIGURE 5.2 Sleep as factor in health and mortality.

stress systems. Insomnia is a major risk factor for depression [24,25] and is a core feature of nearly all psychiatric conditions. Poor sleep has been linked to suicide [26], as has insufficient sleep duration [27] and nocturnal wakefulness [28,29]. There is a growing literature demonstrating the role of sleep in neuroaffective regulation [30,31]. And sleep plays important roles in substance abuse disorders involving alcohol, nicotine, opiates, cannabis, and other substance use disorders.

The impact of sleep loss on cognitive functioning is well-characterized as well. Extensive work has demonstrated that sleep loss impairs attention and ability to remain vigilant [32]. Sleep difficulties have also been associated with processes such as working memory, executive function, and function in other neurocognitive domains [33]. This may underlie other findings showing that sleep loss impairs strategic decision-making [34], risk-based decision-making [35,36], and work productivity [37].

Taken together, the findings described above describe associations between sleep and a number of outcomes. It should be noted that in Fig. 5.2, these outcomes are in a common box; this represents the many intercorrelations among these domains. It should be noted that the model also takes into account the many studies that have shown that poor health states cause disruptions in sleep—either by shortening sleep duration or worsening sleep quality.

Conceptualizing sleep in a social-ecological model

The social-ecological model, outlined above, describes the individual as embedded within the microsystem within which they interact, which is embedded within the mesosystem in which elements of the microsystem interact, which is embedded within the exosystem which includes the structures that surround the mesosystem, and the macrosystem which includes the broader constructs that guide the social environment. For the purposes of the proposed model, sleep is conceptualized along a similar nested system. The proposed model conceptualizes the determinants of sleep to exist on three levels: the individual level, the social level, and the societal level.

Individual level

Fig. 5.3 shows the causal relationship between individual-level factors and sleep. These individual-level factors are conceptualized to reflect aspects of the individual that proximally and/or directly relate to that individual's sleep. These factors represent aspects of the individual that impact sleep, as well as cognitive and behavioral phenomena that

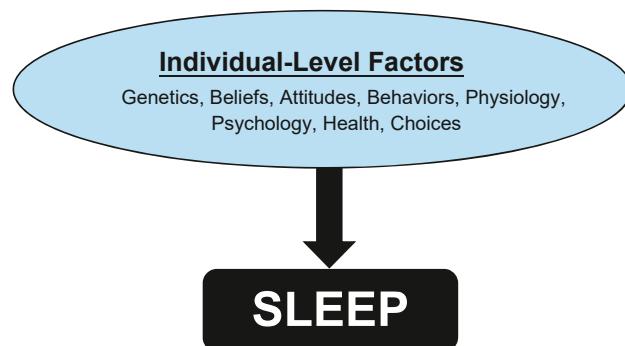


FIGURE 5.3 Individual-level factors, sleep, and health.

impact sleep. This level contains all factors that could fit into this category. For example, this level could include individual genetics, beliefs about sleep, attitudes about sleep, sleep-related behaviors, aspects of individual physiology, health status, and sleep-related choices.

An individual's genotype may exert influence over sleep in many ways. For example, genetics may influence circadian preference, sleep need, resilience against sleep loss, risk for sleep disorders, or even risk for other disorders that may impact sleep. Similarly, some aspects of physiology may impact sleep. For example, individuals who have lowered arousal thresholds may have more difficulty sleeping, as might those with disrupted neuroendocrine stress systems or even raised body temperature. Along these lines, health status is well known to influence sleep. Individuals may experience problems sleeping if they are ill, are in pain, have a sleep disorder, or another medical condition that interferes with sleep. Beliefs about sleep are also important factors at this level. Individuals who believe that they need less sleep, for example, may engage in more sleep-promoting behaviors. Previous studies have shown associations between sleep-related beliefs and sleep health [38], and changing sleep beliefs may impact on sleep-related behaviors. In addition to beliefs, individuals maintain attitudes about sleep. Those who express generally positive attitudes about sleep may be more likely to experience better quality sleep in general [39]. Further, these attitudes may be additional important contributors to behavior. An individual's sleep-related behaviors can encompass a wide range of possibilities, including sleep hygiene practices, bedtime routines, schedules maintained, etc.

Individual-level factors represent the proximal determinants of an individual's sleep, in a specific place, at a specific time. Some of these factors will represent aspects of the individual, some of these factors will represent aspects of the individual's current state, and some will represent aspects of what the individual is believing, thinking, and doing. These factors are conceptualized as generally time-dependent in that their influence on sleep

depends on their characteristics at the time in which they exert influence. Genetics, for example, may not change, but beliefs may change, as might health conditions.

Social level

The proposed model conceptualizes the individual level factors as being embedded within social-level factors. These exist outside of the individual but include the individual. A construct exists at the social level if the individual is part of that construct but that construct would exist whether or not the individual exists. For example, work represents a social level construct, as the workplace represents a construct that contains the individual but would theoretically exist without them. Fig. 5.4 depicts the embedded relationship between the individual and social levels. Some factors that could exist on the social level are also depicted and include home, family, work, school, neighborhood, religion, culture, race/ethnicity, socioeconomic status, and social networks.

The home represents the most proximal social-level factor since it includes many elements, including a sleeping environment, social dynamics, access to other behaviors such as eating, socializing, working, relating to family members, etc. It is (often) the place where people generally sleep, which gives it a prominent place. Many previous studies have described ways in which elements of the home might impact sleep. Related to the home is the family. The family can play an important role in an individual's sleep. The family may represent the source or model for sleep-related beliefs, attitudes, and behaviors. The family may also represent a source for aspects of the individual such as health and even genetics. The family—which represents both the nuclear or extended family—plays many roles in an individual's sleep.

Another key factor at the social level is work or school. This is another complex factor that subsumes schedules, social circles, stresses, expectations, hierarchies, physical

environments, logistics, and other factors. For those in school, school start times have been explored as key determinants of sleep [40–43] and modifying them has been shown to be helpful for promoting sleep. School-related stresses (in many forms) can impact sleep of young children and adolescents alike. For working adults, the workplace similarly can impact sleep—especially by dictating work demands, schedule demands, and sometimes even out-of-work activities (including evening activities). Problems at work can impact sleep and poor sleep can impact performance at work [37].

Aspects of the built environment are also relevant at this level. The built environment represents the buildings, streets, and other man-made elements of the environment. Ways in which these elements may impact sleep can be direct (for example via light or noise) or indirect (for example via crime and stress). The social environment is also relevant at this level. This includes an individual's social network of friends, acquaintances, and other people that may contribute to norming, behaviors, beliefs, and other individual-level factors. It can also represent aspects such as race/ethnicity and socioeconomics, which are also related to sleep at an individual and population level.

The model suggests that it is factors at the social level that are largely responsible for the factors at the individual level. In some cases, the social-level factors represent an explanation for the origin of some of the individual-level factors (e.g., predisposition for a physical or mental health condition). In other cases, individual-level factors are facilitated or impinged on by the social-level factors (e.g., work schedules). Alternatively, social-level factors may more subtly shape individual-level factors (e.g., beliefs, practices, and attitudes). In some cases, a sleep intervention at the individual level will be inert unless social-level factors are considered (e.g., individuals working multiple jobs).

Societal level

Just as the individual is embedded within a social context, these factors, too, are embedded within an even broader societal context. Just as the social level describe the forces that converge to act upon the individual, the societal level represents the forces that impact the social context, and, in turn, the individual. Fig. 5.5 adds the societal layer to the model, listing societal factors such as globalization, 24/7 society, geography, public policy, technology and progress, racism and discrimination, economics, and the natural environment as factors that directly and indirectly affect sleep.

The social level represented constructs that exist outside of the individual but of which the individual is a part (with a key element that if the individual ceased to exist, those structures would still exist). Similarly, the societal level consists of constructs of which the social-level

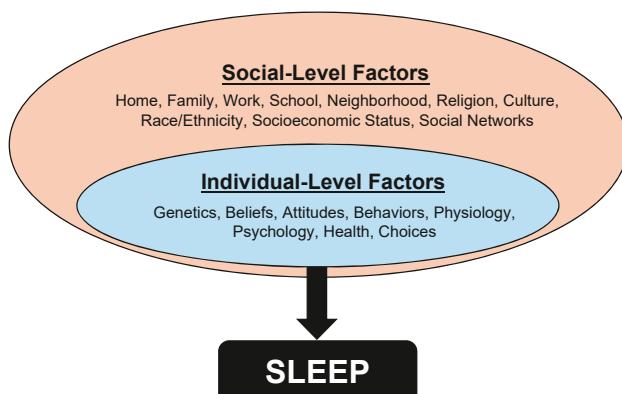


FIGURE 5.4 Role of social factors in sleep and health.

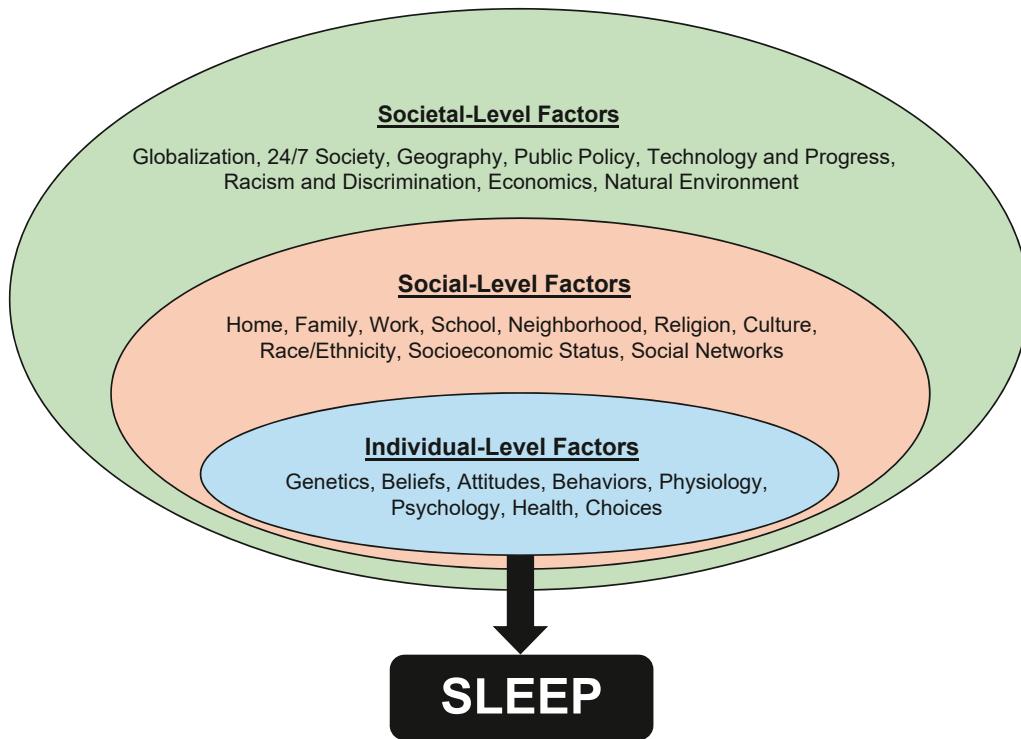


FIGURE 5.5 Individual, social, and societal influences on sleep.

factors are a part and would persist even if those factors would cease to exist. For example, globalization exists outside of any one workplace or organization, but arguably most workplaces and organizations participate in globalization in ways ranging from outsourcing to calling tech support in another country. Similar constructs that exist at a regional, national, and/or global level are included in this level.

Although individual-level factors are proximal and more direct causes of an individual's sleep experience, societal factors are also critically important. Although they may be less readily modifiable, conceptualizing an individual's sleep without considering the role of these factors omits important contextual information. For example, the increased drive toward globalization has interacted with the 24/7 society brought on by automation and the industrial revolution. This has led to products and services available at all hours of the day and, consequently, the awake consumers taking advantage of this opportunity and the shiftworkers employed to meet these demands. Public policy and economics may also impact sleep, whether it be reflected in school start times or regulations about sleep disorders testing, or workplace rules, or light/noise ordinances, or other policies. Factors such as economic stress can impact an individual's sleep whether that stress is felt at the individual level [44], at the level of the neighborhood [45–47], or even at the national level [48,49]. The physical environment and geography may dictate elements that impact sleep such as sunlight duration, weather patterns,

disease risk, local culture, green space, pollution, traffic, or other aspects of the environment. Technology represents a particularly salient factor that indirectly influences sleep. There has been much discussion about the sleep-related effects of using technology in the bedroom [50], which has quickly become ubiquitous in our society.

Taken together, the combined social-ecological model of sleep, represented in [Figs. 5.5 and 5.6](#), attempts to conceptualize the upstream influences on sleep as being primarily driven at the individual level (representing aspects of the individual as well as what the individual thinks/does). But the model recognizes that these individual-level factors exist in a social context, and it is these social-level factors that may dictate many aspects of the individual-level factors. These social factors, though, exist in the context of societal factors that operate at a macro level, influencing communities, workplaces, schools, and families, which then subsequently influence individuals. In this way, a societal-level factor (e.g., development and adoption of mobile technology) influences social-level factors (e.g., workplace emails at all hours of the day), which subsequently influences individual behavior (e.g., sleeping with a smartphone by the bed).

Combining upstream influences and downstream consequences

The role of sleep as a mediator or moderator on aspects of health is still relatively unclear. Sleep could mediate

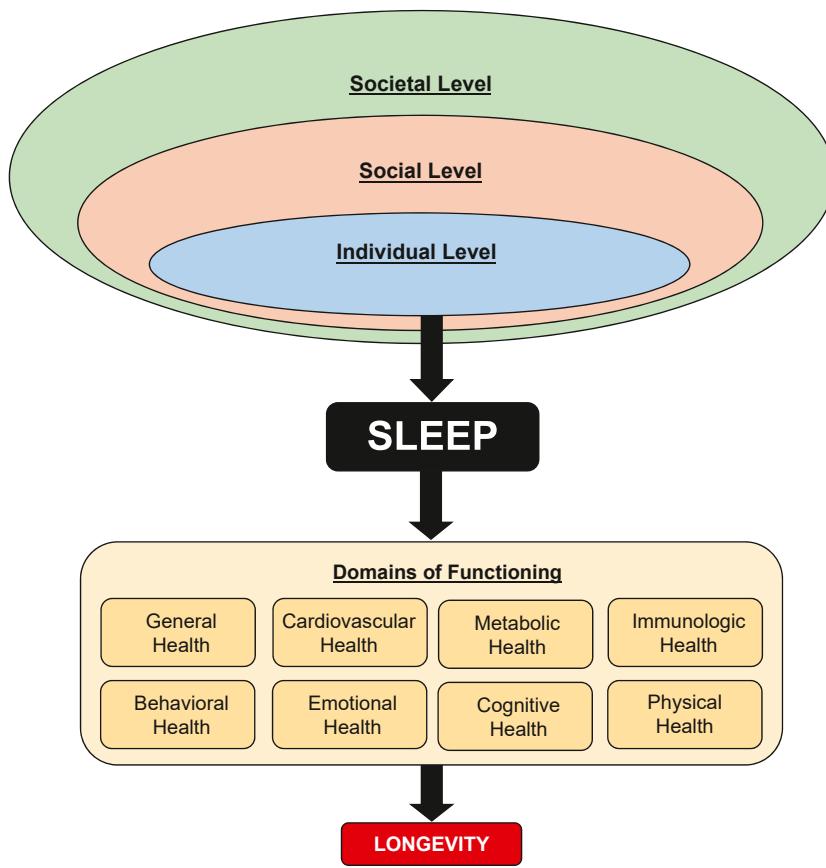


FIGURE 5.6 Full social-ecological model of sleep and health.

or moderate the relationships between individual-level factors and adverse health outcomes. Namely, these relationships could be partly explained by the effects of the individual-level factors on sleep, which, in turn produces adverse outcomes (mediator), or process involved in sleep could change the strength of relationships between individual-level factors and adverse outcomes (moderator). Likely, these relationships are complex. Future research will need to better clarify this. For parsimony, figures only display the mediation relationship, though this is not the only possibility.

Applications of the model

The first version of this model for sleep health and mortality risk was originally proposed by Grandner et al. [2] and has since appeared in various forms in several other publications (e.g. Refs. [16,51,52]). This model has been modified to fit various publications because the concepts underlying it are flexible. For example, the model could be used to develop interventions by examining modifiable targets that account for the social environmental context. The model can also be used to conceptualize the role of

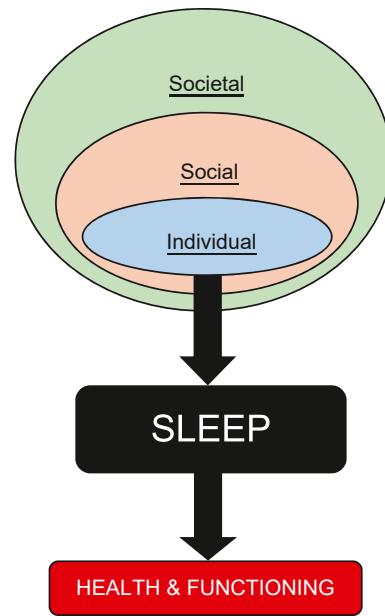


FIGURE 5.7 Simplified social-ecological model of sleep health.

sleep in health, with sleep being more than just a set of physiologic processes.

This is somewhat more evident in the simplified version of the model presented in Fig. 5.7. This version highlights the core of what the model is describing—sleep exists at the intersection of upstream influences (individual, embedded within social, embedded within societal) and downstream influences that encompass the combination of health outcomes and functioning/performance. Although this version is simplified, the core elements remain, including the nested determinants and the explicit implication that health and functioning are inseparably overlapping as outcomes of sleep. Future studies could use this model to better understand the health context of factors related to sleep (such as health disparities, public policy, etc.), to better understand the role of upstream factors in sleep-related outcomes (such as sleep-related cardiometabolic risk), and to better develop and contextualize healthy sleep interventions that aim to improve downstream factors while addressing the contextualized upstream determinants.

References

- [1] Colten HR, Altevogt, Institute of Medicine Committee on Sleep Medicine and Research. *Sleep disorders and sleep deprivation: an unmet public health problem*. National Academies Press; 2006.
- [2] Grandner MA, Hale L, Moore M, Patel NP. Mortality associated with short sleep duration: the evidence, the possible mechanisms, and the future. *Sleep Med Rev* 2010;14(3):191–203. <https://doi.org/10.1016/j.smrv.2009.07.006>.
- [3] Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *J Sleep Res* 2009;18(2):148–58. <https://doi.org/10.1111/j.1365-2869.2008.00732.x>.
- [4] Bronfenbrenner U. Toward an experimental ecology of human development. *Am Psychol* 1977;32(7):513–31. <https://doi.org/10.1037/0003-066x.32.7.513>.
- [5] Chang J, Guy MC, Rosales C, de Zapien JG, Staten LK, Fernandez ML, Carvajal SC. Investigating social ecological contributors to diabetes within Hispanics in an underserved U.S.-Mexico border community. *Int J Environ Res Publ Health* 2013;10(8):3217–32. <https://doi.org/10.3390/ijerph10083217>.
- [6] Sisson SB, Broyles ST. Social-ecological correlates of excessive TV viewing: difference by race and sex. *J Phys Activ Health* 2012;9(3):449–55. <https://doi.org/10.1123/jpah.9.3.449>.
- [7] Hinkley T, Salmon J, Okely AD, Hesketh K, Crawford D. Correlates of preschool children's physical activity. *Am J Prev Med* 2012;43(2).
- [8] Stellefson M, Barry AE, Stewart M, Paige SR, Apperson A, Garris E, Russell A. Resources to reduce underage drinking risks and associated harms: social ecological perspectives. *Health Promot Pract* 2019;20(2):160–6. <https://doi.org/10.1177/1524839918814736>.
- [9] Loewenstein K. Parent psychological distress in the neonatal intensive care unit within the context of the social ecological model: a scoping review. *J Am Psychiatr Nurses Assoc* 2018;24(6):495–509. <https://doi.org/10.1177/1078390318765205>.
- [10] Nyambe A, Van Hal G, Kampen JK. Screening and vaccination as determined by the social ecological model and the theory of triadic influence: a systematic review. *BMC Public Health* 2016;16(1):1–15. <https://doi.org/10.1186/s12889-016-3802-6>.
- [11] Cramer RJ, Kapusta ND. A social-ecological framework of theory, assessment, and prevention of suicide. *Front Psychol* 2017;8:1756. <https://doi.org/10.3389/fpsyg.2017.01756>.
- [12] Golden SD, McLeroy KR, Green LW, Earp JAL, Lieberman LD. Upending the social ecological model to guide health promotion efforts toward policy and environmental change. *Health Educ Behav* 2015;42:8–14. <https://doi.org/10.1177/1090198115575098>.
- [13] Mokdad AH, Marks JS, Stroup, Gerberding JL. Actual causes of death in the United States. *JAMA* 2000;291(10).
- [14] Grandner MA, Alfonso-Miller P, Fernandez-Mendoza J, Shetty S, Shenoy S, Combs D. Sleep: important considerations for the prevention of cardiovascular disease. *Curr Opin Cardiol* 2016;31(5):551–65. <https://doi.org/10.1097/HCO.0000000000000324>.
- [15] Grandner MA, Sands-Lincoln MR, Pak VM, Garland SN. Sleep duration, cardiovascular disease, and proinflammatory biomarkers. *Nat Sci Sleep* 2013;5:93–107. <https://doi.org/10.2147/NSS.S31063>.
- [16] Grandner MA. Addressing sleep disturbances: an opportunity to prevent cardiometabolic disease? *Int Rev Psychiatr* 2014;26(2):155–76. <https://doi.org/10.3109/09540261.2014.911148>.
- [17] Grandner MA. Sleep, health, and society. *Sleep Med Clin* 2017;12(1):1–22. <https://doi.org/10.1016/j.jsmc.2016.10.012>.
- [18] Ge X, Han F, Huang Y, Zhang Y, Yang T, Bai C, Guo X, Sterr A. Is obstructive sleep apnea associated with cardiovascular and all-cause mortality? *PLoS One* 2013;8(7). <https://doi.org/10.1371/journal.pone.0069432>.
- [19] Koren D, Elsie M, Taveras. Association of sleep disturbances with obesity, insulin resistance and the metabolic syndrome. *Metabolism* 2018;84:67–75. <https://doi.org/10.1016/j.metabol.2018.04.001>.
- [20] Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, Wright KP. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Natl Acad Sci U S A* 2013;110(14):5695–700. <https://doi.org/10.1073/pnas.1216951110UnitedStates>.
- [21] Nagai M, Tomata Y, Watanabe T, Kakizaki M, Tsuji I. Association between sleep duration, weight gain, and obesity for long period. *Sleep Med* 2013;14(2):206–10. <https://doi.org/10.1016/j.sleep.2012.09.024>.
- [22] St-Onge MP. The role of sleep duration in the regulation of energy balance: effects on energy intakes and expenditure. *J Clin Sleep Med* 2013;9(1):73–80. <https://doi.org/10.5664/jcsm.2348UnitedStates>.
- [23] St-Onge MP, Roberts AL, Chen J, Kelleman M, O'Keeffe M, RoyChoudhury A, Jones PJH. Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. *Am J Clin Nutr* 2011;94(2):410–6. <https://doi.org/10.3945/ajcn.111.013904UnitedStates>.
- [24] Baglioni C, Riemann D. Is chronic insomnia a precursor to major depression? Epidemiological and biological findings. *Curr Psychiatr Rep* 2012;14(5):511–8. <https://doi.org/10.1007/s11920-012-0308-5>.
- [25] Baglioni C, Spiegelhalder K, Lombardo C, Riemann D. Sleep and emotions: a focus on insomnia. *Sleep Med Rev* 2010;14(4):227–38. <https://doi.org/10.1016/j.smrv.2009.10.007>.
- [26] Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatr* 2012;73(9). <https://doi.org/10.4088/JCP.11r07586>.

- [27] Chakravorty S, Katy Siu HY, Lalley-Chareczko L, Brown GK, Findley JC, Perlis ML, Grandner MA. Sleep duration and insomnia symptoms as risk factors for suicidal ideation in a nationally representative sample. *Prim Care Compan CNS Disord* 2015;17(6). <https://doi.org/10.4088/PCC.13m01551>.
- [28] Perlis ML, Grandner MA, Brown GK, Basner M, Chakravorty S, Morales KH, Gehrman PR, Chaudhary NS, Thase ME, Dinges DF. Nocturnal wakefulness as a previously unrecognized risk factor for suicide. *J Clin Psychiatr* 2016;77(6):e726. <https://doi.org/10.4088/JCP.15m10131>.
- [29] Perlis ML, Grandner MA, Chakravorty S, Bernert RA, Brown GK, Thase ME. Suicide and sleep: is it a bad thing to be awake when reason sleeps? *Sleep Med Rev* 2016;29:101–7. <https://doi.org/10.1016/j.smrv.2015.10.003>.
- [30] Perogamvros L, Schwartz S. The roles of the reward system in sleep and dreaming. *Neurosci Biobehav Rev* 2012;36(8):1934–51. <https://doi.org/10.1016/j.neubiorev.2012.05.010>.
- [31] Van Der Helm E, Walker MP. Sleep and emotional memory processing. *Sleep Med Clin* 2011;6(1):31–43. <https://doi.org/10.1016/j.jsmc.2010.12.010>.
- [32] Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med* 2007;3(5):519–28. <https://doi.org/10.5664/jcsm.26918>.
- [33] Jackson ML, Gunzelmann G, Whitney P, Hinson JM, Belenky G, Rabat A, Van Dongen HPA. Deconstructing and reconstructing cognitive performance in sleep deprivation. *Sleep Med Rev* 2013;17(3):215–25. <https://doi.org/10.1016/j.smrv.2012.06.007>.
- [34] Killgore WDS, Grugle NL, Balkin TJ. Gambling when sleep deprived: don't bet on stimulants. *Chronobiol Int* 2012;29(1):43–54. <https://doi.org/10.3109/07420528.2011.635230>.
- [35] Hisler G, Krizan Z. Sleepiness and behavioral risk-taking: do sleepy people take more or less risk? *Behav Sleep Med* 2019;17(3):364–77. <https://doi.org/10.1080/15402002.2017.1357122>.
- [36] Fraser M, Conduit R, Phillips JG. Effects of sleep deprivation on decisional support utilisation. *Ergonomics* 2013;56(2):235–45. <https://doi.org/10.1080/00140139.2012.760754>.
- [37] Hui SKA, Grandner MA. Trouble sleeping associated with lower work performance and greater health care costs: longitudinal data from Kansas state employee wellness program. *J Occup Environ Med* 2015;57(10):1031–8. <https://doi.org/10.1097/JOM.0000000000000534>.
- [38] Meridew CM, Jaszewski, Newman-Smith K, Killgore WDS, Gallagher C, Miller A-, Gehrels J, Grandner MA. Sleep practices, beliefs, and attitudes associated with overall health. *Sleep* 2016;39:268.
- [39] Grandner MA, Patel NP, Jean-Louis G, Jackson N, Gehrman PR, Perlis ML, Gooneratne NS. Sleep-related behaviors and beliefs associated with race/ethnicity in women. *J Natl Med Assoc* 2013;105(1):4–16. [https://doi.org/10.1016/s0027-9684\(15\)30080-8](https://doi.org/10.1016/s0027-9684(15)30080-8).
- [40] Barnes M, Davis K, Mancini M, Ruffin J, Simpson T, Casazza K. Setting adolescents up for success: promoting a policy to delay high school start times. *J Sch Health* 2016;86(7):552–7. <https://doi.org/10.1111/josh.12405>.
- [41] Millman RP, Boergers J, Owens J. Healthy school start times: can we do a better job in reaching our goals? *Sleep* 2016;39(2):267–8. <https://doi.org/10.5665/sleep.5422>.
- [42] Minges KE, Redeker NS. Delayed school start times and adolescent sleep: a systematic review of the experimental evidence. *Sleep Med Rev* 2016;28:86–95. <https://doi.org/10.1016/j.smrv.2015.06.002>.
- [43] Thacher PV, Onyper SV. Longitudinal outcomes of start time delay on sleep, behavior, and achievement in high school. *Sleep* 2016;39(2):271–81. <https://doi.org/10.5665/sleep.5426>.
- [44] Grandner MA, Patel NP, Gehrman PR, Xie D, Sha D, Weaver T, Gooneratne N. Who gets the best sleep? Ethnic and socioeconomic factors related to sleep complaints. *Sleep Med* 2010;11(5):470–8. <https://doi.org/10.1016/j.sleep.2009.10.006>.
- [45] Hale L, Hill TD, Friedman E, Javier Nieto F, Galvao LW, Engelman CD, Malecki KMC, Peppard PE. Perceived neighborhood quality, sleep quality, and health status: evidence from the Survey of the Health of Wisconsin. *Soc Sci Med* 2013;79(1):16–22. <https://doi.org/10.1016/j.socscimed.2012.07.021>.
- [46] Hale L, Hill TD, Burdette AM. Does sleep quality mediate the association between neighborhood disorder and self-rated physical health? *Prev Med* 2010;51(3–4):275–8. <https://doi.org/10.1016/j.ypmed.2010.06.017>.
- [47] Hill TD, Burdette AM, Hale L. Neighborhood disorder, sleep quality, and psychological distress: testing a model of structural amplification. *Health Place* 2009;15(4):1006–13. <https://doi.org/10.1016/j.healthplace.2009.04.001>.
- [48] Whinnery J, Jackson N, Rattanaumpawan P, Grandner MA. Short and long sleep duration associated with race/ethnicity, sociodemographics, and socioeconomic position. *Sleep* 2014;37(3):601–11. <https://doi.org/10.5665/sleep.3508UnitedStates>.
- [49] Grandner MA, Ruiter Petrov ME, Rattanaumpawan P, Jackson N, Platt A, Patel NP. Sleep symptoms, race/ethnicity, and socioeconomic position. *J Clin Sleep Med* 2013;9(9):897–905. <https://doi.org/10.5664/jcsm.2990UnitedStates>.
- [50] Ko PRT, Kientz JA, Choe EK, Kay M, Landis CA, Watson NF. Consumer sleep technologies: a review of the landscape. *J Clin Sleep Med* 2015;11(12):1455–61. <https://doi.org/10.5664/jcsm.5288>.
- [51] Grandner MA, Williams NJ, Knutson KL, Roberts D, Jean-Louis G. Sleep disparity, race/ethnicity, and socioeconomic position. *Sleep Med* 2016;18:7–18. <https://doi.org/10.1016/j.sleep.2015.01.020>.
- [52] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M, Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL. Joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. *Sleep* 2015;38(8):1161–83. <https://doi.org/10.5665/sleep.4886>.

This page intentionally left blank

Chapter 6

Nocturnal Wakefulness and the Mind After Midnight*

Andrew Scott Tubbs^a, Alisa Huskey^b, Fabian-Xosé Fernandez^c, Michael A. Grandner^b and Michael L. Perlis^d

^aWashington University School of Medicine, Department of Psychiatry, St. Louis, MO, United States; ^bDepartment of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States; ^cEvelyn F. McKnight Brain Institute, Department of Psychology, University of Arizona, Tucson, AZ, United States; ^dUniversity of Pennsylvania Perelman School of Medicine, Department of Psychiatry, Philadelphia, PA, United States

Introduction

Homeostatic sleep pressure and circadian rhythms coordinate sleep and wake with the external environment [1]. Low sleep pressure and rising circadian arousal create an upstate during the day—a time to be awake and pursue goal-directed activity. Elevated sleep pressure and declining circadian arousal create a downstate at night—a time to reduce activity and allow for sleep. Although a robust body of literature now demonstrates how disrupted sleep degrades daytime mood, cognition, behavior, and performance, little is known about wakefulness during the downstate. What happens when an individual pursues goal-directed activity during the biological night? How well does an individual comprehend the world around them, filter competing sources of information, and make well-reasoned decisions when homeostasis and chronobiology promote sleep? Are decisions made during the downstate suboptimal, irrational, or even dangerous? **The Mind After Midnight** hypothesis [2] suggests that this is the case. Risk begins with *nocturnal wakefulness*, a time when central and peripheral neurophysiology are altered. These changes produce the *Mind After Midnight*, a state of compromised affect regulation, risk/reward processing, and executive functions. The consequence of this neuropsychological state is an *increased risk for dysregulated behaviors*, such as self-harm, violence, and substance use. This chapter explores the conceptual and empirical evidence for each component of this hypothesis.

Nocturnal wakefulness: Awake when your nervous system wants to sleep

Nocturnal wakefulness is prolonged wakefulness during an individual's habitual sleep period. For most people, this occurs at night due to the role of (sun)light in promoting wakefulness and entraining circadian rhythms. If an individual's internal/biological sense of day and night is shifted, as in the case of shift workers, then nocturnal wakefulness may occur during the day. Nocturnal wakefulness may occur for many reasons. The awakening may be natural (getting up to use the restroom) or artificial (an alarm). It may be accompanied by significant distress (insomnia, nightmares) or no distress at all. Nocturnal wakefulness may result from substances, partners, technology, or illness. Regardless of cause, this period of wakefulness combines insufficient sleep with circadian changes in neurophysiology that promote sleep. In other words, *the person is awake when they are not prepared to be awake*. The following sections explore these changes in central and peripheral neurophysiology.

Central neurophysiology

Sleep loss disrupts synapses and neurotransmitters during nocturnal wakefulness. Ordinarily, wakefulness continuously strengthens synaptic connections to enable plasticity, learning, and memory. Non-rapid eye movement (NREM) sleep counteracts excessive synaptic strength through downregulation: weak synapses are eliminated, while strong synapses are weakened but retained [3]. Loss of NREM sleep prevents downregulation, which impairs signal transmission, information processing, and higher order cognition. Dopamine levels also peak at night when

* This chapter is adapted from Tubbs A. S., Huskey A., Fernandez F-X. et al. (in press). The Mind After Midnight: Nocturnal Wakefulness and Dysregulated Behaviors. In J. Dzierzewski, D. Kay & S. J. Aton (Eds), The Cambridge Handbook of Sleep Theories and Models. Cambridge University Press.

dopamine receptors downregulate and dopamine transporter activity declines [4]. Reduced dopaminergic activity produces cognitive impairments, and reduced nocturnal D2 receptor expression, by definition, reduces capacity for dopaminergic activity.

Electroencephalographic (EEG) changes suggest circuit-level changes in brain function during nocturnal wakefulness. Slow wave (delta) activity during sleep entails widespread synchronization of cortical activity and is the principal mechanism for synaptic downregulation. Delta activity is proportionate to the duration of prior wakefulness and accumulates predominantly in the frontal cortex [5,6], thus highlighting the prefrontal cortical vulnerability to homeostatic sleep pressure. Nocturnal wakefulness also brings EEG signatures associated with exerting greater cognitive control (theta activity) and with increasing inactivity/inattention (alpha activity). Circadian arousal can support cognitive control and prevent delta intrusions [7], but when wakefulness occurs without this circadian support (e.g., during nocturnal wakefulness), cognitive effort to maintain control rises, and delta intrusions grow more prominent. This may reflect spatial/temporal “microsleeps” that impair ongoing cognitive activities.

These circuit-level changes produce widespread brain dysfunction. Prolonged wakefulness increases global cortical excitability [8,9], which reduces cognitive performance and cortical responsiveness [10]. By contrast, subcortical activity is more dependent on circadian rhythms than elevated sleep pressure, and this may alter activity and connectivity patterns between the cortex and subcortex during nocturnal wakefulness [11]. For example, prefrontal fatigue may weaken top-down regulation of the amygdala. Sleep deprivation may also shift cortical activity from local integration to global synchronization [12,13]. Segregating cortical processes is critical for accurate information processing, so cortical synchronization may impair localized integration of sensory and cognitive information and contribute to cognitive rigidity. Finally, sleep loss alters thalamocortical connectivity [14,15] and increases connectivity between the right insula (which integrates and represents peripheral visceral information) and the anterior cingulate cortex (which processes self-referential information and prioritizes competing information streams) [16]. This shift in connectivity may overvalue negative interoceptive/affective states during decision-making.

Peripheral neurophysiology

The neurovisceral integration model proposes that successful self-regulation depends on the integration of peripheral “bottom-up” and central “top-down” processes [17,18]. Ascending somatic/visceral information, largely provided through vagal activity and the baroreflex system, is

integrated into the central autonomic network, which includes the thalamus, insulae, rostral anterior cingulate, and prefrontal cortices. This information is then translated into a cognitive representation of one’s interoceptive/affective state, which can then be used to regulate autonomic activity.

Consider this example: you come home to find a windowpane broken and the sound of rustling coming from upstairs. Subcortical regions like the amygdala immediately detect the threat of an intruder and marshal a sympathetic response: your blood pressure rises, your heart rate quickens, your muscles tense, and your palms become slightly sweaty. This information feeds back into the brain to confirm your readiness to confront an intruder. Top-down cortical control simultaneously suppresses reflex parasympathetic/vagal actions that would oppose these changes, and the lack of parasympathetic feedback further contributes to a subjective need to act. Once you step inside, however, you discover your toddler accidentally broke the pane and is now hiding upstairs to avoid the consequences. You feel an immediate sense of relief: the prefrontal cortex silences the amygdala and releases parasympathetic suppression, thus allowing a vagal reflex to reduce heart rate and blood pressure and reestablish a resting state. The resulting peripheral autonomic balance feeds back into your brain, enabling you to calmly confront your toddler without devolving into hysterics or rage.

Disintegration of peripheral and central neurophysiology is a transdiagnostic feature of psychiatric illness [19] and may directly affect executive functions such as impulse control. Peripheral neurophysiology is additionally affected by sleep and circadian rhythms. The varying effects of circadian rhythms and sleep homeostasis on cortical and subcortical regions changes the dynamics of the central autonomic network, which affects top-down and bottom-up capacity for self-regulatory control. Heart-rate variability (HRV) is a common noninvasive measure of vagal control; acute sleep deprivation reduces HRV, and reduced HRV predicts impaired vigilant attention during nocturnal wakefulness [20]. Vagal activity is under strong circadian control, with a peak in activity at sleep onset that decreases slowly throughout sleep [21]. Sustained wakefulness, however, causes a rapid decline in vagal activity. By contrast, sympathetic activity increases as a function of homeostatic sleep pressure [22,23], likely to maintain wakefulness. These changes in vagal and sympathetic activity during nocturnal wakefulness may challenge neurovisceral self-regulation.

Nocturnal wakefulness breeds the Mind After Midnight

The synaptic, circuit, and systems-level changes in neurophysiology during nocturnal wakefulness may compromise multiple cognitive processes, including mood and affect, risk/reward processing, and executive functions.

Impaired mood and affect

Mood is constructed from separate systems of positive and negative affect, which exhibit distinct sleep and circadian trends. Positive affect follows a strong circadian pattern with increased activity during the day and reduced activity at night, while negative affect increases more as a function of rising sleep pressure [24]. Nocturnal wakefulness thus combines increased negative affect with decreased positive affect to produce greater negative mood. Studies of emotional content on social media corroborate this peak in nighttime negative emotional content [25,26].

Changes in peripheral neurophysiology have compounding effects on mood. Resting HRV is associated with multiple affective domains and their underlying brain networks [27], and attenuated HRV (as occurs during sleep loss) disrupts threat assessment and affective regulation [27,28]. Moreover, connectivity between prefrontal regions and the amygdala predicts resting HRV, suggesting a role for the prefrontal cortex in regulating the amygdala through vagal control [29]. Reductions in neurovisceral integration during nocturnal wakefulness may thus increase negative affect by increasing physiological arousal, and this hyperarousal may then overemphasize the salience affective states in subcortical structures (e.g., amygdala, right anterior insula) that are less influenced by homeostatic sleep pressure [30].

Changes in affective systems may inappropriately bias processing of emotional information [31], leading neutral or nonemotional stimuli to be interpreted in a more negative/emotionally valent way. Hypoactivity of the prefrontal cortex and rostral anterior cingulate cortex may contribute to further biases in how emotions and personally relevant information are perceived as has been observed in major depressive disorder [32]. Increased insular connectivity with the anterior cingulate cortex at the expense of thalamocortical circuits may allow subcortically overvalued affective states to dominate cortical decision-making by disrupting cognitive control [33] and impairing vigilant attention [16].

Altered reward anticipation and receipt

Nocturnal wakefulness also alters reward processing. Reward anticipation (what you think you will get) and reward receipt (what you get) are largely enacted through subcortical regions that operate under cortical control. Activity within the amygdala, nucleus accumbens, and other components of the reward system demonstrates circadian rhythmicity [34]. Sleep homeostasis also affects reward processing through its influence on the prefrontal cortex, which exerts control over reward processing through regulation of the amygdala [35,36]. This combination of circadian and homeostatic influences creates conditions for optimal reward processing during the afternoon: sensitivity of the nucleus accumbens to reward is greatest at this time [37,38], and discrepancies between

reward anticipation and receipt (based on activation of the left putamen) are minimized [39,40].

Reward processing outside this time, however, is likely compromised. Circadian misalignment and social jetlag are linked to reduced activity in the prefrontal cortex and nucleus accumbens during reward anticipation and receipt [41,42]. Chronotype may also affect reward processing, as evening types may have greater difficulty with delay discounting and substance use due to greater impulsivity, possibly due to changes in activity in the prefrontal cortical and nucleus accumbens [43,44]. Sleep loss impairs prefrontal cortical regulation of reward anticipation and receipt and diminishes sensitivity to loss conditions during risky decision-making [45,46]. Sleep deprivation may also enhance reactivity and change functional connectivity within the mesolimbic reward network to increase assignment of emotional salience [47]. These changes create conditions in which reward anticipation exceeds reward receipt and the negative consequences of reward-driven behaviors are minimized, which may prompt repeated attempts to achieve anticipated reward conditions.

Executive dysfunction—The sleep of reason

Executive functions are higher order cognitive processes that enable humans to control impulses, filter distractions, prioritize tasks, and set and achieve goals. Sleep homeostasis and circadian rhythms exert particular influence over nighttime executive functions because of their preferential effects on the prefrontal cortex [31,48]. Changes in peripheral autonomic systems, including baroreceptor sensitivity [49,50] and HRV [51,52], may also distract or fragment executive functions by increasing cognitive load with ascending visceral information during nocturnal wakefulness. Three major executive functions are considered below: impulse control, cognitive control, and flexible thinking.

Sleep loss reduces impulse control when measured experimentally in go/no-go tasks [48,53]. Impulse control is maximized during the late-morning circadian peak of arousal [54], so a mismatch between wakefulness and circadian arousal at night contributes to impulsivity. This is observed in individuals with evening chronotypes and/or irregular/unstable sleep patterns [55,56]. Inhibitory control is primarily mediated by vagal activity and so concomitant impairments in autonomic (and affective) regulation can further disrupt self-control [57].

Cognitive control over competing information streams emerges from a network of the anterior cingulate, prefrontal, and parietal cortices [58], which are all impacted by nocturnal wakefulness. Sleep and circadian changes in midline theta activity reflect inefficiencies in the anterior cingulate cortex that likely undermine cognitive control [32,33]. Increased connectivity between the right anterior insula and anterior cingulate cortex may also increase the

weight of interoceptive states experienced during nocturnal wakefulness. With cognitive control increasingly costly, these overvalued interoceptive experiences may drown out other information relevant for decision-making.

These nocturnal deficits in inhibitory and cognitive control are further joined by sleep- and circadian-driven declines in flexible/creative thinking [59,60]. During sleep loss, humans rely more on rule-based problem solving [61,62], which combined with increasing negativity, impaired risk/reward calculations, and poor impulse control may precipitate quick, cortically unsupervised decisions. The stress-mediated changes in synaptic function and structure that occur during sleep loss may also attenuate cognitive flexibility by increasing expectation of threat and strengthening fear conditioning [63,64]. Peripheral autonomic dysregulation and decreased frontal activity prevent vagal mitigation of this fear/threat perception [28] and may reinforce feelings of hyperarousal, negativity, and impulsivity.

The Mind After Midnight begets behavioral dysregulation

The proposed deficits in affective regulation, reward processing, and executive function during nocturnal wakefulness translate to risk for dysregulated behaviors, as illustrated in Fig. 6.1. For example, an individual may be confronted with an overvalued sense of negative affect while simultaneously deprived of the autonomic mechanisms to restore affective homeostasis. Unable to tolerate this state, the individual may pursue inflexible and impulsive self-regulatory strategies, especially if such strategies are habitual. Trait-level cognitive inflexibility and impulsivity are commonly associated with past suicide attempts, overweight status, addiction-like eating, problematic Internet use, and gambling [65–69]. As such, an individual compromised by the Mind After Midnight may be more likely to binge eat, use substances, scroll on social media, self-harm, or even attempt suicide/homicide. Although no experimental studies have assessed the Mind After Midnight hypothesis, the following section highlights potential epidemiological and empirical evidence for nighttime increases in risk for suicide, homicide/violence, substance use, and food intake.

Suicide

Hourly suicide rates often peak around noon. Most people are awake at noon, however, and since suicide is a wakeful, volitional behavior, the number of individuals capable of suicide increases at that time. Perlis and colleagues disambiguated behavioral risk from population wakefulness by calculating an “expected” suicide count based on

population wakefulness by time of day [70]. The result was a 3-fold greater risk of suicide between 12 and 6:00 a.m. than expected. Subsequent studies have replicated this finding in Australia [71] and the U.S. [72]. Individuals who express suicidal ideation are more likely to be awake in the early morning (11:00 p.m.–5:00 a.m.) than the general population [73,74] may express more suicidal thoughts at this time [75]. There is also evidence that young adults, who have limited executive functions due to ongoing brain development, are at greater risk of nighttime suicide. Even without adjusting for population wakefulness, young Japanese males were more likely to die in the early morning than any other time of day [76], and young Finnish male railway suicides were most common in the late evening or around midnight [77].

Homicide

Violent behavior may also increase during the Mind After Midnight. Prior reports highlight an elevated risk for death by homicide at night [78–80]. Sexual assault is also more prevalent during the night, with only 28.5% of cases occurring during daylight hours [81]. Nightfall alone may contribute to greater crime rates, perhaps because fewer police are on duty and/or fewer people are awake to witness the crime. Nevertheless, the risk of homicide is nearly 8-fold greater at night after adjusting for population wakefulness [72], and it seems unlikely that this increase in risk is due merely to opportunity. The greater overnight risk among young adults and those intoxicated with alcohol—two groups with limited executive functions—suggests a contribution from the Mind After Midnight.

Substance use

Substance use is likely also influenced by the Mind After Midnight. Despite lower nighttime use of heroin [82], one supervised drug consumption center reported greater risk for heroin overdose at night. If the expectation of reward is high and the actualization of reward is low (as may be the case during the Mind After Midnight), this discrepancy may motivate additional substance use to match the expected hedonic reward, thus increasing the risk of accidental overdose. Craving for alcohol [83] and alcohol use [84] among adolescents may increase at night due to compromised risk/reward processing and executive function. Affective dysregulation and impaired impulse control as part of the Mind After Midnight may also explain why delayed sleep timing in adolescence is associated with cannabis consumption and risky patterns of alcohol use [85] and why nighttime awakenings predict relapse during smoking cessation therapy [86].

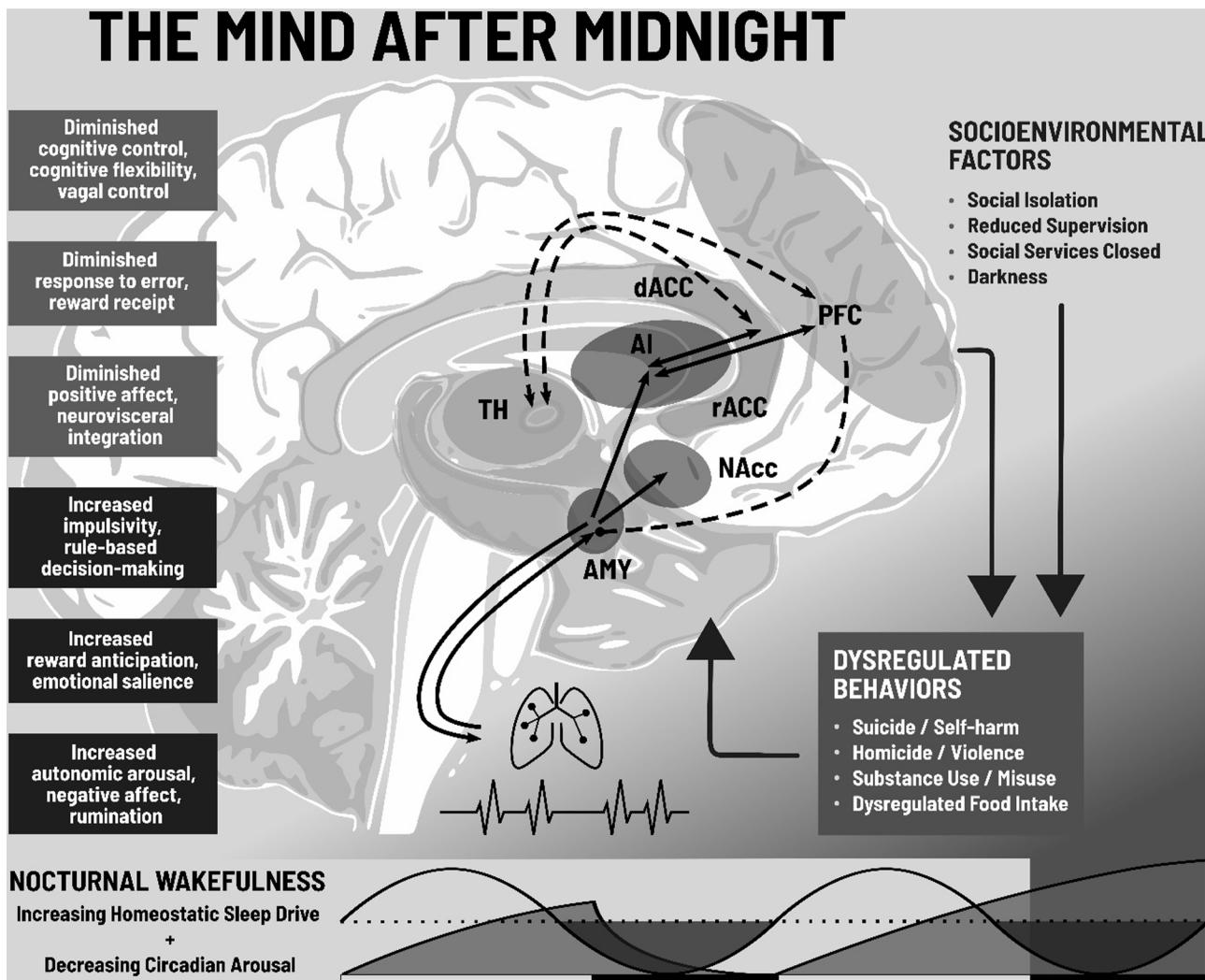


FIGURE 6.1 The Mind After Midnight hypothesis. Nocturnal wakefulness brings sleep- and circadian-dependent changes in neurophysiology. Activity within the rostral and dorsal anterior cingulate cortex (rACC/dACC), prefrontal cortex (PFC), and thalamus (TH) is reduced, as is thalamocortical connectivity. By contrast, activity within subcortical regions such as the amygdala (AMY) and nucleus accumbens (NAcc) is increased, along with increased activity between the anterior insula (AI) and the cortex. Neurovisceral integration is also altered due to heightened sympathetic tone and diminished vagal control exerted by the prefrontal cortex. These changes in physiology are linked to numerous deficits in affect regulation, risk/reward calculations, and executive function. Widespread emotional and cognitive deficits, when combined with socioenvironmental factors that occur at night, may then precipitate risky behaviors. Adapted from Tubbs, Andrew S, Fernandez, Fabian-Xosé, Grandner, Michael A, Perlis, Michael L & Klerman, Elizabeth B. The Mind After Midnight: Nocturnal Wakefulness, Behavioral Dysregulation, and Psychopathology. *Frontiers in Network Physiology* 2022;1. <https://doi.org/10.3389/fnetp.2021.830338>

Food intake

The Mind After Midnight may also influence appetitive behaviors such as food intake. Caloric intake during sleep loss increases beyond energetic needs due to disproportionate consumption of sugars and fats [87–89]. This may reflect a hedonic bias in food choices [90] that emerges from compromised risk/reward calculations and impaired impulse control. Night eating syndrome, a phenomenon characterized by dysregulated nighttime food intake, may also involve changes in reward processing and serotonergic signaling [91,92] during nocturnal wakefulness.

Conclusion

The Mind After Midnight hypothesis proposes a framework by which physiologic and cognitive mechanisms connect nocturnal wakefulness to nighttime risk for dysregulated behaviors. This framework, however, is only the beginning—future studies must explore and confirm these putative mechanisms in the laboratory and the real world. This work would enable subsequent efforts to target evidence-based interventions that reduce morbidity and mortality. An obvious example would be to improve sleep, as there is no Mind After Midnight if there is no nocturnal

wakefulness. Cognitive behavioral therapy for insomnia, bright light and melatonin therapies for circadian dysregulation, and standard pharmacological therapies for disrupted sleep continuity may reduce risk for suicide, violence, and other harmful outcomes. Mitigation of nocturnal wakefulness may also be possible. For instance, placement of blue lights on Japanese train platforms decreased nighttime railway suicides [93,94]. The blue light may have engaged circadian arousal to bring cognitive systems “back online,” thus countering the dysregulated cognition of nocturnal wakefulness. Interventions that leverage autonomic control may also prove useful. Lower HRV is associated with suicidality, intimate partner violence, substance use, and food intake [95–98], and incremental increases in HRV appear to predict decreased suicidal severity [99]. Slow paced breathing may reliably increase parasympathetic activity as measured by HRV [100–102] and could serve as a self-regulatory strategy during nocturnal wakefulness. Such efforts to understand and counteract the Mind After Midnight may bring hope during these darkest hours.

Acknowledgments

We would like to acknowledge the efforts of Elizabeth B. Klerman for her assistance in developing this hypothesis.

References

- [1] Borbély A. The two-process model of sleep regulation: beginnings and outlook. *J Sleep Res* 2022;31(4). <https://doi.org/10.1111/jsr.13598>.
- [2] Tubbs AS, Fernandez F-X, Grandner MA, Perlis ML, Klerman EB. The Mind After Midnight: nocturnal wakefulness, behavioral dysregulation, and psychopathology. *Front Network Physiol* 2022;1. <https://doi.org/10.3389/fnnetp.2021.830338>.
- [3] Tononi G, Cirelli C. Sleep and synaptic down-selection. *Eur J Neurosci* 2020;51(1):413–21. <https://doi.org/10.1111/ejn.14335>.
- [4] Alonso IP, Pino JA, Kortagere S, Torres GE, España RA. Dopamine transporter function fluctuates across sleep/wake state: potential impact for addiction. *Neuropharmacology* 2021;46 (4):699–708. <https://doi.org/10.1038/s41386-020-00879-2>.
- [5] Cajochen C, Foy R, Dijk DJ. Frontal predominance of a relative increase in sleep delta and theta EEG activity after sleep loss in humans. *Sleep Res Online* 1999;2(3):65–9.
- [6] Münch M, Knoblauch V, Blatter K, Schröder C, Schnitzler C, Kräuchi K, Justice AW-, Cajochen C. The frontal predominance in human EEG delta activity after sleep loss decreases with age. *Eur J Neurosci* 2004;20(5):1402–10. <https://doi.org/10.1111/j.1460-9568.2004.03580.x>.
- [7] Cajochen C, Wyatt JK, Czeisler CA, Dijk DJ. Separation of circadian and wake duration-dependent modulation of EEG activation during wakefulness. *Neuroscience* 2002;114(4):1047–60. [https://doi.org/10.1016/S0306-4522\(02\)00209-9](https://doi.org/10.1016/S0306-4522(02)00209-9).
- [8] Huber R, Mäki H, Rosanova M, Casarotto S, Canali P, Casali AG, Tononi G, Massimini M. Human cortical excitability increases with time awake. *Cerebr Cortex* 2013;23(2):1–7. <https://doi.org/10.1093/cercor/bhs014>.
- [9] Ly JQM, Gaggioni G, Chellappa SL, Papachilleos S, Brzozowski A, Borsu C, Rosanova M, Sarasso S, Middleton B, Luxen A, Archer SN, Phillips C, Dijk DJ, Maquet P, Massimini M, Vandewalle G. Circadian regulation of human cortical excitability. *Nat Commun* 2016;7. <https://doi.org/10.1038/ncomms11828>.
- [10] Muto V, Jaspar M, Meyer C, Kussé C, Chellappa SL, Deguelde C, Balteau E, Bourdieu ASL, Luxen A, Middleton B, Archer SN, Phillips C, Collette F, Vandewalle G, Dijk DJ, Maquet P. Local modulation of human brain responses by circadian rhythmicity and sleep debt. *Science* 2016;353(6300):687–90. <https://doi.org/10.1126/science.aad2993>.
- [11] Killgore WDS. Self-reported sleep correlates with prefrontal-amygdala functional connectivity and emotional functioning. *Sleep* 2013;36(11):1597–608. <https://doi.org/10.5665/sleep.3106>.
- [12] Cross NE, Pomares FB, Nguyen A, Perrault AA, Jegou A, Uji M, Lee K, Razavipour F, Ka'b Ali OB, Aydin U, Benali H, Grova C, Dang-Vu TT. An altered balance of integrated and segregated brain activity is a marker of cognitive deficits following sleep deprivation. *PLoS Biol* 2021;19(11). <https://doi.org/10.1371/journal.pbio.3001232>.
- [13] Verweij IM, Romeijn N, Smit DJA, Piantoni G, Van Someren EJW, van der Werf YD. Sleep deprivation leads to a loss of functional connectivity in frontal brain regions. *BMC Neurosci* 2014;15. <https://doi.org/10.1186/1471-2202-15-88>.
- [14] Killgore WDS, Vanuk JR, Knight SA, Markowski SM, Pisner D, Shane B, Fridman A, Alkozei A. Daytime sleepiness is associated with altered resting thalamocortical connectivity. *Neuroreport* 2015;26 (13):779–84. <https://doi.org/10.1097/WNR.0000000000000418>.
- [15] Shao Y, Wang L, Ye E, Jin X, Ni W, Yang Y, Wen B, Hu D, Yang Z, Rao H. Decreased thalamocortical functional connectivity after 36 hours of total sleep deprivation: evidence from resting state fMRI. *PLoS One* 2013;8(10):e78830. <https://doi.org/10.1371/journal.pone.0078830>.
- [16] Fu W, Dai C, Chen J, Wang L, Song T, Peng Z, Xu M, Lin X, Tang Y, Shao Y. Altered insular functional connectivity correlates to impaired vigilant attention after sleep deprivation: a resting-state functional magnetic resonance imaging study. *Front Neurosci* 2022;16. <https://doi.org/10.3389/fnins.2022.889009>.
- [17] Smith R, Thayer JF, Khalsa SS, Lane RD. The hierarchical basis of neurovisceral integration. *Neurosci Biobehav Rev* 2017;75:274–96. <https://doi.org/10.1016/j.neubiorev.2017.02.003>.
- [18] Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord* 2000;61 (3):201–16. [https://doi.org/10.1016/S0165-0327\(00\)00338-4](https://doi.org/10.1016/S0165-0327(00)00338-4).
- [19] Beauchaine TP, Thayer JF. Heart rate variability as a transdiagnostic biomarker of psychopathology. *Int J Psychophysiol* 2015;98(2):338–50. <https://doi.org/10.1016/j.ijpsycho.2015.08.004>.
- [20] Chua ECP, Tan WQ, Yeo SC, Lau P, Lee I, Mien IH, Puwanendran K, Gooley JJ. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. *Sleep* 2012;35(3):325–34. <https://doi.org/10.5665/sleep.1688Singapore>.
- [21] Burgess HJ, Trinder J, Kim Y, Luke D. Sleep and circadian influences on cardiac autonomic nervous system activity. *Am J Physiol Heart Circ Physiol* 1997;273(4):H1761. <https://doi.org/10.1152/ajpheart.1997.273.4.h1761>.

- [22] Liu JCJ, Verhulst S, Massar SAA, Chee MWL. Sleep deprived and sweating it out: the effects of total sleep deprivation on skin conductance reactivity to psychosocial stress. *Sleep* 2015;38(1):155–9. <https://doi.org/10.5665/sleep.4346>.
- [23] Peters AC, Blechert J, Sämann PG, Eidner I, Czisch M, Spoormaker VI. One night of partial sleep deprivation affects habituation of hypothalamus and skin conductance responses. *J Neurophysiol* 2014;112(6):1267–76. <https://doi.org/10.1152/jn.00657.2013>.
- [24] Emens JS, Berman AM, Thosar SS, Butler MP, Roberts SA, Clemons NA, Herzig MX, McHill AW, Morimoto M, Bowles NP, Shea SA. Circadian rhythm in negative affect: implications for mood disorders. *Psychiatry Res* 2020;293. <https://doi.org/10.1016/j.psychres.2020.113337>.
- [25] Dzogang F, Lightman S, Cristianini N. Circadian mood variations in Twitter content. *Brain Neurosci Advan* 2017;1. <https://doi.org/10.1177/2398212817744501>.
- [26] ten Thij M, Bathina K, Rutter LA, Lorenzo-Luaces L, van de Leemput IA, Scheffer M, Bollen J. Depression alters the circadian pattern of online activity. *Sci Rep* 2020;10(1). <https://doi.org/10.1038/s41598-020-74314-3>.
- [27] Mather M, Thayer J. How heart rate variability affects emotion regulation brain networks. *Curr Opin Behav Sci* 2018;19:98–104. <https://doi.org/10.1016/j.cobeha.2017.12.017>. PMID: 29333483; PMCID: PMC5761738.
- [28] Wendt J, Neubert J, Koenig J, Thayer JF, Hamm AO. Resting heart rate variability is associated with inhibition of conditioned fear. *Psychophysiology* 2015;52(9):1161–6. <https://doi.org/10.1111/psyp.12456>.
- [29] Sakaki M, Yoo HJ, Nga L, Lee TH, Thayer JF, Mather M. Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. *Neuroimage* 2016;139:44–52. <https://doi.org/10.1016/j.neuroimage.2016.05.076>.
- [30] Muñoz-Torres Z, Velasco F, Velasco AL, Del Río-Portilla Y, Corsi-Cabrera M. Electrical activity of the human amygdala during all-night sleep and wakefulness. *Clin Neurophysiol* 2018;129(10):2118–26. <https://doi.org/10.1016/j.clinph.2018.07.010>.
- [31] Killgore WDS. Effects of sleep deprivation on cognition. *Prog Brain Res* 2010;185:105–29. <https://doi.org/10.1016/B978-0-444-53702-7.00007-5>.
- [32] Diener C, Kuehner C, Brusniak W, Ubl B, Wessa M, Flor H. A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *Neuroimage* 2012;61(3):677–85. <https://doi.org/10.1016/j.neuroimage.2012.04.005>.
- [33] Harrington MO, Ashton JE, Sankarasubramanian S, Anderson MC, Cairney SA. Losing control: sleep deprivation impairs the suppression of unwanted thoughts. *Clin Psychol Sci* 2021;9(1):97–113. <https://doi.org/10.1177/2167702620951511>.
- [34] Byrne JEM, Tremain H, Leitan ND, Keating C, Johnson SL, Murray G. Circadian modulation of human reward function: is there an evidentiary signal in existing neuroimaging studies? *Neurosci Biobehav Rev* 2019;99:251–74. <https://doi.org/10.1016/j.neubiorev.2019.01.025>.
- [35] Baltazar RM, Coolen LM, Webb IC. Diurnal rhythms in neural activation in the mesolimbic reward system: critical role of the medial prefrontal cortex. *Eur J Neurosci* 2013;38(2):2319–27. <https://doi.org/10.1111/ejn.12224>.
- [36] Womack SD, Hook JN, Reyna SH, Ramos M. Sleep loss and risk-taking behavior: a review of the literature. *Behav Sleep Med* 2013;11(5):343–59. <https://doi.org/10.1080/15402002.2012.703628>.
- [37] Byrne JEM, Murray G. Diurnal rhythms in psychological reward functioning in healthy young men: ‘Wanting’, liking, and learning. *Chronobiol Int* 2017;34(2):287–95. <https://doi.org/10.1080/07420528.2016.1272607>.
- [38] Hasler BP, Forbes EE, Franzen PL. Time-of-day differences and short-term stability of the neural response to monetary reward: a pilot study. *Psychiatr Res Neuroimag* 2014;224(1):22–7. <https://doi.org/10.1016/j.pscyhresns.2014.07.005>.
- [39] Byrne JEM, Hughes ME, Rossell SL, Johnson SL, Murray G. Time of day differences in neural reward functioning in healthy young men. *J Neurosci* 2017;37(37):8895–900. <https://doi.org/10.1523/JNEUROSCI.0918-17.2017>.
- [40] Masterson TD, Kirwan CB, Davidson LE, LeCheminant JD. Neural reactivity to visual food stimuli is reduced in some areas of the brain during evening hours compared to morning hours: an fMRI study in women. *Brain Imag Behav* 2016;10(1):68–78. <https://doi.org/10.1007/s11682-015-9366-8>.
- [41] Hasler BP, Germain A, Nofzinger EA, Kupfer DJ, Krafty RT, Rothenberger SD, James JA, Bi W, Buysse DJ. Chronotype and diurnal patterns of positive affect and affective neural circuitry in primary insomnia. *J Sleep Res* 2012;21(5):515–26. <https://doi.org/10.1111/j.1365-2869.2012.01002.x>.
- [42] Hasler BP, Soehner AM, Wallace ML, Logan RW, Ngari W, Forbes EE, Buysse DJ, Clark DB. Experimentally imposed circadian misalignment alters the neural response to monetary rewards and response inhibition in healthy adolescents. *Psychol Med* 2021;1–9. <https://doi.org/10.1017/S0033291721000787>. Epub ahead of print. PMID: 33729109; PMCID: PMC8935965.
- [43] Evans SL, Norbury R. Associations between diurnal preference, impulsivity and substance use in a young-adult student sample. *Chronobiol Int* 2021;38(1):79–89. <https://doi.org/10.1080/07420528.2020.1810063>.
- [44] Hasler BP, Sitnick SL, Shaw DS, Forbes EE. An altered neural response to reward may contribute to alcohol problems among late adolescents with an evening chronotype. *Psychiatr Res Neuroimag* 2013;214(3):357–64. <https://doi.org/10.1016/j.pscyhresns.2013.08.005>.
- [45] Venkatraman V, Chuah YML, Huettel SA, Chee MWL. Sleep deprivation elevates expectation of gains and attenuates response to losses following risky decisions. *Sleep* 2007;30(5):603–9. <https://doi.org/10.1093/sleep/30.5.603>.
- [46] Venkatraman V, Huettel SA, Chuah LY, Payne JW, Chee MW. Sleep deprivation biases the neural mechanisms underlying economic preferences. *J Neurosci* 2011;31(10):3712–8. <https://doi.org/10.1523/JNEUROSCI.4407-10.2011>. PMID: 21389226; PMC ID: PMC6622793.
- [47] Gujar N, Yoo SS, Hu P, Walker MP. Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. *J Neurosci* 2011;31(12):4466–74. <https://doi.org/10.1523/JNEUROSCI.3220-10.2011>.
- [48] Kuula L, Pesonen AK, Heinonen K, Kajantie E, Eriksson JG, Andersson S, Lano A, Lahti J, Wolke D, Räikkönen K. Naturally occurring circadian rhythm and sleep duration are related to executive functions in early adulthood. *J Sleep Res* 2018;27(1):113–9. <https://doi.org/10.1111/jsr.12581>.

- [49] Duschek S, Werner NS, Reyes del Paso GA. The behavioral impact of baroreflex function: a review. *Psychophysiology* 2013;50(12):1183–93. <https://doi.org/10.1111/psyp.12136>.
- [50] Duschek S, Hoffmann A, Reyes Del Paso GA, Ettinger U. Autonomic cardiovascular control and executive function in chronic hypotension. *Ann Behav Med.* 2017;51(3):442–53. <https://doi.org/10.1007/s12160-016-9868-7>. PMID: 27957701.
- [51] Forte G, Favieri F, Casagrande M. Heart rate variability and cognitive function: a systematic review. *Front Neurosci* 2019;13. <https://doi.org/10.3389/fnins.2019.00710>.
- [52] Nicolini P, Malfatto G, Lucchi T. Heart rate variability and cognition: a narrative systematic review of longitudinal studies. *J Clin Med* 2024;13(1):280. <https://doi.org/10.3390/jcm13010280>.
- [53] Drummond SPA, Paulus MP, Tapert SF. Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. *J Sleep Res* 2006;15(3):261–5. <https://doi.org/10.1111/j.1365-2869.2006.00535.x>.
- [54] May CP, Hasher L. Synchrony effects in inhibitory control over thought and action. *J Exp Psychol Hum Percept Perform* 1998;24(2):363–79. <https://doi.org/10.1037/0096-1523.24.2.363>.
- [55] Gillett G, Watson G, Saunders KE, McGowan NM. Sleep and circadian rhythm actigraphy measures, mood instability and impulsivity: a systematic review. *J Psychiatr Res* 2021;144:66–79. <https://doi.org/10.1016/j.jpsychires.2021.09.043>.
- [56] Kang JI, Park CI, Sohn SY, Kim HW, Namkoong K, Kim SJ. Circadian preference and trait impulsivity, sensation-seeking and response inhibition in healthy young adults. *Chronobiol Int* 2015;32(2):235–41. <https://doi.org/10.3109/07420528.2014.965313>.
- [57] Ottaviani C, Zingaretti P, Petta AM, Antonucci G, Thayer JF, Spitoni GF. Resting heart rate variability predicts inhibitory control above and beyond impulsivity. *J Psychophysiol* 2019;33(3):198–206. <https://doi.org/10.1027/0269-8803/a000222>.
- [58] Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognit Affect Behav Neurosci* 2012;12(2):241–68. <https://doi.org/10.3758/s13415-011-0083-5>.
- [59] May J, Kline P. Measuring the effects upon cognitive abilities of sleep loss during continuous operations. *Br J Psychol* 1987;78(4):443–55. <https://doi.org/10.1111/j.2044-8295.1987.tb02261.x>.
- [60] Craig SN, Dell'Angela K, Jellish SW, Brown IE, Skaredoff M. Residents' performance before and after night call as evaluated by an indicator of creative thought. *J Osteopath Med* 1995;95(10). <https://doi.org/10.7556/jaoa.1995.95.10.600>. 600–600.
- [61] Maddox WT, Glass BD, Wolosin SM, Savarie ZR, Bowen C, Matthews MD, Schnyer DM. The effects of sleep deprivation on information-integration categorization performance. *Sleep* 2009;32(11):1439–48. <https://doi.org/10.1093/sleep/32.11.1439>.
- [62] Slama H, Chylinski DO, Deliens G, Leproult R, Schmitz R, Peigneux P. Sleep deprivation triggers cognitive control impairments in task-goal switching. *Sleep* 2018;41(2). <https://doi.org/10.1093/sleep/zsx200>.
- [63] Woo E, Sansing LH, Arnsten AFT, Datta D. Chronic stress weakens connectivity in the prefrontal cortex: architectural and molecular changes. *Chronic Stress* 2021;5. <https://doi.org/10.1177/24705470211029254>.
- [64] Kathrin Zenses A, Lenaert B, Peigneux P, Beckers T, Boddez Y. Sleep deprivation increases threat beliefs in human fear conditioning. *J Sleep Res* 2020;29(3). <https://doi.org/10.1111/jsr.12873>.
- [65] Liu C, Rotaru K, Lee RSC, Tiego J, Suo C, Yücel M, Albertella L. Distress-driven impulsivity interacts with cognitive inflexibility to determine addiction-like eating. *J Behav Addict* 2021;10(3):534–9. <https://doi.org/10.1556/2006.2021.00027>.
- [66] Coumans JMJ, Danner UN, Ahrens W, Hebestreit A, Intemann T, Kourides YA, Lissner L, Michels N, Moreno LA, Russo P, Stomfai S, Veidebaum T, Adan RAH. The association of emotion-driven impulsiveness, cognitive inflexibility and decision-making with weight status in European adolescents. *Int J Obes* 2018;42(4):655–61. <https://doi.org/10.1038/ijo.2017.270>.
- [67] Leppink EW, Redden SA, Chamberlain SR, Grant JE. Cognitive flexibility correlates with gambling severity in young adults. *J Psychiatr Res* 2016;81:9–15. <https://doi.org/10.1016/j.jpsychires.2016.06.010>.
- [68] Raj K, Segrave R, Verdéjo-García A, Yücel M. Cognitive inflexibility and repetitive habitual actions are associated with problematic use of the internet. *Addict Behav* 2023;139:107600. <https://doi.org/10.1016/j.addbeh.2022.107600>.
- [69] Ram D, Chandran S, Sadar A, Gowdappa B. Correlation of cognitive resilience, cognitive flexibility and impulsivity in attempted suicide. *Indian J Psychol Med* 2019;41(4):362–7. https://doi.org/10.4103/ijpsymp.ijpsymp_189_18.
- [70] Perlis ML, Grandner MA, Brown GK, Basner M, Chakravorty S, Morales KH, Gehrman PR, Chaudhary NS, Thase ME, Dinges DF. Nocturnal wakefulness as a previously unrecognized risk factor for suicide. *J Clin Psychiatr* 2016;77(6):e726. <https://doi.org/10.4088/JCP.15m10131>.
- [71] Mansfield DR, Wasgawatta S, Reynolds A, Grandner MA, Tubbs AS, King K, Johnson M, Mascaro L, Durukan M, Paul E, Drummond SPA, Perlis ML. Nocturnal wakefulness and suicide risk in the Australian population. *J Clin Psychiatr* 2022;83(4). <https://doi.org/10.4088/JCP.21m14275>.
- [72] Tubbs AS, Fernandez F-X, Klerman EB, Karp JF, Basner M, Chakravorty S, Watkins E, Perlis ML, Grandner MA. Risk for suicide and homicide peaks at night: findings from the national violent death reporting system, 35 states, 2003–2017. *J Clin Psychiatr* 2024;85(2). <https://doi.org/10.4088/jcp.23m15207>.
- [73] Tubbs AS, Fernandez FX, Johnson DA, Perlis ML, Grandner MA. Nocturnal and morning wakefulness are differentially associated with suicidal ideation in a nationally representative sample. *J Clin Psychiatr* 2021;82(6). <https://doi.org/10.4088/JCP.20m13820>.
- [74] Tubbs AS, Fernandez FX, Perlis ML, Hale L, Branas CC, Barrett M, Chakravorty S, Khader W, Grandner MA. Suicidal ideation is associated with nighttime wakefulness in a community sample. *Sleep* 2021;44(1). <https://doi.org/10.1093/sleep/zsaa128>.
- [75] Dutta R, George G, Velupillai S, Bakolis I, Stewart R. Temporal and diurnal variation in social media posts to a suicide support forum. *BMC Psychiatr* 2021;21(1). <https://doi.org/10.1186/s12888-021-03268-1>.
- [76] Boo J, Matsubayashi T, Ueda M. Diurnal variation in suicide timing by age and gender: evidence from Japan across 41 years. *J Affect Disord* 2019;243:366–74. <https://doi.org/10.1016/j.jad.2018.09.030>.

- [77] Silla A, Luoma J. Main characteristics of train-pedestrian fatalities on Finnish railroads. *Accid Anal Prev* 2012;45:61–6. <https://doi.org/10.1016/j.aap.2011.11.008>.
- [78] Gibbens TCN. Sane and insane homicide. *J Crim law, Criminol Police Sci* 1958;49(2):110. <https://doi.org/10.2307/1140920>.
- [79] Messner SF, Tardiff K. The social ecology of urban homicide: an application of the “routine activities” approach. *Criminology* 1985;23(2):241–67. <https://doi.org/10.1111/j.1745-9125.1985.tb00336.x>.
- [80] Sisti D, Rocchi MBL, MacCiò A, Preti A. The epidemiology of homicide in Italy by season, day of the week and time of day. *Med Sci Law* 2012;52(2):100–6. <https://doi.org/10.1258/msl.2011.010147>.
- [81] Belknap J. Routine activity theory and the risk of rape: analyzing ten years of national crime survey data. *Crim Justice Policy Rev* 1987;2(4):337–56. <https://doi.org/10.1177/088740348700200403>.
- [82] Montero-Moraga JM, Garrido-Albaina A, Barbaglia MG, Gotsens M, Aranega D, Espelt A, Parés-Badell O. Impact of 24-hour schedule of a drug consumption room on service use and number of non-fatal overdoses. A quasi experimental study in Barcelona. *Int J Drug Pol* 2020;81. <https://doi.org/10.1016/j.drugpo.2020.102772>.
- [83] Hisler GC, Rothenberger SD, Clark DB, Hasler BP. Is there a 24-hour rhythm in alcohol craving and does it vary by sleep/circadian timing? *Chronobiol Int* 2021;38(1):109–21. <https://doi.org/10.1080/07420528.2020.1838532>.
- [84] Comulada WS, Lightfoot M, Swendeman D, Grella C, Wu N. Compliance to cell phone-based EMA among latino youth in outpatient treatment. *J Ethn Subst Abuse* 2015;14(3):232–50. <https://doi.org/10.1080/15332640.2014.986354>.
- [85] Hasler BP, Franzen PL, de Zambotti M, Prouty D, Brown SA, Tapert SF, Pfefferbaum A, Pohl KM, Sullivan EV, De Bellis MD, Nagel BJ, Baker FC, Colrain IM, Clark DB. Eveningness and later sleep timing are associated with greater risk for alcohol and marijuana use in adolescence: initial findings from the National Consortium on alcohol and neurodevelopment in adolescence study. *Alcohol Clin Exp Res* 2017;41(6):1154–65. <https://doi.org/10.1111/acer.13401>.
- [86] Boutou AK, Tsitsa EA, Pataka A, Kontou PK, Pitsiou GG, Argyropoulou P. Smoking cessation in clinical practice: predictors of six-month continuous abstinence in a sample of Greek smokers. *Prim Care Respir J* 2008;17(1):32–8. <https://doi.org/10.3132/pcrj.2008.00009Greece>.
- [87] Knutson KL. Does inadequate sleep play a role in vulnerability to obesity? *Am J Hum Biol* 2012;24(3):361–71. <https://doi.org/10.1002/ajhb.22219>.
- [88] Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, Wright KP. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Natl Acad Sci U S A* 2013;110(14):5695–700. <https://doi.org/10.1073/pnas.1216951110>.
- [89] Shechter A, Grandner MA, St-Onge MP. The role of sleep in the control of food intake. *Am J Lifestyle Med* 2014;8(6):371–4. <https://doi.org/10.1177/1559827614545315>.
- [90] Broussard JL, Cauter EV. Disturbances of sleep and circadian rhythms: novel risk factors for obesity. *Curr Opin Endocrinol Diabetes Obes* 2016;23(5):353–9. <https://doi.org/10.1097/MED.0000000000000276>.
- [91] Mendoza J. Food intake and addictive-like eating behaviors: time to think about the circadian clock(s). *Neurosci Biobehav Rev* 2019;106:122–32. <https://doi.org/10.1016/j.neubiorev.2018.07.003>.
- [92] Stunkard AJ, Allison KC, Lundgren JD, O'Reardon JP. A biobehavioural model of the night eating syndrome. *Obes Rev* 2009;10(s2):69–77. <https://doi.org/10.1111/j.1467-789x.2009.0068.x>.
- [93] Matsubayashi T, Sawada Y, Ueda M. Does the installation of blue lights on train platforms prevent suicide? A before-and-after observational study from Japan. *J Affect Disord* 2013;147 (1–3):385–8. <https://doi.org/10.1016/j.jad.2012.08.018>.
- [94] Matsubayashi T, Sawada Y, Ueda M. Does the installation of blue lights on train platforms shift suicide to another station?: Evidence from Japan. *J Affect Disord* 2014;57–60. <https://doi.org/10.1016/j.jad.2014.07.036>. Epub 2014 Aug 7. PMID: 25151192.
- [95] Passler S, Noack A, Poll R, Fischer WJ. Validation of the use of heart rate variability measurements during meal intake in humans. *Comput Cardiol* 2013;40.
- [96] Moon SJE, Schlenk EA, Lee H. Heart rate variability in adults with substance use disorder: a comprehensive narrative review. *J Am Psychiatr Nurses Assoc* 2024;30(2):240–51. <https://doi.org/10.1177/10783903221145142>.
- [97] Kang GE, Patriquin MA, Nguyen H, Oh H, Rufino KA, Storch EA, Schanzer B, Mathew SJ, Salas R, Najafi B. Objective measurement of sleep, heart rate, heart rate variability, and physical activity in suicidality: a systematic review. *J Affect Disord* 2020;273:318–27. <https://doi.org/10.1016/j.jad.2020.03.096>.
- [98] Fink BC, Claus ED, Cavanagh JF, Hamilton DA, Biesen JN. Heart rate variability may index emotion dysregulation in alcohol-related intimate partner violence. *Front Psychiatr* 2023;14. <https://doi.org/10.3389/fpsy.2023.1017306>.
- [99] Sheridan DC, Baker S, Dehart R, Lin A, Hansen M, Tereshchenko LG, Le N, Newgard CD, Nagel B. Heart rate variability and its ability to detect worsening suicidality in adolescents: a pilot trial of wearable technology. *Psychiatr Investigat* 2021;18 (10):928–35. <https://doi.org/10.30773/pi.2021.0057>.
- [100] Kromenacker BW, Sanova AA, Marcus FI, Allen JJB, Lane RD. Vagal mediation of low-frequency heart rate variability during slow yogic breathing. *Psychosom Med* 2018;80(6):581–7. <https://doi.org/10.1097/PSY.0000000000000603>.
- [101] Laborde S, Allen MS, Borges U, Dosseville F, Hosang TJ, Iskra M, Mosley E, Salvotti C, Spolverato L, Zammit N, Javelle F. Effects of voluntary slow breathing on heart rate and heart rate variability: a systematic review and a meta-analysis. *Neurosci Biobehav Rev* 2022;138:104711. <https://doi.org/10.1016/j.neubiorev.2022.104711>.
- [102] Tsai HJ, Kuo TBJ, She Lee G, Yang CH. Efficacy of paced breathing for insomnia: enhances vagal activity and improves sleep quality. *Psychophysiology* 2015;52(3):388–96.

This page intentionally left blank

Part II

Contextual factors related to sleep

This page intentionally left blank

Chapter 7

Race, socioeconomic position and sleep

Girardin Jean-Louis^{a, b, c}, Judite Blanc^c and Douglas M. Wallace^{d, e}

^aNYU Langone Health, Department of Population Health, New York, NY, United States; ^bNYU Langone Health, Department of Psychiatry, New York, NY, United States; ^cUniversity of Miami Miller School of Medicine, Department of Psychiatry & Behavioral Sciences, Center for Translational Sleep and Circadian Sciences, Miami, FL, United States; ^dDepartment of Neurology, Sleep Medicine Division, University of Miami Miller School of Medicine, Miami, FL, United States; ^eMiami VA HealthCare System, Sleep Disorders Laboratory, Miami, FL, United States

Abbreviations

ACT	actigraphy
DFA	difficulty falling asleep
DMS	difficulty maintaining sleep
EDS	excessive daytime sleepiness
EMA	early morning awakening
LS	long sleep
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NRS	nonrestorative sleep
OSA	obstructive sleep apnea
PLMS	periodic limb movements during sleep
PSG	polysomnography
RLS	restless leg syndrome
SC	sleep complaints
SDB	sleep disordered breathing
SES	socioeconomic status
SL	sleep latency
SS	short sleep
TST	total sleep time
WASO	wake after sleep onset

Much of the history of thinking about inequality in the United States, including health inequality, has usually been framed in terms of race or class, but seldom both.

[1, 347, pp.]

Introduction

There is no doubt that the US economy has experienced strong growth. Broadly defined as a measure of economic well-being [2], the gross domestic product (GDP) is approximately 4.2%, an 18% increase from the 2009

financial crisis [2]. The unemployment rate is 4%, also approaching the same rate as in 2009 [3]. Lamentably, only a small segment of the population has benefited from this recent economic growth. For example, Blacks with a college degree earn less than their white counterparts without a college degree [4]. Only 70% of Native Americans/Alaska Natives earned a high school diploma in 4 years compared to 87% of whites [5]. The total household income of Blacks has remained relatively unchanged over the past 30 years [6]. In 2015, the total household income of Hispanics was less than it was in 1972 and 1 in 4 Hispanics were living at the US federal poverty level [6]. Black and white Americans have significant differences in life expectancy. Life expectancy at birth for white men is 76.1, approximately 4 years longer than Black men and in 2016 white women were expected to live until age 81 compared to Black women at 77.9 [7]. Hispanics make up the highest percentage of Americans without health insurance coverage (19.5%) whereas only 6% of non-Hispanic whites do not have health insurance coverage. Given that there are disparities at nearly every level of socioeconomic status (SES) and racial/ethnic disparities by nearly every indicator of health status, addressing these persistent health disparities has become one of the most pressing public health challenges.

Beginning with Healthy People 2010 (officially launched in January 2000), the nation's public health agenda has included the broad goal of eliminating disparities [8]. Healthy People 2020 includes sleep health objectives, specifically to increase sleep duration among adults and adolescents and to increase the proportion of adults seeking a medical evaluation for obstructive sleep apnea [5]. Aligned

with the overarching goals, the inclusion of the sleep health objectives provides an important opportunity for the sleep community to: (1) address health disparities, (2) identify the complex conditions that contribute to and/or exacerbate these disparities, and (3) develop, evaluate, and implement evidenced-based interventions for achieving these objectives among socioeconomically disadvantaged Americans and racial/ethnic minorities.

The purpose of this chapter is not to present an exhaustive and comprehensive review of the literature, because several reviews about sleep among racial/ethnic minorities have been conducted [9–11]. Rather, we describe the current landscape in health disparities science in the United States. First, we provide a brief overview of health disparities. Second, we summarize the available influential published studies on inadequate sleep duration, poor sleep quality, and a selection of the sleep disorders. Finally, we identify gaps in the literature and suggestions for future inquiry.

(Brief) history and definition of health disparities

Presumably, the earliest remark of a “health disparity” in the United States was noted in the Secretary’s Task Force on Black and Minority Human Services. Congress convened the report in 1984 in order to comprehend the health of minority populations [5]. In the report, former Secretary of the Department of Health and Human Services, Margaret Heckler, described “... the disparity has existed ever since accurate federal record keeping began.” The definition of disparity was best defined as “excess deaths,” or “the difference between the number of deaths observed in minority populations and the number of deaths which would have been expected in the minority population and the same age- and sex-specific death rate as the non-minority population [5].” While the Secretary’s remarks stated that the report should serve as a “generating force” for a “national assault on the persisting health disparity, (p. 1),” the disparities widened.

In 1999, Congress requested that the National Academy of Medicine (formerly known as the Institute of Medicine), to convene its seminal study that synthesized the evidence of disparities in health care [12]. In this work titled, “Unequal Treatment: What Healthcare Providers need to Know about Racial and Ethnic Disparities in Health Care” the committee defined disparities in healthcare as “racial or ethnic differences in the quality of healthcare that are not due to access-related factors or clinical needs, preferences, and appropriateness of interventions.” The Committee reviewed over 100 published studies and concluded that even among the insured, there were differences in health

care utilization and treatment and these differences occurred beyond the traditional individual level factors such as smoking and patients’ attitudes about treatment. Rather, these differences could be attributed to factors within the healthcare system, prejudice and discrimination and clinical uncertainty [12]. Moreover, eliminating these disparities is possible. In contrast to efforts in monitoring disparities in the United States, European countries consistently report health status by SES indicators [13]. For example, the Whitehall studies of British civilian workers were most striking as it related to SES and health inequities. In those studies, a homogeneous sample, with access to national health insurance, demonstrated that SES was related to age-adjusted mortality in 10 years and that there was an SES-gradient effect for nearly every cause of death. That is, higher-ranking employees had a lower relative risk of mortality compared to lower ranking employees [14]. These studies have demonstrated the importance of exploring disparities not only by educational level and income but also occupation status and within various economic strata to assess whether relationships are graded.

Sleep characteristics

Self-reported sleep duration across racial/ethnic groups

Population-based studies have shown that individuals belonging to minority racial/ethnic groups are more likely to experience self-reported extremes in sleep duration than white individuals. In the Alameda County Health and Ways of Living Study, Stamatakis et al. found that disparities among minorities for habitual short sleep (SS; ≤ 6 h daily) have existed for several decades and have widened over time [15]. In 1965, Blacks had nearly a twofold higher odds for SS while non-Hispanic individuals of other race–ethnicity had a 40% increased odds for SS than whites (Table 7.1) [15]. Over the 34 years of the study (1965–99), the age-adjusted mean probability of SS among black (26%–54%) and Hispanic (12%–37%) individuals grew disproportionately relative to whites (15%–25%). In a nationally representative sample (National Health Interview Survey 1990 data) adjusting for individual SES factors, health behaviors, and urban living environments, Hale and Do found that individuals of black, non-Mexican Hispanic, and other non-Hispanic race–ethnicity had increased odds of SS relative to whites (Table 7.1) [16]. Blacks also had increased odds of long sleep (LS; ≥ 9 h; OR 1.62 [1.40–1.88]) relative to whites. On examining more recent data from the National Health and Interview Survey (NHIS) (2004–07), Krueger et al. reported similar

TABLE 7.1 Representative studies examining sleep duration in adult racial/ethnic minorities and lower SES populations.

Study	Design/source	Sample	Racial/ethnic/SES group (% of sample)	Sleep duration assessment	Sleep duration definitions (h/night)	Covariates	Findings (racial/ethnic reference group is white unless specified)
Stamatakis et al. [15]	Longitudinal; Alameda County Health and Ways of Living Study (1965–99)	N = 6928 (1965); N = 2123 (1999); age: 16–94	Black: 12.4 Hispanic: 3.9 Other: 4.7 White: 78.9 — Lowest income quintile: 20	Self-report at each study wave	Short: ≤6 Reference: 7–8 Excluded: ≥9	Age, BMI, living conditions, health behaviors, health status, depression, insomnia	<i>Short sleep (<6 h):</i> Black OR 1.97 (1.7–2.3) Other OR 1.4 (1.1–1.9) — <i>Lowest income quintile OR 1.6 (1.3–1.9) relative to highest quintile</i>
Hale and Do [16]	Cross-sectional; National Health Interview Survey 1990	N = 32,749; 52% women; age 43	Black: 10.1 Mex-Amer: 4.1 Other Hispanic: 3.5 Other non-Hisp: 3.3 White: 79.0	Self-report: “total hours slept over 24-h day”	Short: ≤6 Reference: 7–8 Long sleep: ≥9	Age, sex, individual SES, health conditions/behaviors, residence type, urban environment characteristics	<i>Short sleep (<6 h):</i> Black OR 1.4 (1.3–1.6) Other Hispanic OR 1.3 (1.1–1.5) Other non-Hispanic OR 1.4 (1.1–1.6) <i>Long sleep(>9 h):</i> Black OR 1.6 (1.4–1.9)
Whinnery et al. [17]	Cross-sectional; National Health and Nutrition Examination Survey 2007–08	N = 4850; 52% women; age 25–64: 71%	Black: 11.4 Mex-Amer: 8.5 Other Hispanic: 5.0 Asian/other: 6.0 White: 69.2 Income <20K: 16.4 >75K: 33.4	Self-report: “sleep on weekday or workday nights”	Very short: <5 Short: 5–6 Normal: 7–8 Long: ≥9	Demographics, self-rated health, country of origin, language, income, education, health insurance, food security	<i>Very short sleep(<5 h):</i> Black OR 2.3 (1.6–3.4) Other Hispanic OR 2.7 (1.1–6.3) Asians/others OR 3.99 (1.7–9.5) <i>Short sleep (5–6 h):</i> Black OR 1.85 (1.5–2.2) Asians/others OR 2.1 (1.3–3.3) <i>Long sleep(≥9 h):</i> Mex-Amer OR 0.4 (0.1–0.9)
Krueger and Friedman [18]	Cross-sectional; National Health Interview Survey 2004–07	N = 110,441	NR	Self-report: “total hours slept over 24-h day”	5, 6, 8, 9 7 (reference)	Demographics, foreign born status, family structure, SES, health behaviors, health status	6 vs 7 h: Blacks OR 1.5 (1.4–1.6) Other Hispanics OR 1.15 (1.03–1.3) Other non-Hispanic OR 1.4 (1.2–1.5)

Continued

TABLE 7.1 Representative studies examining sleep duration in adult racial/ethnic minorities and lower SES populations.—cont'd

Study	Design/source	Sample	Racial/ethnic/SES group (% of sample)	Sleep duration assessment	Sleep duration definitions (h/night)	Covariates	Findings (racial/ethnic reference group is white unless specified)
							9 vs 7 h Blacks OR 1.5 (1.3–1.6) Mex-Amer OR 1.4 (1.3–1.6)
Lauderdale et al. [19]	Cross-sectional; CARDIA 2003–04	N = 669; 58% women; age 43 ± 4	Black: 44 White: 56	3 days of ACT	Continuous	Age, BMI, individual SES, employment, household, health behaviors, SDB-risk, shift work	White women 6.5 (6.0–6.9) h White men 5.8 (5.3–6.3) h Black women 5.9 (5.5–6.3) h Black men 5.1 (4.6–5.6) h
Mezick et al. [20]	Cross-sectional; Pittsburgh Sleep SCORE	N = 187; 47% women; age 60 ± 7	Black: 41 White/Asians: 59 (Asians; n = 3)	9 days of ACT; 2-nights of home PSG	Continuous	Age, sex, medication use	ACT: black 5.4 ± 0.8 vs white/Asian 6.0 ± 0.9 h PSG: black 5.8 ± 1.1 vs white/Asian 6.2 ± 0.9 h
Hall et al. [21]	Cross-sectional; Study of Women's Health Across the Nation (SWAN) Sleep ancillary	N = 368 adults; 100% women; age 51 ± 2	Black: 37.5 Chinese: 16.0 White: 46.5 – Difficulty paying for basics: 27.4	3-nights of home PSG (1st night excluded)	Continuous	Age, menopausal status, vasomotor symptoms, BMI, depression, perceived health, sleep meds	Beta for blacks: <i>p</i> 0.27 Beta for Chinese: –0.04; <i>P</i> = NS Beta for difficulty paying for basics: 0.02; <i>P</i> = NS
Song et al. [22]	Cross-sectional; Outcomes of Sleep Disorders in Older Men Study (MrOs Sleep)	N = 2862 adults; 100% men; age 76 ± 6	Black: 3.4 Hispanic: 1.9 Asian-Amer: 2.9 Other: 1.1 White: 90.8	5 days of ACT	Continuous	Age, social status, BMI, education, marital status, health behaviors/conditions, study site	Black: 6.1 (5.8–6.3) Hispanic: 6.7 (6.4–7.0) Asian-Amer: 6.1 (5.8–6.4) Other: 6.5 (6.1–7.0) White: 6.4 (6.4–6.5)

Chen et al. [23]	Cross-sectional; Multi-Ethnic Study of Atherosclerosis (MESA) Sleep cohort	$N = 2230$ adults; 54% women; age 68 ± 9	Black: 28.0 Hispanic: 23.9 Chinese: 12.1 White: 36.1	7 days of ACT	Short: <6,6–7 Reference: 7–8 Long: >8	Age, sex, and site	<i>Short sleep (<6 h):</i> Blacks OR 4.95 (3.6–6.9) Hispanics OR 1.80 (1.3–2.6) Chinese OR 2.3 (1.5–3.6) <i>Long sleep (>8 h):</i> No racial differences
Carnethon et al. [24]	Cross-sectional; Chicago Area Sleep Study (CASS)	$N = 496$ adults; 60% women; age 48 ± 8	Black: 31.3 Hispanic: 20.8 Asian: 22.0 White: 26.0	7 days of ACT	Continuous	Age, sex, BMI, education, shift work, health behaviors, depression	Black: 6.7 (6.5–6.8) h Hispanic: 6.9 (6.6–7.1) h Asian: 6.8 (6.6–7.1) h White: 7.5 (7.3–7.7) h
Dudley et al. [25]	Cross-sectional; Hispanic Community Health Study/Study of Latinos (HCHS/SOL)	$N = 2087$ adults; 64.6% women; age 47 ± 12	Mexico: 26.9 Central Am: 13.6 Cuban: 18.1 Dominican: 12.5 Puerto Rico: 20.7 South Am: 8.2	5–7 days of ACT	Continuous	Age, sex, education, employment status, shift work status, income, BMI, SDB, depression, health behaviors, sleep medication, season	<i>Regression coeff beta [SE] min</i> Mexico (reference) Central Am: – 13.2 [5.2] Cuban – 5.2 [4.9] Dominican: – 10.5 [5.1] Puerto Rico: – 12.4 [6.7] South Am: – 19.3 [6.7]

Data presented as mean \pm SD, mean [SE], or OR (95% CI). **Bolded values** represent $P < 0.05$; ACT, actigraphy; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; LS, long sleep; OR, odds ratio; SDB, sleep disordered breathing; SES, socioeconomic; SOL, sleep onset latency; SS, short sleep; VSS, very short sleep.

racial/ethnic findings for SS. However, they also found that Blacks (OR 1.46 [1.33–1.59]) and Mexican-Americans (1.42 [1.27–1.60]) were more likely to report LS [18,26]. In the National Health and Nutrition Examination Survey (NHANES), Whinnery et al. examined the relationship between racial/ethnic groups and extremes of sleep duration while adjusting not only for individual SES characteristics but also including homeownership, health insurance, food insecurity, and acculturation measures [17]. Blacks and non-Mexican Hispanics were more than two times the odds to report very SS (<5 h nightly) compared to whites, while Asians/individuals of other race/ethnicity were nearly four times more likely to report very SS relative to whites (Table 7.1). Blacks and Asians/others also reported about two times the odds of SS (5–6 h) compared to whites. In contrast, Mexican-Americans were about one-third as likely to report LS (>9 h) relative to whites. Finally, Jean-Louis et al. examined 3 decades of data from NHIS (1977–2007), among whites, the prevalence of VSS increased from 1.5% in 1977 to 2.3% in 2009, and the prevalence of SS increased from 19.3% to 25.4%, whereas prevalence among blacks, the prevalence of VSS increased from 3.3% to 4.0%, and the prevalence of SS increased from 24.6% to 33.7% [27].

These nationally representative self-reported data suggest that specific racial/ethnic groups may be at greater risk for very SS, SS, and LS than whites and that these disparities in sleep duration may have widened over time.

Objective reported sleep duration across racial/ethnic groups

In addition to self-reported measures, some population-based studies have employed objective measures of total sleep time (TST). Objective measures of TST is important because (1) the disparity between subjectively and objectively measured TST can exceed 1 h and (2) comorbid sleep disorders (e.g., undiagnosed sleep disordered breathing) can influence an individual's perception of sleep duration). Using three nights of actigraphy (ACT) in black and white participants aged 39–50 years, Lauderdale et al. examined race-sex interactions for sleep measures in the Coronary Artery Risk Development in Young Adults (CARDIA) study [19]. In models adjusting for individual SES factors, employment, health behaviors, and sleep disordered breathing (SDB) risk, white women slept 6.5 h while black men slept 5.1 h with white men and black women having similar intermediate sleep durations (Table 7.1). Mezick et al. used two nights of home polysomnography (PSG) and nine nights of ACT finding that Blacks, on average, had significantly shorter TST (about 30 min less) than white/

Asian participants by both methods [20] (Table 7.1). In the Study of Women's Health Across the Nation (SWAN) sleep cohort, participants completed three nights of home PSG in a diverse sample of middle-aged women from seven US cities [21]. Adjusting for financial strain and education attainment, black, but not Chinese, women had significantly shorter PSG-measured TST than white women. Similarly, Song et al. assessed the sleep characteristics of older men (>65 years of age) enrolled in the Outcomes of Sleep Disorders in Older Men study (MrOs Sleep) using 5 days of ACT and one night of PSG to measure TST and SDB, respectively [22]. In adjusted models accounting for social status and a number of health factors, black men slept less than white men (6.0 vs. 6.4 h) while Hispanic men [28] slept more than black (6.0 h) and Asian American (6.1 h) participants. Similar results were observed in further analyses adjusting for SDB. More recently, Chen et al. used 7 days of ACT to measure TST and home PSG to assess for SDB in the Multi-Ethnic Study of Atherosclerosis (MESA) in participants from six US cities [23]. After adjusting for age, sex, and study site, Blacks were nearly five times as likely to have objectively SS (<6 h) compared to whites while Hispanics and Chinese had nearly twice the odds of SS relative to white participants. These racial differences in odds for SS persisted despite additional adjustments for SDB and insomnia. As in CARDIA, the shortest sleep duration was found among black men who on average slept 75 min less than white women. Black women on average slept 43 min less than white women. Finally, Carnethon et al. expanded the results of CARDIA by examining additional racial/ethnic groups (Hispanics and Asians), and screening for SDB with PSG in the Chicago Area Sleep Study [24,29]. Using 7 days of ACT, Carnethon et al. found that, in adjusted analyses, Blacks, Asians, and Hispanics each had significantly shorter TST than whites (Table 7.1). Most, but not all, studies using objective TST and accounting for comorbid sleep disorders suggest individuals of minority background have greater risk for shorter sleep duration than whites. Consistently across these studies with varying adjustments (e.g., SES), black men and women had the shortest objective TST relative to their white counterparts.

Sleep duration within racial/ethnic groups

There are fewer data concerning heterogeneity of sleep duration within racial/ethnic groups. Recently, the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) has provided detailed sleep characteristics concerning intra-ethnic variability within US Hispanics from the Bronx, Chicago, San Diego, and Miami [25]. Using 7 days of ACT in participants evaluated for SDB with PSG, Dudley et al.

found that mean TST for US Hispanics was >30 min longer than for non-Hispanic Blacks and whites who participated in CARDIA. In age- and sex-adjusted analyses, Mexican Americans had the longest TST (6.82 h) while individuals of Puerto Rican (6.57 h) and South American (6.44 h) heritage had the shortest TST (Table 7.1).

Sleep duration across SES groups

Above and beyond the effects of race–ethnicity, there is evidence for individuals belonging to lower SES groups having greater risk for extremes of TST than individuals from higher SES groups. For example, in the Alameda County Health and Ways of Living Study, individuals in the lowest income quintile had over a 60% increased odds of SS relative to those in the highest quintile [15] (Table 7.1). In the Nurses Health Study II, Patel et al. observed that the odds of subjective LS (>9 h) relative to normal sleep duration (7–8 h) was increased for never having been married (OR 1.4 [1.2,1.5]), unemployment (OR 2.4 [2.3,2.6]), and having an annual income less than \$30,000 [30]. In NHANES, Whinnery et al. reported that lower educational attainment and very low food security was associated with SS, while having public health insurance relative to being uninsured was associated with LS [17]. Within US Hispanics ($n = 11,860$), Patel found that having full-time employment and less than a high school education predicted self-reported SS (<7 h); whereas unemployment, less than a high school education, and household income (<\$10,000 annually) predicted LS (>9 h) [31]. A similar association between lower SES position and LS (>9 h) has been reported within US Blacks in the Jackson Heart Study (JHS) [32]. In contrast, among middle aged women in the SWAN study, financial strain was not associated with PSG-measured TST in adjusted analyses [21]. In CARDIA, ACT-defined TST was not associated to traditional SES measures (income, education) but was associated with other employment factors (i.e., unemployment, shift work) [19]. In a sample of healthcare workers, Ertel et al. used 7 days of ACT to compare the sleep duration of black Caribbean/African immigrants to those of whites [33]. In age- and gender-adjusted analyses, the sleep duration disparity between black Caribbean/African immigrants was >1 h relative to whites, which was attenuated by 41% with adjustment for individual economic indicators and occupational characteristics [34]. Finally, in a nationally representative sample (NHIS), a race by occupation/industry interaction has been observed for SS. With increasing professional/managerial roles, SS increases among Blacks but decreases among whites [35]. These data suggest that psychosocial measures of SES

(e.g., workplace, social, and environmental features) may be more closely linked to sleep duration for racial/ethnic groups than traditional measures of SES. Of note, these studies used objective measures of TST, which may be more accurate than self-reported sleep duration [19].

Sleep architecture and continuity across racial/ethnic groups

Most studies examining sleep architecture and continuity across racial/ethnic groups have shown that minority individuals tend to have “lighter” and more fragmented sleep than whites [36,37]. For example, Redline et al. used home PSG to characterize sleep architecture in the Sleep Heart Health Study (SHHS) [38] (Table 7.2). In analyses adjusting for demographics, health comorbidities and SDB, American Indians had higher percentage N1 sleep than Blacks (6.7% vs. 5.3%, $P = 0.01$) or whites (6.7% vs. 5.4%, $P < 0.001$). Additionally, American Indians had higher percentage N2 sleep than Hispanics (65.1% vs. 58.4%, $P < 0.001$) or whites (65.1% vs. 58.4%, $P < 0.001$). The same group also had significantly less percentage of N3 (deep) sleep than any other racial and ethnic group. Blacks had higher percentage of N2 sleep than whites (62.2% vs. 58.4%, $P < 0.001$) or Hispanics (62.2% vs. 58.4%, $P = 0.02$) and lower N3 sleep than whites (11.0% vs. 14.8%) or Hispanics (11.0% vs. 15.1%). In a study examining sleep architecture in the sleep laboratory, Tomfohr et al. found that Blacks spent approximately 4.5% more TST in N2 sleep and 4.7% less in N3 sleep than whites [46]. Similar sleep architecture findings were reported in the MrOs Sleep study (one night of home PSG) where black men had less N3 sleep than white men (4.9% vs. 8.8%, $P < 0.001$) [22]. Actigraphic measures also found that black men had longer sleep latencies (28.7 vs. 21.9 min, $P = 0.02$) and lower sleep efficiencies (80.6% vs. 83.4%, $P = 0.02$). Similarly, in CASS, Carnethon et al. reported that Blacks significantly increased sleep fragmentation index and greater wake after sleep onset time (50.2 vs. 41.2 min, $P < 0.01$) than whites. However, these sleep parameters were similar in Asians and Hispanics relative to whites [24]. In the SWAN sleep study, using home PSG, black women had longer sleep latency, poorer sleep efficiency, lower N3 stage sleep than white women [21]. Chinese women also had significantly lower N3 sleep than white women. Additionally, this study used EEG spectral analysis to quantify sleep microstructural differences and found that beta power, a marker of hyperarousal during sleep, was significantly higher in black women than white women [21]. Using ACT in CARDIA, white women had shorter sleep latency (34 vs. 48 min,

TABLE 7.2 Representative studies examining sleep disordered breathing in racial/ethnic minorities and low SES populations.

Study	Design/source	Sample	Racial/ethnic/SES (% of sample)	SDB assessment	SDB definition	Covariates	Findings; OR (95% CI) (reference racial/ethnic group is white)		
Young et al. [39,40]	Cross-sectional; Sleep Heart Health Study (SHHS)	N = 5615; 53% women; age 64 ± 11	Black: 7.4 American Indian: 10.4 Other: 5.0 White: 77.1	1-night home PSG	AHI ≥15	Age, sex	Black 1.23 (0.97–1.6) American Indian 1.70 (1.4–2.1) Other 0.94 (0.65–1.37)		
Fulop et al. [41]	Cross-sectional; Jackson Heart Study (JHS)	N = 5301; 63% women; age 55 ± 13	Black: 100 Annual income <25K: 27.5	5 items: sex, snoring, witnessed apneas, BMI, age	SDB risk score	None	<i>High SDB risk:</i> women 16.8% men 3.5% <i>Habitual loud snoring:</i> women 58.1% men 66.3% <i>Excessive daytime sleepiness:</i> women 61.4% men 68.6%		
Johnson et al. [42]	Cross-sectional; Jackson Heart Study (JHS)	N = 825; 66% women; age 63 ± 11	Black: 100	1-night home PSG	AHI 5–15; AHI 15–30; AHI ≥30	None	Mild SDB 38.4% Moderate SDB 21.3% Severe SDB 15.8%		
Chen et al. [23]	Cross-sectional; Multi-Ethnic Study of Atherosclerosis (MESA) Sleep cohort	N = 2230; 54% women; age 68 ± 9	Black: 28.0 Hispanic: 23.9 Chinese: 12.1 White: 36.1	1-night home PSG	SAS: AHI ≥5 and ESS ≥10 Severe SDB: AHI ≥30	Age, sex, and site	Black	SAS	AHI ≥30
Mihaere et al. [43]	Cross-sectional; New Zealand	N = 358; 27% women; age 30–59	Maori: 46.4 White: 53.6	1-night of home PSG	RDI ≥15	Age, sex	Maori 4.26 (1.31–13.9)		
Kripke et al. [44]	Cross-sectional; San Diego, CA	N = 355; 54% women; age 40–64	Black: 3.4 Hispanic: 12.4 Other: 3.9 White: 80.3	4-nights of oximetry and actigraphy	ODI 4 ≥ 20	None	Black 16.7 Hispanic 15.9 Other 21.5 White 5.6		
Redline et al. [45] Cross-sectional; Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Central Am Cuba Dom Rep Puerto Rico South Am Mexico mixed	N = 14,440; 60% women; age 46 ± 12	Central Am: 10.3 Cuba: 13.2 Dom Rep: 8.9 Puerto Rico: 15.9 South Am: 6.5 Mexico: 42.3 Mixed: 2.8 Annual income <30K: 64	1-night of home PSG	AHI ≥15	Age, BMI		Men	Women	
							15.2	4.9	
							17.8	6.1	
							16.0	4.9	
							11.7	7.0	
							13.0	5.5	
							14.4	5.8	
							16.4	4.6	

Data presented as means ± SD, frequency (95% CI) or OR (95% CI). **Bolded values** represent P < 0.05 for Chi-square comparisons. AHI, apnea-hypopnea index (events/h of sleep); BMI, body mass index; ESS, Epworth sleepiness scale; PSG, polysomnography; RDI, respiratory disturbance index; SAS, sleep apnea syndrome; SDB, sleep disordered breathing; SES, socioeconomic status.

$P < 0.01$) and greater sleep efficiency (77% vs. 69%, $P < 0.01$) than black men [19]. White men and black women had similar intermediate sleep latency and sleep efficiency. In a metaanalysis of studies comparing subjective and objective sleep parameters [47] and among Black ($n = 1010$) and white ($n = 3156$) healthy sleepers, Ruiter et al. reported that Blacks had significantly shorter TST (objective and subjective), longer sleep latency (SL) greater N2 and lower N3 sleep percentage than whites [48]. However, racial/ethnic differences in many of these variables disappeared when studies examined participants in sleep laboratories and excluded participants with (1) undiagnosed mental illness or (2) using prescription medications. Finally, the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) has shown that there is significant heterogeneity in ACT sleep patterns among US Hispanics [25]. In SES-adjusted models, Dudley et al. showed that individuals of Mexican heritage had the most consolidated sleep and healthiest sleep schedule while individuals of Puerto Rican descent had the most fragmented sleep and irregular sleep. To our knowledge, there are no other objective sleep data examining sleep heterogeneity within other US racial/ethnic minority groups.

Sleep architecture and continuity across SES groups

Currently, sparse data concerning the influence of SES factors on sleep architecture and continuity independent of race/ethnicity exists in the literature. In ACT-measured sleep in CARDIA, analyses adjusting for education and employment status showed that lower income was associated with longer SL and lower sleep efficiency [19]. In Pittsburgh, lower SES (assessed by a composite of education and income) was associated with longer ACT SL and greater PSG wake after sleep onset (WASO) time [20]. Similarly, in the SWAN study, financial strain was associated with poorer PSG-assessed sleep continuity and efficiency and this relationship was equivalent across race–ethnicity [21]. Thus, using multiple proxies for SES, most existing data suggest more disruptive and less efficient sleep in lower SES individuals.

Sleep disorders

Sleep disordered breathing (SDB)

SDB encompasses a number of chronic breathing abnormalities occurring during sleep, of which OSA is the most common [49]. Diagnosis of SDB requires PSG with

detection of breathing abnormalities (>5 per hour of sleep) associated with sleep irregularities/daytime consequences [49]. Estimates of the prevalence of moderate to severe SDB (apnea–hypopnea index [AHI] ≥ 15) in the US middle-aged (50–70 years of age) population are 17% for men and 9% for women [50].

Symptoms of and risk factors for sleep disordered breathing across racial/ethnic groups

Population-based studies have shown that SDB symptoms may vary across racial/ethnic groups. In the Sleep Heart Health Study, habitual loud snoring was significantly more common among Black (OR 1.6 [1.1–2.1]) and Hispanic (OR 2.3 [1.5–3.4]) women than among white women [51]. Hispanic men had more than twice the odds (OR 2.3 [1.4–3.7]) of reporting loud snoring than white men; However, the prevalence of loud snoring was similar among Black, Asian/Pacific islander, American Indian and white men [51]. Subjective excessive daytime sleepiness (EDS), one of the hallmark consequences of SDB, varies by racial/ethnic groups and assessment method. In analyses adjusted for demographics, medical comorbidities, sleep and psychosocial variables in the MESA study, Baron et al. found that Blacks had significantly higher odds (OR 1.5 [1.2–1.9]) for EDS (Epworth sleepiness scale >12) than whites [52]. The odds of reporting EDS (ESS >12) among Hispanics and Chinese participants was similar to that of whites. However, when EDS was measured as frequency reporting feeling excessively sleepy on 5 days or more over the previous month, Black (OR 0.57 [0.5–0.7]) and Hispanic (OR 0.62 [0.5–0.8]) participants were less likely to report EDS than whites. These contradictory data may suggest cultural differences in the interpretations of questions assessing sleepiness or normative levels of daytime sleepiness [52,53]. Normalization of the consequences of the nocturnal symptoms may lead to lower screening for SDB among racial/ethnic individuals.

Some recognized risk factors for SDB may vary among racial/ethnic groups compared to whites. For example, one of the strongest risk factors for SDB is obesity, which is prevalent among US Blacks, Hispanics, and American Indians [32,54–56]. In age- and gender-adjusted analysis of SHHS, Blacks and American Indians had a significantly higher odds of moderate to severe SDB (AHI ≥ 15) [39]. However, after adjusting for body habitus, racial/ethnic background was no longer associated with increased risk for SDB relative to whites. Thus, much of the increased risk of SDB among racial/ethnic individuals may be

attributable to increased prevalence of obesity. Also, racial/ethnic individuals may distribute excess body fat differently. Therefore, typical body mass index (BMI) definitions of obesity (i.e., 30 kg/m^2) may not adequately measure SDB risk across racial/ethnic groups. As Asians store greater amounts of body fat at the same level of BMI, the World Health Organization has recommended using a lower BMI threshold (i.e., 25 kg/m^2) to define obesity in Asian populations [57]. Data from MESA shows that each unit BMI increase may have a greater effect on AHI in Asian Americans than among other US racial/ethnic groups [58]. Thus, alternative measurements of obesity among racial/ethnic individuals should be considered in SDB risk-stratification.

Racial/ethnic differences in craniofacial anatomy have also been implicated in differential risk for SDB among racial/ethnic groups. Studies have suggested that soft tissue factors (e.g., tongue size, soft palate, tonsils) may be more relevant in predicting SDB risk among Blacks while skeletal components of the upper airways (e.g., maxillary-mandibular shape, inferior hyoid position) may be more important among Asians [59]. Studies comparing the anatomical differences between Blacks and whites have noted that the volume of the tongue is significantly larger among Blacks with SDB [60]. Relative to whites, Asian individuals have been found to have greater skeletal restrictions assessed by shorter cranial base as well as decreased thyromental distance and larger thyromental angles, suggesting the presence of these skeletal features contributed to their upper airway obstruction [61]. Among the Maori of New Zealand, reductions in mandibular prognathism and wider bony nasal aperture were associated with SDB, while reduced retropalatal airway size was more important among whites participants [62]. Less is known about Hispanic craniofacial structure and SDB risk. One cephalometric study found that Hispanics had greater bimaxillary retroposition relative to whites, but another failed to find any anatomical differences between Hispanics and whites [63,64]. However, these anatomical data are limited by the relatively small sample size ($n < 100$) of these studies.

Diagnosis of SDB across and within racial/ethnic groups

The prevalence of SDB among some racial/ethnic groups has been reported to be higher than among whites. For example, in the SHHS, the prevalence of moderate to severe SDB ($\text{AHI} \geq 15$) was 23%, 20%, and 17% among American Indians, Blacks, and whites, respectively [40]. A metaanalysis examining studies of SBD between Blacks

and whites ($n = 10$ studies) found a small but significant effect size for Blacks having more prevalent and severe SDB relative to whites [65]. A recent study ($n = 512$; 48% women; 66% black) has specifically identified that this Black–white difference in SDB severity may be primarily driven by younger [66] and middle-aged (50–59 years of age) Black men [67]. In the Jackson Heart Study ($n = 5301$), Fulop et al. reported that 16.8% of Black women and 3.5% of Black men were at high risk for SDB and that individual symptoms of SDB were extremely common [41] (Table 7.2). In a subset of this cohort completing PSG ($n = 825$), 37.1% of this sample had moderate to severe SDB.

Early studies that explored diverse samples suggested that Hispanics may carry an excessive burden of SDB relative to their white counterparts. In a population-based study in San Diego, Kripke et al. showed that Hispanic participants ($n = 44$, mainly of Mexican-descent) had higher prevalence of moderate to severe SDB than whites (15.9% vs. 5.6%) [44]. In the MESA study, US Hispanics had more than twice the odds of severe SDB than whites [23]. Recently, data from the HCHS/SOL ($n = 14,440$) showed that the large heterogeneity within US Hispanics regarding SDB [45]. Overall, 19% of Hispanic women and 33% of Hispanic men had at least mild SDB ($\text{AHI} \geq 5$) with 6% of women and 14% of men having moderate to severe SDB ($\text{AHI} \geq 15$). However, among US Hispanic men, moderate to severe SDB was most common among Cubans and least common among those of South American and Puerto Rican background (Table 7.2). Among Hispanic women, SDB was most prevalent among individuals of Puerto Rican heritage and least common among women of South American background [45]. Thus, although the overall SDB estimates among US Hispanics may be similar to that of the US general population, these data suggest that specific Hispanic subgroups may be particularly high risk for SDB.

There is also evidence of heterogeneity in the prevalence of SDB within individuals of Asian descent. Early studies comparing SDB among white and Asian individuals (ethnicity not reported) presenting to a sleep center reported that Asians had significantly greater prevalence of severe SDB (25% vs. 11%, $P = 0.03$) [68]. In the MESA study, adjusted analyses revealed that Chinese individuals were 37% more likely to have severe SDB ($\text{AHI} \geq 30$) than whites [23]. However, a cross-cultural SDB comparison study between individuals from Japan ($n = 978$) and the US (Hispanics $n = 211$; whites $n = 246$) found that the prevalence of SDB ($\text{RDI} \geq 15$) among the Japanese (18.4%) was significantly lower than among US Hispanics (36.5%) or whites (33.3%) [69]. The SDB

prevalence differences in these groups were largely explained by differences in their BMIs. There are few data for direct SDB comparison studies of other Asian ethnic subgroups living in the United States. Finally, in population-based studies from New Zealand, the Maori people have been reported to have four times the risk of moderate to severe SDB than white individuals (6% vs. 1.5%) [43]. However, in analyses that adjusted for BMI, the association between ethnicity and SDB disappears. This suggests that increased body habitus among the Maori, as in US racial/ethnic groups, imparts greater SDB risk. Overall, these studies propose that a great deal of heterogeneity for SDB may exist in individuals of Asian descent.

SDB symptoms and diagnosis across SES groups

Beyond the risk factors of race/ethnicity, low SES individuals may have higher risk for SDB mediated by increased obesity rates, unhealthy behaviors (e.g., smoking, alcohol use), toxic environmental exposure, or other factors [20,32,42,70]. However, as seen in Table 7.2, most epidemiological studies examining PSG-verified SDB among racial/ethnic groups have not adjusted for SES measures [23,40,44,68]. Indirect evidence for SDB comparisons among socioeconomically diverse samples may be gained from randomized clinical trials that eliminate some of the financial barriers associated with sleep testing. For example, in the Home PAP study (seven US cities; $n = 183$) [71], individuals who lived in the poorest neighborhoods had similar SDB severity to those who lived in more affluent neighborhoods ($AHI 43 \pm 28$ vs. 44 ± 26 , $P = 0.81$). In other smaller studies (SWAN, Sleep Score Table 7.1), different SES measures have not been found to be associated with SBD severity [20,21]. In NHANES analyses ($N = 4081$; household income <\$20,000 annually; 15.5% of the sample) adjusting for demographics, income, and other SES factors, Grandner et al. described an inverse relationship between habitual snoring and educational attainment with those achieving higher educational degrees reporting lower odds of snoring relative to highly educated individuals [72]. In addition, low household food security (vs. high) was associated to greater odds of symptoms suggestive of SDB [73]. Similarly, analyses from the JHS adjusting for demographics, health behaviors, and comorbidities, Fulop et al. reported that lower SES individuals and physical inactivity were associated with high SDB risk among Blacks [41]. To date, the prevalence of PSG-diagnosed SDB between different SES levels has not been comprehensively studied.

Insomnia

Approximately 33% of the US general population reports insomnia complaints, including difficulty falling asleep, maintaining sleep, and/or premature awakening [74]. Even when more stringent diagnostic criteria are used, the prevalence of chronic insomnia disorder ranges from 6% to 15% [75]. Most population-based studies have focused on insomnia complaints (nocturnal symptoms alone) as opposed to insomnia disorder (complaints associated with daytime impairments) [49]. We have included studies examining sleep quality in this section in accordance with one presentation of insomnia: non-restorative sleep.

Insomnia complaints across racial/ethnic groups

Studies assessing insomnia complaints in racially/ethnically diverse samples have used a varying assessment of insomnia symptoms. One of the first studies was conducted among Blacks and whites living in a small county in Florida ($n = 1645$) [76]. In that study, 58% reported on survey questionnaire insomnia complaints, and this finding was greater among lower SES, but unrelated to race. An early population-based study concerning racial/ethnic differences in sleep complaints was the Established Populations for Epidemiologic Studies of the Elderly Study [77]. Using a racially diverse sample representing older individuals from North Carolina ($n = 3976$, 54% Black), Blazer et al. evaluated sleep complaints using questions: difficulty falling asleep (DFA), difficulty maintaining sleep (DMS), early morning awakenings (EMA), and non-restorative sleep (NRS). Whites were significantly more likely to endorse all insomnia complaints than Blacks (Table 7.3). In addition, among those with high levels of insomnia complaints, whites were more likely to be prescribed sedative-hypnotic medications than Blacks (83% vs. 17%, $P < 0.001$) [77]. Significant Black–white disparity in insomnia complaints were also found in the Atherosclerosis Communities at Risk (ARIC) study, a population-based study of cardiovascular risk in four US cities [78]. Assessing symptoms of DFA, DMS, or NRS, Phillips and Mannino found that Blacks had significantly lower odds of reporting DFA or DMS (OR 0.8 [0.7–0.9] for both sleep complaints) [78]. In an analysis of the Women's Health Initiative ($n = 98,705$; 8% Black, 3% Hispanic, 4% other), Kripke et al. assessed the frequency of sleep complaints [81] in the previous month in post-menopausal women [82]. Black, Hispanic, and women of

other racial/ethnic minorities reported more DFA but less DMS and use of sleep aids. Similarly, in sample of older women in Brooklyn, Jean Louis et al. ($n = 1274$, 72% Black) found that white women reported insomnia complaints more often than Black women (74% vs. 46%, $P < 0.001$). Specifically, white women complained of greater rates of DFA (42% vs. 16%, $P < 0.01$), DMS (64% vs. 40%, $P < 0.01$), EMA (53% vs. 27%, $P < 0.01$), and regular use of sleep medicine (19% vs. 4%, $P < 0.01$) than Black women [83]. In a metaanalysis comparing insomnia studies among Black and whites ($n = 13$ studies; 21,685 Black, 108,964 white participants), Ruiter et al. found small negative effect sizes for sleep complaints and subjectively measured wake after sleep onset (WASO) and terminal wakefulness but not for subjective SL [65]. These data show that Blacks report significantly less sleep complaints and report less subjective time awake after falling asleep than whites.

Other community-based and nationally representative samples have been able to provide data on insomnia complaints of other racial/ethnic groups. Analyzing the 2006 Behavioral Risk Factor Surveillance System (BRFSS), Grandner et al. used responses to the question “Over the last 2 weeks, how many days have you had trouble falling asleep or staying asleep or sleeping too much?” to categorize sleep complaints (SC) and their association with social determinants [79]. Participants categorized with SCs were those reporting problems most days of the week. In adjusted models for age, education, income, marital status, and unemployment, Asian/other men had significantly lower odds (OR 0.43 [0.24–0.76]) of reporting SCs than white men. The odds for SC in men of other racial/ethnic groups (Black, Asian/other, Hispanic) were equivalent to those of white men [79]. For women, Black, Asian/other, and Hispanic women all had significantly lower odds of reporting SCs than white women. In contrast, multiracial women had increased odds of SCs (OR 1.67 [1.09–2.55]) compared to white women. Similar results were found in the MESA study, where Chen et al. used the Women’s Health Initiative Insomnia Rating Scale (WHIIRS) to diagnose insomnia complaints over the previous 4 weeks [23]. Black and Hispanic participants had similar odds of insomnia than whites while Chinese participants had lower odds of insomnia (OR 0.66 [0.44–1.00]) than whites. In NHANES, Grandner et al. assessed insomnia complaints via two methods: (1) asking how long it took an individual to fall asleep and (2) inquiring about frequency of *difficulty* with falling asleep, maintaining sleep, premature awakenings, or non-restorative sleep [73]. Mexican Americans and other Hispanic individuals had a 40% and 30%, respectively, lower

odds of having DFA than whites. In addition, Mexican Americans had 20% lower odds of reporting DMS. Relative to whites, Blacks had greater odds of reporting SL > 30 min but lower odds of reporting DFA, DMS, EMA, or NRS (Table 7.3) [73]. These data among minority individuals suggest that the wording of insomnia assessment may influence results among racially/ethnically diverse individuals.

In a community-based sample of three indigenous North American groups (56% women, age 43 ± 1 years) [56], Froese et al. found that 17% of this sample reported insomnia symptoms (DFA, DMS, EMA, or NRS) “every night or almost every night.” Using the Pittsburgh Sleep Quality Index in participants from eight rural Indian reservations ($n = 386$, 54% women, age 31 ± 14 years), Ehlers et al. reported that slightly $>50\%$ of the sample had SL > 30 min and reported overall poor sleep quality (PSQI score >5) [84]. In age-, gender-, and SES-adjusted analyses in New Zealand, Maori ethnicity was associated with greater odds of DMS and EMA complaints than among whites [80].

Insomnia complaints across SES groups

Many of the same studies evaluating insomnia complaints or poor sleep among racial/ethnic groups have also explored their associations with SES variables. Among elderly individuals in EPSES, lower education was associated with greater insomnia complaints after adjustment for demographics, health status, depression, cognitive impairment, and use of sedative-hypnotics [77]. In a study using sleep diaries and daytime impairments to define insomnia disorder ($n = 575$, 50% women, 27% Black), Gellis et al. found that individuals with lower educational attainment had greater odds of insomnia (Table 7.3) [85]. Compared to college graduates, high school drop outs were 3.9 times more likely to have insomnia and high school graduates were 2.3 times more likely to have insomnia. Analyzing data from the BRFSS, Grandner et al. found that having lower educational attainment, living in poverty (annual income $< \$10,000$), or unemployment were all associated with significantly greater odds of SS than college graduates, earning more than \$75,000 annually, or having full-time employment [79]. An inverse linear relationship was noted between education, income, and SS with increasing odds for SS as income and education categories each decreased. Similarly, in NHANES, Grandner et al. reported that long SL was associated with lower educational attainment, lacking private insurance, and food insecurity [73]. In nationally representative sample of New Zealand, after adjusting for ethnicity and demographic

TABLE 7.3 Representative studies examining insomnia in adult racial/ethnic minority and lower SES populations.

Study	Design/source	Sample	Racial/ethnic/ SES (% of sample)	Insomnia assessment	Insomnia definition	Covariates	Findings; OR (95% CI) (refer- ence racial/ethnic group is white)		
Blazer et al. [77]	Cross-sectional; Established Popula-tions for Epidemiologic Studies of the Elderly study (EPESES)	N = 3976; 65% women; age 73 ± 7	Black: 54.2 White: 45.8	4 items; no data on symptom duration	DFA, DMS, EMA, NRS	None	<u>DFA</u> <u>White</u> 16.3% vs black 13.4%		
Phillips and Man-nino [78]	Cross-sectional; Atherosclerosis Risk in Community Study (ARIC) 1990–92 wave	N = 13,563; 55% women; age 50–59: 53%	Black: 23.7 White: 76.3 Annual in- come <16K: 19.1	3 items; no data on symptom duration or frequency	DFA, DMS, or NRS	Age, sex, BMI, indi- vidual SES factors, health behaviors, comorbidities, depression, hypnotic use, menopausal status	<u>DFA</u> <u>Black</u> 0.8 (0.7–0.9)		
Grandner et al. [79]	Cross-sectional; Behavioral Risk Factor Surveillance System (BRFSS)	N = 159,856; 60% women; age 52 ± 16	Black: 8.9 Hispanic: 17.4 Asian/other: 4.8 Multirace: 1.8 White: 67.1	Telephone survey items	1 item: “trouble fall-ing asleep, staying asleep, or sleeping too much” over 2 weeks	Age, education, in- come, marital sta-tus, employment, interactions	OR (95% CI)	<u>Women</u>	<u>Men</u>
Chen et al. [23]	Cross-sectional; Multi-Ethnic Study of Atherosclerosis (MESA) Sleep cohort	N = 2230 adults; 54% women; age 68 ± 9	Black: 27.4 Hispanic: 23.7 Chinese: 11.7 White: 37.1	5 items: Women’s Health Initiative Insomnia Rating Scale	WHIIRS >10	Age, sex, and site	<u>Black</u> 1.11 (0.86–1.45) <u>Hispanic</u> 1.28 (0.95–1.72) <u>Chinese</u> 0.66 (0.44–1.00)		

Continued

TABLE 7.3 Representative studies examining insomnia in adult racial/ethnic minority and lower SES populations.—cont'd

Study	Design/source	Sample	Racial/ethnic/ SES (% of sample)	Insomnia assessment	Insomnia definition	Covariates	Findings; OR (95% CI) (refer- ence racial/ethnic group is white)
Patel et al. [30]	Cross-sectional; Philadelphia Health Management Corporation	<i>N</i> = 9553; 67% women; age 40–64:51%	Black: 21.1 Hispanic: 10.6 Other: 2.6 White: 65.7 Poor: 26.8	Telephone survey item	1 item: "How would you rate quality of sleep in past week?"	Age, sex, BMI, education, employment, marital status, general and mental health, health behaviors	OR (95% CI) Black, not poor 1.45 (1.1–1.9) Black, poor 1.2 (0.9–1.5) Hispanic, not poor 1.3 (0.8–2.1) Hispanic, poor 1.05 (0.7–1.5) Other, not poor 1.01 (0.5–2.1) Other, poor 0.67 (0.2–2.3) White, poor 4.20 (3.3–5.4)
Grandner et al. [72,73]	Cross-sectional; National Health and Nutrition Examination Survey 2007–08	<i>N</i> = 4081; 48% women; age 47 ± 17	Black: 10.3 Mex-Amer: 7.6 Other Hisp: 4.6 Asian/other: 4.8 White: 72.8 Income <20K: 13.5	5 items; "How long does it take to fall asleep at bedtime?"; "In the past month, how often had you had difficulty with"	SOL >30 min, DFA, DMS, EMA, or NR sleep	Age, sex, marital status, individual SES factors, marital status, immigrant status, physical and mental health	<u>SOL</u> >30 min Black 1.6 (1.3–2.0) <u>DFA</u> Black 0.6 (0.5–0.7) Mex-Amer 0.6 (0.5–0.8) Other Hispanic 0.7 (0.5–0.9) <u>DMS</u> Black 0.8 (0.7–0.98) Mex-Amer 0.8 (0.6–0.98) <u>EMA</u> Black 0.8 (0.7–0.96) <u>NRS</u> Black 1.6 (1.3–2.0)
Paine et al. [80]	Cross-sectional; New Zealand	<i>N</i> = 2670; 56% women; age 20–59	Maori: 45.8 White: 54.2	Mailed questionnaire	DFA, DMS, EMA, NRS	Age, sex, shift work, employment status, SES deprivation score	<u>DMS</u> Maori 1.2 (1.0–1.5) <u>EMA</u> Maori 1.4 (1.2–1.7) Unemployed vs employed <u>DFA</u> 1.4 (1.1–1.7) <u>DMS</u> 1.4 (1.2–1.9)

Data presented as means ± SD or OR (95% CI). **Bolded values** represent $P < 0.05$ for Chi-square comparisons. *AHI*, apnea-hypopnea index; *BMI*, body mass index; *DFA*, difficulty falling asleep; *DMS*, difficulty maintaining sleep; *EMA*, early morning awakening; *NRS*, nonrestorative sleep; *SES*, socioeconomic status; *SOL*, sleep onset latency; *WASO*, wake after sleep onset; *WHIIRS*, women's health initiative insomnia rating scale.

factors, living in areas of socioeconomic deprivation and being unemployed were also associated with increased odds of DFA and DMS complaints [80].

Studies that have utilized sleep quality as a proxy for insomnia have produced similar findings. In the SWAN Sleep study cohort, analyses adjusted for demographics, health status, depression, and sleep medications showed that greater financial strain was related to more sleep quality complaints [21]. Similarly, in Pittsburgh, Mezick et al. found that a lower SES composite score (income and education) was associated with poorer sleep quality [20]. In another study focusing on sleep quality, Patel et al. examined the relationship between sociodemographic factors and perceived poor sleep [30]. In models adjusting for education, employment, and health covariates, impoverished whites (OR 4.20 [3.3–5.4]) and nonpoor Blacks (OR 1.45 [1.1–1.9]) had significantly increased odds of poor sleep quality than nonpoor whites. These covariates mediated the association of poor sleep quality among poor Blacks observed in unadjusted analyses. These data suggest a complex relationship between SES measures and perceived sleep health that may vary by racial/ethnic background. Not all studies have found an association between insomnia and SES. For example, in a diverse sample of low-income individuals in Brooklyn ($n = 1118$; mean income $< \$20,000$ annually), adjusting for health status, social support, and demographics, neither education nor income predicted a composite sleep disturbance index score [86]. These contradictory data suggest that the relationship with SES and insomnia may vary in racial/ethnic samples. They may also indicate a need for comprehensive measures of SES and/or measurement of protective factors (e.g., coping style, social networks) that may explain the moderation of race on the relationship between SES and insomnia symptoms.

Restless leg syndrome (RLS) and periodic limb movements during sleep (PLMS)

The prevalence of RLS and PLMS is estimated to be between over 1% and 15% in the general population, depending on the diagnostic criteria used [87]. Almost all patients with RLS exhibit PLMS [88]. In a comprehensive sleep study including 24-h PSG, 592 participants from Detroit ($n = 186$ Blacks) completed subjective and objective sleep measurements to determine racial/ethnic differences in the prevalence of PLMS. The authors found a lower prevalence of PLMS in Blacks compared to whites (4.3% vs. 9.3%, $P < 0.05$) [89]. While the other racial/ethnic groups were too small to analyze, they included American Indian or Alaskan Native, Asian and “other racial” groups. The “other” racial category had similar

prevalence of PLMS to whites. Given that lower stores in the blood is associated with PLMS/RLS [90], one study examined serum ferritin—a protein that stores iron—and complaints of RLS in dialysis patients comparing Blacks with whites. Using a combination of in-person interviews and medical chart review, 210 chronic kidney disease patients (48% Black) were asked: “During the past 4 weeks, to what extent were you bothered by restless legs?” Blacks had a lower odds of complaint or “bothered by restless legs symptoms” compared with whites. Blacks also had a lower odds of reporting RLS than white patients (OR, 0.44; $P = 0.03$) [91]. The results were similar to an earlier investigation conducted by the same group. In that study, 48% of older Blacks reported a complaint of RLS compared to 68% of whites ($P = 0.0006$). The findings remained significant after adjusting for gender, education, BMI, cardiovascular disease (CVD) morbidity, hours receiving hemodialysis treatment, and months receiving hemodialysis treatment [92].

Most recently, in a large representative cohort of veterans, Molnar et al. conducted a 1:1 propensity score matched analysis in a cohort consisting of 3696 patients (17% Black) in each group. In adjusted analysis, Black, Hispanic, and “other race” was associated with a decreased risk of incident RLS than whites. In an assessment of clinical outcomes, Blacks reported a similar risk to whites for CVD and stroke, but reduced risk for mortality. No other racial/ethnic group was included in the analysis. Finally, incident RLS was associated with an 88% increased hazard ratio of mortality across all racial groups, except for Blacks [87].

Using data from the Baltimore Health and Mental Health Study, which included a seven-item RLS validated questionnaire, unadjusted results revealed similar prevalence rates of RLS (4.7%) in Blacks and (3.8%) whites. After adjusting for age, gender, SES, and medical comorbidities, there were no differences in rates of RLS found between Blacks and whites [93]. The authors speculated that a phenotypically difference in RLS symptoms could be different in Blacks than other racial groups. Given the lower prevalence of RLS and/or PLMS among Blacks, one group of investigators speculated that Blacks are less likely to seek treatment for RLS/PLMS. This may partly explain the lower prevalence [93], but to our knowledge, this hypothesis has not been tested.

The Sleep Health and Knowledge in US Hispanics Project conducted the first population-based study to assess RLS in Hispanics [94]. 1754 Hispanics of Mexican descent and 1913 non-Hispanic whites in San Diego, were queried about RLS, based on the four diagnostic criteria from the International Restless Legs Syndrome Study Group [95]. Hispanics had a lower prevalence of RLS than whites

(14.4% vs. 18.3%, $P = 0.002$). Koo et al. analyzed data from the MESA sleep study, and found that Blacks had less PLMS (10.5%) than other ethnic groups. A higher prevalence of PLMS was found in whites (18.8%), Hispanics (20.1%), and Chinese Americans (19.1%). When analyzing race/ethnicity and prevalence of hypertension among those with PLMS, middle aged to older Blacks had 20% increase in their odds of having hypertension and Chinese Americans had a 10% increase in their odds of having hypertension relative to whites [96]. In sensitivity analysis, PLMS was associated with 2.47 mmHg systolic and as high as 3.71 mmHg systolic, depending on the unit of PLMS (periodic leg movement index [97] 10-unit vs. PLMAI 1-unit) ($P < 0.0001$). Similar findings were reported for Chinese Americans, 10-unit increase in PLMI was associated with 1.31 mmHg higher SBP ($P = 0.03$). For diastolic blood pressure, there were modest significant findings with PLMI among Blacks and Chinese Americans ($P = 0.09$ and $P = 0.08$) but not for Hispanics.

To summarize, in all previous studies Blacks have reported lower prevalence of RLS and PLMS, other racial/ethnic groups have similar prevalence of PLMS compared to whites, and all studies compared one racial/ethnic group (e.g., Blacks to whites) with the exception of the MESA study. The clinical outcomes suggest that despite lower risk, when the disorder is present it confers greater morbidity among racial/ethnic minorities. Given that there are few studies on these conditions, and because not all studies have adjusted for the same set of covariates, and population differences (e.g., older men only, hemodialysis patients), it is too soon to definitively make an assessment about the lower prevalence of RLS/PLMS in Blacks compared to whites. Notably, none of the aforementioned studies investigated the role of SES.

Narcolepsy

The first study to assess the prevalence of narcolepsy in the United States was conducted among young (16–34 years of age) naval recruit men at the US Marine Corps in North Carolina [98]. In this study, the prevalence of narcolepsy was estimated to be 19 cases out of 10,000 recruits [98]. The author described Black men as “constantly in a state of readiness for sleep” and referenced an impoverished environment as potential contributions to narcolepsy among Black men. Later in 2002, Okun et al. conducted a retrospective study of patient data at the Stanford Sleep Clinic ($n = 64$ Blacks, $n = 353$ whites, $n = 32$ Asians, $n = 26$ Latinos, $n = 9$ mixed ethnicity). There were no differences across ethnic groups in symptomatology and severity [99]. In 2009, a population-based study was conducted in King County, Washington to determine the

prevalence of narcolepsy among a diverse patient population. Patients were recruited from local sleep centers, neurologists, or self-referred. Patients were eligible if they reported a diagnosis by a physician of narcolepsy. Blacks (42.8%) had the highest prevalence of narcolepsy followed by whites (32.2%), Asians (15.0%), and other races (27.9%) [100]. At Stanford University, the largest study to date that compared ethnic differences ($n = 839$ whites, $n = 182$ Blacks, $n = 35$ Asians, $n = 41$ Latinos) in the clinical presentation of narcolepsy type 1 [100] and type 2 [101] was conducted. Adjusting for age, sex and BMI, Black patients with narcolepsy type 1 and patients with narcolepsy type 2 were diagnosed at an earlier age and scored higher on the Epworth Sleepiness Scale ($P < 0.001$) than whites, Asians, and Hispanics [101]. In a subgroup analysis, Hispanics with type 2 also presented at an earlier age ($P < 0.003$). Blacks with narcolepsy type 2 exhibited cerebrospinal fluid (CSF) hypocretin-1 deficiency and lower mean CSF hypocretin-1 levels than whites (45.7 ± 22.1 pg/mL vs. 262.6 ± 16.4 pg/mL). The sample size was too small among other groups to analyze CSF hypocretin-1 levels. Importantly, from this data, genetic typing of human leukocyte antigen (HLA) DQB1*0602 allele, was analyzed. HLA DQB1*06:02 positivity was significantly higher in blacks than other ethnicities (91.6% vs. 77.4%, 80.4%, and 71.7%, respectively; $P < 0.001$). Blacks were also obese and of younger age. The early age finding is likely related to a strong genetic component and a difference in clinical presentation of the disorder in Blacks versus whites. Another interesting finding is that Blacks were less likely to report complaints of cataplexy. It is plausible that there is overlap between cataplexy and other psychological problems (e.g., nightmares, trauma) leading to an underestimation of cataplexy among Blacks.

Circadian rhythms

The results on the circadian processes of racial/ethnic minorities compared with whites is mixed. Among a multi-ethnic cohort of postmenopausal women, circadian rhythm was measured by 24-h collection of urine specimens for melatonin and an Actillume wrist monitor worn for up to 1 week. Daily sleep logs and 1 week of actigraphic recording measured subjective sleep duration. Findings revealed that ethnicity was significantly associated with illumination and European Americans received greater illumination than Blacks, Hispanics and American Indian/Alaska Native ($P < 0.001$). Melatonin secretion was not significantly related to ethnicity and declined with increasing age ($P < 0.001$) [82]. Jean-Louis et al. analyzed data from a group of men and women from San Diego and found no differences in activity patterns, illumination, and timing of

sleep between non-Hispanic whites and minorities [102]. More recent studies suggest that Blacks have a shorter free-running (τ) period. One study conducted by Eastman et al. included 94 healthy adults. Participants provided saliva every 30 min over the course of 5 days and slept in windowless rooms. Data collection was conducted in dim light (<5 lx). Findings revealed that Black women had a τ that was approximately 14 min shorter than white women [103]. The authors' findings were confirmed based on a previous analysis conducted in an earlier study which found that Blacks have larger phase shifts than whites [104]. In another study conducted by Eastman's group, researchers observed Blacks and whites in a laboratory and conducted phase sleep shift (i.e., changing their sleep time as if on eastern time zone). The authors explored cognition and found that Blacks performed less on cognitive assessments than whites [105]. But these findings were in contrast to a later study in which Blacks and whites performed equally on cognitive tasks [106]. While these studies have been conducted in the laboratory environment and with small samples, these early findings raise important questions as circadian sleep-wake processes can have a profound effect on the trajectory of psychiatric disorders [107] and metabolic health [108,109]. Additional research is needed to understand the mechanisms of how these processes influence the development and outcomes of psychiatric and medical morbidity and how these vary by race/ethnicity and sex.

Why do minority Americans have poor sleep?

Thomas et al. [110] described health disparities research occurring across generations including first, second, third, and fourth (see Fig. 7.1). First generation was characterized as measuring the gap in a health outcome based on epidemiological, observational studies using cohort studies and large population data sets. Second generation focused on identifying the mechanisms, third generation focused on designing or identifying solutions to address challenges, and fourth and current generation focuses on taking action and addressing health equity. In the field of sleep medicine, significant work has been done as part of first and second generation, which we have outlined in this chapter. Far less has been done with respect to third and fourth generation research. In the next section, we highlight a select set of potential mediators that could explain disparities: acculturation, discrimination, worry and risk perception, and sleep opportunity, as well as potential solutions.

Acculturation

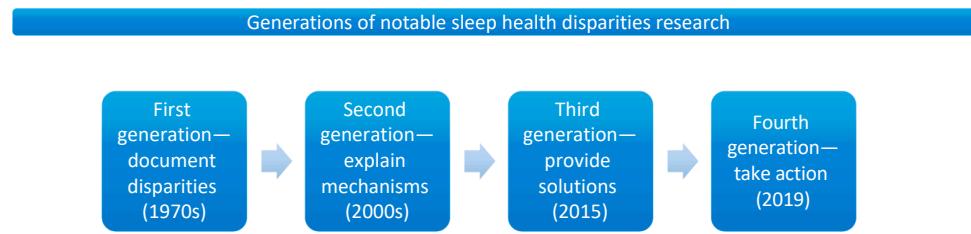
Acculturation is a multidimensional process in which migrants maintain aspects of their culture of origin while

adopting elements of their new cultural group. Acculturation has been measured via multiple proxies (e.g., nativity, language) in studies examining its relationship to sleep [55]. In the NHIS, foreign-born individuals had lower risk for SS (6 h OR 0.92 [0.85–0.99]) and LS (9 h OR 0.85 [0.76–0.95]) than US-born individuals [18]. Similarly, in NHANES, individuals who were born in Mexico reported less SS and those who spoke Spanish only at home reported less very SS (<5 h) compared to whites [17]. In the SWAN study cohort, Hale et al. reported that US-born Latinas, Japanese, and Chinese women were more likely to report SC than their first generation ethnic counterparts [54]. In addition, language acculturation mediated 40% of the association between immigrant status and SC. Among US Hispanics in the HCHS/SOL, greater levels of acculturation stress have been linked to lower ACT-measured TST, greater sleep fragmentation, and more variable sleep timing [111]. Although individuals in the Sleep Health and Knowledge in US Hispanics Project [94] reported a lower prevalence of RLS than whites, additional analyses revealed that among Hispanics with high acculturation, prevalence of RLS was greater than Hispanics with a lower acculturation score (17.4% vs. 12.8%, $P = 0.008$). Highly acculturated individuals had similar prevalence to whites (17.4% vs. 18.3%, $P = 0.637$). There was also a difference in acculturation and gender with high acculturated younger men reporting higher prevalence of RLS than low acculturated younger men (15.5% vs. 7.4%, $P = 0.003$) [94]. In general, greater acculturation is associated with worsened sleep quantity and quality possibly via adoption of unhealthy lifestyle factors of the new culture (e.g., electronics use, lower levels of physical activity) or weakening of protective factors associated with the culture of origin (e.g., social cohesion).

Perceived discrimination

Racial/ethnic minorities experience perceived discrimination and several studies have documented that perceived discrimination is associated with sleep duration and sleep quality [112]. In a review by Slopen et al. [112], absent from these studies were sufficient objective measurements of sleep; 13 out of 17 studies used self-report to measure sleep. Of those studies using an objective measure, the results were inconsistent. In addition, these studies lacked a richness of measures of discrimination and none explored the role of coping including racial/ethnic identity development, which could serve as protective factors [113]. One peer reviewed abstract reported that experiences of racial identity may moderate the relationship between sleep duration and discrimination [114]. Additional evidence on potential mediators to explain this relationship as well as more novel race-discrimination factors including internalized racism and structural racism should be explored. Studying this further may be particularly important as many investigations have described the physiological and

FIGURE 7.1 Historical timeline of notable studies examining sleep and race/ethnicity and health disparities research. Adapted from Thomas SB, Quinn SC, Butler J, Fryer CS, Garza MA. Toward a fourth generation of disparities research to achieve health equity. *Annu Rev Public Health*. 2011;32:399–416. WOS:000290776200022.



psychological consequences of discrimination [115–117], which could have significant implications for sleep health.

Worry and risk perception

Worry and risk perception in the health psychology literature are often seen as contradictory but overlapping constructs [118,119]. One potential reason is that cognitive risk perception (the degree of perceived susceptibility) and worry (affective perceptions) may influence health behavior differently and may also interact in influencing health behavior. These psychosocial variables have been shown to influence cancer screening [120] and uptake of flu vaccination [121]. Little is known about risk perception and worry in sleep medicine. Understanding the role of these factors in sleep is important because these could influence the uptake of screening for PSG, the ability to engage in healthy sleep and adherence to treatment for sleep disorders.

Sleep opportunity

Optimizing sleep entails a balance in sleep opportunity (how much time you spend in bed) and sleep ability (how long you are able to sleep) [122]. If there is a mismatch between sleep ability (low) and opportunity by habitual napping and sleeping in (high) it is likely that the individual will experience too little sleep, too much sleep, NRS, or low sleep efficiency [123]. For example, if you are in bed for 10 h and you can only sleep 5 h then there is a mismatch. This hypothesis has been tested in *Drosophila* flies where extending a dark period (sleep) from 12 to 14 and 16 h resulted in impaired sleep [123]. Indeed, when sleep opportunity is aligned with sleep ability, as is done through sleep restriction, individuals achieve improved sleep efficiency and quality sleep. This research is a promising beginning and raises the importance to test this model in human populations.

Future directions and summary

Converging evidence from several studies over the past 2 decades demonstrate that racial/ethnic minorities report inadequate sleep, experience poor sleep quality, and have a

greater risk for certain sleep disorders, than their white counterparts. Four broad questions remain: First, most of the sleep disparities literature has focused on Blacks, but some studies have described the experience of other racial/ethnic groups. There is a marked paucity in good data on other racial/ethnic groups, rural populations and sexual minorities. How will researchers engage these populations in order to recruit and retain a rich and diverse sample for further inquiry? Second, few studies provide sufficient data to understand the mechanisms of sleep symptoms and sleep disorders by race/ethnicity and SES limiting the ability to infer causality. How will researchers argue for large-scale multiethnic epidemiological studies with long-term follow-up to fully elucidate potential mechanisms that may contribute to disparities in sleep? Simultaneously, intensive naturalistic studies with a smaller sample size could also be undertaken. Third, as there is increasing national, local and global recognition of social determinants of health (SDH), the question for the sleep community is: how do we act on the SDH and implement important public health policy as it relates to closing the disparities gap? Fourth, as we work to determine a strategy to assess these important challenges, at the same time, there is an urgent need to test the efficacy of evidence-based sleep interventions (e.g., PAP adherence, sleep extension, cognitive behavioral therapy for insomnia) to improve health and well-being (e.g., obesity, impaired glucose intolerance, depression, and quality of life). A few investigators have reported on evidence-based sleep interventions and results are promising [124,125]. But, the question still holds which is how does the community ensure that established efficacious treatments (e.g., cognitive behavioral therapy for insomnia) for sleep disorders are generalizable and also personalized to the needs of vulnerable populations? Overall, more could be done to explore variability in sleep disorders by race/ethnicity, SES, and the inclusion of sexual minorities. Importantly, studies must be designed with the explicit purpose of addressing these questions.

In our observation, the field of sleep medicine could advance the discussion by examining both racial/ethnic disparities and SES. In the pursuit of effective policy that could close the disparities gap, we hope that the materials outlined in this chapter will move the field forward.

References

- [1] Kawachi I, Daniels N, Robinson DE. Health disparities by race and class: why both matter—we must link efforts to address the injuries of race and class simultaneously if we are to reduce health disparities. *Health Aff* 2005;24(2):343–52. WOS:000227835700008.
- [2] Analysis BoE. Gross domestic product: second quarter 2018. 2018.
- [3] Analysis BoE. Available from: <https://www.bea.gov/news/2018/gross-domestic-product-second-quarter-2018-second-estimate-corporate-profits-second>; 2018.
- [4] Musu-Gillette L, de Brey C, McFarland J, Hussar W, Sonnenberg W. Status and trends in the education of racial and ethnic groups. Education Do. Washington, DC: National Center for Education Statistics; 2017.
- [5] USDHHS. Healthy People 2020. 2014. Available from: <http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicid=38>.
- [6] Bureau USC. QuickFacts. Income and poverty in the United States: 2017. 2018. Available from, <https://www.census.gov/content/dam/Census/library/publications/2018/demo/p60-263.pdf>.
- [7] Services UDoHaH. Health, United States, 2012: with special feature on emergency care. Hyattsville, MD: National Center for Health Statistics; 2013.
- [8] MMWR. Health objectives for the Nation Healthy People 2000: National Health Promotion and Disease Prevention Objectives for the year 2000. Washington, DC: U.S. Department of Health and Human Services; 1990. p. 695–7.
- [9] Grandner MA, Alfonso-Miller P, Fernandez-Mendoza J, Shetty S, Shenoy S, Combs D. Sleep: important considerations for the prevention of cardiovascular disease. *Curr Opin Cardiol* 2016;31(5):551–65. WOS:000382559100011 [English].
- [10] Grandner MA, Williams NJ, Knutson KL, Roberts D, Jean-Louis G. Sleep disparity, race/ethnicity, and socioeconomic position. *Sleep Med* 2016;18:7–18. WOS:000371837500003.
- [11] Petrov ME, Lichstein KL. Differences in sleep between black and white adults: an update and future directions. *Sleep Med* 2016;18:74–81. WOS:000371837500010.
- [12] Smedley BD, Stith AY, Nelson AR, Smedley BD, Stith AY, Nelson AR, editors. Unequal treatment: confronting racial and ethnic disparities in health care (with CD). The National Academies Press; 2003.
- [13] Adler N. Socioeconomic status and health. The challenge of the gradient effect. *Am Psychol* 1994;49:15–24.
- [14] Marmot MG, Shipley MJ, Rose G. Inequalities in death—specific explanations of a general pattern? *Lancet* 1984;1(8384):1003–6. 6143919, [eng].
- [15] Stamatakis KA, Kaplan GA, Roberts RE. Short sleep duration across income, education, and race/ethnic groups: population prevalence and growing disparities during 34 years of follow-up. *Ann Epidemiol* 2007;17(12):948–55. 17855122. [Epub 2007/09/15. eng].
- [16] Hale L, Do P. Racial differences in self-reports of sleep duration in a population-based study. *Sleep* 2007;30(9):1096–103. WOS:000249293000006 [English].
- [17] Whinnery J, Jackson N, Rattanaumpawan P, Grandner MA. Short and long sleep duration associated with race/ethnicity, socio-demographics, and socioeconomic position. *Sleep* 2014;37(3):601. WOS:000332520400021.
- [18] Krueger PM, Friedman EM. Sleep duration in the United States: a cross-sectional population-based study. *Am J Epidemiol* 2009;169(9):1052–63. 19299406. [Epub 2009/03/21. eng].
- [19] Lauderdale DS, Knutson KL, Yan LJL, Rathouz PJ, Hulley SB, Sidney S, et al. Objectively measured sleep characteristics among early-middle-aged adults—the CARDIA study. *Am J Epidemiol* 2006;164(1):5–16. WOS:000238536900002. [English].
- [20] Mezick EJ, Matthews KA, Hall M, Strollo PJ, Buysse DJ, Kamarck TW, et al. Influence of race and socioeconomic status on sleep: Pittsburgh SleepScore project. *Psychosom Med* 2008;70(4):410–6. WOS:000255922400004. [English].
- [21] Hall MH, Matthews KA, Kravitz HM, Gold EB, Buysse DJ, Bromberger JT, et al. Race and financial strain are independent correlates of sleep in midlife women: the SWAN Sleep Study. *Sleep* 2009;32(1):73–82. WOS:000262075600013. [English].
- [22] Song YS, Ancoli-Israel S, Lewis CE, Redline S, Harrison SL, Stone KL. The association of race/ethnicity with objectively measured sleep characteristics in older men. *Behav Sleep Med* 2012;10(1):54–69. WOS:000300169500005. [English].
- [23] Chen XL, Wang R, Zee P, Lutsey PL, Javaheri S, Alcantara C, et al. Racial/ethnic differences in sleep disturbances: the multi-ethnic study of atherosclerosis (MESA). *Sleep* 2015;38(6):877–88. WOS:000355617000009. [English].
- [24] Carnethon MR, De Chavez PJ, Zee PC, Kim KYA, Liu K, Goldberger JJ, et al. Disparities in sleep characteristics by race/ethnicity in a population-based sample: Chicago Area Sleep Study. *Sleep Med* 2016;18:50–5. WOS:000371837500006. [English].
- [25] Dudley KA, Weng J, Sotres-Alvarez D, Simonelli G, Feliciano EC, Ramirez M, et al. Actigraphic sleep patterns of US Hispanics: the Hispanic community health study/study of Latinos. *Sleep* 2017;40(2):8. WOS:000394129900012. [English].
- [26] Altman NG, Izci-Balserak B, Schopfer E, Jackson N, Rattanaumpawan P, Gehrmann PR, et al. Sleep duration versus sleep insufficiency as predictors of cardiometabolic health outcomes. *Sleep Med* 2012;13(10):1261–70. WOS:000311940400010.
- [27] Jean-Louis G, Grandner MA, Youngstedt SD, Williams NJ, Zizi F, Sarpong DF, et al. Differential increase in prevalence estimates of inadequate sleep among black and white Americans. *BMC Public Health* 2015;15. WOS:000365476300002.
- [28] Chen X, Gelaye B, Williams MA. Sleep characteristics and health-related quality of life among a national sample of American young adults: assessment of possible health disparities. *Qual Life Res Int J Qual Life Asp Treat Care Rehab* 2014;23(2):613–25. MEDLINE:23860850.
- [29] Edwards C, Mukherjee S, Simpson L, Palmer LJ, Almeida OP, Hillman DR. Depressive symptoms before and after treatment of obstructive sleep apnea in men and women. *J Clin Sleep Med* 2015;11(9):1029–38. WOS:000366292600010.
- [30] Patel NP, Grandner MA, Xie DW, Branas CC, Gooneratne N. “Sleep disparity” in the population: poor sleep quality is strongly associated with poverty and ethnicity. *BMC Public Health* 2010;10(11). WOS:000282236700002. [English].
- [31] Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. *Sleep* 2006;29(7):881–9. WOS:000238961500004. [English].
- [32] Johnson DA, Lisabeth L, Hickson D, Johnson-Lawrence V, Samdarshi T, Taylor H, et al. The social patterning of sleep in African Americans: associations of socioeconomic position and neighborhood

- characteristics with sleep in the Jackson Heart Study. *Sleep* 2016;39(9):1749–59. WOS:000384333400015. [English].
- [33] Ertel KA, Berkman LF, Buxton OM. Socioeconomic status, occupational characteristics, and sleep duration in African/Caribbean immigrants and US White health care workers. *Sleep* 2011;34(4):509–18. WOS:000289061800016.
- [34] Akerstedt T, Fredlund P, Gillberg M, Jansson B. Work load and work hours in relation to disturbed sleep and fatigue in a large representative sample. *J Psychosom Res* 2002;53(1):585–8. WOS:000177230200009.
- [35] Jackson CL, Redline S, Kawachi I, Williams MA, Hu FB. Racial disparities in short sleep duration by occupation and industry. *Am J Epidemiol* 2014;178(9):1442–51. WOS:000326642300012.
- [36] Giles DE, Kupfer DJ. Effects of race on EEG sleep in major depression. *Biol Psychiatry* 1995;37(9):624. WOS:A1995QX03700114.
- [37] Rao U, Poland RE, Lutchmansingh P, Ott GE, McCracken JT, Lim KM. Relationship between ethnicity and sleep patterns in normal controls: implications for psychopathology and treatment. *J Psychiatr Res* 1999;33(5):419–26. WOS:000082296000007.
- [38] Redline S, Kirchner L, Quan SF, Gottlieb DJ, Kapur V, Newman A. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med* 2004;164(4):406–18. WOS:000189148600008.
- [39] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea—a population health perspective. *Am J Respir Crit Care Med* 2002;165(9):1217–39. WOS:000175314900009.
- [40] Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults—the sleep heart health study. *Arch Intern Med* 2002;162(8):893–900. WOS:000175039400005. [English].
- [41] Fulop T, Hickson DA, Wyatt SB, Bhagat R, Rack M, Gowdy O, et al. Sleep-disordered breathing symptoms among African-Americans in the Jackson heart study. *Sleep Med* 2012;13(8):1039–49. WOS:000309038300011. [English].
- [42] Johnson DA, Simonelli G, Moore K, Billings M, Mujahid MS, Rueschman M, et al. The neighborhood social environment and objective measures of sleep in the Multi-Ethnic Study of Atherosclerosis. *Sleep* 2017;40(1):8. WOS:000394125700016. [English].
- [43] Mihaere KM, Harris R, Gander PH, Reid PM, Purdie G, Robson B, et al. Obstructive sleep apnea in New Zealand adults: prevalence and risk factors among Maori and non-Maori. *Sleep* 2009;32(7):949–56. WOS:000268126000015.
- [44] Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ. Prevalence of sleep-disordered breathing in ages 40–64 years: a population-based survey. *Sleep* 1997;20(1):65–76. WOS:A1997WV60300011. [English].
- [45] Redline S, Sotres-Alvarez D, Loredo J, Hall M, Patel SR, Ramos A, et al. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds the Hispanic community health study/study of Latinos. *Am J Respir Crit Care Med* 2014;189(3):335–44. WOS:000331793400016. [English].
- [46] Tomfohr L, Pung MA, Edwards KM, Dimsdale JE. Racial differences in sleep architecture: the role of ethnic discrimination. *Biol Psychol* 2012;89(1):34–8. WOS:000299714500004. [English].
- [47] Yon A, Scogin F, DiNapoli EA, McPherron J, Arean PA, Bowman D, et al. Do manualized treatments for depression reduce insomnia symptoms? *J Clin Psychol* 2014;70(7):616–30. WOS:000337623800002.
- [48] Ruiter ME, Decoster J, Jacobs L, Lichstein KL. Normal sleep in African-Americans and Caucasian-Americans: a meta-analysis. *Sleep Med* 2011;12(3):209–14. 21317037. [eng].
- [49] Medicine AAoS. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
- [50] Peppard PE, Young T, Barnet JH, Palta M, Hagen E, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177(9):1006–14. WOS:000318576300019.
- [51] O'Connor GT, Lind B, Eea L. Variation in symptoms of sleep-disordered breathing with race and ethnicity: the Sleep Heart Health Study. *Sleep* 2003;26:74–9.
- [52] Baron KG, Liu KA, Chan CL, Shahar E, Hasnain-Wynia R, Zee P. Race and ethnic variation in excessive daytime sleepiness: the Multi-Ethnic Study of Atherosclerosis. *Behav Sleep Med* 2010;8(4):231–45. WOS:000282578800005. [English].
- [53] Hayes AL, Spilsbury JC, Patel SR. The Epworth score in African American populations. *J Clin Sleep Med* 2009;5(4):344–8. WOS:000270263300009.
- [54] Hale L, Troxel WM, Kravitz HM, Hall MH, Matthews KA. Acculturation and sleep among a multiethnic sample of women: the Study of Women's Health Across the Nation (SWAN). *Sleep* 2014;37(2):309–17. WOS:00032519100011. [English].
- [55] Loredo JS, Soler X, Bardwell W, Ancoli-Israel S, Dimsdale JE, Palinkas LA. Sleep health in US Hispanic population. *Sleep* 2010;33(7):962–7. WOS:000279365600016. [English].
- [56] Froese CL, Butt A, Mulgrew A, Cheema R, Speirs MA, Gosnell C, et al. Depression and sleep-related symptoms in an adult, Indigenous, North American population. *J Clin Sleep Med* 2008;4(4):356–61. WOS:000209777000010. [English].
- [57] WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363(9403):157–63. MEDLINE:14726171. [English].
- [58] Chen XL, Wang R, Lutsey PL, Zee PC, Javaheri S, Alcantara C, et al. Racial/ethnic differences in the associations between obesity measures and severity of sleep-disordered breathing: the Multi-Ethnic Study of Atherosclerosis. *Sleep Med* 2016;26:46–53. WOS:000390720900009. [English].
- [59] Sutherland K, Lee RWW, Cistulli PA. Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: impact of ethnicity. *Respirology* 2012;17(2):213–22. WOS:000299416100004. [English].
- [60] Cakirer B, Hans MG, Graham G, Aylor J, Tishler PV, Redline S. The relationship between craniofacial morphology and obstructive sleep apnea in whites and in African-Americans. *Am J Respir Crit Care Med* 2001;163(4):947–50. WOS:000168057700032. [English].
- [61] Lam B, Ip MSM, Tench E, Ryan CF. Craniofacial profile in Asian and white subjects with obstructive sleep apnoea. *Thorax* 2005;60(6):504–10. WOS:000229433900013. [English].
- [62] Coltman R, Taylor DR, Whyte K, Harkness M. Craniofacial form and obstructive sleep apnea in Polynesian and Caucasian men. *Sleep* 2000;23(7):943–50. WOS:000165175500011. [English].
- [63] Will MJ, Ester MS, Ramirez SG, Tiner BD, McAnear JT, Epstein L. Comparison of cephalometric analysis with ethnicity in

- obstructive sleep apnea syndrome. *Sleep* 1995;18(10):873–5. WOS:A1995TQ23600008. [English].
- [64] Lee JJ, Ramirez SG, Will MJ. Gender and racial variations in cephalometric analysis. *Otolaryngol Head Neck Surg* 1997;117(4):326–9. WOS:A1997YA33900006. [English].
- [65] Ruiter ME, DeCoster J, Jacobs L, Lichstein KL. Sleep disorders in African Americans and Caucasian Americans: a meta-analysis. *Behav Sleep Med* 2010;8(4):246–59. 20924837. [eng].
- [66] Zanobetti A, Redline S, Schwartz J, Rosen D, Patel S, O'Connor GT, et al. Associations of PM10 with sleep and sleep-disordered breathing in adults from seven US Urban areas. *Am J Respir Crit Care Med* 2010;182(6):819–25. WOS:000282162100015.
- [67] Pranathiageswaran S, Badr MS, Severson R, Rowley JA. The influence of race on the severity of sleep disordered breathing. *J Clin Sleep Med* 2013;9(4):303–9. WOS:000318604100002.
- [68] Ong KC, Clerk AA. Comparison of the severity of sleep-disordered breathing in Asian and Caucasian patients seen at a sleep disorders center. *Respir Med* 1998;92(6):843–8. WOS:000075263000007. [English].
- [69] Yamagishi K, Ohira T, Nakano H, Bielinski SJ, Sakurai S, Imano H, et al. Cross-cultural comparison of the sleep-disordered breathing prevalence among Americans and Japanese. *Eur Respir J* 2010;36(2):379–84. WOS:000281601800023. [English].
- [70] Billings ME, Rosen CL, Wang R, Auckley D, Benca R, Foldvary-Schaefer N, et al. Is the relationship between race and continuous positive airway pressure adherence mediated by sleep duration? *Sleep* 2013;36(2):221–7. WOS:000314393700011.
- [71] Billings ME, Auckley D, Benca R, Foldvary-Schaefer N, Iber C, Redline S, et al. Race and residential socioeconomics as predictors of CPAP adherence. *Sleep* 2011;34(12):1653–8. 22131602. [eng].
- [72] Grandner MA, Jackson N, Gerstner JR, Knutson KL. Dietary nutrients associated with short and long sleep duration. Data from a nationally representative sample. *Appetite* 2013;64:71–80. WOS:000317325500010.
- [73] Grandner MA, Petrov MER, Rattanaumpawan P, Jackson N, Platt A, Patel NP. Sleep symptoms, race/ethnicity, and socioeconomic position. *J Clin Sleep Med* 2013;9(9):897–905. WOS:000324375100009. [English].
- [74] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6(2):97–111. WOS:000176231600003.
- [75] Roth T, Drake C. Evolution of insomnia: current status and future direction. *Sleep Med* 2004;5:S23–30. WOS:000222352700005. [English].
- [76] Karacan I, Thornby JI, Anch M, Holzer CE, Warheit GJ, Schwab JJ, et al. Prevalence of sleep disturbance in a primarily Urban Florida County. *Soc Sci Med* 1976;10(5):239–44. WOS: A1976CB00600006.
- [77] Blazer DG, Hays JC, Foley DJ. Sleep complaints in older adults—a racial comparison. *J Gerontol A Biol Sci Med Sci* 1995;50(5):M280–4. WOS:A1995RY60500019.
- [78] Phillips B, Mannino D. Correlates of sleep complaints in adults: the ARIC study. *J Clin Sleep Med* 2005;1(3):277–83. MEDLINE:17566189.
- [79] Grandner MA, Patel NP, Gehrmann PR, Xie DW, Sha DH, Weaver T, et al. Who gets the best sleep? Ethnic and socioeconomic factors related to sleep complaints. *Sleep Med* 2010;11(5):470–8. WOS:000277878500008. [English].
- [80] Paine SJ, Gander PH, Harris R, Reid P. Who reports insomnia? Relationships with age, sex, ethnicity, and socioeconomic deprivation. *Sleep* 2004;27(6):1163–9. , WOS:000224445600017.
- [81] Barile JP, Reeve BB, Smith AW, Zack MM, Mitchell SA, Kobau R, et al. Monitoring population health for Healthy People 2020: evaluation of the NIH PROMIS (R) Global Health, CDC Healthy Days, and satisfaction with life instruments. *Qual Life Res* 2013;22(6):1201–11. WOS:000322735700004.
- [82] Kripke DF, Jean-Louis G, Elliott JA, Klauber MR, Rex KM, Tuunainen A, et al. Ethnicity, sleep, mood, and illumination in post-menopausal women. *BMC Psychiatry* 2004;4:8. 15070419. [eng].
- [83] Jean-Louis G, Magai C, Consedine NS, Pierre-Louis J, Zizi F, Casimir GJ, et al. Insomnia symptoms and repressive coping in a sample of older Black and White women. *BMC Womens Health* 2007;7(1). MEDLINE:17261187.
- [84] Ehlers CL, Wills DN, Lau P, Gilder DA. Sleep quality in an adult American Indian community sample. *J Clin Sleep Med* 2017;13(3):385–91. WOS:000397051100006. [English].
- [85] Gellis LA, Lichstein KL, Scarinci IC, Durrence HH, Taylor DJ, Bush AJ, et al. Socioeconomic status and insomnia. *J Abnorm Psychol* 2005;114(1):111–8. WOS:000227146600011.
- [86] Jean-Louis G, Magai C, Cohen C, Zizi F, von Gizycki H, DiPalma J, et al. Ethnic differences in self reported sleep problems in older adults. *Sleep* 2001;926–33.
- [87] Molnar M. Association of incident restless legs syndrome with outcomes in a large cohort of US veterans. *J Sleep Res* 2016;25(1):47–56.
- [88] Chesson AL, Wise M, Davila D, Johnson S, Littner M, Anderson WM, et al. Practice parameters for the treatment of Restless Legs Syndrome and periodic limb movement disorder. *Sleep* 1999;22(7):961–8. WOS:000083566100015.
- [89] Scofield H, Roth T, Drake C. Periodic limb movements during sleep: population prevalence, clinical correlates, and racial differences. *Sleep* 2008;31(9):1221–7. WOS:000258891100005.
- [90] O'Brien LM, Koo J, Fan L, Owusu JT, Chotinaiwattarakul W, Felt BT, et al. Iron stores, periodic leg movements, and sleepiness in obstructive sleep apnea. *J Clin Sleep Med* 2009;5(6):525–31. WOS:000272780400006.
- [91] Kutner NG, Zhang R, Huang YJ, Bliwise DL. Racial differences in restless legs symptoms and serum ferritin in an incident dialysis patient cohort. *Int Urol Nephrol* 2012;44(6):1825–31. WOS:000313523000030.
- [92] Kutner NG, Bliwise DL. Restless legs complaint in African-American and Caucasian hemodialysis patients. *Sleep Med* 2002;3:497–500.
- [93] Lee HB, Hening WA, Allen RP, Earley CJ, Eaton WW, Lyketsos CG. Race and restless legs syndrome symptoms in an adult community sample in east Baltimore. *Sleep Med* 2006;7(8):642–5. WOS:000243272500008.
- [94] Sawanyawisuth K, Palinkas LA, Ancoli-Israel S, Dimsdale JE, Loredo JS. Ethnic differences in the prevalence and predictors of restless legs syndrome between Hispanics of Mexican descent and non-Hispanic Whites in San Diego county: a population-based study. *J Clin Sleep Med* 2013;9(1):47–53. 23319904. [eng].
- [95] Allen RP. Race, iron status and restless legs syndrome. *Sleep Med* 2002;3(6):467–8. MEDLINE:14592139. [English].
- [96] Koo BB. Restless leg syndrome across the globe: epidemiology of the restless legs syndrome/Willis-Ekbom disease. *Sleep Med Clin* 2015;10(3):189. WOS:000218432500003.

- [97] Koo BB, Blackwell T, Ancoli-Israel S, Stone KL, Stefanick ML, Redline S, et al. Association of incident cardiovascular disease with periodic limb movements during sleep in older men outcomes of sleep disorders in older men (MrOS) study. *Circulation* 2011;124(11):1223–31. WOS:000294779000016.
- [98] Solomon P. Narcolepsy in negroes. *Dis Nerv Syst* 1945;6:179–83.
- [99] Okun ML, Lin L, Pelin Z, Hong S, Mignot E. Clinical aspects of narcolepsy-cataplexy across ethnic groups. *Sleep* 2002;25(1):27–35. 11833858. [eng].
- [100] Longstreth WT, Ton TG, Koepsell T, Gersuk VH, Hendrickson A, Velde S. Prevalence of narcolepsy in King County, Washington, USA. *Sleep Med* 2009;10(4):422–6. 19013100. [Epub 2008/11/13. eng].
- [101] Kawai M, O'Hara R, Einen M, Lin L, Mignot E. Narcolepsy in African Americans. *Sleep* 2015;38(11):1673–81. 26158891. [Epub 2015/11/01. eng].
- [102] Jean-Louis G, Kripke DF, Ancoli-Israel S, Klauber MR, Sepulveda RS, Mowen MA, et al. Circadian sleep, illumination, and activity patterns in women: influences of aging and time reference. *Physiol Behav* 2000;68(3):347–52. 10716544. [eng].
- [103] Eastman CI, Molina TA, Dziepak ME, Smith MR. Blacks (African Americans) have shorter free-running circadian periods than whites (Caucasian Americans). *Chronobiol Int* 2012;29(8):1072–7. WOS:000308654000010.
- [104] Smith MR, Burgess HJ, Fogg LF, Eastman CI. Racial differences in the human endogenous circadian period. *PLoS One* 2009;4(6). WOS:000267515700001.
- [105] Eastman CI, Suh C, Tomaka VA, Crowley SJ. Circadian rhythm phase shifts and endogenous free-running circadian period differ between African-Americans and European-Americans. *Sci Rep* 2015;5. WOS:000349240000005.
- [106] Emens JS, Eastman CI. Diagnosis and treatment of non-24-h sleep-wake disorder in the blind. *Drugs* 2017;77(6):637–50. WOS:000398036100004.
- [107] Boivin DB. Influence of sleep-wake and circadian rhythm disturbances in psychiatric disorders. *J Psychiatry Neurosci* 2000;25(5):446–58. WOS:000165383200004.
- [108] Gu D, Sautter J, Pipkin R, Zeng Y. Sociodemographic and health correlates of sleep quality and duration among very old Chinese. *Sleep* 2010;33(5):601–10. 20469802. [Epub 2010/05/18. eng].
- [109] Dinges DF, Douglas SD, Hamarman S, Zaugg L, Kapoor S. Sleep-deprivation and human immune function. *Adv Neuroimmunol* 1995;5(2):97–110. WOS:A1995RR29300002.
- [110] Thomas SB, Quinn SC, Butler J, Fryer CS, Garza MA. Toward a fourth generation of disparities research to achieve health equity. *Annu Rev Public Health* 2011;32:399–416. WOS:000290776200022.
- [111] Alcantara C, Patel SR, Carnethon M, Castaneda S, Isasi CR, Davis S, et al. Stress and sleep: results from the Hispanic Community Health Study/Study of Latinos Sociocultural Ancillary Study. *SSM Popul Health* 2017;3:713–21. MEDLINE:29104908. [English].
- [112] Slopen N, Williams DR. Discrimination, other psychosocial stressors, and self-reported sleep duration and difficulties. *Sleep* 2014;37(1):147–56. 24381373. [eng].
- [113] Brondolo E, ver Halen NB, Pencille M, Beatty D, Contrada RJ. Coping with racism: a selective review of the literature and a theoretical and methodological critique. *J Behav Med* 2009;32(1):64–88. WOS:000262434000005.
- [114] Williams NJ, Nuru-Jeter A. Does racial identity moderate the association between racial discrimination and sleep quality? *Psychosom Med* 2017;79(4):A81. WOS:000401250500216.
- [115] Krieger N. Embodying inequality: a review of concepts, measures, and methods for studying health consequences of discrimination. *Int J Health Serv* 1999;29(2):295–352. WOS:000080804700004.
- [116] Williams DR, Williams-Morris R. Racism and mental health: the African American experience. *Ethn Health* 2000;5(3–4):243–68. WOS:000168231000006.
- [117] Harrell JP, Hall S, Taliaferro J. Physiological responses to racism and discrimination: an assessment of the evidence. *Am J Public Health* 2003;93(2):243–8. WOS:000180721000017.
- [118] Acheson LS, Wang C, Zyzanski SJ, Lynn A, Ruffin MT, Gramling R, et al. Family history and perceptions about risk and prevention for chronic diseases in primary care: a report from the family healthcare impact trial. *Genet Med* 2010;12(4):212–8. 20216073. [eng].
- [119] Lipkus IM, Skinner CS, Dement J, Pompeii L, Moser B, Samsa GP, et al. Increasing colorectal cancer screening among individuals in the carpentry trade: test of risk communication interventions. *Prev Med* 2005;40(5):489–501. 15749130. [eng].
- [120] Leventhal H, Kelly K, Leventhal EA. Population risk, actual risk, perceived risk, and cancer control: a discussion. *J Natl Cancer Inst Monogr* 1999;(25):81–5. 10854461. [eng].
- [121] Quinn SC, Jamison A, Freimuth VS, An J, Hancock GR, Musa D. Exploring racial influences on flu vaccine attitudes and behavior: results of a national survey of White and African American adults. *Vaccine* 2017;35(8):1167–74. 28126202. [Epub 2017/01/17. eng].
- [122] Smith MT, Perlis ML. Who is a candidate for cognitive-behavioral therapy for insomnia? *Health Psychol* 2006;25(1):15–9. WOS:000235123300003.
- [123] Belfer S, Perlis M, Kayser M. A neurobiological basis for behavioral therapy using *Drosophila*. *Biol Psychiatry* 2017;81(10):S69. WOS:000400348700168.
- [124] Jean-Louis G, Newsome V, Williams NJ, Zizi F, Ravenell J, Ogedegbe G. Tailored behavioral intervention among Blacks with metabolic syndrome and sleep apnea: results of the MetSO trial. *Sleep* 2017;40(1). WOS:000394125700008.
- [125] Cukor D, Pencille M, Ver Halen N, Primus N, Gordon-Peters V, Fraser M, et al. An RCT comparing remotely delivered adherence promotion for sleep apnea assessment against an information control in a black community sample. *Sleep Health* 2018;4(4):369–76. WOS:000439075900011.

Chapter 8

Neighborhood factors associated with sleep health

Lauren Hale^a, Sarah James^b, Qian Xiao^c, Martha E. Billings^d and Dayna A. Johnson^e

^aProgram in Public Health, Department of Family, Population, and Preventive Medicine, Stony Brook University School of Medicine, Stony Brook, NY, United States; ^bDepartment of Sociology and Office of Population Research, Princeton University, Princeton, NJ, United States; ^cDepartment of Health and Human Physiology and Department of Epidemiology, University of Iowa, Iowa City, IA, United States; ^dDivision of Pulmonary, Critical Care & Sleep Medicine, University of Washington, Seattle, WA, United States; ^eDivision of Sleep and Circadian Disorders, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

Neighborhoods and sleep health

Sleep, a modifiable health behavior, is increasingly recognized as integral for optimal health and well-being [1,2]. One-third of Americans report obtaining <7 h of sleep: an insufficient amount according to expert consensus panels [3,4]. Highly prevalent sleep disorders such as sleep apnea and insomnia [5,6] are underdiagnosed and a pressing public health burden [7]. In addition, there are substantial disparities in sleep health; insufficient sleep and unrecognized and undertreated sleep disorders are highly prevalent among racial/ethnic minorities and lower socioeconomic status populations who disproportionately reside in underresourced neighborhoods [8,9]. In this chapter, we first present a theoretical justification for the link between neighborhoods and sleep health, review current literature on the neighborhood determinants of sleep among children and adolescents, followed by a separate section on neighborhoods and sleep among adults. We conclude with opportunities and challenges for advancing the research on neighborhoods and sleep health and their implications for developing interventions and reducing health disparities.

Theoretical justification for neighborhoods and sleep health

As part of the emerging literature on the social determinants of sleep health, one active line of research investigates the neighborhood factors that are associated with sleep health across the life course [10]. The high prevalence of poor sleep health, particularly among vulnerable

populations, is associated with neighborhood features such as noise disturbances, crime, crowding, excess light, and social isolation; these same factors are also associated with poor health outcomes [11,12]. The theoretical rationale for such an association is rooted in an evolutionary understanding of sleep as being highly contextually dependent [13]. When an external threat puts a sleeping individual at risk, we can expect sleep to be affected through a reduction in sleep quality or duration to minimize the time vulnerable to threats [14,15]. Thus, the study of sleep health must embrace a socioecological model in which neighborhood factors are a key component [2].

A growing number of studies have evaluated the association between neighborhood factors and sleep outcomes [10–12,16–22]. As with other neighborhood research, associations between neighborhoods and an outcome of interest may be due to causal processes or due simply to compositional differences across the neighborhoods. Insufficient sleep may be a cause of poor health outcomes observed among residents of disadvantaged neighborhoods [18,23,24]. Previous research has identified key environmental factors that may be causally linked to sleep quality and duration, including (1) safety concerns, (2) neighborhood socioeconomic status (NSES), (3) noise, (4) temperature, (5) neighborhood disorder, (6) pollution, and (7) cultural factors. For example, the regional clustering of insufficient sleep, such as in American Appalachia, may be related to poor health behaviors, reduced access to health care, and/or economic disparity [25]. In contrast, a compositional explanation for the association between neighborhood characteristics and sleep means that individuals with less or poorer quality sleep are more likely

to live in the same neighborhoods, and it is not the features of the neighborhoods themselves that contribute to the sleep outcomes. That is, there may be collinearity of disadvantage with other causal environmental factors contributing to sleep health (such as pollution, noise, and disorder, or other items listed before) [26,27]. Therefore, in this chapter, we limit our discussion to articles that adjust for individual risk factors to minimize the role of compositional explanations for the associations between neighborhood factors and sleep outcomes.

Neighborhood factors associated with pediatric sleep

Research on the association between neighborhood factors and pediatric sleep health has shown that a variety of neighborhood factors are associated with child and adolescent sleep outcomes. These factors include urbanicity and neighborhood density, neighborhood disadvantage, low walkability, and neighborhood violence.

Urbanicity and population density

Infants, children, and adolescents living in more urban areas and/or areas with higher population density have shorter sleep durations [28,29], higher odds of inadequate sleep [29,30], and higher rates of obstructive sleep apnea [31] than do children living in less urban or dense areas.

Neighborhood socioeconomic status (NSES)

Low NSES and related measures of neighborhood disadvantage are consistently associated with worse sleep health among both children and adolescents. Children and adolescents living in disadvantaged neighborhoods have shorter nightly sleep durations [32,33] and greater odds of inadequate sleep [30] than do children and adolescents living in more advantaged neighborhoods. Notably, one recent study of children ages 5–10 years living in urban California counties found that children living in neighborhoods with 40-year histories of consistently high poverty have higher odds of inadequate sleep than children living in neighborhoods with consistently low- or moderate-poverty trajectories [34]; the same study finds that current neighborhood poverty is not associated with sleep adequacy [34]. In addition, adolescents living in more disadvantaged neighborhoods have more variable sleep times [35] and more sleep problems [36,37] than those living in more advantaged neighborhoods. Finally, obstructive sleep apnea is also substantially more common [31,38] and the sleep apnea severity is greater [39] among children living in disadvantaged neighborhoods compared with more advantaged areas.

Neighborhood access to physical activity

The association between neighborhoods and sleep may partially operate through the promotion of physical activity, which is necessary for good sleep. Using data from the National Survey of Children's Health, including waves from 2003, 2007, and 2011–12, Singh and Kenney [30] found that children ages 6–17 years residing in neighborhoods with fewer amenities—such as a lack of parks/playgrounds, recreation/community center, or access to a library/bookmobile—had higher odds of inadequate sleep than their peers living in neighborhoods with these amenities. A smaller study of adolescents living in the Southeast found that recreation facilities located closer to the adolescent's home lead to higher physical activity, which in turn predicted more daily sleep minutes, better-quality sleep, and less variability in sleep schedules [40]. Relatedly, sleep is more variable for adolescents living on busier streets [35].

Neighborhood violence and safety concerns

Exposure to violence within the neighborhood may also impact sleep. Concerns about violence and crime or exposure to community violence are associated with a range of sleep problems and inadequate sleep among children and adolescents [36,37,41–47]. Similarly, concerns about school and community violence are associated with poorer sleep quality in a sample of adolescents living in the Southeastern United States, with stronger associations for girls than boys. In less violent settings, girls slept longer each night than boys but in violent contexts there was no sex difference in nightly sleep duration [45]. Finally, acute exposure to violent events is associated with delayed sleep timing and shorter duration [48]. Using a rigorous within-person study design in a small sample of adolescents, Heissel et al. [48] found that adolescents go to sleep 30 min later and sleep for 39 min less on the night after a violent crime occurred within half a mile of their home.

Neighborhood factors associated with adult sleep

Social characteristics of the neighborhood environment (e.g., social cohesion, safety, violence, and disorder) are associated with sleep duration, daytime sleepiness, sleep difficulties, and a sleep quality among adults [12,17,18,20,49,50]. Adverse neighborhood social environments—those low in social cohesion and high in violence and disorder—are associated with sleeping between 7 and 11 min less per night on average, after adjustment for age and sex [12,50,51]. Perceived neighborhood safety and social cohesion are associated with both self-reported and

objectively measured sleep duration, with longer sleep in safer and more cohesive neighborhoods [12,50]. Neighborhood features are also associated with common adult sleep problems as detailed as follows: inadequate sleep duration and sleep timing, insomnia, and obstructive sleep apnea.

Inadequate sleep duration and delayed sleep timing

Physical neighborhood features such as artificial light, vehicular traffic, and noise related to crowding all impact sleep. Traffic (including air, road, and rail), and other urban noise (such as that of alarms, construction, sirens, etc.) can lead to sleep fragmentation, delay sleep onset, or contribute to early awakenings. Bright light exposure from street lights, houses, business, and commercial space can similarly impact sleep timing, typically delaying sleep onset (circadian phase delay) [52–59]. Excess artificial light may depress melatonin secretion, which impacts the initiation of sleep by causing circadian phase delay and prolonging sleep latency [60]. In a US study, those with greater nighttime exposure to outdoor lights had a 28% greater odds of a circadian phase delay. Similarly, those living in areas that are brighter at night (typically dense cities) have a later bedtime [61]. Thus, city dwellers often sleep less than their rural counterparts as a result of these physical features of urban neighborhoods.

Other features of the built neighborhood environment, such as walkability, green space, density, street connectivity, and mixed land use, may also impact sleep. Observational studies show that adults living in neighborhoods with more green space or natural water features have a lower likelihood of insufficient sleep [62,63]. However, data from the Multi-Ethnic Study of Atherosclerosis showed that living in neighborhoods with higher street smart walk scores, more social engagement destinations, street intersections, and population density are associated with 17%–23% higher odds of short sleep duration (≤ 6 h) [64]. This finding demonstrates the complex relation of the built environment with health—while built environment features may be favorable for physical activity [65,66] simultaneously there may be a cost to sleep opportunity.

Insomnia

An estimated 10% of adults suffer from chronic insomnia with 35% of the adult population experiencing insomnia symptoms annually. Insomnia, a clinical diagnosis, is characterized as difficulty initiating and/or maintaining sleep, awakening too early, with a resulting daytime impairment [67]. Contextual features of the neighborhood likely contribute to insomnia. Living in disadvantaged neighborhoods is associated with insomnia symptoms

[9,12,19,68]. Objective measures of insomnia such as a greater period of wake after sleep onset are also associated with neighborhood disadvantage [69]. One possible mechanism underlying the association of neighborhood features with insomnia symptoms may be that crime, noise, disorder promote hypervigilance and lead to increased trouble falling asleep, staying asleep, among other sleep disturbances [11,23]. Neighborhood physical disorder and low social cohesion are associated with greater odds of difficulty falling asleep among older adults [70]. Neighborhood disadvantage may also have an indirect association with sleep through increased psychosocial distress, which is associated with insufficient sleep [71,72]. Residing in an adverse neighborhood environment, fear of crime and violence, discrimination, and/or social disorganization may increase anxiety or depression, which may lead to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, impacting biological rhythms and mood [73].

Neighborhood light and noise pollution can also foster insomnia in susceptible urbanites. A study in Oslo, Norway found a 5% greater odds of difficulty falling asleep and too early awakenings per 5 dB increase in traffic noise. Loud noises from trucks, trains, planes, sirens, and highways—all sounds related to a high population density—also disrupt sleep and may lead to insomnia symptoms [53,54,74,75]. For example, noisy neighborhoods were associated with a 4% greater prevalence of insomnia symptoms in a US national epidemiological study of Hispanics and Latinos [19]. In the elderly, artificial light exposure at night can decrease melatonin secretion and lead to increased objective sleep disturbance and subjective insomnia [76].

Obstructive sleep apnea (OSA)

Neighborhood features which promote obesity, sedentary behaviors, and metabolic disease [77,78] likely increase the risk of OSA. Sleep apnea is highly correlated with obesity, with greater prevalence and severity among the morbidly obese [6]. Neighborhood-built characteristics associated with body mass index (BMI) and physical activity levels include walkability, access to healthy food, recreation, street connectivity, and green spaces [65,66,79–81]. Living in neighborhoods with lower-rated walking environments is associated with a greater severity of OSA, with stronger associations in persons with obesity [16]. Neighborhood crowding is also associated with OSA, and BMI partially mediates the association [82].

Neighborhood physical features such as traffic and ambient air pollution are associated with OSA. Individuals exposed to higher levels of ozone and particulate matter have a greater severity of OSA, particularly in the summer [83–85]. In a recent study in Taiwan, higher exposure to traffic pollution is associated with a 4%–5% greater OSA

severity. Similarly, proximity to traffic is associated with greater OSA symptoms such as snoring and daytime sleepiness, possibly through noise and air pollution mechanisms [86,87]. An adverse physical environment with greater inflammatory irritants may also increase OSA propensity [88,89].

Current limitations and future directions

Though recent research has generated a growing body of evidence supporting an important role of neighborhood environment in sleep health, we have identified several gaps in the current literature. Specifically, the field would benefit from more studies that (1) characterize long-term neighborhood conditions, (2) evaluate evidence from quasi- or natural experiments that use statistical methods to strengthen the argument for causality, and (3) use technological advances to objectively measure neighborhood characteristics at a larger spatial scale.

Studying long-term trajectories of neighborhood conditions and sleep

The vast majority of the literature on neighborhood factors associated with pediatric and adult sleep health examined neighborhood conditions at a single time point. Yet neighborhoods are not static and people are mobile, both of which may lead to changes in neighborhood environment that may impact sleep behaviors. Similarly, sleep health may be differently influenced by exposure to neighborhood factors at different points in the lifespan (such as during childhood). However, only a few studies have sought to understand the impact of long-term exposure patterns to neighborhood conditions on sleep. In one study, compared with neighborhoods with historically high poverty, neighborhoods that showed upward mobility over 1 decade were associated with lower odds of insufficient sleep [90]. In another study of middle-to-older aged adults, a decrease in NSES was associated with very short sleep (<5 h) in women; while an improvement in NSES was associated with long sleep (≥ 9 h) in men [91]. Additional studies with this longitudinal approach could help better characterize neighborhood-related sleep disparities in the population and identify vulnerable groups that are at a high risk of adverse health outcomes related to sleep deficiency.

Evaluating evidence from natural experiments and other causal methods

Most of the empirical studies of neighborhood factors and sleep health have relied on observational data. However, observational studies are plagued by residual confounding

from individual backgrounds, which limit their ability to make causal inferences [92]. Due to the scarcity of interventional studies that change neighborhood conditions, quasi-experimental studies take advantage of public policy, funding, and physical environmental changes to examine the impact of neighborhood factors on health behaviors and related outcomes. Many such studies have provided valuable insight about designing interventions that aim at improving environmental conditions to reduce health disparities related to physical activity and nutrition [93]. Using a similar approach, the effect of neighborhood factors on sleep could be more accurately assessed. In addition, some studies use methods designed to approximate causal estimates, such as propensity score analysis, marginal structural models, and fixed effect models, to examine neighborhood conditions and health behaviors and outcomes longitudinally [94–97]. The application of such methods in the research of neighborhood and sleep is limited, with the notable exception of a recent paper that examined neighborhood disorders and sleep problems in older adults using fixed-effect models to control for confounding of unmeasured personal traits [98]. Future research on the neighborhood determinants of sleep health would be strengthened by evaluating evidence from experimentally designed studies and the use of more rigorous statistical methods.

Using technological advances to studying neighborhoods and sleep at a larger scale

Though recent studies have taken advantage of satellite imagery, national exposure maps, and other technologies to investigate environmental exposures associated with health outcomes [99–101], these data have been underutilized to understand sleep health. Because many population-based studies have collected both sleep data and participants' addresses, more large-scale epidemiological studies could link information such as street connectivity, land use, vegetation, environmental pollutants, and outdoor light and noise exposures to participants' neighborhoods [102]. For example, two recent studies examined satellite measurements of nighttime outdoor artificial light as predictors of sleep health variables and found that a higher level of outdoor light at night was associated with insufficient sleep in Korean adults [103], and a stronger evening-type orientation in adolescents in Germany [104]. In addition, widespread use of commercial sleep-tracking devices may allow objective assessments of sleep on a large-scale population level [105,106]. More studies are needed to link sleep data with large-scale exposure databases, and such linkages will provide novel means of assessing the environmental determinants of sleep in the population.

Are there interventions and policies to improve neighborhoods and sleep health?

Substantial evidence demonstrates that adverse physical and social neighborhood environments negatively impact sleep health and likely contribute to sleep health disparities. Thus, there is a clear need for community interventions and policies to improve neighborhood conditions and promote healthy sleep. Governmental agencies (e.g., World Health Organization and US Centers for Disease Control and Prevention) have highlighted the need to improve housing and neighborhood conditions as a strategy to improve health and address health disparities [107–111]. Although limited, there are examples in the sleep research literature that have demonstrated that interventions which consider the neighborhood environment or the neighborhood environment in combination with household factors may improve sleep outcomes. A randomized controlled trial of households in five communities in New Zealand found that children in the intervention group (installation of nonpolluting, more effective home heater before winter) had less sleep disturbed by wheezing than children in the control group [112]. Another in the Peruvian Andes showed reduced sleep apnea symptoms with less indoor air pollution by modifying biomass exposure [113]. Cross-sectional data have shown that access to neighborhood green space is associated with a lower risk of short sleep [62,114]; therefore, policies that promote green spaces may also promote healthy sleep. As a result of home and neighborhood structures, exposure to daylight may be limited; thus, interventions that include light boxes in the home can be efficacious in community settings for improving sleep [115,116]. Also, interventions that target walking outside can also have a positive effect on sleep. For example, results of a small randomized controlled trial among individuals with Alzheimer's disease ($n = 132$) showed that a combination of walking and light exposure were effective treatments for improving sleep in terms of reduced actigraphic total wake time at night [115]. However, for neighborhood interventions to be successful, walkable and safe neighborhoods are necessary. Racial/ethnic minorities and lower SES populations disproportionately reside in adverse neighborhoods [117], which may impact the uptake of neighborhood-sleep interventions. Based on evidence that neighborhood factors are more adverse for the sleep health of minority populations [30,33,50,64,69,118], there is a clear need for policy that will increase safety and development in the neighborhood that promotes physical activity, social cohesion, and improved esthetics. Such policy changes could potentially address sleep health disparities. Furthermore, interventions that target changes in the

environment to promote healthy sleep should be developed, tested, and evaluated as possible pathways for ameliorating sleep health disparities and subsequently health disparities. Interventions to improve sleep should target the home sleeping environment (e.g., shades, thermal comfort, and smart home lighting), the physical neighborhood (e.g., traffic, light, noise, and pollution reduction; access to parks), and the social atmosphere neighborhood (e.g., improved neighborhood safety and social cohesion). Targeting these salient neighborhood factors will help to identify priorities for public health intervention and policies. Improving the neighborhood environment has the potential to improve sleep health as well as population health.

Conclusions and public health significance

Identifying the mechanisms underlying the association between neighborhood characteristics and sleep health may provide opportunities to reduce population health disparities, as adequate and high-quality sleep are fundamental to physical and mental health. To further advance this field, rigorous experimental studies with urban planning and policy interventions are necessary to confirm how neighborhood context might be modified to improve sleep health and reduce overall health disparities.

Acknowledgments

Funding: Research reported in this publication was supported by the Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD) R01 HD073352 (to LH), The Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number P2CHD047879 (for SJ) and by the National Heart, Lung, and Blood Institute, (NHLBI) K01HL138211 (to DAJ).

References

- [1] Czeisler CA. Duration, timing and quality of sleep are each vital for health, performance and safety. *Sleep Health* 2015;1(1):5–8. <https://doi.org/10.1016/j.slehd.2014.12.008>.
- [2] Grandner MA, Hale L, Moore M, Patel NP. Mortality associated with short sleep duration: the evidence, the possible mechanisms, and the future. *Sleep Med Rev* 2010;14(3):191–203. <https://doi.org/10.1016/j.smrv.2009.07.006>.
- [3] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M, Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep* 2015;38(6):843–4. <https://doi.org/10.5665/sleep.4716>.

- [4] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Adams Hillard PJ, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC. National Sleep Foundation's updated sleep duration recommendations: final report. *Sleep Health* 2015;1(4):233–43. <https://doi.org/10.1016/j.sleb.2015.10.004>.
- [5] Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med* 2007;3(5 Suppl. I). <https://doi.org/10.5664/jcsm.26929>.
- [6] Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177(9):1006–14. <https://doi.org/10.1093/aje/kws342>.
- [7] Rosen RC, Zozula R, Jahn EG, Carson JL. Low rates of recognition of sleep disorders in primary care: comparison of a community-based versus clinical academic setting. *Sleep Med* 2001;2(1):47–55. [https://doi.org/10.1016/S1389-9457\(00\)00043-5](https://doi.org/10.1016/S1389-9457(00)00043-5).
- [8] Grandner MA, Williams NJ, Knutson KL, Roberts D, Jean-Louis G. Sleep disparity, race/ethnicity, and socioeconomic position. *Sleep Med* 2016;18:7–18. <https://doi.org/10.1016/j.sleep.2015.01.020>.
- [9] Patel NP, Grandner MA, Xie D, Branas CC, Gooneratne N. Sleep disparity in the population: poor sleep quality is strongly associated with poverty and ethnicity. *BMC Public Health* 2010;10:2010.
- [10] Hale L, Emanuele E, James S. Recent updates in the social and environmental determinants of sleep health. *Curr Sleep Med Rep* 2015;1(4):212–7.
- [11] Hill TD, Trinh HN, Wen M, Hale L. Perceived neighborhood safety and sleep quality: a global analysis of six countries. *Sleep Med* 2016;18:56–60.
- [12] Desantis AS, Diez Roux AV, Moore K, Baron KG, Mujahid MS, Nieto FJ. Associations of neighborhood characteristics with sleep timing and quality: the multi-ethnic study of atherosclerosis. *Sleep* 2013;36(10):1543–51.
- [13] Nunn CL, Samson DR, Krystal AD. Shining evolutionary light on human sleep and sleep disorders. *Evol Med Public Health* 2016;2016(1):227–43.
- [14] Samson DR, Crittenden AN, Mabulla IA, Mabulla AZP, Nunn CL. Chronotype variation drives night-time sentinel-like behaviour in hunter-gatherers. *Proc Biol Sci* 1858;2017:284.
- [15] Dahl RE. The regulation of sleep and arousal: development and psychopathology. *Dev Psychopathol* 1996;8(1):3–27.
- [16] Billings ME, Johnson DA, Simonelli G, et al. Neighborhood walking environment and activity level are associated with OSA: the multi-ethnic study of atherosclerosis. *Chest* 2016;150(5):1042–9.
- [17] Johnson DA, Brown DL, Morgenstern LB, Meurer WJ, Lisabeth LD. The association of neighborhood characteristics with sleep duration and daytime sleepiness. *Sleep Health* 2015;1:148–55.
- [18] Hale L, Hill TD, Friedman E, et al. Perceived neighborhood quality, sleep quality, and health status: evidence from the Survey of the Health of Wisconsin. *Soc Sci Med* 2013;79:16–22.
- [19] Simonelli G, Dudley KA, Weng J, et al. Neighborhood factors as predictors of poor sleep in the Sueno Ancillary Study of the Hispanic Community Health Study/Study of Latinos. *Sleep* 2017;40(1).
- [20] Bassett E, Moore S. Neighbourhood disadvantage, network capital and restless sleep: is the association moderated by gender in urban-dwelling adults? *Soc Sci Med* 2014;108:185–93.
- [21] Chambers EC, Pichardo MS, Rosenbaum E. Sleep and the housing and neighborhood environment of urban Latino adults living in low-income housing: the AHOME study. *Behav Sleep Med* 2016;14(2):169–84.
- [22] Simonelli G, Patel SR, Rodriguez-Espinola S, et al. The impact of home safety on sleep in a Latin American country. *Sleep Health* 2015;1(2):98–103.
- [23] Hale L, Hill TD, Burdette AM. Does sleep quality mediate the association between neighborhood disorder and self-rated physical health? *Prev Med* 2010;51(3–4):275–8.
- [24] Curtis DS, Fuller-Rowell TE, El-Sheikh M, Carnethon MR, Ryff CD. Habitual sleep as a contributor to racial differences in cardiometabolic risk. *Proc Natl Acad Sci U S A* 2017;114(33):8889–94.
- [25] Grandner MA, Smith TE, Jackson N, Jackson T, Burgard S, Branas C. Geographic distribution of insufficient sleep across the United States: a county-level hotspot analysis. *Sleep Health* 2015;1(3):158–65.
- [26] Hajat A, Diez-Roux AV, Adar SD, et al. Air pollution and individual and neighborhood socioeconomic status: evidence from the multi-ethnic study of atherosclerosis (MESA). *Environ Health Perspect* 2013;121(11–12):1325–33.
- [27] Ross CE, Mirowsky J. Neighborhood disadvantage, disorder, and health. *J Health Soc Behav* 2001;42(3):258–76.
- [28] Bottino CJ, Rifas-Shiman SL, Kleinman KP, et al. The association of urbanicity with infant sleep duration. *Health Place* 2012;18(5):1000–5.
- [29] Patte KA, Qian W, Leatherdale ST. Sleep duration trends and trajectories among youth in the COMPASS study. *Sleep Health* 2017;3(5):309–16.
- [30] Singh GK, Kenney MK. Rising prevalence and neighborhood, social, and behavioral determinants of sleep problems in US children and adolescents, 2003–2012. *Sleep Disord* 2013;2013:394320.
- [31] Brouillette RT, Horwood L, Constantin E, Brown K, Ross NA. Childhood sleep apnea and neighborhood disadvantage. *J Pediatr* 2011;158(5):789–95.
- [32] McLaughlin Crabtree V, Beal Korhonen J, Montgomery-Downs HE, Faye Jones V, O'Brien LM, Gozal D. Cultural influences on the bedtime behaviors of young children. *Sleep Med* 2005;6(4):319–24.
- [33] Bagley EJ, Fuller-Rowell TE, Saini EK, Philbrook LE, El-Sheikh M. Neighborhood economic deprivation and social fragmentation: associations with children's sleep. *Behav Sleep Med* 2016;1:1–13.
- [34] Sheehan C, Powers D, Margerison-Zilko C, McDevitt T, Cubbin C. Historical neighborhood poverty trajectories and child sleep. *Sleep Health* 2018;4(2):127–34.
- [35] Marco CA, Wolfson AR, Sparling M, Azuaje A. Family socioeconomic status and sleep patterns of young adolescents. *Behav Sleep Med* 2011;10(1):70–80.
- [36] Rubens SL, Gudino OG, Fite PJ, Grande JM. Individual and neighborhood stressors, sleep problems, and symptoms of anxiety and depression among Latino youth. *Am J Orthopsychiatr* 2018;88(2):161–8.

- [37] Rubens SL, Fite PJ, Cooley JL, Canter KS. The role of sleep in the relation between community violence exposure and delinquency among Latino adolescence. *J Commun Psychol* 2014;42(6):723–34.
- [38] Spilsbury JC, Storfer-Isser A, Kirchner HL, et al. Neighborhood disadvantage as a risk factor for pediatric obstructive sleep apnea. *J Pediatr* 2006;149(3):342–7.
- [39] Wang R, Dong Y, Weng J, et al. Associations among neighborhood, race, and sleep apnea severity in children. A Six-City analysis. *Ann Am Thorac Soc* 2017;14(1):76–84.
- [40] Philbrook LE, El-Sheikh M. Associations between neighborhood context, physical activity, and sleep in adolescents. *Sleep Health* 2016;2(3):205–10.
- [41] Kliewer W, Lepore SJ. Exposure to violence, social cognitive processing, and sleep problems in urban adolescents. *J Youth Adolesc* 2015;44(2):507–17.
- [42] Umlauf MG, Bolland JM, Lian BE. Sleep disturbance and risk behaviors among inner-city African-American adolescents. *J Urban Health* 2011;88(6):1130–42.
- [43] Umlauf MG, Bolland AC, Bolland KA, Tomek S, Bolland JM. The effects of age, gender, hopelessness, and exposure to violence on sleep disorder symptoms and daytime sleepiness among adolescents in impoverished neighborhoods. *J Youth Adolesc* 2015;44(2):518–42.
- [44] McHale SM, Kim JY, Kan M, Updegraff KA. Sleep in Mexican-American adolescents: social ecological and well-being correlates. *J Youth Adolesc* 2011;40(6):666–79.
- [45] Bagley EJ, Tu KM, Buckhalt JA, El-Sheikh M. Community violence concerns and adolescent sleep. *Sleep Health* 2016;2(1):57–62.
- [46] Smaldone A, Honig JC, Byrne MW. Sleepless in America: inadequate sleep and relationships to health and well-being of our nation's children. *Pediatrics* 2007;119(Suppl. 1):S29–37.
- [47] Cooley-Quille M, Lorion R. Adolescents exposure to community violence: sleep and psychophysiological functioning. *J Commun Psychol* 1999;27(4):367–75.
- [48] Heissel JA, Sharkey PT, Torrats-Espinosa G, Grant K, Adam EK. Violence and vigilance: the acute effects of community violent crime on sleep and cortisol. *Child Dev* 2017;89(4):e323–31.
- [49] Hill TD, Burdette AM, Hale L. Neighborhood disorder, sleep quality, and psychological distress: testing a model of structural amplification. *Health Place* 2009;15(4):1006–13.
- [50] Johnson DA, Simonelli G, Moore K, et al. The neighborhood social environment and objective measures of sleep in the multi-ethnic study of atherosclerosis. *Sleep* 2017;40(1).
- [51] Johnson DA, Lisabeth L, Hickson D, et al. The social patterning of sleep in African Americans: associations of socioeconomic position and neighborhood characteristics with sleep in the Jackson Heart Study. *Sleep* 2016;39(9):1749–59.
- [52] Basner M, Brink M, Elmenhorst EM. Critical appraisal of methods for the assessment of noise effects on sleep. *Noise Health* 2012;14(61):321–9.
- [53] Basner M, Muller U, Elmenhorst EM. Single and combined effects of air, road, and rail traffic noise on sleep and recuperation. *Sleep* 2011;34(1):11–23.
- [54] Halonen JI, Vahtera J, Stansfeld S, et al. Associations between nighttime traffic noise and sleep: the Finnish public sector study. *Environ Health Perspect* 2012;120:1391–6.
- [55] Hume KI, Brink M, Basner M. Effects of environmental noise on sleep. *Noise Health* 2012;14(61):297–302.
- [56] Muzet A. Environmental noise, sleep and health. *Sleep Med Rev* 2007;11(2):135–42.
- [57] Pirrera S, De Valck E, Cluydts R. Nocturnal road traffic noise: a review on its assessment and consequences on sleep and health. *Environ Int* 2010;36(5):492–8.
- [58] Pirrera S, De Valck E, Cluydts R. Field study on the impact of nocturnal road traffic noise on sleep: the importance of in- and outdoor noise assessment, the bedroom location and nighttime noise disturbances. *Sci Total Environ* 2014;500:84–90.
- [59] Perron S, Plante C, Ragettli MS, Kaiser DJ, Goudreau S, Smargiassi A. Sleep disturbance from road traffic, railways, airplanes and from total environmental noise levels in montreal. *Int J Environ Res Publ Health* 2016;13(8).
- [60] Cho Y, Ryu SH, Lee BR, Kim KH, Lee E, Choi J. Effects of artificial light at night on human health: a literature review of observational and experimental studies applied to exposure assessment. *Chronobiol Int* 2015;32(9):1294–310.
- [61] Ohayon MM, Milesi C. Artificial outdoor nighttime lights associate with altered sleep behavior in the American general population. *Sleep* 2016;39(6):1311–20.
- [62] Grigsby-Toussaint DS, Turi KN, Krupa M, Williams NJ, Pandi-Perumal SR, Jean-Louis G. Sleep insufficiency and the natural environment: results from the US behavioral risk factor surveillance system survey. *Prev Med* 2015;78:78–84.
- [63] Bodin T, Bjork J, Ardo J, Albin M. Annoyance, sleep and concentration problems due to combined traffic noise and the benefit of quiet side. *Int J Environ Res Publ Health* 2015;12(2):1612–28.
- [64] Johnson DA, Hirsh JA, Moore KA, Redline S, Diez Roux AV. Associations between the built environment and objective measures of sleep: the multi-ethnic study of atherosclerosis (MESA). *Am J Epidemiol* 2018;187(5):941–50.
- [65] Lovasi GS, Hutson MA, Guerra M, Neckerman KM. Built environments and obesity in disadvantaged populations. *Epidemiol Rev* 2009;31:7–20.
- [66] Papas MA, Alberg AJ, Ewing R, Helzlsouer KJ, Gary TL, Klassen AC. The built environment and obesity. *Epidemiol Rev* 2007;29:129–43.
- [67] Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest* 2014;146(5):1387–94.
- [68] Riedel N, Fuks K, Hoffmann B, et al. Insomnia and urban neighbourhood contexts—are associations modified by individual social characteristics and change of residence? Results from a -population-based study using residential histories. *BMC Public Health* 2012;12:810.
- [69] Fuller-Rowell TE, Curtis DS, El-Sheikh M, Chae DH, Boylan JM, Ryff CD. Racial disparities in sleep: the role of neighborhood disadvantage. *Sleep Med* 2016;27–28:1–8.
- [70] Chen-Edinboro LP, Kaufmann CN, Augustinavicius JL, et al. Neighborhood physical disorder, social cohesion, and insomnia: results from participants over age 50 in the health and retirement study. *Int Psychogeriatr* 2014;1:1–8.
- [71] Akerstedt T. Psychosocial stress and impaired sleep. *Scand J Work Environ Health* 2006;32(6):493–501.
- [72] Johnson DA, Lisabeth L, Lewis TT, et al. The contribution of psychosocial stressors to sleep among African Americans in the Jackson Heart Study. *Sleep* 2016;39(7):1411–9.

- [73] Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: from physiological to pathological conditions. *Sleep Sci* 2015;8(3):143–52.
- [74] Evandt J, Oftedal B, Hjertager Krog N, Nafstad P, Schwarze PE, Marit AG. A population-based study on nighttime road traffic noise and insomnia. *Sleep* 2017;40(2).
- [75] Kim M, Chang SI, Seong JC, et al. Road traffic noise: annoyance, sleep disturbance, and public health implications. *Am J Prev Med* 2012;43(4):353–60.
- [76] Obayashi K, Saeki K, Kurumatani N. Association between light exposure at night and insomnia in the general elderly population: the HEIJO-KYO cohort. *Chronobiol Int* 2014;31(9):976–82.
- [77] Diez Roux AV, Mair C. Neighborhoods and health. *Ann N Y Acad Sci* 2010;1186:125–45.
- [78] Christine PJ, Auchincloss AH, Bertoni AG, et al. Longitudinal associations between neighborhood physical and social environments and incident type 2 diabetes mellitus: the multi-ethnic study of atherosclerosis (MESA). *JAMA Intern Med* 2015;175(8):1311–20.
- [79] Auchincloss AH, Mujahid MS, Shen M, Michos ED, Whitt-Glover MC, Diez Roux AV. Neighborhood health-promoting resources and obesity risk (the multi-ethnic study of atherosclerosis). *Obesity* 2013;21(3):621–8.
- [80] Fish JS, Ettner S, Ang A, Brown AF. Association of perceived neighborhood safety with [corrected] body mass index. *Am J Public Health* 2010;100(11):2296–303.
- [81] Brownson RC, Hoehner CM, Day K, Forsyth A, Sallis JF. Measuring the built environment for physical activity: state of the science. *Am J Prev Med* 2009;36(4 Suppl. 1):S99–123.e112.
- [82] Johnson DA, Drake C, Joseph CL, Krajenta R, Hudgel DW, Cassidy-Bushrow AE. Influence of neighbourhood-level crowding on sleep-disordered breathing severity: mediation by body size. *J Sleep Res* 2015;24(5):559–65.
- [83] Zanobetti A, Redline S, Schwartz J, et al. Associations of PM10 with sleep and sleep-disordered breathing in adults from seven U.S. urban areas. *Am J Respir Crit Care Med* 2010;182(6):819–25.
- [84] DeMeo DL, Zanobetti A, Litonjua AA, Coull BA, Schwartz J, Gold DR. Ambient air pollution and oxygen saturation. *Am J Respir Crit Care Med* 2004;170(4):383–7.
- [85] Shen YL, Liu WT, Lee KY, Chuang HC, Chen HW, Chuang KJ. Association of PM2.5 with sleep-disordered breathing from a -population-based study in Northern Taiwan urban areas. *Environ Pol* 2017;233:109–13.
- [86] Gerbase MW, Dratva J, Germond M, et al. Sleep fragmentation and sleep-disordered breathing in individuals living close to main roads: results from a population-based study. *Sleep Med* 2014;15(3):322–8.
- [87] Gislason T, Bertelsen RJ, Real FG, et al. Self-reported exposure to traffic pollution in relation to daytime sleepiness and habitual snoring: a questionnaire study in seven north-European cities. *Sleep Med* 2016;24:93–9.
- [88] Mehra R, Redline S. Sleep apnea: a proinflammatory disorder that coaggregates with obesity. *J Allergy Clin Immunol* 2008;121(5):1096–102.
- [89] Lopez-Jimenez F, Sert Kuniyoshi FH, Gami A, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *Chest* 2008;133(3):793–804.
- [90] Sheehan CM, Cantu PA, Powers DA, Margerison-Zilko CE, Cubbin C. Long-term neighborhood poverty trajectories and obesity in a sample of California mothers. *Health Place* 2017;46:49–57.
- [91] Xiao Q, Hale L. Neighborhood socioeconomic status, sleep duration and napping in middle-to-old aged US men and women. *Sleep* 2018;41(7).
- [92] Oakes JM, Andrade KE, Biyow IM, Cowan LT. Twenty years of neighborhood effect research: an assessment. *Curr Epidemiol Rep* 2015;2(1):80–7.
- [93] Mayne SL, Auchincloss AH, Michael YL. Impact of policy and built environment changes on obesity-related outcomes: a systematic review of naturally occurring experiments. *Obes Rev* 2015;16(5):362–75.
- [94] Hearst MO, Oakes JM, Johnson PJ. The effect of racial residential segregation on black infant mortality. *Am J Epidemiol* 2008;168(11):1247–54.
- [95] Oakes JM, Forsyth A, Schmitz KH. The effects of neighborhood density and street connectivity on walking behavior: the twin cities walking study. *Epidemiol Perspect Innovat* 2007;4:16.
- [96] Glymour MM, Mujahid M, Wu Q, White K, Tchetgen Tchetgen EJ. Neighborhood disadvantage and self-assessed health, disability, and depressive symptoms: longitudinal results from the health and retirement study. *Ann Epidemiol* 2010;20(11):856–61.
- [97] Jokela M. Are neighborhood health associations causal? A 10-year prospective cohort study with repeated measurements. *Am J Epidemiol* 2014;180(8):776–84.
- [98] Bierman A, Lee Y, Schieman S. Neighborhood disorder and sleep problems in older adults: subjective social power as mediator and moderator. *Gerontol* 2018;58(1):170–80.
- [99] James P, Bertrand KA, Hart JE, Schernhammer ES, Tamimi RM, Laden F. Outdoor light at night and breast Cancer incidence in the Nurses' health study II. *Environ Health Perspect* 2017;125(8):087010.
- [100] Sarkar C. Residential greenness and adiposity: findings from the UK biobank. *Environ Int* 2017;106:1–10.
- [101] Casey JA, Morello-Frosch R, Mennitt DJ, Fistrup K, Ogburn EL, James P. Race/ethnicity, socioeconomic status, residential segregation, and spatial variation in noise exposure in the contiguous United States. *Environ Health Perspect* 2017;125(7):077017.
- [102] Johnson DA, Hirsch JA, Moore KA, Redline S, Diez Roux AV. Associations between the built environment and objective measures of sleep: the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2018;187(5):941–50.
- [103] Koo YS, Song JY, Joo EY, et al. Outdoor artificial light at night, obesity, and sleep health: cross-sectional analysis in the KoGES study. *Chronobiol Int* 2016;33(3):301–14.
- [104] Vollmer C, Michel U, Randler C. Outdoor light at night (LAN) is correlated with eveningness in adolescents. *Chronobiol Int* 2012;29(4):502–8.
- [105] Baron KG, Duffecy J, Berendsen MA, Cheung Mason I, Lattie EG, Manalo NC. Feeling validated yet? A scoping review of the use of consumer-targeted wearable and mobile technology to measure and improve sleep. *Sleep Med Rev* 2017;40:151–9.
- [106] Ko PR, Kientz JA, Choe EK, Kay M, Landis CA, Watson NF. Consumer sleep technologies: a review of the landscape. *J Clin Sleep Med* 2015;11(12):1455–61.

- [107] Kjellstrom T, Mercado S, Sami M, Havemann K, Iwao S. Achieving health equity in urban settings. *J Urban Health* 2007;84(3 Suppl. 1):i1–6.
- [108] Services UTfOCP. Recommendations to promote healthy social environments. *Am J Prev Med* 2003;24(3):4.
- [109] Shaw M. Housing and public health. *Annu Rev Publ Health* 2004;25:397–418.
- [110] Howden-Chapman P. Housing and inequalities in health. *J Epidemiol Community Health* 2002;56(9):645–6.
- [111] Services TFoCP. Recommendations to promote healthy social environments. *Am J Prev Med* 2003;24(3S):21–4.
- [112] Howden-Chapman P, Pierse N, Nicholls S, et al. Effects of improved home heating on asthma in community dwelling children: randomised controlled trial. *Br Med J* 2008;337:a1411.
- [113] Castaneda JL, Kheirandish-Gozal L, Gozal D, Accinelli RA. Pampa Cangallo Instituto de Investigaciones de la Altura research G. Effect of reductions in biomass fuel exposure on symptoms of sleep apnea in children living in the peruvian Andes: A preliminary field study. *Pediatr Pulmonol* 2013;48(10):996–9.
- [114] Astell-Burt T, Feng X, Kolt GS. Does access to neighbourhood green space promote a healthy duration of sleep? Novel findings from a cross-sectional study of 259 319 Australians. *BMJ Open* 2013;3(8).
- [115] McCurry SM, Pike KC, Vitiello MV, Logsdon RG, Larson EB, Teri L. Increasing walking and bright light exposure to improve sleep in community-dwelling persons with Alzheimer's disease: results of a randomized, controlled trial. *J Am Geriatr Soc* 2011;59(8):1393–402.
- [116] McCurry SM, Gibbons LE, Logsdon RG, Vitiello MV, Teri L. Nighttime insomnia treatment and education for Alzheimer's disease: a randomized, controlled trial. *J Am Geriatr Soc* 2005;53(5):793–802.
- [117] Reardon SF, Fox L, Townsend J. Neighborhood income composition by household race and income, 1990–2009. *Ann Am Acad Polit Soc Sci* 2015;660(1):78–97.
- [118] Hale L, Do DP. Racial differences in self-reports of sleep duration in a population-based study. *Sleep* 2007;30(9):1096–103.

This page intentionally left blank

Chapter 9

Environmental exposures affected by long-term weather pattern changes in relation to sleep health

Rupsha Singh^a, Symielle A. Gaston^a and Chandra L. Jackson^{a, b}

^aEpidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, United States; ^bDivision of Intramural Research, National Institute on Minority Health and Health Disparities, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, United States

Acronyms and abbreviations

ALAN	Artificial light at night
C	Celsius
CVD	Cardiovascular disease
dB	Decibel
EDI	Effective daylight illuminance
F	Fahrenheit
HHCM	High heat capacity mattress
JHS	Jackson Heart Study
LED	Light emitting diode
LHCM	Low heat capacity mattress
MESA	Multi-Ethnic Study of Atherosclerosis
mm/s	Millimeter per second
nm	Nanometer
REM	Rapid eye movement
SDB	Sleep-disordered breathing
SEP	Socioeconomic position
SES	Socioeconomic status
SWS	Slow-wave sleep
WASO	Wake after sleep onset

The physical environment and sleep

Sleep is an essential human need for maintaining biological homeostasis. While many internal biological mechanisms act in concert to regulate sleep–wake cycles, sleep is not entirely endogenous. In fact, many naturally occurring and anthropogenic external factors can impact sleep. Fig. 9.1 displays our conceptual framework for how physical and social environments across the life course may influence a person's health behaviors (e.g., sleep) that are related to risk and resiliency and “get under their skin” to subsequently influence health conditions (e.g., cardiovascular

disease). Of note, individuals spend the 24-hour period in either their residential, work and/or school, or recreational environments. These environments have structural factors, both social and material resources, community stressors (e.g., low social cohesion), and potential environmental hazards/pollutants (e.g., light and/or noise pollution) that could either directly or indirectly impact human health through various pathways.

Long-term weather pattern changes, driven by the escalating levels of greenhouse gas emissions resulting from human activities (e.g., fossil fuel burning), poses a threat for the environment as well as human health and well-being, including sleep health. The long-term shifts in atmospheric conditions related to environmental changes (e.g., rising temperature and precipitation) play a pivotal role in exacerbating the frequency, duration, and severity of various hazards (e.g., heat and cold waves, wildfires) [1], which results in direct and indirect consequences for both the physical and social environments that impact sleep [2]. Consequences in the physical environment include exacerbation of hazardous environmental exposures, such as worsened air quality [3,4].

In this section of the chapter, we describe the most salient known—albeit understudied—exposures in the physical environment (i.e., light, temperature, noise, vibrations, air quality, seasonality, and latitude/longitude) that are exacerbated by long-term weather pattern changes and influence sleep health. We also summarize prior observational and experimental studies (including interventions) that have investigated the impact of these external exposures on sleep before providing future directions based on gaps in our current understanding.

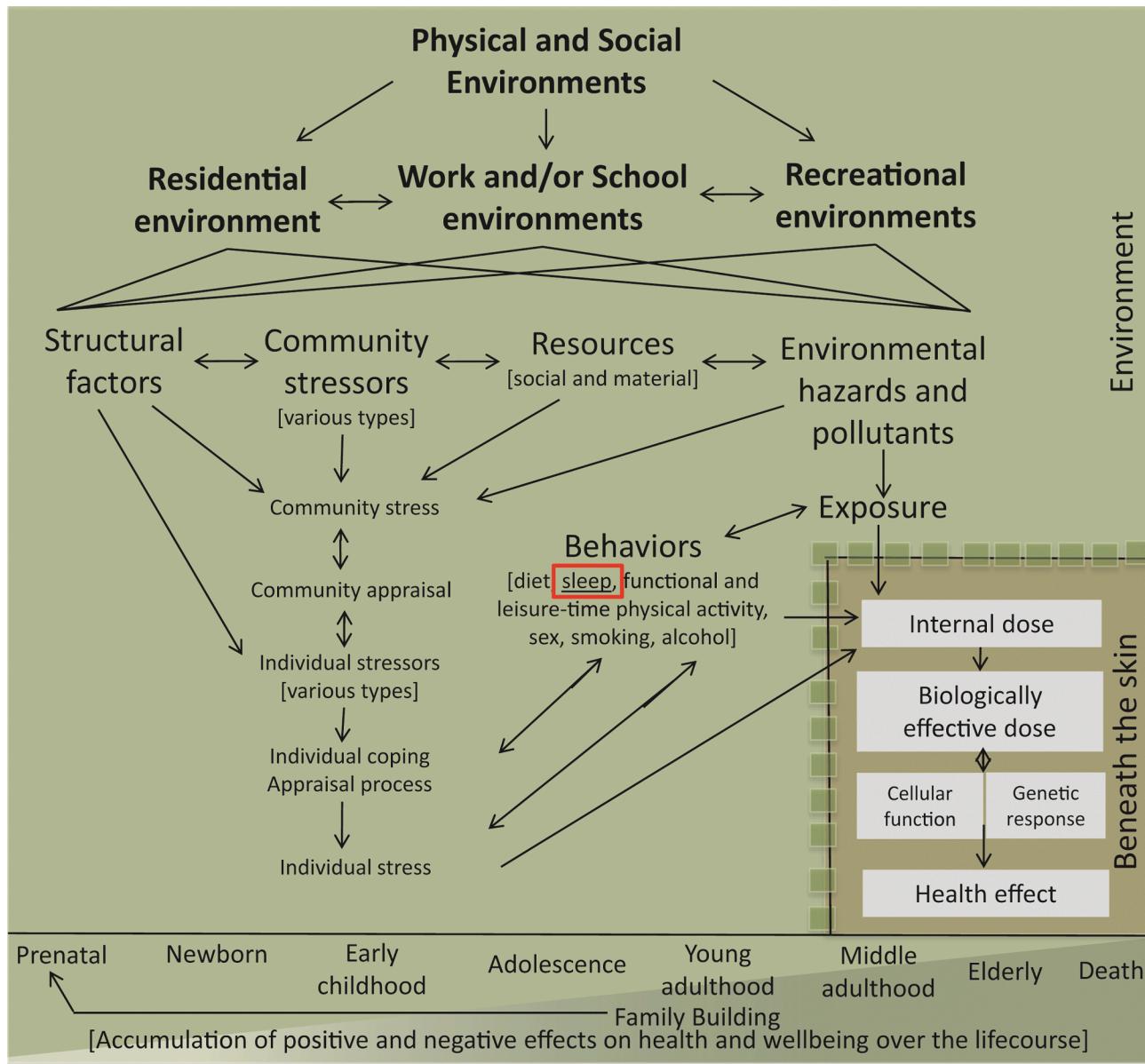


FIGURE 9.1 How risk, protective, and resiliency factors in the physical and social environments may “get under the skin” to influence health behaviors and subsequently impact health outcomes. *Permissions Adapted conceptual framework (permission granted in the original version).*

The impact of light on sleep

Greatly influencing human health and well-being, environmental light is the strongest synchronizing agent between the external physical environment and a person's circadian clock, which helps regulate internal biological systems [5–7]. As one of the most pervasive and fastest growing forms of environmental pollution with an annual increase of approximately 2%, excessive light has become a substantial public health concern [8]. Light pollution is generally considered artificial lighting that is either (1) unnecessary or inefficient (e.g., not targeted for a specific task and that can trespass into homes and bedrooms), (2)

brighter than natural light like lighting often used for advertising commercial goods and services such as gas stations and shopping centers, (3) uncomfortable/annoying to the human eye, and/or (4) unsafe (e.g., causes glare among drivers and pedestrians) [9–11]. Various forms include over illumination, light trespass, glare, and sky glow [10]. In addition to wasting energy by shining nontargeted light upward into space and creating sky glow above cities that obscures views of the stars and other planets, light pollution can even harm the biological integrity of ecosystems and has been shown to affect both flora and fauna [11].

Although outdoor light pollution thresholds have not been officially established, the International Astronomical Union recommends considering light pollution as artificial sky brightness greater than 10% of the natural sky brightness above 45 degrees of elevation [12]. It is also recommended that the visible light spectrum wavelength range (i.e., 440–540 nm) that corresponds to the maximum scotopic vision (responsible for night vision) sensitivity serve as the established protected range. Therefore, unrecommended outdoor lamps with a wavelength that exceeds 15% of the energy flux emitted in the photopic (responsible for daytime vision) response pass band (measured in watts) and where emissions in the scotopic response pass band that exceeds two-thirds of that emitted in the photopic response pass band (measured in lumens) [13]. Indoor light exposure recommendations based on expert consensus were recently established by the Second International Workshop on Circadian and Neurophysiological Photometry in 2019 [14]. Daytime light recommendations for indoor environments suggest maintaining a minimum melanopic Effective Daylight Illuminance (EDI) of 250 lux at eye level when seated, with a preference for natural daylight when possible [14]. If additional electric lighting is needed, it should ideally mimic natural daylight by having a spectrum enriched in shorter wavelengths [14]. During the evening, especially in the 3 h leading up to bedtime, it is recommended to limit melanopic EDI to a maximum of 10 lux at eye level [14]. This can be achieved by using white light sources with reduced short-wavelength content. During sleep, the recommended maximum ambient melanopic EDI is just 1 lux at the eye, emphasizing the importance of a dark sleep environment [14]. However, if nighttime activities require some illumination, it should be limited to a maximum of 10 lux at eye level [14].

Regarding potential biological mechanisms linking light pollution to poor sleep, humans are genetically adapted to a natural environment consisting of sunlight during the day and darkness at night, thus, making biological processes in rhythm with the 24-h light/dark cycle [15]. However, artificial light has replaced natural sunlight during the day and artificial light at night (ALAN) has also replaced darkness at night. Exposure to ALAN now begins in early life, continues throughout one's lifespan, and presumably affects biological processes in ways that raise the risk of poor sleep and health conditions like diabetes, certain cancers (e.g., breast), depression, and cardiovascular disease (CVD) [16,17]. Inopportune light exposure could lead to misalignment between one's external environment and their internal biological circadian clock. Circadian rhythm mechanisms that may underlie or contribute to the aforementioned health conditions include: melatonin synthesis suppression, circadian disruption/misalignment, 24-h sleep-wake cycle perturbations, sleep deprivation, or a combination thereof.

ALAN (based on both light intensity and wavelength) has been shown to suppress melatonin production, which is a hormone secreted by the pineal gland in the epithalamus of the brain that helps regulate sleeping patterns by, for instance, enhancing sleep onset. Human health can be negatively affected due to inhibited melatonin production because of exposure to bright light at night, especially blue light (described in greater detail later) since it, in particular, disrupts normal melatonin rhythms. Of note, bedroom illumination that is typical for most homes in the US is sufficient to reduce and delay melatonin production.

Schulmeister et al. found that monochromatic red light at 100 lux would take 403 h to suppress melatonin exposure by 50% and other sources take a much shorter time period: candle (66 min), 60 W incandescent bulb (39 min), 58 W deluxe daylight fluorescent light (15 min), and pure white high-output light emitting diode (LED) (13 min) [18]. LED light is an important source of light pollution that emits a large amount of blue light, which actually appears white to the naked human eye. LED light can cause glare and reduces visibility or the ability to resolve spatial detail. This glare is considered worse than conventional lighting and can create a safety hazard when, for example, drivers are affected. The main advantage of popular LED lighting is energy efficiency (in terms of reduced energy consumption and a decrease in fossil fuel use) and cost savings (although it takes years to accrue cost savings).

Previous studies have found that bright residential lighting from LED, for example, is associated with reduced sleep time, dissatisfaction with sleep quality, night-time awakenings, excessive sleepiness, impaired daytime functioning, and obesity [19,20]. Therefore, outdoor LED lighting may contribute to chronic disease risk in cities where they are installed. Outdoor ALAN has been positively associated with an increased risk of breast cancer among women and prostate cancer in men [21–23]. However, there have been no relevant correlations or links between outdoor ALAN and melatonin levels (based on a urinary biomarker) in cross-sectional studies [16]. Also, the threshold of light intensity that triggers a response in human health effects is currently unknown, which is an important topic for future research.

In terms of indoor illumination levels, melatonin levels have been found to be significantly lower in nurses who work nights versus day shifts [24–26]. Nurses working night shifts were exposed to more light during sleep. Rotating shift workers with erratic light exposure also had abnormal melatonin levels. Intense ALAN was also associated with a higher prevalence of self-reported insomnia symptoms [20]. It has been proposed that interventions among night-shift workers could seek to reset circadian rhythms to match work schedules with dark/light cycles by using bright light exposure during work and avoiding light

exposure before sleep. A recent meta-analysis found blue-enriched white light with a color temperature exceeding 5000 K to be effective in reducing nighttime sleepiness among night-shift workers [27]. Additionally, entrainment to scheduled time cues for food and exercise may reduce health effects despite disrupted photoperiods. Night workers could also curtail nonessential shift work and establish or maintain good sleep hygiene practices (e.g., regular sleep-wake schedule, avoid stimulants before bed) [10,11,28], but more research is needed. Indoor LAN has also been associated with short sleep duration and sleep disturbances [29]. Increased evening and nighttime light exposure also significantly associated with sleep-onset latency in an adolescent population [30]. Bright light 1 m away from eyes during sleep was associated with less deep sleep as demonstrated by periodic arousal and altered brain activity [31]. ALAN was also associated with delayed sleep initiation and reduced overall sleep quality and fatigue [32,33]. Of note, an increase in duration of exposure to bright light at night may be more important than intensity [16], and melatonin levels were negatively affected by blue light exposure, in particular. Blue light exposure was associated with decreased sleepiness and raised alertness [31,34].

Overall, some evidence supports a long-term increase in risk of obesity, diabetes, certain cancers (e.g., breast and prostate), and CVD from chronic sleep disruption or shift work associated with exposure to brighter light in the evening and at night although more research is warranted [35,36]. One study found low bedroom brightness was associated with reduced obesity rates in children [37]. Another study that examined the association between LAN and obesity among 113,343 women in the United Kingdom found that body mass index, waist-to-hip ratio, waist-to-height ratio, and waist circumference increased with increasing lightness of the room that the person sleeps in at night, even after adjusting for factors like sleep duration [38]. Similarly, ALAN was associated with obesity risk among a cohort of 43,722 US women [39]. The worldwide rise of obesity and use of electric lighting have paralleled each other, and both epidemiological evidence and animal experimental models support the belief that electric lighting is not merely a marker for a developed society in which behavioral factors (e.g., increased consumption, less energy expenditure) increase likelihood of obesity. Chronic circadian disruption from a 24-h light-dark cycle could mediate increased susceptibility to obesity, and more studies of, for instance, gene-by-environment interactions that take lighting and other environmental factors into account are needed since obesity and internal circadian clocks both have a high genetic component.

To protect sleep and avoid over lighting (greater than the minimum required for the task at hand), it is recommended by Falchi et al. that indoor light be dim and limited

to the area that needs illumination before being turned off when deemed unnecessary. The light also needs to have wavelengths toward the red, yellow, and orange rather than the blue end of the spectrum [10]. For instance, incandescent lights are preferred over fluorescent lights although they are considered less energy efficient [10]. International Dark Sky Association recommends use of low-pressure sodium lights generally and high-pressure sodium lights when color perception is important [10]. Ultimately, there are various types of lighting recommended in the following order from the most to least recommended: low pressure sodium, high pressure sodium, incandescent, metal halide, and LEDs are the least recommended because of their scotopic-to-photopic ratios and melatonin suppression effects [10]. Vision provided by rods and cones has sensitivity to certain wavelengths. Practically, there should be complete darkness during sleep; therefore, televisions and other devices should not remain on during the sleep period. A randomized controlled trial found that wearing amber versus clear lenses 2 h before bed was associated with reduced severity in insomnia symptoms and significant improvements in sleep, which may represent one effective intervention if behaviors prove difficult to change [40]. Blinds should be closed to keep illumination from street lights out.

Furthermore, recommendations for limiting outdoor ALAN includes avoiding the over lighting of outdoor spaces by turning lights off when not in use and banning outdoor emission of light at wavelengths shorter than 540 nm to reduce the adverse health effects of decreased melatonin production and circadian rhythm disruption in both humans and animals [10]. Also, luminaires should not send any light directly at and above the horizontal plane [10]. While it is important to note that some suggested interventions are counter to “public safety” (e.g., mall parking lots, lighting to deter crime—even though not proven effective), these recommendations should be evaluated for effectiveness in improving sleep. A study sought to identify protected areas that could be a refuge from light pollution and daily noise in European countries using spatial mapping and regression modeling to define areas without light pollution and that are quiet [41]. However, future studies should go beyond finding refuge from light and noise pollution toward finding ways to reduce these forms of pollution. Future studies should also use more advanced mapping tools to create finer map scales and define classes of areas needed beyond dichotomous levels of lit versus unlit.

There are several gaps in the literature that can serve as important directions for future research. For instance, more longitudinal studies assessing, for example, the impact of ALAN on melatonin and subsequent poor sleep and disease risk are needed. More research is needed to determine how varying levels of bedroom illumination affect

melatonin production in different types of sleepers, which may be especially important for people with sleep disorders (e.g., insomnia) and disparities in sleep architecture [11]. We need more research on illumination levels, duration, and colors of the light spectrum required to suppress human melatonin production. Furthermore, more research should be conducted on indoor light pollution, and sleep studies should ascertain outdoor and indoor ALAN along with their independent and combined effects. Future research should also study communities and cities that have adopted outdoor LED lighting and investigate its impact on sleep and health conditions affected by light-dark cycles. Additional recommended strategies are outlined in a National Heart, Lung, and Blood Institute workshop report on circadian health and light [42].

The impact of temperature on sleep

In addition to light, outdoor, indoor, and an individual's core body temperature can also affect sleep health, which has noteworthy implications for disease risk [43–45]. The core body temperature of humans is regulated by the thermoregulatory control center (known as the preoptic-anterior-hypothalamus), and is typically 37.0°C (or 98.6°Fahrenheit) [46]. There is an overlap in neurons sensitive to heat and neurons changing their firing pattern before and during sleep [47], and control of both body and brain temperature is closely tied to sleep regulation [48]. During normal sleep, a 2°F decrease in core body temperature occurs from the person's peak in body temperature in the early evening to its lowest point before waking up [47]. External factors can influence core body temperature, and distal skin temperature appears to be more important than the proximal skin temperature for sleep regulation. For instance, air conditioners are usually unnecessarily low at night (when compared to thermal comfort temperatures) [49]. Humidity at night/during sleep increases heart rate, sweat rate, and thermal load, which suppress slow wave sleep (SWS) and increase wakefulness [50]. Effects of humidity vary by time of sleep with stronger effects observed during the initial versus later sleeping period [50]. Negative effects of heat exposure are aggravated by other factors such as high humidity, as compromised air flow can reduce the heat load and wakefulness in warm, humid climates. Even exposure to bright light at night maintains high skin as well as rectal temperature and increases both heart rate and systolic blood pressure [50]. Although cycling temperatures within the thermoneutral temperature range do not significantly affect sleep stages, the thermal environment is one of the primary causes of sleep disturbance, and rapid-eye movement (REM) sleep is more vulnerable to thermal discomfort than other sleep stages [50]. Cold temperatures can increase the number and duration of wakefulness periods

and the length of REM cycles. Furthermore, high temperature can reduce total sleep time, duration of REM, and SWS and increase sleep onset latency as well as wakefulness. Higher ambient air temperatures have been associated with afternoon rest periods, but there was no relationship between afternoon resting periods (and ambient air pollution) when temperatures were lower than an 18–25°C threshold [51].

A recent study linked over 10 billion repeated sleep measurements from sleep-tracking wristbands comprising 7.4 million sleep records from 47,628 adults in 68 countries to daily meteorological information specific to each local area. The authors found that increasing nighttime temperatures, driven by long-term weather pattern changes, can have a substantial negative impact on sleep duration and timing after controlling for individual, seasonal, and time-varying confounders [52]. Specifically, sleep duration decreased by 14.08 min on very warm nights (>30°C), and temperatures >25°C were associated with <7 h of sleep [52]. Rising temperatures were also associated with shorter sleep duration due to delay in sleep onset when minimum temperatures rose above –10°C and advance in sleep offset when nighttime temperatures rose above 15°C [52]. The impact of temperature on sleep loss was notably greater for individuals in lower-income countries and older age groups, with females being more susceptible than males [52]. Those living in warmer regions showed a notably greater sleep loss with each degree of temperature increase. The authors also projected that by the year 2099, insufficient temperatures may lead to a reduction of 50–58 h of sleep per person per year [52].

A thermal neutral temperature for sleeping people has not been established. Bed microenvironments vary by person, season, location, indoor air temperature, bedding, clothing, etc. Therefore, room temperature measurements are not sufficient to describe thermal environment. Furthermore, females have been shown to be more sensitive to ambient air temperature than males [53]. While there is no threshold for outdoor temperature, the minimum recommended indoor threshold for European homes is approximately 18°C (17–19°C in winter and 23–25°C in summer) [54]. Limitations of current thresholds include thermal standards being defined for waking people, but the thermal comfort/neutral temperature is often warmer for sleeping compared to awake individuals. There is also important natural and unnatural variation in thermal comfort/neutral temperature that is difficult to capture.

A previous study sought to examine the impact of a high heat capacity mattress (HHC) compared to a low heat capacity mattress (LHC) on sleep and to determine whether core body temperature decline is enhanced and SWS is increased under gentle core body cooling on a HHC. The investigators found that participants on an HHC had significantly reduced core body temperature,

proximal skin temperatures on the back, and mattress surface temperature compared to participants on an LHC. They also had significantly increased N3 (or slow wave) sleep (27% of total sleep time for HHCM vs. 23% for LHC, $P = .03$) [55].

Future interventions could focus on changing the indoor environment in ways that meet the varied thermal comfort requirements throughout the sleep period. Interventions that address energy insecurity are particularly important due its contribution to extreme indoor temperatures and, consequently, sleep health [56]. Although more research is needed, bedside personalized ventilation systems could help with thermal comfort maintenance in addition to improved indoor air quality. Ventilation systems are also considered energy efficient. In addition to fan air ventilation, opening windows is associated with lower carbon monoxide levels and subjective sleep quality although there have been weak or nonsignificant associations with objective sleep as measured by wrist actigraphy [57]. Furthermore, stoves with external versus internal exhaust also appear to be an effective intervention to help address parent-reported child sleep problems [58].

Important gaps in the literature on temperature and sleep currently exist. For instance, objective measures of both the environment and sleep are necessary. It is important to measure heart rate variability and skin temperature concurrently with sleep to monitor human thermal comfort state as comfort reported during subjective sleep can be influenced by emotional or psychological stress, which may affect associations if sleep is subjectively measured. More studies of the microenvironment/climate of bed and its interaction with, for example, ventilation systems are needed to define a comfortable thermal neutral zone or sleep environment.

The impact of noise on sleep

Excessive natural and anthropogenic noise is an environmental pollutant and increasingly recognized public health issue that can negatively impact sleep health, which is considered the most serious nonauditory effect of excessive noise [59]. Noise is perceived by the auditory system in humans, and important studied sources of outdoor noise include traffic on the road, railways, and aircraft near homes [60]. Indoor noise/sound pollution is considered >35 dB and outdoor noise at night is >40 dB [61], but even ambient noise from external stimuli can be processed by the sleeper's sensory functions despite a nonconscious perception of their presence [60]. Environmental noise (and other external environmental events) can also activate processes during sleep that lead to eventual consciousness [62].

Previous studies have found that noise can negatively affect sleep architecture [60]. For instance, one study

concluded that railway noise was associated with a higher percentage of people self-reporting sleep disturbance compared to those exposed to the same amount of road noise [63]. In addition to railway noise leading to sleep disturbance [64], studies have also found delayed sleep onset, induced awakenings, earlier final awakening or nocturnal awakenings, arousals along with hormonal responses, as well as acute autonomic and cardiac activations that may explain associations between noise and compromised cardiovascular conditions [60,65,66]. In addition to reductions in REM sleep [67], there are also reports of a greater likelihood of taking sleep medications and experiencing objectively measured body movements during sleep [64,68], increased wakefulness [64], performance decrements [69], and impaired daytime functioning in terms of increased tiredness, daytime sleepiness, and need for compensatory resting periods [65]. Railway noise exposure has even been linked with a higher risk for certain types of breast cancer compared to nonexposure to railway noise [63]. Moreover, freight train noise may be particularly deleterious as it has been shown to cause more frequent awakenings [70,71], a stronger cardiac response [66], and greater night time annoyance compared to passenger trains [72]. Wind turbine noise also has the potential to adversely affect sleep through frequent physiological activation in response to disturbance; however, prior studies have had inconsistent results and additional systematic studies are needed [73].

In a meta-analysis of pooled data from 28 data sources, Miedema and Vos investigated the association between night-time noise and sleep disturbance to both establish functions that specify self-reported sleep disturbance in relation to night-time transportation noise exposure (ranging from 45 to 65 dB) and to quantify the impact of transportation types (air, road, rail) [74]. The authors found that exposure to nighttime transportation noise was related to self-reported sleep in a dose-response manner [74]. Also, aircraft noise was associated with more self-reported sleep disturbance than road traffic, and road traffic noise had a stronger association with sleep disturbance than railways. The association of noise-induced sleep disturbance with age had an inverse U-shape, with the strongest reaction found between 50 and 56 years of age. The investigators concluded that this counterintuitive finding could be due to hearing decline in older age. Another study investigating the single and combined effects of air, road, and rail traffic noise on sleep and recuperation, found small changes in SWS latency (+8.3 min), stage 1 sleep (+4 min), and SWS (-6 min) associated with traffic noise [65]. Changes in sleep continuity were also significant in that small noise-induced changes affected subjective assessments of sleep quality but did not affect daytime performance. Road traffic noise led to the most prominent changes in sleep structure and continuity even though

nights with air and rail traffic noise were reported as being more disturbing than road traffic noise [65]. Relatively moderate cumulative effects of noise on sleep structure were only observed for REM latency, SWS latency, and time spent in REM. Awakening probability decreased in the order of rail, rod, and air traffic noise, which is the reverse order for annoyance rankings reported during the day. A study of hospitalized patients found a new-onset insomnia prevalence of 36%, and that noise/brightness were contributors following frequent blood draws and vital sign checks due to their illnesses [75].

Furthermore, in a recent review of 48 articles assessing the impact of occupational noise exposure on sleep quality, there was consistent evidence of associations between various occupational noise and poorer sleep among workers across different occupations [76]. All of the high-quality studies included in the review showed that noise (mean noise exposure level = 78.68 dB, mean noise duration = 7.43 h) was associated with sleep disturbance, poor sleep quality, insomnia, and sleepiness with odds ratios ranging from 1.39 to 3.52 [76]. Most moderate quality studies also reported similar associations as well as associations with obstructive sleep apnea with odds ratios ranging from 1.07 to 2.28 [76].

Challenges associated with research on noise and sleep include the association being modified by personal/nonauditory factors including sensitivity to noise. Also, sound levels in communities constantly change. Intermittent noise is more likely to affect sleep (than constant noise), which can vary by source like rail versus road versus aircrafts. Moreover, bedroom noise depends on a variety of factors (e.g., insulation of house, sounds of household appliances, if windows are open) and is difficult to measure. Overall, for this type of research to advance, it is necessary for some fundamental questions to be answered regarding whether environmental noise has long-term detrimental effects on health and quality of life and, if so, what these effects are for night-time noise-exposed populations. Studies of individual differences in sensitivity to noise and effects of daytime noise on shift/night workers are also needed. Moreover, future studies should include the elderly who may be more affected by noise than younger adults (because SWS is shorter among the elderly), people with severe disease likely to be disturbed by noise, children (because studies are sparse), and night workers since they must sleep during the day when it is noisier. Furthermore, additional longitudinal studies need to study how sleep is affected by noise and its impact on CVD. Future research should also focus on long-term effects of night-time noise exposure among different populations, specific subgroups that are “at risk” (e.g., children, elderly people, self-estimated sensitive people, people with insomnia or other sleep disorders, night and

shift workers), and the combined effects of noise exposure and other physical agents or stressors during sleep.

The impact of vibrations on sleep

Noise is often accompanied by vibrations. Ground-born vibration from railway movements, as an example, is created by the interaction between the wheels and the rail, where regularities from either surface can generate considerable vibration energy [77]. Ground vibrations near railway lines are often in the range of 0.4–1.5 mm/s [78]. Previous studies have found that increasing vibration results in increased reporting of waking during the night and waking too early in the morning [79]. Annoyance due to railway vibration is higher during the evening than the day and higher during night than evening [80]. Both lower sleep quality and alertness have been reported following the night after vibration exposure of 1.4 mm/s compared to nights with vibration of 0.4 mm/s. This finding corresponded with more restlessness, greater difficulty falling asleep, and more awakenings once asleep [80]. Although stronger vibrations from railway freight were associated reduced subjective sleep quality and increased self-reported sleep disturbance [81], self-reported sleep variables do not necessarily correlate strongly with actual physiological responses [82]. Like with noise, even minor sleep disturbances due to vibrations can cause degradation of executive functions despite a lack of subjective response [83]. In addition to exposure level per se, there is some evidence that the number of trains can influence human response as annoyance was found to be higher in areas with a greater number of trains [78,84]. Pass-by frequency during the night has also been linked to self-reported noise-induced disturbances [64]. However, the number of nocturnal pass-bys was not found to be statistically significantly associated with wakefulness and light sleep time as objectively determined by polysomnography [64]. The vibration amplitude contributed to arousal as well as awakening and sleep stage change probabilities. A number of trains during the night led to self-reports of sleep disturbance at moderate vibration amplitudes. Both vibration amplitude and the number of trains contributed to effects on sleep architecture, whereby the number of sleep depth changes, SWS continuity, and nocturnal wakefulness were negatively affected during the high vibration condition with a high number of trains. Furthermore, some studies also suggest that low-frequency vibration (like from a car or inside a train) can, in turn, induce sleep [85]. Nonetheless, future studies need to investigate the long-term effect of nocturnal vibrations, examine the combined impact of noise and vibration, and elucidate mechanisms involved in potential vibration habituation or sensitization.

The impact of air quality on sleep

It is biologically plausible that elevations in ambient air pollution may affect sleep through pollutant-associated effects on central or peripheral neurotransmitters that influence sleep state stability, upper airway patency, and/or ventilatory control. Pollutants may directly contribute to nasal/pharyngeal inflammatory and oxidative stress responses that increase upper and lower airway resistance and reduce airway patency, which could lead to oxyhemoglobin desaturation [86]. Fine and ultrafine particles may alter ventilation–perfusion relations, exacerbating the hypoxia of SDB [86,87], and pollution may increase SDB through influencing central ventilatory control centers. In patients with asthma and SDB, elevated air pollution has been demonstrated to worsen lower airway inflammation and airflow obstruction through allergic and nonallergic mechanisms [88]; this may also contribute to the propensity for desaturation with sleep-associated reductions in ventilation. In patients with hay fever, upper airflow obstruction may worsen on an allergic basis when air pollution particles also contain allergen fragments [86,87]. Pollutants entering the blood could have an effect on the brain and hence the regulation of breathing.

Of the few studies that have investigated the relationship between outdoor air pollution and sleep apnea or sleep disordered breathing (SDB), results have been inconsistent among adults [89–92]. Among US adults (≥ 39 years), an interquartile increase in short-term exposure to fine particulate matter $\leq 10 \mu\text{m}$ (PM_{10}) in diameter was associated with an approximately 12% increase in the percentage of sleep time at less than 90% oxygen saturation as well as a 1% decrease in sleep efficiency (affected by sleep state stability) [89]. However, population-based studies among German and Taiwanese adults observed no associations between PM_{10} and sleep apnea severity [90,91]. In the German study, however, short-term exposure to ozone was associated with sleep apnea severity [91]. Yet, in Taiwan, Shen et al. found no relationship between sleep apnea severity and ozone, but observed positive associations between sleep apnea severity and both short-term and annual exposure to particulate matter with aerodynamic diameters ≤ 2.5 ($\text{PM}_{2.5}$) as well as nitrogen dioxide (NO_2) [90]. These associations were stronger in the winter and spring. There also may be associations between $\text{PM}_{2.5}$ and average sleep duration. For instance, a prospective study of 12,291 college freshman in China found that students reported longer sleep duration (in hours) for each standard deviation (36.5 mg/m^3) increase in $\text{PM}_{2.5}$ exposure (1.07 [95% CI: 1.04–1.11]) [93].

A review highlighting studies of air pollution and SDB among children found that Australian and Italian children with high exposure to NO_2 and PM_{10} (Italian children only for PM_{10}) were more likely to report or have objectively

measured SDB [92]. Similarly, a study of elementary-aged children in Iran suggested that odds of subjectively measured habitual snoring were higher among children more exposed to air pollution compared to children exposed to less pollution [92]. Conversely, Abou-Khadra et al. did not observe a relationship between PM_{10} exposure and SDB among Egyptian elementary school-aged children [92].

In a review of 15 studies on impact of air pollution on sleep quality, Cao et al. found that exposure to $\text{PM}_{2.5}$, PM_{10} , NO_2 was associated with decreased sleep duration among adults [94]. Among preschool aged children (4–5 years), prenatal exposures to $\text{PM}_{2.5}$ during weeks 1–8 of gestation were associated with decreased sleep efficiency and during weeks 31–35 was associated with decreased sleep duration, while exposure of $\text{PM}_{2.5}$ during weeks 39–40 was associated with increased sleep duration [95]. Further, one study in China reported that one standard deviation increase in the air quality index (calculated with $\text{PM}_{2.5}$, PM_{10} , NO_2 , SO_2 , O_3 , and CO) was associated with 0.68 h reduction in sleep duration per day [96]. In a recent large study from the UK Biobank ($N = 378,223$), Li et al. also found associations between ambient air pollution and poor sleep after adjusting for noise [97].

While the relationship between outdoor air pollution and sleep may prove important, humans spend approximately 80%–90% of their time indoors with approximately 34% of their day in the sleep microenvironment [98–100], which is characterized as the space with a mattress, pillow, bedding materials, bed frame, and breathing zone as well as buoyant thermal plume [101,102]. This environment (especially beds as reservoirs for a complex mixture of chemical- and non-chemical-laden dust) can harbor diverse indoor pollutants like house dust mites comprising a wide range of organisms and their associated allergens, fungi, bacteria (mainly from human origins [e.g., skin, intestinal, genital]), volatile organic compounds, plasticizers like phthalates, flame retardants such as polybrominated diphenyl ethers in and on mattresses, pillows, and bed sheets (as accumulation zones) [101]. Inhalation and dermal absorption of these potentially detrimental chemical and nonchemical environmental exposures, while sleeping could be hazardous to health. In fact, data suggest that the sleep microenvironment may even play a critical role in characterizing exposures of very young children to indoor pollutants. Of note, if a child and an adult are exposed to the same breathing zone concentration of a pollutant released from, for example, a mattress, then the child-normalized dose will be much greater than the adult.

There are several key factors in the sleep microenvironment that contribute to a source-proximity effect, including the spatial proximity of the breathing zone to the source of the exposure, incomplete mixing and common poor ventilation of bedroom air that leads to concentration

gradients in the space near an actively emitting source, the personal cloud due to human body movement-induced particle resuspension, the buoyant human thermal plume, heat transfer from the human body to the source (which may elevate the emissions of gaseous pollutants), and direct dermal contact with the source [102]. Sleep microenvironments are important, but they have not been extensively researched in contrast to exposures in other types of indoor environments, such as classrooms, kitchens, and occupational workplaces. To investigate subsequent health effects and to develop strategies to promote healthy bedrooms, more research is needed to understand the pollutants commonly found in sleep microenvironments, the mechanisms by which pollutants are transported around the human body to an individual's breathing zone, pollutant concentrations and exposure levels that individuals experience while sleeping, and the total amount of pollutants that are inhaled or absorbed via dermal exposure. As summarized by Boor et al., future research should focus on personal exposure monitoring of particles and gases, which will permit more reliable associations with health outcomes beyond basic mattress dust sampling/analysis [102]. Studies should also investigate the contribution of early-life sleep exposures to microbes, allergens, and semi-volatile organic compounds as well as total exposures to these agents. A systematic review found an overall positive association between allergic rhinitis and SDB among children [103]. It is also important to understand variation in exposures during sleep among ethnically diverse populations and age groups as well as to elucidate the impact of human exposure to the full range (indoor and outdoor) of particulate and gaseous air pollutants. Investigators should also identify the role of multiple bed partners since 48%–72% of Americans sleep with a significant other and 2%–16% with their pets [102]. Studies should also evaluate the impact of bedside personalized ventilation systems helping to filter and deliver fresh air in addition to providing thermal comfort maintenance. Lastly, indoor air quality and its effects on sleep quality as well as special settings for sleep microenvironments (e.g., hospital beds, camping tents, dormitories) should be studied.

The impact of seasonality and latitude/longitude on sleep

Although the health effects are not well understood, seasonal variation in sleep/wake cycles likely exist due to differences in photoperiod, which refers to variability in hours of light throughout the four weather seasons [104]. Since light entrains circadian rhythms that depend on when the light exposure occurs, exposure prior to the normal temperature nadir will phase-delay the circadian rhythm and exposure to light after the normal temperature nadir will phase-advance the circadian rhythm [105]. During

summer sleep times, core body temperature and melatonin secretion tend to be slightly advanced due to the longer photoperiods. Users of a smartphone ENTRAIN app found that later sunset times were associated with longer sleep duration among more than 20 different countries located around the globe [106]. They also found that those reporting being typically exposed to outdoor light go to sleep earlier and sleep more than those who reported more indoor light exposure [106]. A retrospective study investigating seasonal variation in sleep of patients who underwent polysomnography found REM sleep to be longer during winter than spring, shorter REM latency in winter and early autumn compared to late spring and late autumn, as well as decrease in SWS during autumn [107].

Furthermore, seasonal changes during the year are more marked in extreme Arctic and Antarctic latitudes than in Equatorial regions. Thus, people living at higher latitudes have a higher variability of sunlight duration, depending on the season. Even in preindustrial societies, the specific photopic period related to latitude seems to markedly influence sleep duration [104]. For instance, geographic latitude showed significant associations with self-reported sleep duration in a large population-based sample of people living between 18°29'S and 53°18'S in Chile. Those individuals who lived nearer to the Antarctic Circle had significantly longer sleep durations compared to their counterparts who resided closer to the equator. This association was stronger in men and especially for sleep during weekends. People living in latitudes more proximal to the equator had a greater than threefold odds of being short sleepers during weekends than those living near the Antarctic Circle [108]. Another study investigated the impact of seasonality on sleep by comparing Norway and Ghana where Norway experiences large seasonal variation while Ghana does not (due to its position near the equator). While not found in Ghana, the bed and wake times were earlier in the summer while insomnia, fatigue, and poor mood were more common in the winter [109]. Furthermore, Stothard et al. aimed to (1) quantify the impact of a week-long exposure to the natural winter light-dark cycle compared to exposure to modern electrical lighting on the timing of the human circadian clock and (2) quantify the circadian response to a weekend of exposure to the natural summer light-dark cycle [110]. Investigators found that the beginning of the biological night and sleep occurred earlier after a week's exposure to a natural winter light-dark cycle as compared to the modern electrical lighting environment [110]. They also found that the human circadian clock was sensitive to seasonal changes in the natural light-dark cycle in that it was longer in the winter than the summer [110]. Circadian and sleep timing occurred earlier after spending a week camping in a summer natural light-dark cycle compared to a typical weekend in the modern environment; thus, the circadian clock appears timed later in the modern

environment in both the winter and the summer. Participants in cities along the same latitude had similar resting periods, and resting periods over the year reflected the length of the night throughout the year [51]. Since better characterizing the impact of seasonality on sleep health could lead to more effective interventions, more research in this area is warranted.

The social environment and sleep

In addition to naturally occurring and man-made exposures in the physical environment (i.e., light, temperature, noise, vibrations, air quality in the microenvironment, seasonality, latitude/longitude) affecting sleep health, many factors in one's social environment are important determinants of sleep health. The social environment includes social conditions, policies, and institutions (e.g., culture, the economic system), the surrounding community (e.g., neighborhood), along with interpersonal factors (e.g., social context and relationships) [111]. Notably, long-term weather pattern changes will likely contribute to worsening social environments [3,4]. Social impacts of hazards related to long-term weather pattern changes may include, for instance, heightened food insecurity, as well as social challenges, such as displacement and forced migration in the aftermath of disasters, adverse economic impacts, community disruptions, and civil conflicts. Moreover, extreme weather-related disasters can have direct (e.g., posttraumatic stress disorder) and indirect (e.g., eco-anxiety—anxiety stemming from the looming threats posed by long-term weather pattern changes) effects on community psychosocial and individual-level psychological stress, further contributing to sleep problems [3,4].

With psychosocial stress as the main, overarching driver connecting the social environment to poor sleep, this section of the chapter summarizes prior observational studies that have investigated how sleep is impacted by psychosocial stressors one may experience within multiple social contexts and in various settings within the social environment (e.g., neighborhood/home, workplace, social/recreational environment). For example, we discuss relationships between sleep and low socioeconomic status; suboptimal neighborhood characteristics like low safety and high disorder; racism and other forms of discrimination at multiple levels (e.g., institutional and interpersonal); suboptimal work-related conditions like shift work and job strain; as well as interpersonal factors such as family structure and trauma.

Psychosocial stress and sleep

A detrimental social environment whether at the policy, community, or interpersonal level can lead to psychosocial

stress in individuals. Defined as stress that occurs when an individual perceives that the external demands of a stressor exceed their ability to cope with the stressor [112], there are two types of psychosocial stress: acute stress (e.g., major event like a flood) and chronic stress (e.g., the aftermath of such disasters like homelessness or financial strain). Chronic stress is associated with increased vulnerability to disease [113], and poor sleep may be on the causal pathway from stress to disease.

Each form of psychosocial stress has the potential to affect sleep as shown in the results of a recent review [114]. Although most of the investigated stressors have been chronic, acute stress has been associated with worse sleep efficiency, frequent awakenings, decreased REM sleep, and less SWS [114]. Particularly, major stressful life events can affect sleep through decreases in REM latency, increased REM sleep percentage, and reduced SWS [114]. It has been difficult to observe consistent patterns between diverse chronic stressors and sleep, likely due to differences in study populations and the daily life stressors measured; yet, everyday emotional stress was found to be consistently associated with unfavorable changes in sleep architecture, namely less SWS [114]. Since a variety of acute and chronic, everyday psychosocial stressors within an individual's social environment can affect sleep, we summarize many factors that have been investigated in the sleep literature.

Social conditions, policies, and institutions: The impact of socioeconomic status and racism on sleep

Socioeconomic status (SES) is a fundamental cause and strong driver of differences in population health, and it likely affects sleep by determining an individual's physical as well as social environmental exposures [115]. Within several studies highlighted in literature reviews, lower socioeconomic position (SEP) has been associated with higher rates of sleep disturbance, such as difficulty falling asleep, staying asleep, waking too early, and worse sleep quality [115,116]. SES characteristics associated with worse sleep include not graduating from college, lower household income, unemployment, a lack of access to private health insurance, and food insecurity [116–119]. Studies also suggest a negative association between educational attainment and insomnia [120] and that lower childhood SEP is associated with decreased SWS and increased stage 2 sleep in adulthood [121].

Discussed in greater detail in Chapter 7, many racial and ethnic groups are disproportionately represented in lower socioeconomic status groups, which is likely a manifestation of discriminatory practices on the societal level. Discrimination is generally defined as differential or unfair treatment based on actual or perceived membership

in a group [122] and can occur based on race along with ethnicity, national origin, religion, gender, sexual orientation, SES, or other social factors [123]. In fact, the pervasive, widespread observation of racial and ethnic disparities across a range of health outcomes likely results from a race-based or -conscious society involving systematic discrimination across institutions and cultural practices on the basis of race and/or ethnicity [124,125]. In terms of sleep, minoritized racial and ethnic groups are more likely to experience poor sleep than their White counterparts, especially African–Americans [115,126]. For instance, certain minoritized racial and ethnic groups in the US are generally 2–4 times more likely than their White counterparts to report shorter and longer sleep duration [115,126], both of which are associated with suboptimal health. Racial and ethnic minorities are also more likely to experience suboptimal sleep architecture and quality [115,126]. One manifestation of an individual living in a stressful/oppressive environment is known as John Henryism in the epidemiological literature. It is the hypothesis that members of marginalized groups are routinely exposed to psychosocial stressors (e.g., discrimination, job strain) that require the engagement in a high level of active coping or use of considerable energy daily to manage the psychosocial stress [127]. When continual engagement in effortful active coping and ambitions or interests is not met with support or resources, strain ensues. This strain or stress can lead to disrupted sleep, which may (as an example) lead to less SWS and nondipping of blood pressure during normal sleep [128]. Discriminatory practices (e.g., residential segregation; employment; education) based on race likely play an important role in determining differential exposure to environmental features that promote or harm health.

Community: The impact of neighborhood social and physical environments on sleep

Described in greater detail in [Chapter 8](#), the neighborhood environment has been linked to individual health outcomes and sleep may be on the causal pathway through which factors in the environment—both physical and social—affect health. In short, psychosocial stress in the neighborhood (like relative social disadvantage and a lack of social cohesion, social capital, and/or safety) can affect sleep health and subsequent risk of disease. Aspects of the neighborhood environment are measured differently across studies, but most suggest that suboptimal neighborhood conditions can contribute to poor sleep. However, they are often cross-sectional and rely on self-reported data. Therefore, more research with longitudinal designs and objective measures are needed.

Nonetheless, neighborhood physical and social disorder was associated with self-reported trouble falling asleep and

waking too early [129] as well as shorter sleep duration [130]. No social or physical neighborhood factors were associated with insomnia symptoms in one study [130], but insomnia symptoms were found to be more prevalent in noisy compared to non-noisy neighborhoods in another study [131]. Johnson et al. found that neither sleep fragmentation nor sleep efficiency varied by social environment, but participants residing in increasingly more favorable social environments had approximately 6 min longer sleep duration and earlier sleep midpoint [132]. Lower neighborhood social cohesion has been found to be associated with self-reported trouble falling asleep and feeling unrested [129] and worse sleep quality [133,134], and a cohesive, positive social environment was suggested as being associated with less daytime sleepiness [130].

Studies about neighborhood socioeconomic factors and sleep have had mixed results. Neighborhood disadvantage, measured by census tract-level data (e.g., percentage of residents with Bachelor's degree, median home value, median household income), was not associated with sleep duration in the Jackson Heart Study (JHS) after adjustment for individual-level SES factors, demographic factors, and health characteristics [133]. However, Fang and colleagues observed that participants with low- and middle-neighborhood SES had higher odds of very short and short sleep compared to individuals in high SES neighborhoods in Boston communities [135]. Furthermore, DeSantis et al. showed higher neighborhood SES was associated with less daytime sleepiness within US adults enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) [130]. Similarly, Xiao and Hale found that adults residing in lower-SES neighborhoods were more likely to report very short sleep, long sleep, and long (≥ 1 h) napping [136].

Neighborhood and sleep relationships may vary by sex. For instance, neighborhood disadvantage has been associated with higher odds of restless sleep among women and not men, but census tract density was associated with higher odds of restless sleep among men and not women [137]. An individual's perception as well as outsiders' perceptions of their neighborhood may also affect sleep, but such relationships vary by neighborhood perceptions measured. Perceived low neighborhood quality was associated with fair/poor sleep quality [138,139] and prolonged sleep latency [139]. Studies have shown perceived neighborhood safety was not associated with sleep disruption [140] or insomnia symptoms [131] while perceiving the neighborhood as unsafe was associated with short sleep and insomnia symptoms in another study [141]. Moreover, neighborhood safety was associated with longer sleep duration in a different study [130]. High levels of neighborhood violence were associated with insomnia symptoms among Hispanics/Latinos [131] as well as shorter sleep duration and poor sleep quality among

African–Americans in JHS [133]. In JHS, participants with perceptions of neighborhood problems like traffic, trash/litter, and lack of parks had lower sleep quality than participants with more positive neighborhood perceptions, which remained after adjustment for individual-level sociodemographic and socioeconomic factors as well as health characteristics [133]. Neighborhood stigma in the form of negative media perception was negatively associated with self-reported sleep duration and quality among 120 Hispanic/Latino adults enrolled in the New York City Low Income Housing, Neighborhoods, and Health Study [142].

Physical features of the neighborhood environment may be associated with sleep. Low neighborhood walkability was associated with greater severity of sleep apnea, especially in male obese individuals [143], greater built environment was associated with shorter average sleep duration, and larger intersection density was associated with lower sleep efficiency [144]. Neighborhood-level crowding has also been suggested as a factor related to increased severity of sleep disrupted breathing [145].

Community: Work environment and sleep

The workplace is an important setting for potential exposure to suboptimal physical and social environmental factors that can negatively affect sleep, which are described in greater detail in Chapter 37. Briefly, shift work has been identified as a probable human carcinogen [146], and shift workers have been shown to have long sleep latency, decreased SWS, increased REM, and shorter REM latency, which is attributed largely to emotional stress or worry regarding the next morning [114]. A meta-analysis of three longitudinal studies suggested that steady shift work was a risk factor for future sleep disturbances [147]. Shift work can also lead to circadian misalignment, resulting in deleterious outcomes like chronic sleep loss, shift work disorder (a clinically diagnosed circadian rhythm sleep disorder), and morbidity [28]. Shift workers are more likely to have low SES and be nonwhite (particularly, African–American), which has several implications regarding racial/ethnic and socioeconomic sleep disparities discussed previously.

Meta-analyses of longitudinal and cross-sectional studies provide evidence that stressful work environments may lead to poor sleep [147–149]. Higher job demands are positively associated with sleep disturbances and lower sleep quality in longitudinal studies [147,148]. In terms of job control, there is strong evidence that higher job control is positively associated with higher sleep quality in longitudinal studies [148]. Positive associations have also been observed between job control and lower levels of sleep disturbances in fixed effects models, although the relationship was no longer significant in the random effects

model [147]. Job strain may be a risk factor for future sleep disturbances [147]. Conversely, a meta-analysis states there is moderately strong evidence that social support within the work environment may induce better sleep quality [148] and lower frequency of sleep disturbances [147]. Effort-reward imbalance (imbalance between the effort to perform a job and the reward it provides), though negatively associated with sleep quality [148], was not found to influence future sleep disturbances [147]. However, self-reported and actual workplace bullying was positively associated with future sleep disturbances [147]. Lastly, organizational justice/influence over decisions was positively related to better sleep quality and lack thereof was related to future sleep disturbances [147,148]. Despite these findings among longitudinal studies, no significant effect of changes to psychosocial work characteristics on sleep quality could be established [148].

Interpersonal relationships and sleep

In addition to the aforementioned institutional discrimination, interpersonal discrimination occurs in ways that have been shown to affect sleep. For instance, there are consistent positive associations between various forms of interpersonal discrimination and self-reported sleep difficulties as well as insomnia [123,150]. However, one study among older adult participants aged 50 and older in the Health and Retirement Study reported no longitudinal association between discrimination and sleep quality [151]. Findings related to sleep duration are inconsistent and vary by type of discrimination (major vs. everyday discrimination). Among four studies that used PSG or actigraphy, one study found that everyday discrimination was associated with shorter sleep duration, but no significant association was observed in the other studies [123].

In terms of sleep architecture, within four studies of objectively measured sleep, discrimination was positively associated with wake after sleep onset (WASO) in two studies as well as a smaller proportion of REM sleep in one study, and experiencing discrimination was inversely related to the proportion of SWS (stages 3 and 4) in two studies [123]. One study found a positive relationship between discrimination and light (stage 2) sleep [123]. Of the three studies that examined discrimination and sleep efficiency, two reported no association with discrimination, but one suggested an inverse relationship [123]. Associations between discrimination and sleep were generally attenuated after adjustment for depressive symptoms [123].

An additional social stressor that may affect sleep is acculturation, the process by which immigrants adopt, internalize, and exhibit the behaviors of the host society [152]. Among Hispanics/Latinos, one's level of acculturation has been associated with changes in health status when living in the US [153]. Most studies regarding

acculturation and sleep among the US population have focused on Hispanics/Latinos, were cross-sectional, and investigated associations with self-reported sleep [118,152–159]. Although the measure of acculturation varied across studies, less acculturation was consistently associated with better sleep. Among adolescents, middle-aged adults, and older adults, less acculturated Hispanic/Latinos were more likely to report longer sleep duration and better sleep quality and were also less likely to report very short sleep, short sleep, and insomnia symptoms—although relationships with insomnia symptoms were attenuated after adjustment for sociodemographic and behavioral characteristics [118,152,159,160]. Furthermore, greater acculturation and acculturation stress were marginally associated with long sleep and positively associated with poor sleep quality including daytime sleepiness, short sleep (prior to adjustment for socio-demographic and behavioral factors), and more sleep complaints [154,156–158]. One repeated measures study among Mexican-American pregnant women found that women with higher acculturation reported more nighttime disruptions in sleep compared to less acculturated women throughout pregnancy [155]. Further research regarding acculturation inclusive of non-Mexicans and other immigrant populations with longitudinal study designs and objective measures of sleep throughout the life course are warranted.

Beyond neighborhood-related stigma, there are few studies with focus on personal stigma and sleep; however, stigma may be associated with worse sleep. For instance, in a study of HIV infected individuals, internalized (integration of others attitudes and opinions into one's identity/sense of self) HIV stigma was indirectly associated with poorer sleep quality through depression and loneliness [161]. Similarly, among 64 adults aged 18–64 years that reported substance abuse, internalized stigma mediated the positive association between perceived stigma and self-reported poorer sleep [162].

In terms of trauma as a stressor that appears to affect sleep, a systematic review conducted by Kajeepeeta et al. shows significant associations between history of childhood adversity and a variety of sleep disorders including sleep apnea, narcolepsy, nightmare distress, sleep paralysis, and psychiatric sleep disorders in adulthood among women [163]. The strengths of the associations increased with the number and severity of experiences [163]. These findings, particularly among adult women of childbearing age, have potential implications for child health because poor maternal mental health may be associated with WASO among infants [164]. Another early life trauma, bullying victimization at 8 and 10 years, has also been associated with nightmares, night terrors, sleepwalking, and any type of parasomnia at age 12 years [164]. Furthermore, there is evidence that peer victimization is

associated with insomnia symptoms over time among both preschool aged children and adolescents [165,166]. In terms of violence, a review of literature investigating relationships between community violence and physical health outcomes among youth aged 0–18 years, found that exposure to community violence was associated with sleep problems in all of the included studies [167]. Bailey et al. reported that children who were victims of community violence had 94% increased risk of self-reported sleep difficulty [168]. Youth who reported witnessing a homicide had a two-fold increase of WASO at baseline in one of the studies, but associations were no longer statistically significant at follow-up [169]. One study suggests that relationships between witnessing violence and sleep problems may be stronger among females compared to males [170]. Lastly, high exposure to violence was also associated with self-reports of short sleep and sleep interruption among the mothers of young children [140].

Family structure or dynamics are important for sleep throughout the life course as noted in a review by Meltzer and Montgomery-Downs [171]. During pregnancy and in the postpartum period, mothers are likely to experience less sleep, lower sleep efficiency, less deep sleep, and more daytime sleepiness and have more frequent awakenings [172–174]. Newborn sleep is often fragmented; thus, the parents' sleep will be fragmented. Conversely, parents are considered the main agents affecting infant sleep [175]. Therefore, there may be a bidirectional relationship between parent and infants' sleep [171]. Toddler, preschool-aged, and school-aged children's sleep problems can disrupt parents' sleep and family functioning, but sleep disruption, sleep quality, and sleep duration may affect marital conflict [171]. Among adolescents, there may be bidirectional relationships between adolescent sleep quantity, quality, and sleep problems and family factors including parenting style, family problems, and the home atmosphere [171]. Adolescent behaviors and activities like being involved in late extracurricular activities/events can affect parents' ability to initiate and maintain sleep [171]. Conversely, adolescent sleep can also be affected by parent behaviors: parents are not typically involved with adolescent sleep routines; however, total sleep time increased with parental rules like setting bedtimes [176]. Additionally, when parents are more involved with monitoring adolescents, adolescents experience less psychosocial distress and greater sleep efficiency [177]. Single parent family structure has also been found to be associated with worse sleep efficiency and shorter sleep duration among black and white adolescents [178]. Relationships between family conflict and sleep may remain when children reach adulthood: family conflict at ages 7–15 years was associated with higher odds of insomnia in adulthood [163].

Most adults share a bed with a partner or spouse, and there is evidence that couple-level variables affect sleep

(such as through relational conflicts, abuse, differing preferences for morningness–eveningness, timing of sleep–wake cycles) [179]. Sleep can be affected by other relationships such as those with caregivers, including parents of infants and children, healthcare professionals, and family or other informal caregivers of individuals with physical or cognitive disabilities. In a study of caregivers who live with adult care-receivers, in addition to predisposing risk factors (e.g., female sex and chronic health conditions, and precipitating events like menopause), factors like reduced physical activity and irregular sleep/wake schedules due to caregiving could lead to sleep problems such as insomnia in caregivers [180].

Attachment or early attachment style, defined as the interpersonal style that develops during childhood based on the type of bond and amount of trust with primary caregivers, may be associated with sleep throughout the life course [181]. In all studies except for one among 2–18 year-olds, lower attachment was associated with poorer subjective and objective sleep measures, and studies also suggest a bidirectional relationship among parental attachment, emotional security, and sleep in children [181]. Of 14 studies among individuals 18–64 years old, only one had a longitudinal design, and the majority identified a relationship between insecure attachment and poorer sleep as well as differences in sleep architecture [181]. Among studies of individuals >65 years of age, two studies found that those with high attachment reported better sleep, but less securely attached individuals were more likely to report daytime napping, use of sleep-inducing medication, and tended to sleep less at night [181].

Lastly, a variety of other social factors may affect sleep, but additional studies are warranted. Social support is considered a protective factor against a variety of poor health outcomes, which is also plausible regarding sleep given that studies show lack of social support as being associated with shorter subjective sleep [182–184]. A study using actigraphy among US adults aged 24–81 years enrolled in the MacArthur Study on Aging: Midlife in the United States found that neither social support nor social strain were associated with total sleep time, but social strain, defined as strained aspects of the individual's social network, was associated with lower sleep efficiency and night-to-night sleep variability [185]. Other psychosocial factors like financial strain, social isolation, low emotional support, and negative social interactions were related to reported sleep problems in a cross-sectional study of 736 men and women aged 58–72 years in the Whitehall II civil servants cohort [186].

In conclusion, this chapter has nonexhaustively discussed many physical and social environmental factors that can either positively or negatively impact the integrity of sleep, which is important for maintaining and restoring health across the lifespan. Some organizations

or investigators have provided recommendations for certain exposures in the physical environment like light or temperature that are based on scientific evidence or expert opinion. We have compiled a nonexhaustive list of potential pollution definitions and safety thresholds (see Table 9.1), but recommendations for defining and determining the maximum acceptable level across the range of factors that impact sleep health and subsequent risk of disease are desperately needed. There are many gaps in our current understanding of environmental exposures and sleep, and we have provided directions for future research, but a wide range of experimental studies and interventions in multiple contexts from the individual-to-society-level and across the lifespan can be designed and evaluated to optimize the impact of the physical and social environments on sleep health.

Glossary

Air pollution Term representing ambient concentrations of particulate matter, ozone, nitrogen dioxide, and sulfur dioxide

Buoyant thermal plume Upwelling and downwelling features in an element (e.g., fluid) that are maintained by thermal buoyancy, which is the ability or tendency to float in water, air, or some other fluid

Circadian misalignment The incorrect arrangement or position of the sleep–wake cycle to the biological night; incorrect arrangement or position of feeding rhythms to the sleep–wake cycle; internal misalignment of central and peripheral rhythms

Circadian rhythm A daily rhythmic activity cycle, based on 24-hour intervals, that is exhibited by many organisms

Circadian time structure disruption or circadian disruption Disturbance or problems that interrupt naturally recurring 24-hour cycles of biological processes

Effort-reward imbalance “High cost/low gain” situation at work, in which individuals spend high effort while receiving low rewards (in terms of monetary gratification, career opportunities, esteem, respect, and job security)

Environment The complex physical, chemical, and biotic factors that act upon an organism or an ecological community and ultimately determine its form and survival; the aggregate of social and cultural conditions that influence the life of an individual or community

Glare A visual sensation caused by excessive and uncontrolled brightness

Health disparity A type of difference in health that is closely linked with social or economic disadvantage and negatively affects groups of people who have systematically experienced greater social or economic obstacles to health. These obstacles stem from characteristics historically linked to discrimination or exclusion such as race or ethnicity, religion, socioeconomic status, gender, mental health, sexual orientation, or geographic location. Other characteristics include cognitive, sensory, or physical disability

Health inequity A difference or disparity in health outcomes that is systematic, avoidable, and unjust

Job control Two theoretically distinct subdimensions of decision latitude, namely skill discretion and decision authority

TABLE 9.1 Potential pollution definitions and thresholds.

	Definition of pollution	Threshold	Organization defining threshold
Light			
Indoor	Not defined	Daytime: melanopic effective daylight illuminance (EDI) < 250 lux measured at the eye in the vertical plane at approximately 1.2 m height Evening: melanopic EDI >10 lux measured at the eye in the vertical plane at approximately 1.2 m height, within 3 h of bedtime Nighttime: melanopic EDI >1 lux measured at the eye. For nighttime activities requiring vision, melanopic EDI >10 lux measured at the eye in the vertical plane at approximately 1.2 m height [14]	The Second International Workshop on Circadian and Neurophysiological Photometry
Outdoor	Light that is not targeted for a specific task, is bright and uncomfortable to the human eye, causes unsafe glare, trespasses in homes and bedrooms, or creates sky glow above cities [9,11].	Artificial brightness >10% of the natural sky brightness above 45 degrees of elevation [187]	International Astronomical Union
Noise			
Indoor	Not defined	Indoor A-weighted sound equivalent level >35 dB [188]	World Health Organization
Outdoor	Not defined	Outdoor noise at night >40 dB [61]	World Health Organization Occupational and Environmental Health Team
Temperature			
Indoor	Not defined	1. minimum: 18°C [189] 2. 17–19°C in winter and 23–25°C in summer [54] 3. minimum for heating: 20°C and maximum for cooling: 26°C [190]	1. World Health Organization Regional Office for Europe 2. Chartered Institution of Building Services Engineers 3. Comité Européen de Normalisation
Outdoor	Not defined	No threshold	
Vibration			
Outdoor	Indoor and outdoor - Ground-borne vibration from railway movements created by the interaction between the wheels and the rail, where regularities from either surface can generate considerable vibration energy [77].	No threshold	
Air			
Indoor	Indoor air quality defined as the air quality within and around buildings and structures, especially as it relates to the health and comfort of building occupants [191].	State-specific (for the United States) indoor air quality information is available at: https://www.epa.gov/indoor-air-quality-iaq/epa-regional-office-and-state-indoor-air-quality-information	US Environmental Protection Agency
Outdoor	Air pollution represents ambient concentrations of particulate matter, ozone, nitrogen dioxide, and sulfur dioxide.	Air quality guidelines for particulate matter, ozone, nitrogen dioxide, and sulfur dioxide are found online: 1. World Health Organization- https://www.who.int/publications/i/item/9789240034228 2. US Environmental Protection Agency- https://www.epa.gov/report-environment/outdoor-air-quality	1. World Health Organization 2. US Environmental Protection Agency

Permissions Adapted conceptual framework (permission granted in the original version).

Job demands	Stressors present in the work environment
Job strain	Work condition that occurs when job demand is greater than job control
Light pollution	Light that is not targeted for a specific task, is bright and uncomfortable to the human eye, causes unsafe glare, trespasses in homes and bedrooms, or creates sky glow above cities
Light trespass	Light that is cast where it is not wanted
Microenvironment	A small or relatively small usually distinctly specialized and effectively isolated habitat or environment
Noise pollution	Annoying or harmful noise (as of automobiles or jet airplanes) in an environment
Organizational justice	A multidimensional concept, which refers to the fairness of decision-making processes, how equally supervisors treat employees and share information, and whether employees themselves perceive that their viewpoints are taken into account
Overillumination	Excessive light supplied beyond the amount required for a given task that can produce glare, annoyance, and adverse health effects
Photopic	Relating to or being vision in bright light with light-adapted eyes that is mediated by the cones of the retina
Scotopic	Relating to or being vision in dim light with dark-adapted eyes which involves only the retinal rods as light receptors
Sky glow	A glow in the night sky deriving from an artificial source
Sleep onset latency	The length of time that it takes to accomplish the transition from full wakefulness to sleep, which is normally to the lightest of the non-REM sleep stages
Thermal comfort/neutral temperature	Satisfaction with thermal environment assessed by subjective evaluation
Thermal neutral zone	An endotherm's temperature tolerance range where the basal rate of heat production is in equilibrium with the rate of heat loss to the external environment

Acknowledgments

This work was funded by the Intramural Program at the NIH, National Institute of Environmental Health Sciences (ZIAES103325).

References

- [1] Hidalgo J, Baez AA. Natural disasters. *Crit Care Clin* 2019;35(4):591–607. <https://doi.org/10.1016/j.ccc.2019.05.001>.
- [2] Rifkin DI, Long MW, Perry MJ. Climate change and sleep: a systematic review of the literature and conceptual framework. *Sleep Med Rev* 2018;42:3–9. <https://doi.org/10.1016/j.smrv.2018.07.007>.
- [3] Gaston SA, Singh R, Jackson CL. The need to study the role of sleep in climate change adaptation, mitigation, and resiliency strategies across the life course. *Sleep* 2023;46(7). <https://doi.org/10.1093/sleep/zsad070>.
- [4] Gaston SA, Singh R, Jackson CL. Health disparities in sleep and mental health: Examining the role of sleep disturbances in the relationship between climate change-related traumatic childhood experiences and mental health as an exemplar. In: Jackson ML, Drummond SPA, editors. *Advances in the psychobiology of sleep and circadian rhythms*. Routledge; 2024. p. 175–94.
- [5] Emens JS, Burgess HJ. Effect of light and melatonin and other melatonin receptor agonists on human circadian physiology. *Sleep Med Clin* 2015;10(4):435–53. <https://doi.org/10.1016/j.jsmc.2015.08.001>.
- [6] Pendergast JS, Yamazaki S. Effects of light, food, and methamphetamine on the circadian activity rhythm in mice. *Physiol Behav* 2014;128:92–8. <https://doi.org/10.1016/j.physbeh.2014.01.021>.
- [7] Blume C, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and mood. *Somnologie* 2019;23(3):147–56. <https://doi.org/10.1007/s11818-019-00215-x>.
- [8] Kyba CCM, Kuester T, De Miguel AS, Baugh K, Jechow A, Höller F, Bennie J, Elvidge CD, Gaston KJ, Guanter L. Artificially lit surface of Earth at night increasing in radiance and extent. *Sci Adv* 2017;3(11). <https://doi.org/10.1126/sciadv.1701528>.
- [9] Chepesiuk R. Missing the dark: health effects of light pollution. *Environ Health Perspect* 2009;117(1):A20. <https://doi.org/10.1289/ehp.117-a20>.
- [10] Falchi F, Cinzano P, Elvidge CD, Keith DM, Haim A. Limiting the impact of light pollution on human health, environment and stellar visibility. *J Environ Manag* 2011;92(10):2714–22. <https://doi.org/10.1016/j.jenvman.2011.06.029>.
- [11] Pauley SM. Lighting for the human circadian clock: recent research indicates that lighting has become a public health issue. *Med Hypothes* 2004;63(4):588–96. <https://doi.org/10.1016/j.mehy.2004.03.020>.
- [12] Smith FG. Report and recommendations of IAU. In: Commission reports on Astronomy, IAU Trans. XVIIIA. vol 218; 1979. p. 1979.
- [13] Falchi F, Cinzano P, Duriscoe D, Kyba CCM, Elvidge CD, Baugh K, Portnov BA, Rybnikova NA, Furgoni R. The new world atlas of artificial night sky brightness. *Sci Adv* 2016;2(6). <https://doi.org/10.1126/sciadv.1600377>.
- [14] Brown TM, Brainard GC, Cajochen C, Czeisler CA, Hanifin JP, Lockley SW, Lucas RJ, Münch M, O'Hagan JB, Peirson SN, Price LLA, Roenneberg T, Schlangen LJM, Skene DJ, Spitschan M, Vetter C, Zee PC, Wright KP. Recommendations for daytime, evening, and nighttime indoor light exposure to best support physiology, sleep, and wakefulness in healthy adults. *PLoS Biol* 2022;20(3):e3001571. <https://doi.org/10.1371/journal.pbio.3001571>.
- [15] Turner PL, Van Someren EJW, Mainster MA. The role of environmental light in sleep and health: effects of ocular aging and cataract surgery. *Sleep Med Rev* 2010;14(4):269–80. <https://doi.org/10.1016/j.smrv.2009.11.002>.
- [16] Cho YM, Ryu S-H, Lee BR, Kim KH, Lee E, Choi J. Effects of artificial light at night on human health: a literature review of observational and experimental studies applied to exposure assessment. *Chronobiol Int* 2015;32(9):1294–310. <https://doi.org/10.3109/07420528.2015.1073158>.
- [17] Haus E, Smolensky M. Biological clocks and shift work: circadian dysregulation and potential long-term effects. *Cancer Causes Control* 2006;17(4):489–500. <https://doi.org/10.1007/s10552-005-9015-4>.
- [18] Schulmeister K, Weber M, Bogner W, Schernhammer E. Application of melatonin action spectra on practical lighting issues. Proceedings from the 5th International Symposium on Light and Human Health: November 3–5, 2002, Orlando, Florida—EPRI Lighting Research Office. Palo Alto, CA: Electric Power Research Institute; 2004.
- [19] Koo YS, Song JY, Joo EY, Lee HJ, Lee E, Lee SK, Jung KY. Outdoor artificial light at night, obesity, and sleep health: cross-sectional analysis in the KoGES study. *Chronobiol Int* 2016;33(3):301–14. <https://doi.org/10.3109/07420528.2016.1143480>.

- [20] Obayashi K, Saeki K, Kurumatani N. Association between light exposure at night and insomnia in the general elderly population: the HEIJO-KYO cohort. *Chronobiol Int* 2014;31(9):976–82. <https://doi.org/10.3109/07420528.2014.937491>.
- [21] Peter J, Bertrand KA, Hart JE, Schernhammer ES, Tamimi RM, Laden F. Outdoor light at night and breast cancer incidence in the nurses' health study II. *Environ Health Perspect* 2017;125(8). <https://doi.org/10.1289/ehp935>.
- [22] Al-Naggar RA, Anil S. Artificial light at night and cancer: global study. *Asian Pac J Cancer Prev APJCP* 2016;17(10):4661–4. <https://doi.org/10.7314/APJCP.2016.17.10.4661>.
- [23] Spivey A. Light at night and breast cancer risk worldwide. *Environ Health Perspect* 2010;118(12):A525. <https://doi.org/10.1289/ehp.118-a525undefined>.
- [24] Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. *Science* 1980;210 (4475):1267–9. <https://doi.org/10.1126/science.7434030>.
- [25] Bojkowski CJ, Aldhous ME, English J, Franey C, Poulton AL, Skene DJ, Arendt J. Suppression of nocturnal plasma melatonin and 6-sulphatoxymelatonin by bright and dim light in man. *Horm Metab Res* 1987;19(9):437–40. <https://doi.org/10.1055/s-2007-1011846>.
- [26] Trinder J, Armstrong S, O'Brien C, Luke D, Martin M. Inhibition of melatonin secretion onset by low levels of illumination. *J Sleep Res* 1996;5(2):77–82. <https://doi.org/10.1046/j.1365-2869.1996.00011.x>.
- [27] Wu CJ. Effects of lighting interventions to improve sleepiness in night-shift workers: a systematic review and meta-analysis. *Healthcare* 2022;10(8).
- [28] Schaefer EW, Williams MV, Zee PC. Sleep and circadian misalignment for the hospitalist: a review. *J Hosp Med* 2012;7 (6):489–96. <https://doi.org/10.1002/jhm.1903>.
- [29] Sweeney MR, Nichols HB, Jones RR, Olshan AF, Keil AP, Engel LS, James P, Sandler DP, White AJ, Jackson CL. Exposure to indoor light at night in relation to multiple dimensions of sleep health: findings from the Sister Study. *Sleep* 2024;47(2). <https://doi.org/10.1093/sleep/zsd100>.
- [30] Gamble AL, D'Rozario AL, Bartlett DJ, Williams S, Sun Bin Y, Grunstein RR, Marshall NS, Federici S. Adolescent sleep patterns and night-time technology use: results of the Australian Broadcasting Corporation's big sleep survey. *PLoS One* 2014;9(11):e111700. <https://doi.org/10.1371/journal.pone.0111700>.
- [31] Cho JR, Joo EY, Koo DL, Hong SB. Let there be no light: the effect of bedside light on sleep quality and background electroencephalographic rhythms. *Sleep Med* 2013;14(12):1422–5. <https://doi.org/10.1016/j.sleep.2013.09.007>.
- [32] Martin JS, Hébert M, Ledoux E, Gaudreault M, Laberge L. Relationship of chronotype to sleep, light exposure, and work-related fatigue in student workers. *Chronobiol Int* 2012;29 (3):295–304. <https://doi.org/10.3109/07420528.2011.653656>.
- [33] Auger RR, Burgess HJ, Dierkhising RA, Sharma RG, Slocumb NL. Light exposure among adolescents with delayed sleep phase disorder: a prospective cohort study. *Chronobiol Int* 2011;28(10):911–20. <https://doi.org/10.3109/07420528.2011.619906>.
- [34] Silvani MI, Werder R, Perret C. The influence of blue light on sleep, performance and wellbeing in young adults: a systematic review. *Front Physiol* 2022;13. <https://doi.org/10.3389/fphys.2022.943108>.
- [35] Touitou Y, Reinberg A, Touitou D. Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: health impacts and mechanisms of circadian disruption. *Life Sci* 2017;173:94–106. <https://doi.org/10.1016/j.lfs.2017.02.008>.
- [36] Smolensky MH, Sackett-Lundeen LL, Portaluppi F. Nocturnal light pollution and underexposure to daytime sunlight: complementary mechanisms of circadian disruption and related diseases. *Chronobiol Int* 2015;32(8):1029–48. <https://doi.org/10.3109/07420528.2015.1072002>.
- [37] Pattinson CL, Allan AC, Staton SL, Thorpe KJ, Smith SS, Vinciguerra M. Environmental light exposure is associated with increased body mass in children. *PLoS One* 2016;11(1):e0143578. <https://doi.org/10.1371/journal.pone.0143578>.
- [38] McFadden E, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. The relationship between obesity and exposure to light at night: cross-sectional analyses of over 100,000 women in the breakthrough generations study. *Am J Epidemiol* 2014;180 (3):245–50. <https://doi.org/10.1093/aje/kwu117>.
- [39] Park YMM, White AJ, Jackson CL, Weinberg CR, Sandler DP. Association of exposure to artificial light at night while sleeping with risk of obesity in women. *JAMA Intern Med* 2019;179 (8):1061–71. <https://doi.org/10.1001/jamainternmed.2019.0571>.
- [40] Shechter A, Kim EW, St-Onge M-P, Westwood AJ. Blocking nocturnal blue light for insomnia: a randomized controlled trial. *J Psychiatr Res* 2018;96:196–202. <https://doi.org/10.1016/j.jpsychires.2017.10.015>.
- [41] Votsi NP, Kallimanis AS, Pantis ID. An environmental index of noise and light pollution at EU by spatial correlation of quiet and unlit areas. *Environ Pollut* 2017;221:459–69. <https://doi.org/10.1016/j.envpol.2016.12.015>.
- [42] Mason IC, Boubekri M, Figueiro MG, Hasler BP, Hattar S, Hill SM, Nelson RJ, Sharkey KM, Wright KP, Boyd WA, Brown MK, Laposky AD, Twery MJ, Zee PC. Circadian health and light: a report on the National Heart, Lung, and Blood Institute's Workshop. *J Biol Rhythms* 2018;33(5):451–7. <https://doi.org/10.1177/0748730418789506>.
- [43] Bach V, Telliez F, Chardon K, Tourneux P, Cardot V, Libert JP. Thermoregulation in wakefulness and sleep in humans. *Handb Clin Neurol* 2011;98:215–27. <https://doi.org/10.1016/B978-0-444-52006-7.00014-9>.
- [44] Krauchi K, Deboer T. The interrelationship between sleep regulation and thermoregulation. *Front Biosci* 2010;15(2):604–25. <https://doi.org/10.2741/3636>.
- [45] Chevance G. A systematic review of ambient heat and sleep in a warming climate. *Sleep Med Rev* 2024;25.
- [46] Boulant JA. Role of the preoptic-anterior hypothalamus in thermoregulation and fever. *Clin Infect Dis* 2000;31(5):S157–61. <https://doi.org/10.1086/317521>.
- [47] Van Someren EJW. More than a marker: interaction between the circadian regulation of temperature and sleep, age-related changes, and treatment possibilities. *Chronobiol Int* 2000;17(3):313–54. <https://doi.org/10.1081/CBI-100101050>.
- [48] Kharakoz DP. Brain temperature and sleep. *Zh Vyssh Nerv Deiatelnosti Im I P Pavlova* 2013;63(1):113–24. <https://doi.org/10.7868/S0044467713010061>.
- [49] Song C, Liu Y, Zhou X, Liu J. Investigation of human thermal comfort in sleeping environments based on the effects of bed climate. *Procedia Eng* 2015;121:1126–32. <https://doi.org/10.1016/j.proeng.2015.09.118>.
- [50] Okamoto-Mizuno K, Mizuno K. Effects of thermal environment on sleep and circadian rhythm. *J Physiol Anthropol* 2012;31 (1):1–9. <https://doi.org/10.1186/1880-6805-31-14>.
- [51] Monsivais D, Bhattacharya K, Ghosh A, Dunbar RIM, Kaski K. Seasonal and geographical impact on human resting periods. *Sci Rep* 2017;7(1). <https://doi.org/10.1038/s41598-017-11125-z>.

- [52] Minor K, Bjerre-Nielsen A, Jonasdottir SS, Lehmann S, Obradovich N. Rising temperatures erode human sleep globally. *One Earth* 2022;5(5):534–49. <https://doi.org/10.1016/j.oneear.2022.04.008>.
- [53] Xiong J, Lian Z, Zhou X, You J, Lin Y. Investigation of gender difference in human response to temperature step changes. *Physiol Behav* 2015;151:426–40. <https://doi.org/10.1016/j.physbeh.2015.07.037>.
- [54] Butcher KJ (Ed). Environmental design: CIBSE Guide A. 7th. London: CISBE; 2006.
- [55] Kräuchi K, Fattori E, Giordano A, Falbo M, Iadarola A, Agli F, Tribolo A, Mutani R, Cicolini A. Sleep on a high heat capacity mattress increases conductive body heat loss and slow wave sleep. *Physiol Behav* 2018;185:23–30. <https://doi.org/10.1016/j.physbeh.2017.12.014>.
- [56] Hernández D. Understanding ‘energy insecurity’ and why it matters to health. *Soc Sci Med* 2016;167:1–10. <https://doi.org/10.1016/j.socscimed.2016.08.029>.
- [57] Strøm-Tejsen P, Zukowska D, Wargozi P, Wyon DP. The effects of bedroom air quality on sleep and next-day performance. *Indoor Air* 2016;26(5):679–86. <https://doi.org/10.1111/ina.12254>.
- [58] Accinelli RA, Llanos O, López LM, Pino MI, Bravo YA, Salinas V, Lazo M, Noda JR, Sánchez-Sierra M, Zárate L, da Silva J, Gianella F, Kheirandish-Gozal L, Gozal D. Adherence to reduced-polluting biomass fuel stoves improves respiratory and sleep symptoms in children. *BMC Pediatr* 2014;14(1). <https://doi.org/10.1186/1471-2431-14-12Peru>.
- [59] Basner M, Babisch W, Davis A, Brink M, Clark C, Janssen S, Stansfeld S. Auditory and non-auditory effects of noise on health. *Lancet* 2014;383(9925):1325–32. [https://doi.org/10.1016/s0140-6736\(13\)61613-x](https://doi.org/10.1016/s0140-6736(13)61613-x).
- [60] Muzet A. Environmental noise, sleep and health. *Sleep Med Rev* 2007;11(2):135–42. <https://doi.org/10.1016/j.smrv.2006.09.001>.
- [61] Berglund B, Lindvall T, Schwela DH, Team WHO/OEH. Guidelines for community noise. Geneva: World Health Organization; 1999. <http://www.who.int/iris/handle/10665/66217>.
- [62] Tavakoli P, Varma S, Campbell K. Highly relevant stimuli may passively elicit processes associated with consciousness during the sleep onset period. *Conscious Cognit* 2018;58:60–74. <https://doi.org/10.1016/j.concog.2017.10.012>.
- [63] Sørensen M, Ketzel M, Overvad K, Tjønneland A, Raaschou-Nielsen O. Exposure to road traffic and railway noise and post-menopausal breast cancer: a cohort study. *Int J Cancer* 2014;134(11):2691–8. <https://doi.org/10.1002/ijc.28592>.
- [64] Aasvang GM, Øverland B, Ursin R, Moum T. A field study of effects of road traffic and railway noise on polysomnographic sleep parameters. *J Acoust Soc Am* 2011;129(6):3716–26. <https://doi.org/10.1121/1.3583547>.
- [65] Basner M, Müller U, Elmenhorst EM. Single and combined effects of air, road, and rail traffic noise on sleep and recuperation. *Sleep* 2011;34(1):11–23. <https://doi.org/10.1093/sleep/34.1.11>.
- [66] Munzel T, Gori T, Babisch W, Basner M. Cardiovascular effects of environmental noise exposure. *Eur Heart J* 2014;35(13):829–36. <https://doi.org/10.1093/euroheartj/ehu030>.
- [67] Halperin D. Environmental noise and sleep disturbances: a threat to health? *Sleep Sci* 2014;7(4):209–12. <https://doi.org/10.1016/j.slsci.2014.11.003>.
- [68] Lercher P, Brink M, Rudißer J, Van Renterghem T, Botteldooren D, Baulac M, Baulac J. The effects of railway noise on sleep medication intake: results from the ALPNAP-study. *Noise Health* 2010;12(47):110. <https://doi.org/10.4103/1463-1741.63211>.
- [69] Stansfeld S, Hygge S, Clark C, Alfred T. Night time aircraft noise exposure and children’s cognitive performance. *Noise Health* 2010;12(49):255–62. <https://doi.org/10.4103/1463-1741.70504>.
- [70] Saremi M, Grenèche J, Bonnefond A, Rohmer O, Eschenlauer A, Tassi P. Effects of nocturnal railway noise on sleep fragmentation in young and middle-aged subjects as a function of type of train and sound level. *Int J Psychophysiol* 2008;70(3):184–91. <https://doi.org/10.1016/j.ijpsycho.2008.08.002>.
- [71] Elmenhorst EM, Pennig S, Rolny V, Quehl J, Mueller U, Maass H, Basner M. Examining nocturnal railway noise and aircraft noise in the field: sleep, psychomotor performance, and annoyance. *Sci Total Environ* 2012;424:48–56. <https://doi.org/10.1016/j.scitotenv.2012.02.024>.
- [72] Pennig S, Quehl J, Mueller U, Rolny V, Maass H, Basner M, Elmenhorst E-M. Annoyance and self-reported sleep disturbance due to night-time railway noise examined in the field. *J Acoust Soc Am* 2012;132(5):3109–17. <https://doi.org/10.1121/1.4757732>.
- [73] Gorica M, Zajamsek B, Leon L, Hansen K, Doolan C, Hansen C, Vakulin A, Lovato N, Bruck D, Chai-Coetzer CL, Mercer J, Catcheside P. A review of the potential impacts of wind farm noise on sleep. *Acoust Aust* 2018;46(1):87–97. <https://doi.org/10.1007/s40857-017-0120-9>.
- [74] Miedema HME, Vos H. Associations between self-reported sleep disturbance and environmental noise based on reanalyses of pooled data from 24 studies. *Behav Sleep Med* 2007;5(1):1–20. https://doi.org/10.1207/s15402010bsm0501_1.
- [75] Ho A, Raja B, Waldhorn R, Baez V, Mohammed I. New onset of insomnia in hospitalized patients in general medical wards: incidence, causes, and resolution rate. *J Community Hosp Intern Med Perspect* 2017;7(5):309–13. <https://doi.org/10.1080/2000966.2017.1374108>.
- [76] Yazdanirad S, Hossein Khoshakhlagh A, Sulaie SA, Drake CL, Wickwire EM. The effects of occupational noise on sleep: a systematic review. *Sleep Med Rev* 2023;72:101846. <https://doi.org/10.1016/j.smrv.2023.101846>.
- [77] Guidelines for the assessment of noise from rail infrastructure. 2013. p. 2013.
- [78] Gidlöf-Gunnarsson A, Ögren M, Jerson T, Öhrström E. Railway noise annoyance and the importance of number of trains, ground vibration, and building situational factors. *Noise Health* 2012;14 (59):190–201. <https://doi.org/10.4103/1463-1741.99895>.
- [79] Klæboe R, et al. Vibration in dwellings from road and rail traffic — Part II: exposure–effect relationships based on ordinal logit and logistic regression models. *Appl Acoust* 2003;64(1):89–109. [https://doi.org/10.1016/S0003-682X\(02\)00053-1](https://doi.org/10.1016/S0003-682X(02)00053-1).
- [80] Peris E, Woodcock J, Sica G, Moorhouse AT, Waddington DC. Annoyance due to railway vibration at different times of the day. *J Acoust Soc Am* 2012;131(2):EL191. <https://doi.org/10.1121/1.3679390>.
- [81] Smith MG, Croy I, Ögren M, Kerstin Persson W, Sun Q. On the influence of freight trains on humans: a Laboratory investigation of the impact of nocturnal low frequency vibration and noise on sleep and heart rate. *PLoS One* 2013;8(2):e55829. <https://doi.org/10.1371/journal.pone.0055829>.
- [82] Baker FC, Maloney S, Driver HS. A comparison of subjective estimates of sleep with objective polysomnographic data in healthy men and women. *J Psychosom Res* 1999;47(4):335–41. [https://doi.org/10.1016/S0022-3999\(99\)00017-3](https://doi.org/10.1016/S0022-3999(99)00017-3).

- [83] Griefahn B, Marks A. Associations between noise sensitivity and sleep, subjectively evaluated sleep quality, annoyance, and performance after exposure to nocturnal traffic noise. *Noise Health* 2007;9(34):1. <https://doi.org/10.4103/1463-1741.34698>.
- [84] Seidler A, Schubert M, Mehrjerdian Y, Krapf K, Popp C, van Kamp I, Ögren M, Hegewald J. Health effects of railway-induced vibration combined with railway noise – a systematic review with exposure-effect curves. *Environ Res* 2023;233:116480. <https://doi.org/10.1016/j.envres.2023.116480>.
- [85] Kimura H, Kuramoto A, Inui Y, Inou N. Mechanical bed for investigating sleep-inducing vibration. *J Healthc Eng* 2017;2017:1–9. <https://doi.org/10.1155/2017/2364659>.
- [86] Mehra R, Redline S. Sleep apnea: a proinflammatory disorder that coaggregates with obesity. *J Allergy Clin Immunol* 2008;121(5):1096–102. <https://doi.org/10.1016/j.jaci.2008.04.002>.
- [87] DeMeo DL, Zanobetti A, Litonjua AA, Coull BA, Schwartz J, Gold DR. Ambient air pollution and oxygen saturation. *Am J Respir Crit Care Med* 2004;170(4):383–7. <https://doi.org/10.1164/rccm.200402-244OC>.
- [88] Jerrett M, Shankardass K, Berhane K, James Gauderman W, Künzli N, Avol E, Gilliland F, Lurmann F, Molitor JN, Molitor JT, Thomas DC, Peters J, McConnell R. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect* 2008;116(10):1433–8. <https://doi.org/10.1289/ehp.10968>.
- [89] Zanobetti A, Redline S, Schwartz J, Rosen D, Patel S, George T, O'Connor, Lebowitz M, Coull BA, Gold DR. Associations of PM 10 with sleep and sleep-disordered breathing in adults from seven U.S. Urban areas. *Am J Respir Crit Care Med* 2010;182(6):819–25. <https://doi.org/10.1164/rccm.200912-1797oc>.
- [90] Shen YL, Liu WT, Lee KY, Chuang HC, Chen HW, Chuang KJ. Association of PM2.5 with sleep-disordered breathing from a population-based study in Northern Taiwan urban areas. *Environ Pollut* 2018;233:109–13. <https://doi.org/10.1016/j.envpol.2017.10.052>.
- [91] Weinreich G, Wessendorf TE, Pundt N, Weinmayr G, Hennig F, Moebus S, Möhlenkamp S, Erbel R, Jöckel K-H, Teschler H, Hoffmann B. Association of short-term ozone and temperature with sleep disordered breathing. *Eur Respir J* 2015;46(5):1361–9. <https://doi.org/10.1183/13993003.02255-2014>.
- [92] Tenero L, Piacentini G, Nosetti L, Gasperi E, Piazza M, Zaffanello M. Indoor/outdoor not-voluntary-habit pollution and sleep-disordered breathing in children: a systematic review. *Transl Pediatr* 2017;6(2):104–10. <https://doi.org/10.21037/tp.2017.03.04>.
- [93] An R, Yu H. Impact of ambient fine particulate matter air pollution on health behaviors: a longitudinal study of university students in Beijing, China. *Public Health* 2018;159:107–15. <https://doi.org/10.1016/j.puhe.2018.02.007>.
- [94] Cao B, Chen Y, McIntyre RS. Comprehensive review of the current literature on impact of ambient air pollution and sleep quality. *Sleep Med* 2021;79:211–9. <https://doi.org/10.1016/j.sleep.2020.04.009>.
- [95] Bose S, Ross KR, Rosa MJ, Mathilda Chiu Y-H, Just A, Kloog I, Wilson A, Thompson J, Svensson K, Rojo MMT, Lourdes S, Osorio-Valencia E, Oken E, Wright RO, Wright RJ. Prenatal particulate air pollution exposure and sleep disruption in preschoolers: windows of susceptibility. *Environ Int* 2019;124:329–35. <https://doi.org/10.1016/j.envint.2019.01.012>.
- [96] Yu C, Gordon P, Yu W. The association between air pollution and sleep duration: a cohort study of freshmen at a University in Beijing, China. *Int J Environ Res Publ Health* 2019;16(18):3362. <https://doi.org/10.3390/ijerph16183362>.
- [97] Li D, Wang L, Yang Y, Hu Y, Wang Y, Tian Y, Wang F. Associations of long-term exposure to ambient air pollution and road traffic noise with sleep health in UK Biobank. *J Affect Disord* 2022;310:1–9. <https://doi.org/10.1016/j.jad.2022.04.136>.
- [98] Klepeis NE, Nelson WC, Ott WR, Robinson JP, Tsang AM, Switzer P, Behar JV, Hern SC, Engelmann WH. The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. *J Expo Anal Environ Epidemiol* 2001;11(3):231–52. <https://doi.org/10.1038/sj.jea.7500165>.
- [99] Odeh I, Hussein T. Activity pattern of urban adult students in an Eastern Mediterranean Society. *Int J Environ Res Publ Health* 2016;13(10):960. <https://doi.org/10.3390/ijerph13100960>.
- [100] Schweizer C, Edwards RD, Bayer-Oglesby L, James Gauderman W, Ilacqua V, Jantunen MJ, Lai HKan, Nieuwenhuijsen M, Künzli N. Indoor time-microenvironment-activity patterns in seven regions of Europe. *J Expo Sci Environ Epidemiol* 2007;17(2):170–81. <https://doi.org/10.1038/sj.jes.7500490>.
- [101] Boor BE, Järnström H, Novoselac A, Xu Y. Infant exposure to emissions of volatile organic compounds from crib mattresses. *Environ Sci Technol* 2014;48(6):3541–9. <https://doi.org/10.1021/es405625q>.
- [102] Boor BE, Spilak MP, Corsi RL, Novoselac A. Characterizing particle resuspension from mattresses: chamber study. *Indoor Air* 2015;25(4):441–56. <https://doi.org/10.1111/ina.12148>.
- [103] Lin SY, Melvin TAN, Boss EF, Ishman SL. The association between allergic rhinitis and sleep-disordered breathing in children: a systematic review. *Int Forum Aller Rhinol* 2013;3(6):504–9. <https://doi.org/10.1002/alr.21123>.
- [104] Yetish G, Kaplan H, Gurven M, Wood B, Pontzer H, Manger PR, Wilson C, McGregor R, Siegel JM. Natural sleep and its seasonal variations in three pre-industrial societies. *Curr Biol* 2015;25(21):2862–8. <https://doi.org/10.1016/j.cub.2015.09.046>.
- [105] Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol* 2003;549(3):945–52. <https://doi.org/10.1113/jphysiol.2003.040477>.
- [106] Walch OJ, Cochran A, Forger DB. A global quantification of “normal” sleep schedules using smartphone data. *Sci Adv* 2016;2(5). <https://doi.org/10.1126/sciadv.1501705>.
- [107] Seidler A, Weihrich KS, Bes F, de Zeeuw J, Kunz D. Seasonality of human sleep: polysomnographic data of a neuropsychiatric sleep clinic. *Front Neurosci* 2023;17. <https://doi.org/10.3389/fnins.2023.1105233>.
- [108] Brockmann PE, Gozal D, Villarroel L, Damiani F, Nuñez F, Cajochen C. Geographic latitude and sleep duration: a population-based survey from the Tropic of Capricorn to the Antarctic Circle. *Chronobiol Int* 2017;34(3):373–81. <https://doi.org/10.1080/07420528.2016.1277735>.
- [109] Friberg O, Bjørvatn B, Ampomah B, Pallesen S. Associations between seasonal variations in day length (photoperiod), sleep timing, sleep quality and mood: a comparison between Ghana (5°) and Norway (69°). *J Sleep Res* 2012;21(2):176–84. <https://doi.org/10.1111/j.1365-2869.2011.00982.x>.

- [110] Stothard ER, McHill AW, Depner CM, Birks BR, Moehlman TM, Ritchie HK, Guzzetti JR, Chinoy ED, LeBourgeois MK, Axelsson J, Wright KP. Circadian entrainment to the natural light-dark cycle across seasons and the weekend. *Curr Biol* 2017;27(4):508–13. <https://doi.org/10.1016/j.cub.2016.12.041>.
- [111] Warnecke RB, Oh A, Breen N, Gehlert S, Paskett E, Tucker KL, Lurie N, Rebbeck T, Goodwin J, Flack J, Srinivasan S, Kerner J, Heurtin-Roberts S, Abeles R, Tyson FL, Patmios G, Hiatt RA. Approaching health disparities from a population perspective: the National Institutes of Health Centers for Population Health and Health Disparities. *Am J Publ Health* 2008;98(9):1608–15. <https://doi.org/10.2105/AJPH.2006.102525>.
- [112] Lazarus RS. Theory-based stress measurement. *Psychol Inq* 1990;1(1):3–13. https://doi.org/10.1207/s15327965pli0101_1.
- [113] Pitsavos C, Panagiotakos DB, Papageorgiou C, Tsetsekou E, Soldatos C, Stefanidis C. Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA Study. *Atherosclerosis* 2006;185(2):320–6. <https://doi.org/10.1016/j.atherosclerosis.2005.06.001>.
- [114] Kim EJ, Dimsdale JE. The effect of psychosocial stress on sleep: a review of polysomnographic evidence. *Behav Sleep Med* 2007;5(4):256–78. <https://doi.org/10.1080/15402000701557383>.
- [115] Grandner MA, Williams NJ, Knutson KL, Roberts D, Jean-Louis G. Sleep disparity, race/ethnicity, and socioeconomic position. *Sleep Med* 2016;18:7–18. <https://doi.org/10.1016/j.sleep.2015.01.020>.
- [116] Etindele Sosso FA, Holmes SD, Weinstein AA. Influence of socioeconomic status on objective sleep measurement: A systematic review and meta-analysis of actigraphy studies. *Sleep Health* 2021;7(4):417–28. <https://doi.org/10.1016/j.slehd.2021.05.005>.
- [117] Grandner MA, Patel NP, Gehrman PR, Xie D, Sha D, Weaver T, Gooneratne N. Who gets the best sleep? Ethnic and socioeconomic factors related to sleep complaints. *Sleep Med* 2010;11(5):470–8. <https://doi.org/10.1016/j.sleep.2009.10.006>.
- [118] Whinnery J, Jackson N, Rattanaumpawan P, Grandner MA. Short and long sleep duration associated with race/ethnicity, socio-demographics, and socioeconomic position. *Sleep* 2014;37(3):601–11. <https://doi.org/10.5665/sleep.3508>.
- [119] Alhasan DM, Riley NM, Jackson II WB, Jackson CL. Food insecurity and sleep health by race/ethnicity in the United States. *J Nutr Sci* 2023;12:e59. <https://doi.org/10.1017/jns.2023.18>.
- [120] Gellis LA, Lichstein KL, Scarinci IC, Durrence HH, Taylor DJ, Bush AJ, Riedel BW. Socioeconomic status and insomnia. *J Abnorm Psychol* 2005;114(1):111–8. <https://doi.org/10.1037/0021-843X.114.1.111>.
- [121] Tomfohr LM, Ancoli-Israel S, Dimsdale JE. Childhood socioeconomic status and race are associated with adult sleep. *Behav Sleep Med* 2010;8(4):219–30. <https://doi.org/10.1080/15402002.2010.509236>.
- [122] Williams DR, Lavizzo-Mourey R, Warren RC. The concept of race and health status in America. *Publ Health Rep* 1994;109(1):26–41.
- [123] Slopen N, Lewis TT, Williams DR. Discrimination and sleep: a systematic review. *Sleep Med* 2016;18:88–95. <https://doi.org/10.1016/j.sleep.2015.01.012>.
- [124] Reskin B. The race discrimination system. *Annu Rev Sociol* 2012;38(1):17–35. <https://doi.org/10.1146/annurev-soc-071811-145508>.
- [125] Bailey ZD, Krieger N, Agénor M, Graves J, Linos N, Bassett MT. Structural racism and health inequities in the USA: evidence and interventions. *Lancet* 2017;389(10077):1453–63. [https://doi.org/10.1016/S0140-6736\(17\)30569-X](https://doi.org/10.1016/S0140-6736(17)30569-X).
- [126] Johnson DA, Jackson CL, Williams NJ, Alcántara C. Are sleep patterns influenced by race/ethnicity – a marker of relative advantage or disadvantage? Evidence to date. *Nat Sci Sleep* 2019;11:79–95. <https://doi.org/10.2147/NSS.S169312>.
- [127] James SA. John Henryism and the health of African-Americans. *Cult Med Psychiatr* 1994;18(2):163–82. <https://doi.org/10.1007/BF01379448>.
- [128] Barksdale DJ, Woods-Giscombé C, Logan JG. Stress, cortisol, and nighttime blood pressure dipping in nonhypertensive Black American Women. *Biol Res Nurs* 2013;15(3):330–7. <https://doi.org/10.1177/1099800411433291>.
- [129] Chen-Edinboro LP, Kaufmann CN, Augustinavicius JL, Mojtabai R, Parisi JM, Wennberg AMV, Smith MT, Spira AP. Neighborhood physical disorder, social cohesion, and insomnia: results from participants over age 50 in the Health and Retirement Study. *Int Psychogeriatr* 2015;27(2):289–96. <https://doi.org/10.1017/S1041610214001823>.
- [130] De Santis AS, Roux AVD, Moore K, Baron KG, Mujahid MS, Javier Nieto F. Associations of neighborhood characteristics with sleep timing and quality: the multi-ethnic study of atherosclerosis. *Sleep* 2013;36(10):1543–51. <https://doi.org/10.5665/sleep.3054India>.
- [131] Simonelli G, Dudley KA, Jia W, Gallo LC, Perreira K, Shah NA, Alcantara C, Zee PC, Ramos AR, Llabre MM, Sotres-Alvarez D, Wang R, Patel SR. Neighborhood factors as predictors of poor sleep in the Sueño Ancillary Study of the Hispanic Community Health Study/Study of Latinos. *Sleep* 2017;40(1). <https://doi.org/10.1093/sleep/zsw025>.
- [132] Johnson DA, Simonelli G, Moore K, Billings M, Mujahid MS, Rueschman M, Kawachi I, Redline S, Roux AVD, Patel SR. The neighborhood social environment and objective measures of sleep in the multi-ethnic study of atherosclerosis. *Sleep* 2017;40(1). <https://doi.org/10.1093/sleep/zsw016>.
- [133] Johnson DA, Lisabeth L, Hickson D, Johnson-Lawrence V, Samdarshi T, Taylor H, Diez Roux AV. The social patterning of sleep in African Americans: associations of socioeconomic position and neighborhood characteristics with sleep in the Jackson heart study. *Sleep* 2016;39(9):1749–59. <https://doi.org/10.5665/sleep.6106>.
- [134] Alhasan DM, Gaston SA, Jackson WB, Williams PC, Kawachi I, Jackson CL. Neighborhood social cohesion and sleep health by age, sex/gender, and race/ethnicity in the United States. *Int J Environ Res Publ Health* 2020;17(24):1–23. <https://doi.org/10.3390/ijerph17249475>.
- [135] Fang SC, Subramanian SV, Piccolo R, Yang M, Klar Yaggi H, Bliwise DL, Araujo AB. Geographic variations in sleep duration: a multilevel analysis from the Boston Area Community Health (BACH) survey. *J Epidemiol Commun* 2015;69(1):63–9. <https://doi.org/10.1136/jech-2013-203256>.
- [136] Xiao Q, Hale L. Neighborhood socioeconomic status, sleep duration, and napping in middle-to-old aged US men and women. *Sleep* 2018;41(7). <https://doi.org/10.1093/sleep/zsy076>.
- [137] Bassett E, Moore S. Neighbourhood disadvantage, network capital and restless sleep: is the association moderated by gender in urban-

- dwelling adults? *Soc Sci Med* 2014;108:185–93. <https://doi.org/10.1016/j.socscimed.2014.02.029>.
- [138] Hale L, Hill TD, Friedman E, Javier Nieto F, Galvao LW, Engelman CD, Malecki KMC, Peppard PE. Perceived neighborhood quality, sleep quality, and health status: evidence from the Survey of the Health of Wisconsin. *Soc Sci Med* 2013;79 (1):16–22. <https://doi.org/10.1016/j.socscimed.2012.07.021>.
- [139] Chambers EC, Pichardo MS, Rosenbaum E. Sleep and the housing and neighborhood environment of urban Latino adults living in low-income housing: the AHOME Study. *Behav Sleep Med* 2016;14 (2):169–84. <https://doi.org/10.1080/15402002.2014.974180>.
- [140] Johnson SL, Solomon BS, Shields WC, McDonald EM, McKenzie LB, Gielen AC. Neighborhood violence and its association with mothers' health: assessing the relative importance of perceived safety and exposure to violence. *J Urban Health* 2009;86 (4):538–50. <https://doi.org/10.1007/s11524-009-9345-8>.
- [141] Gaston SA, Alhasan DM, Johnson DA, Hale L, Harmon QE, Baird DD, et al. Perceived childhood neighborhood safety and sleep health during childhood and adulthood among a cohort of African American women. *Sleep Med* 2024;117:115–22. <https://doi.org/10.1016/j.sleep.2024.03.004>.
- [142] Ruff RR, Ng J, Jean-Louis G, Elbel B, Chaix B, Duncan DT. Neighborhood stigma and sleep: findings from a pilot study of low-income housing residents in New York City. *Behav Med* 2016;44 (1):48–53. <https://doi.org/10.1080/08964289.2016.1203754>.
- [143] Billings ME, Johnson DA, Simonelli G, Moore K, Patel SR, Diez Roux AV, Redline S. Neighborhood walking environment and activity level are associated with OSA: the multi-ethnic study of atherosclerosis. *Chest* 2016;150(5):1042–9. <https://doi.org/10.1016/j.chest.2016.06.012>.
- [144] Johnson DA, Hirsch JA, Moore KA, Redline S, Diez Roux AV. Associations between the built environment and objective measures of sleep. *Am J Epidemiol* 2018;187(5):941–50. <https://doi.org/10.1093/aje/kwx302>.
- [145] Johnson DA, Drake C, Joseph CLM, Krajenta R, Hudgel DW, Cassidy-Bushrow AE. Influence of neighbourhood-level crowding on sleep-disordered breathing severity: Mediation by body size. *J Sleep Res* 2015;24(5):559–65. <https://doi.org/10.1111/jsr.12305>.
- [146] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Painting, Firefighting, and Shiftwork. In: IARC monographs on the evaluation of carcinogenic risks to humans. Lyon (FR): International Agency for Research on Cancer; 2010. <https://www.ncbi.nlm.nih.gov/books/NBK326814/>.
- [147] Linton SJ, Kecklund G, Franklin KA, Leissner LC, Sivertsen B, Lindberg E, Svensson AC, Hansson SO, Sundin Ö, Hetta J, Björkelund C, Hall C. The effect of the work environment on future sleep disturbances: a systematic review. *Sleep Med Rev* 2015;23:10–9. <https://doi.org/10.1016/j.smrv.2014.10.010>.
- [148] Van Laethem M, Beckers DGJ, Kompier MAJ, Dijksterhuis A, Geurts SAE. Psychosocial work characteristics and sleep quality: a systematic review of longitudinal and intervention research. *Scand J Work Environ Health* 2013;39(6):535–49. <https://doi.org/10.5271/sjweh.3376>.
- [149] Yang B, Wang Y, Cui F, Huang T, Sheng P, Shi T, Huang C, Lan Y, Huang Y-N. Association between insomnia and job stress: a meta-analysis. *Sleep Breath* 2018;22(4):1221–31. <https://doi.org/10.1007/s11325-018-1682-y>.
- [150] Gaston SA, Feinstein L, Slopen N, Sandler DP, Williams DR, Jackson CL. Everyday and major experiences of racial/ethnic discrimination and sleep health in a multiethnic population of U.S. women: findings from the Sister Study. *Sleep Med* 2020;71:97–105. <https://doi.org/10.1016/j.sleep.2020.03.010>.
- [151] Bierman A, Lee Y, Schieman S. Chronic discrimination and sleep problems in late life: religious involvement as buffer. *Res Aging* 2018;40(10):933–55. <https://doi.org/10.1177/0164027518766422>.
- [152] Ebin VJ, Sned CD, Morisky DE, Rotheram-Borus MJ, Magnusson AM, Malotte CK. Acculturation and interrelationships between problem and health-promoting behaviors among Latino adolescents. *J Adolesc Health* 2001;28(1):62–72. [https://doi.org/10.1016/S1054-139X\(00\)00162-2](https://doi.org/10.1016/S1054-139X(00)00162-2).
- [153] Loredo JS, Soler X, Bardwell W, Ancoli-Israel S, Dimsdale JE, Palinkas LA. Sleep health in U.S. Hispanic population. *Sleep* 2010;33(7):962–7. <https://doi.org/10.1093/sleep/33.7.962>.
- [154] Alcantara C, Patel SR, Carnethon M, Castañeda SF, Isasi CR, Davis S, Ramos AR, Arredondo E, Redline S, Zee PC, Gallo LC. Stress and sleep: results from the hispanic community health study/study of Latinos Sociocultural Ancillary Study. *SSM - Populat Health* 2017;3:713–21. <https://doi.org/10.1016/j.ssmph.2017.08.004>.
- [155] D'Anna-Hernandez KL, Garcia E, Coussons-Read M, Laudenslager ML, Ross RG. Sleep moderates and mediates the relationship between acculturation and depressive symptoms in pregnant Mexican-American Women. *Matern Child Health J* 2016;20(2):422–33. <https://doi.org/10.1007/s10995-015-1840-9>.
- [156] Ehlers CL, Gilder DA, Criado JR, Caetano R. Sleep quality and alcohol-use disorders in a select population of young-adult Mexican Americans. *J Stud Alcohol Drugs* 2010;71(6):879–84. <https://doi.org/10.15288/jasad.2010.71.879>.
- [157] Hale L, Rivero-Fuentes E. Negative acculturation in sleep duration among Mexican immigrants and Mexican Americans. *J Immigr Minor Health* 2011;13(2):402–7. <https://doi.org/10.1007/s10903-009-9284-1>.
- [158] Hale L, Troxel WM, Kravitz HM, Hall MH, Matthews KA. Acculturation and sleep among a multiethnic sample of women: the Study of Women's Health across the Nation (SWAN). *Sleep* 2014;37(2):309–17. <https://doi.org/10.5665/sleep.3404>.
- [159] Roberts RE, Lee ES, Hernandez M, Solari AC. Symptoms of insomnia among adolescents in the Lower Rio Grande Valley of Texas. *Sleep* 2004;27(4):751–60. <https://doi.org/10.1093/sleep/27.4.751>.
- [160] Kachikis AB, Breitkopf CR. Predictors of sleep characteristics among women in southeast Texas. *Womens Health Iss* 2012;22(1): e99. <https://doi.org/10.1016/j.whi.2011.07.004>.
- [161] Fekete EM, Williams SL, Skinta MD. Internalised HIV-stigma, loneliness, depressive symptoms and sleep quality in people living with HIV. *Psychol Health* 2017;33(3):398–415. <https://doi.org/10.1080/08870446.2017.1357816>.
- [162] Birtel MD, Wood L, Kempa NJ. Stigma and social support in substance abuse: implications for mental health and well-being. *Psychiat Res* 2017;252:1–8. <https://doi.org/10.1016/j.psychres.2017.01.097>.
- [163] Kajeepeta S, Gelaye B, Jackson CL, Williams MA. Adverse childhood experiences are associated with adult sleep disorders: a systematic review. *Sleep Med* 2015;16(3):320–30. <https://doi.org/10.1016/j.sleep.2014.12.013>.

- [164] Oh DL, Jerman P, Silvério Marques S, Koita K, Purewal Boparai SK, Burke Harris N, Bucci M. Systematic review of pediatric health outcomes associated with childhood adversity. *BMC Pediatr* 2018;18(1). <https://doi.org/10.1186/s12887-018-1037-7>.
- [165] Bilodeau F, Brendgen M, Vitaro F, Côté SM, Tremblay RE, Touchette E, Montplaisir J, Boivin M. Longitudinal association between peer victimization and sleep problems in preschoolers: the moderating role of parenting. *J Clin Child Adolesc Psychol* 2018;47(1):S555. <https://doi.org/10.1080/15374416.2018.1469091>.
- [166] Chang LY, Chang HY, Lin LN, Wu CC, Yen LL. Transitions in sleep problems from late adolescence to young adulthood: a longitudinal analysis of the effects of peer victimization. *Aggress Behav* 2018;44(1):69–82. <https://doi.org/10.1002/ab.21725>.
- [167] Wright AW, Austin M, Booth C, Kliwer W. Systematic review: exposure to community violence and physical health outcomes in youth. *J Pediatr Psychol* 2017;42(4):364–78. <https://doi.org/10.1093/jpepsy/jsw088>.
- [168] Bailey BN, Delaney-Black V, Hannigan JH, Ager J, Sokol RJ, Covington CY. Somatic complaints in children and community violence exposure. *J Dev Behav Pediatr* 2005;26(5):341–8. <https://doi.org/10.1097/00004703-200510000-00001>.
- [169] Spilsbury JC, Babineau DC, Frame J, Juhas K, Rork K. Association between children's exposure to a violent event and objectively and subjectively measured sleep characteristics: a pilot longitudinal study. *J Sleep Res* 2014;23(5):585–94. <https://doi.org/10.1111/jsr.12162>.
- [170] Umlauf MG, Bolland AC, Bolland KA, Tomek S, Bolland JM. The effects of age, gender, hopelessness, and exposure to violence on sleep disorder symptoms and daytime sleepiness among adolescents in impoverished neighborhoods. *J Youth Adolesc* 2015;44(2):518–42. <https://doi.org/10.1007/s10964-014-0160-5>.
- [171] Meltzer LJ, Montgomery-Downs HE. Sleep in the family. *Pediatr Clin* 2011;58(3):765–74. <https://doi.org/10.1016/j.pcl.2011.03.010>.
- [172] Schulmeister K. Application of melatonin action spectra on practical lighting issues. In: Proceedings from the 5th International Symposium on light and human health; 2002.
- [173] Lee KA, Ellen Zaffke M, Mcenany G. Parity and sleep patterns during and after pregnancy. *Obstet Gynecol* 2000;95(1):14–8. <https://doi.org/10.1097/00006250-200001000-00003>.
- [174] Lauren PH, Rychnovsky JD, Yount SM. A Selective review of maternal sleep characteristics in the postpartum period. *J Obstet Gynecol Neonatal Nurs* 2009;38(1):60–8. <https://doi.org/10.1111/j.1552-6909.2008.00309.x>.
- [175] Tikotzky L. Parenting and sleep in early childhood. *Curr Opin Psychol* 2017;15:118–24. <https://doi.org/10.1016/j.copsyc.2017.02.016>.
- [176] Adam EK, Snell EK, Pendry P. Sleep timing and quantity in ecological and family context: a nationally representative time-diary study. *J Fam Psychol* 2007;21(1):4–19. <https://doi.org/10.1037/0893-3200.21.1.4>.
- [177] Cousins JC, Bootzin RR, Stevens SJ, Ruiz BS, Haynes PL. Parental involvement, psychological distress, and sleep: a preliminary examination in sleep-disturbed adolescents with a history of substance abuse. *J Fam Psychol* 2007;21(1):104–13. <https://doi.org/10.1037/0893-3200.21.1.104>.
- [178] Troxel WM, Lee L, Hall M, Matthews KA. Single-parent family structure and sleep problems in black and white adolescents. *Sleep Med* 2014;15(2):255–61. <https://doi.org/10.1016/j.sleep.2013.10.012>.
- [179] Rogojanski J, Carney CE, Monson CM. Interpersonal factors in insomnia: a model for integrating bed partners into cognitive behavioral therapy for insomnia. *Sleep Med Rev* 2013;17(1):55–64. <https://doi.org/10.1016/j.smrv.2012.02.003>.
- [180] McCurry SM, Song Y, Martin JL. Sleep in caregivers: what we know and what we need to learn. *Curr Opin Psychiatr* 2015;28(6):497–503. <https://doi.org/10.1097/YCO.0000000000000205>.
- [181] Adams GC, Stoops MA, Skomro RP. Sleep tight: exploring the relationship between sleep and attachment style across the life span. *Sleep Med Rev* 2014;18(6):495–507. <https://doi.org/10.1016/j.smrv.2014.03.002>.
- [182] Glenn C. Social support and sleep symptoms in US adults. *J Clin Sleep Med* 2015;11(8).
- [183] Grandner MA, Jackson NJ, Izci-Balserak B, Gallagher RA, Murray-Bachmann R, Williams NJ, Patel NP, Jean-Louis G. Social and behavioral determinants of perceived insufficient sleep. *Front Neurol* 2015;6(MAY). <https://doi.org/10.3389/fneur.2015.00112>.
- [184] Williams NJ, Grandner MA, Wallace DM, Cuffee Y, Airihenbuwa C, Okuyemi K, Ogedegbe G, Jean-Louis G. Social and behavioral predictors of insufficient sleep among African Americans and Caucasians. *Sleep Med* 2016;18:103–7. <https://doi.org/10.1016/j.sleep.2015.02.533>.
- [185] Chung J. Social support, social strain, sleep quality, and actigraphic sleep characteristics: evidence from a national survey of US adults. *Sleep Health* 2017;3(1):22–7. <https://doi.org/10.1016/j.slehd.2016.10.003>.
- [186] Steptoe A, O'Donnell K, Marmot M, Wardle J. Positive affect, psychological well-being, and good sleep. *J Psychosom Res* 2008;64(4):409–15. <https://doi.org/10.1016/j.jpsychores.2007.11.008>.
- [187] Cinzano P, Falchi F, Elvidge CD. The first World Atlas of the artificial night sky brightness. *Mon Not Roy Astron Soc* 2001;328(3):689–707. <https://doi.org/10.1046/j.1365-8711.2001.04882.x>.
- [188] WHO. Night Noise Guidelines for Europe. Copenhagen: World Health Organization Regional Office for Europe; 2009. http://www.eruo.who.int/_data/assets/pdf_file/0017/43316/E92845.pdf.
- [189] Ranson RP. Guidelines for healthy housing. Copenhagen: WHO Regional Office for Europe; 1988. p. 244. <http://www.who.int/iris/handle/10665/191555>.
- [190] CEN. Indoor environmental input parameters for design and assessment of energy performance of buildings. Addressing Indoor Air Quality, Thermal Environment, Lighting, and Acoustics. Brussels: C.E.e.d. Normalisation; 2007. http://www.cres.gr/greenbuilding/PDF/prend/set4/WI_31_Pre-FV_version_prEN_15251_Indoor_Environment.pdf.
- [191] EPA. Indoor air pollution and health. In: Introduction to indoor air quality. EPA; 2018. p. 2018. <https://www.epa.gov/indoor-air-quality-iaq/introduction-indoor-air-quality>.

Chapter 10

Sleep health during the perinatal period: From pregnancy to postpartum

Anna L. MacKinnon^{a,b}, Makayla Freeman^c, Jasleen Kaur^d, Katherine Silang^e, Dana Watts^e and Lianne Tomfohr-Madsen^c

^aDépartement de psychiatrie et d'addictologie, Université de Montréal, Montréal, QC, Canada; ^bCentre de recherche Azrieli du CHU Sainte-Justine, Montréal, QC, Canada; ^cDepartment of Educational and Counselling Psychology, and Special Education, University of British Columbia, Vancouver, BC, Canada; ^dDepartment of Psychology, University of Regina, Regina, SK, Canada; ^eDepartment of Psychology, University of Calgary, Calgary, AB, Canada

Introduction

In the mental health context, the perinatal period is typically defined as spanning from conception to 1 year after childbirth [1]. There are several changes to sleep health that occur throughout pregnancy and the postpartum, which are related to an interplay of physiological and psychosocial factors during this time of transition to parenthood. While sleep disturbances and poor sleep quality are common across the perinatal period, the development of insomnia disorder is concerning as it can have implications for both the birthing parent¹ and their child's health. This chapter provides an overview of sleep changes and insomnia during pregnancy and the postpartum, as well as considerations for the assessment and treatment of insomnia in the perinatal context.

Sleep changes during pregnancy

With respect to sleep quality, findings from a meta-analysis reported that nearly half (45.7%) of individuals reported poor sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI) across pregnancy, with the highest rates (69.6%) in the third trimester [2]. Longitudinal findings suggest that self-reported sleep problems on the PSQI significantly increase from early to late pregnancy [3].

1. Gender-inclusive language is used throughout this chapter in accordance with recommendations for inclusive perinatal research and practice [32], as many of the cited sources do not report the self-identified gender of their participants. Future research should follow recommendations [159], such as those provided by the Centre for Gender and Sexual Equity to ensure accurate reporting of their sample characteristics.

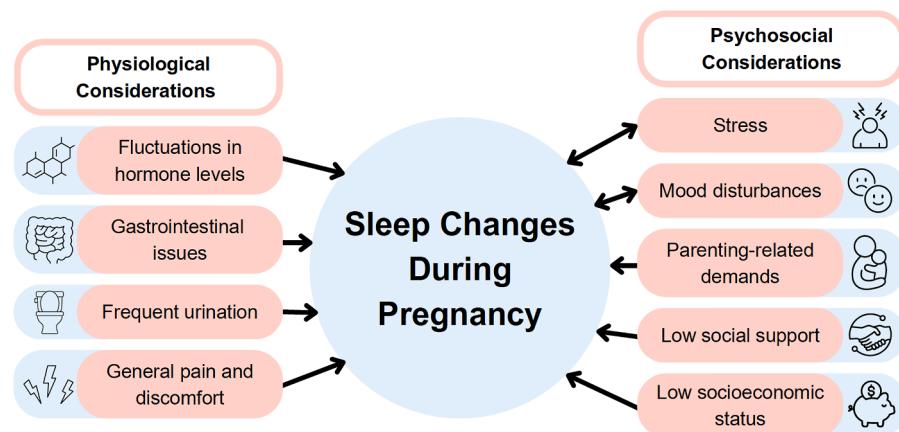
Cross-sectional polysomnography (PSG) studies indicated that pregnant individuals spend more time awake after sleep onset (WASO) or in lighter stages of sleep (non-REM 1) and less time in rapid eye-movement (REM) and deeper (slow-wave) stages of sleep, compared to nonpregnant control groups [4,5]. Longitudinal PSG studies have demonstrated that these patterns of poor sleep are more pronounced in late pregnancy (e.g., 27–39 weeks) compared to early pregnancy (e.g., 8–14 weeks) [6,7]. Taken together, findings from both subjective and objective measures suggest that pregnancy is characterized by less restorative and more disturbed sleep.

Physiological considerations

A number of physiological changes occur during pregnancy, which may impact both the quality and quantity of sleep of the pregnant individual (see Fig. 10.1). Typical physiological changes include fluctuations in hormone levels and increased physical demands related to carrying the developing fetus [8]. Resulting effects of these changes commonly include gastrointestinal issues, general pain and discomfort, more frequent urination, and sleep-disordered breathing, all of which may have a downstream impact on the quality and quantity of sleep for the pregnant individual.

Hormonal fluctuations, particularly in progesterone, throughout pregnancy may impact sleep in a variety of ways. Changes in hormones may occur as early as the first trimester, which may result in increased levels of sleepiness [9–11]. Peaks in oxytocin levels in late pregnancy may result in sleep fragmentation [12]. Gastrointestinal issues, such as heartburn, nausea, vomiting, and gastroesophageal

FIGURE 10.1 Influence of physiological and psychosocial factors on sleep changes during pregnancy.



reflux disease (GERD), can occur during pregnancy [13]. Pregnant individuals experiencing symptoms of GERD report significant negative impact on sleep [14], with symptoms of GERD being generally related to worse sleep quality and duration [15]. As pregnancy progresses, the developing fetus applies increasing pressure to the pregnant individual's bladder, reducing the bladder's functional capacity. As a result, pregnant individuals report needing to wake up more frequently throughout the night to urinate [16]. Among a sample of 2427 pregnant individuals, the most cited cause of sleep disruption was frequent urination [17]. Finally, pregnant individuals report increased difficulty in finding a comfortable sleeping position and report this lack of comfort as disruptive to their sleep [8].

The prevalence of sleep disorders increases during pregnancy, including restless leg syndrome (RLS) [18] and sleep-disordered breathing (SDB), which refers to irregularities in sleep including obstructive sleep apnea (OSA) and snoring [19]. RLS is condition in which the individual experiences an unpleasant sensation, urging the individual to move their legs [12]. This sensation is worsened during periods of inactivity, such as periods of rest during the evening [12], which explains sleep interruptions. Additionally, physical changes during pregnancy, including increased pressure on the lungs and varying degrees of airway compromise, may lead to SDB [8,19]. Prevalence of sleep-disordered breathing is estimated between 10% and 32%, varying based on stage of pregnancy [20].

Psychosocial considerations

Social and emotional factors also impact sleep during pregnancy (see Fig. 10.1). Higher levels of stress and symptoms of anxiety and depression are related to poorer sleep during pregnancy [3,21–23], particularly subjective sleep disturbances [24]. The relationship between sleep and mood disturbances is bidirectional, meaning that these

challenges are often co-occurring and further exacerbate one another. Pregnant individuals have reported that their thoughts, such as worries about sleep or the health of their baby, are one of the leading causes for difficulties in falling or staying asleep during pregnancy [16]. Pregnancy-related anxiety, vivid dreams, and worry about the baby, pregnancy, labor/delivery, and the transition to parenthood can disrupt sleep across all months of pregnancy [25–27]. Additionally, poor sleep quality or insomnia during pregnancy have been associated with higher rates of post-traumatic stress disorder after a difficult birth experience [28].

Parity has been found to be significantly correlated with sleep during pregnancy. Multiparous pregnant people are likely to have other young children at home and experience more external parenting-related demands (e.g., childcare and child sleep schedules), which may impact sleep duration and efficiency during pregnancy [27,29]. Other social contextual factors known to exacerbate stress, such as low social support and low socioeconomic status, have also been associated with worse sleep quality during pregnancy [3,30]. Further research is required to determine how the unique social-contextual factors experienced during pregnancy by marginalized populations, such as racialized groups [31], sexual minorities and gender-diverse pregnant people [32], and incarcerated individuals [33], impact sleep health.

Sleep changes during the postpartum

Sleep continues to be of worse quality and quantity for many after childbirth. Indeed, 67.8% of individuals reported poor sleep quality across the first 6 months postpartum [34]. Sleep fragmentation, reduced total sleep time, and increased feelings of fatigue are common during the postpartum period, with sleep disturbances often related to newborn sleep patterns and feeding schedules [35,36].

Physiological considerations

Some individuals experience ongoing pain and discomfort following the prenatal period and birthing process. For example, individuals with persistent low back and pelvic pain (LBPP) in the postpartum period commonly report experiencing sleep disturbances [37]. In addition, hormonal fluctuations also continue to occur in the postpartum period, with lower level of progesterone (as compared to the end of pregnancy) related to significantly shorter REM latency [38]. See Fig. 10.2.

Psychosocial considerations

The demands of childcare, infant feeding, and nighttime wakings significantly affect sleep efficiency and duration during the postpartum period [8]. Parents with pre-existing sleep difficulties or whose infants have sleep difficulties may be even more impacted by postpartum sleep fragmentation and have reported more severe sleep disturbance, greater fatigue, and poorer postpartum well-being [39,40]. The bidirectional relationship between sleep and mental health continues in the postpartum, wherein stress and symptoms of depression and anxiety have been identified as both symptoms of and risk factors for postpartum sleep difficulties [8,41,42]. Worry about the baby, the transition to parenting, sleeping arrangements, and exhaustion from labor and delivery have all been reported to disrupt new parents' perceptions of postpartum sleep quality [43]. For birthing parents who have difficult or traumatic birth experiences, postpartum sleep difficulties can both contribute to and be maintained by childbirth-related post-traumatic stress symptoms [44,45]. This bidirectional relationship can also have a negative impact on postpartum mental health and parenting stress [44,45]. For parents with infants in the neonatal intensive care unit (NICU), spending time at the NICU and experiencing higher levels of stress and/or depressive symptoms is

associated with greater sleep disturbances [46], see Fig. 10.2. Further research is needed to characterize the postpartum experiences of underserved and diverse populations.

Partners' sleep in the perinatal period

Sleep changes during pregnancy and postpartum do not often occur in isolation and may significantly impact partners of pregnant individuals [47–49]. This may be the result of shared sleep environments, as sleep disturbances of pregnant individuals affect their partners through behaviors such as tossing and turning in a shared bed [35]. Additionally, during the postpartum period, partners' sleep may be disrupted in response to infant crying or nighttime caregiving duties, such as feedings and diaper changes [48,50]. Previous research has demonstrated strong associations between sleep outcomes of birthing and non-birthing parents [51,52], with limited evidence suggesting a causal influence of partners' sleep during pregnancy on birthing parents' sleep in the postpartum [53]. The subsequent impact of poor sleep on individual and family functioning renders consideration of partner sleep important in the present context. Discussions regarding partner sleep concerns during pregnancy and postpartum, the role of gendered divisions of labor, relationships between sleep and mental health, and implications for family functioning are especially warranted.

Explorations of partner sleep concerns across the perinatal period are scarce in comparison to similar research among pregnant individuals. However, the limited research available facilitates an examination of the topic through both quantitative and qualitative methodologies. In an Australian study, individual interviews revealed that 76.9% of partners described experiencing sleep disturbances during the perinatal period [54]. In comparison, studies using self-report questionnaires of partners have

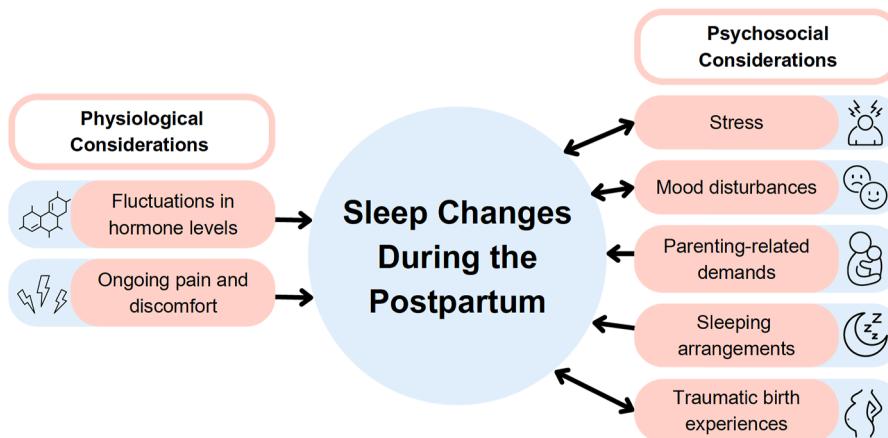


FIGURE 10.2 Influence of physiological and psychosocial considerations on sleep changes during postpartum.

demonstrated clinically significant sleep disturbance rates of 29.6% during pregnancy and 44.7% at 2 months postpartum in Canada [55], 30.4% during pregnancy and 24.6% at 3 months postpartum in Germany [53], and 26.4% during pregnancy, 36.4% at 6 weeks postpartum, and 27.3% at 6 months postpartum in China [56]. Taken together, this data suggest that sleep disturbances are relatively common among partners during the perinatal period across multiple countries. Additionally, during the perinatal period, approximately 7%–10% of partners present with clinical levels of insomnia, while approximately 40% meet criteria for a sub-clinical threshold [51].

Subjective and objective sleep measures have examined similarities and differences in sleep indices among pregnant individuals and partners. During the prenatal period, pregnant individuals and their partners receive comparable amounts of sleep [35,51]. This changes during the postpartum, as partners of pregnant individuals experience less total sleep, but pregnant individuals experience more fragmented sleep [35,51,57,58]. These differences may be related to gendered divisions of labor, such as in couples of cisgender women and cisgender men wherein the mother tends to be responsible for nighttime feedings [50]. Nighttime feedings may subsequently contribute to fragmented sleep [59], with catch up occurring through daytime naps while the infant is asleep [35]. Nonbirthing partners may not have similar opportunities to catch up on sleep debt as they typically return to work shortly after the birth of their infant [35,54].

The potential implications of poor partner sleep for individual functioning are expansive. Transitions to parenthood reflect a difficult time for partners of pregnant individuals due to increased risks for mental health concerns, with approximately 8.4% presenting with depression and 10.7% presenting with anxiety [60,61]. Associations between partners' own sleep and mental health, particularly depression, are of special importance due to the bidirectional relationship where poor sleep is considered both a predictor and consequence of poor mental health [52,54,55,62,63] (see Fig. 10.3). A longitudinal investigation demonstrated the nuanced nature of this relationship,

wherein partners' depression assessed at 1-month postpartum predicted their sleep quality assessed at 6-months postpartum, which subsequently predicted depression assessed at 1-year postpartum [52].

Examinations of the relationship between partner and pregnant individual's sleep have been an emerging area of interest. Prior research has demonstrated associations between birthing and nonbirthing parent's sleep duration, sleep quality, and frequency of nighttime awakenings [51,52]. Additionally, a recent study utilizing dyadic data demonstrated that birthing parents' sleep quality, sleep duration, sleep efficiency, and frequency of nighttime awakenings at 3-months postpartum was influenced by the corresponding sleep characteristics of their partner during pregnancy [53]. In contrast, partners' sleep at 3 months' postpartum was not influenced by the sleep characteristics of the birthing parent during pregnancy [53].

In one study that has longitudinally examined relationships between birthing and nonbirthing parents' sleep and mental health. This investigation demonstrated significant associations between birthing parents' sleep quality assessed at 6-months postpartum and nonbirthing parents' depression symptoms assessed at 6-months and 12-months postpartum [52]. Based on these findings, poor birthing parent sleep quality has been conceptualized as a potential mechanism for conferring risks for nonbirthing parent mental health concerns [52]. Additionally, the study reported significant correlations between nonbirthing parents' sleep at 6-month postpartum and birthing parents' depression symptoms at 1-month, 6-month, and 12-month postpartum [52]. However, when analyzed with a longitudinal model, these associations were not significant [52].

Research on relationships between partner sleep and family functioning has received limited attention. Most pertinent to the present discussion, disruptions to partner sleep have been associated with poorer relationship satisfaction [64], which subsequently relates to less partner involvement in infant care [65]. Although further research in this area is needed, it is apparent that partners should be considered when examining sleep changes during pregnancy and the postpartum.

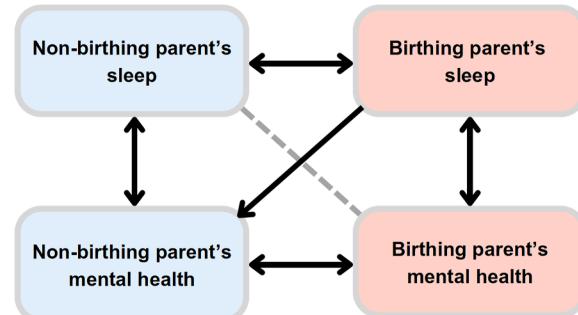


FIGURE 10.3 Relationships between birthing parent and nonbirthing parent's sleep and mental health.

Insomnia in pregnancy and postpartum

Insomnia is a prevalent sleep disorder characterized by persistent difficulty falling asleep, staying asleep, or experiencing restorative sleep, despite adequate opportunities for rest [66]. Insomnia is categorized based on various factors, including how often a person experiences insomnia symptoms (frequency), whether the insomnia is short-term or chronic (chronicity), and the subtype of insomnia. Subtypes, describe different patterns of insomnia, such as initial (difficulty initiating sleep), middle (difficulty maintaining sleep at night), late (difficulty sustaining sleep into the morning or early awakenings), or mixed insomnia (combination of difficulties). Historically, insomnia was merely seen as a symptom of an underlying medical or psychiatric condition, and the assumption was that resolving the underlying disorder would alleviate the associated insomnia. Now, chronic insomnia is recognized as an independent disorder. In line with a stress-diathesis model of insomnia [67], pregnancy represents a period of stress, particularly related to health and family changes, that can increase the risk of experiencing insomnia.

Prevalence

Pregnancy introduces a unique set of changes (i.e., physiological, vascular, and psychological), with a significant number of expecting parents grappling with sleep disturbances. A meta-analysis conducted by Sedov et al. [68] indicated that during pregnancy, approximately 38.2% of individuals experience insomnia, where symptoms occur more frequently in the third trimester (39.7%) in comparison to the first (25.3%) and the second (27.2%) trimester [68] (see Fig. 10.4). Consistent with this, results from a

longitudinal trajectory analyses of insomnia during the perinatal period demonstrated that symptoms of insomnia remained fairly stable in early and mid-pregnancy until increasing in late pregnancy, after which symptoms tend to decrease in the postpartum period [69].

During the postpartum period, insomnia continues to be a significant concern for many birthing parents. The challenges of caring for a newborn, adjusting to a new routine, and hormonal fluctuations can contribute to sleep disturbances. Furthermore, these sleep disturbances may persist into the postpartum period with around 20.4% of pregnant individuals reporting enduring, chronic insomnia issues [70]. Understanding prenatal and postpartum insomnia is vital for comprehensive healthcare strategies aimed at promoting parental and child well-being.

Risk and protective factors

The development of insomnia during pregnancy is influenced by a multitude of factors. Hormonal fluctuations [71], physiological discomfort (such as back pain and fetal movement) [72], obesity [73], rumination regarding childbirth and parenthood [26], and the trimester in pregnancy [68], all contribute to the likelihood of experiencing insomnia. Following birth, parents encounter new challenges that contribute to postpartum insomnia. Disrupted sleep patterns due to infant care [74], hormonal fluctuations as the body adjusts to postpregnancy physiology [75], and the stress of adapting to parenthood all play a role in the development of insomnia. Conversely, employing relaxation techniques, maintaining a healthy lifestyle [73], and the use of evidence-based therapeutic interventions like cognitive behavioral therapy for insomnia (CBT-I) [76] can help mitigate the adverse effects of insomnia during pregnancy and the postpartum period.

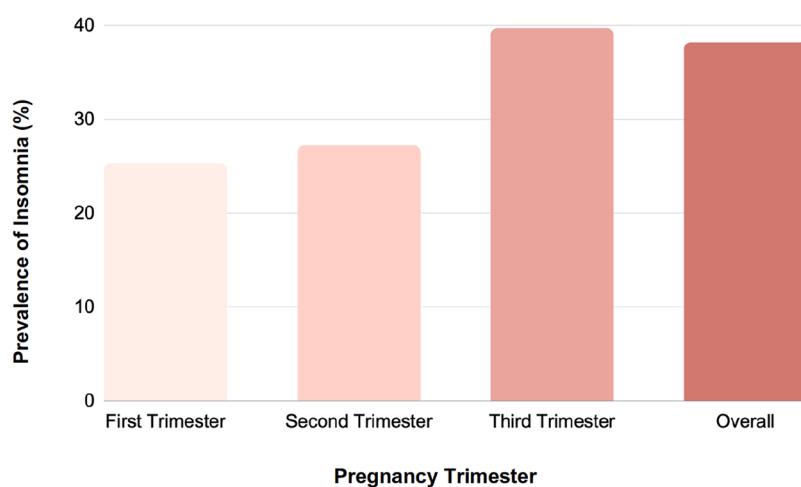


FIGURE 10.4 Prevalence of insomnia grouped by pregnancy trimester. Based on data from Sedov ID, Anderson NJ, Dhillon AK, Tomfohr-Madsen LM. Insomnia symptoms during pregnancy: A meta-analysis. *Journal of Sleep Research* 2021;30(1). <https://doi.org/10.1111/jsr.13207>.

Consequences for parent and child

Insomnia during pregnancy can exert a significant toll on both the pregnant parent and the developing fetus. Untreated insomnia during pregnancy has been associated with adverse obstetrical complications, including pre-eclampsia and growth retardation [77,78] more prolonged, painful labor, and caesarean delivery [12,79,80], as well as a higher risk of preterm birth and low birth weight [81–83]. These poor birth outcomes are associated with long-term impacts on child health and development [84]. Prenatal insomnia also confers risk for the onset and recurrence of depression and anxiety [85–87]. These consequences underline the importance of addressing insomnia early in the perinatal period to safeguard both parent and infant health.

Insomnia during the post-partum period also has significant consequences for both parents and their infants. Parents often contend with heightened fatigue, irritability, and impaired cognitive functioning [8], which can make the demanding task of caring for a newborn even more challenging. Insomnia during the postpartum period may also negatively influence infant sleep, as well as parent-infant bonding [88,89]. Furthermore, postpartum insomnia has been found to be associated with the worsening and/or development of postpartum depression [90], which can have negative impacts on child wellbeing [91,92].

Comorbid mental health problems

Insomnia during pregnancy and postpartum frequently co-occurs with mental health conditions such as depression and anxiety. In fact, compared to those without an insomnia diagnosis, pregnant patients with insomnia have a substantially higher prevalence of major mental health disorders (53.5% vs. 5.5%) [93]. The co-morbidity of disorders like depression and anxiety alongside insomnia during pregnancy and postpartum may be more likely, given that sleep and mood typically worsen as pregnancy progresses. Insomnia is widely recognized as a risk factor for psychiatric disorders in general and is implicated in increasing the risk for depression and anxiety during pregnancy specifically [94]. Insomnia may commonly co-occur with these disorders because they share many of the same symptoms or clinical presentation, such as depressed mood, worry, fatigue, and difficulty concentrating. For example, a core feature of anxiety, depression, and insomnia is emotional dysregulation. Sleep is essential to the ability to regulate emotions, and, when emotions are dysregulated, this leads to both mental health and sleep disturbances [95]. Individuals with insomnia are more likely to experience emotion dysregulation and use maladaptive emotion regulation strategies such as suppression and rumination, which are common features of both

anxiety and depressive disorders [96,97]. Consistent with this explanation, studies have found a significant relationship between poor sleep quality and maladaptive emotion regulation strategies during pregnancy [98]. Although it can be argued that this relationship between sleep and emotion regulation may be true in the general population as well, it is important to consider that individuals in pregnancy are faced with various physiological and hormonal changes, which have been noted to affect cognition, subjective affect, emotional sensitivity, emotion regulation, and sleep [99]. Further, a recent review on emotion regulation in parents has provided evidence from various studies to suggest that there are important differences at a neurobiological level (i.e., elevated oxytocin, increase in gray matter volume in the prefrontal cortex, higher levels of activation in brain networks associated with emotion information processing) in emotion regulation when comparing parents to nonparents (general population) [100]. This review emphasizes the importance of understanding the complex interplay between sleep and mental health in pregnancy and postpartum as this unique period of time is associated with various changes and stressors separate from that in the general population. Additionally, exploring the relationship between sleep and mental health in pregnancy and postpartum specifically will help inform clinicians and researchers of early interventions that address these interconnected issues.

Comorbid depressive disorders

Major depressive disorder (MDD) is a complex and prevalent condition characterized by episodes of depressed mood and/or anhedonia lasting at least 2 weeks [66]. Major depressive episodes (MDEs) often bring significant changes in weight, sleep patterns, psychomotor activity, fatigue, feelings of worthlessness or guilt, and concentration difficulties. These symptoms can be difficult to differentiate from pregnancy-related changes; however, depression severely impacts daily functioning and causes substantial distress. Based on a systematic review, the combined period prevalence indicated that as many as 19.2% of birthing parents had a depressive episode (MDE) during the first 3 months postpartum [101].

Despite growing evidence that insomnia plays a role beyond being a symptom of depression, the exact mechanisms linking insomnia during pregnancy and depression remain unclear. The relationship between insomnia and depression generally has been suggested to be bidirectional, where insomnia has been observed to be a risk factor for depression, and depression has been noted to be a predictor of insomnia [102]. However, in the context of pregnancy and postpartum, most research has focused on insomnia in pregnancy and postpartum being predictive of postpartum depressive symptoms [103,104], which suggest

that the relationship between insomnia symptoms and depressive symptoms in pregnancy and postpartum may not be bidirectional as originally hypothesized. This is supported by a trajectory analysis suggesting that poor prenatal sleep precedes postpartum depressive symptoms [69,105]. Using a growth processing model, another study looking at the relationship between sleep and depression reported findings demonstrating that shorter sleep duration, higher sleep disturbance, and more sleep-related impairments were predictive of a slower decline in depressive symptoms over time [106]. Insomnia may serve as a risk factor for MDD during pregnancy and postpartum through abnormalities in REM sleep, which likely interfere with arousal and affective systems implied in emotion regulation [107,108]. While the precise nature and role of these biological mechanisms in the connection between pregnancy-related insomnia and depression remain unclear, they represent promising areas for future research in this context.

Comorbid anxiety disorders

Anxiety disorders, broadly defined, share characteristics such as intense feelings of fear, avoidance behaviors, and susceptibility to stress triggers [66]. Although not as extensively studied as depression during the perinatal period, features of anxiety also overlap with insomnia, possibly explaining the comorbidity between the insomnia and anxiety [25]. One study found that nearly 12% of individuals experiencing insomnia during pregnancy also had met criteria for an anxiety diagnosis based on a semi-structured interview, compared to 7.4% among those without insomnia [25]. Evidence also suggests that insomnia in pregnancy may act as a potential risk factor for postpartum anxiety and later sleep problems [25,40,106,109]. The parallel relationship that insomnia has with anxiety and depression may point to disruptions in sleep as a transdiagnostic mechanism through which it influences other mental health concerns [110].

Assessment of insomnia during the perinatal period

Assessment of insomnia and sleep difficulties should take into account the context of pregnancy and the transition to parenthood, as well as cultural considerations about sleep practices and beliefs. Indeed, wholistic and collaborative assessment of insomnia during the perinatal period enables a more accurate and empathic understanding of an individual's symptoms and experience, as well as for better evaluation of changes and tracking of treatment progress.

Questionnaires can be a useful way for individuals to self-report their insomnia symptoms. While few screening scales have been validated for use during the perinatal

period, the Insomnia Severity Index (ISI) [111] has been used reliably in research with pregnant populations. The seven-item ISI corresponds to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for insomnia disorder [112] and has been used to show response to treatment in clinical trials of therapy during pregnancy [113–115]. The Pittsburgh Sleep Quality Index (PSQI) [116] is useful for monitoring sleep problems. This 19-item questionnaire has been validated against polysomnography and used reliably among pregnant populations [117–119]. Given the PSQI tends to identify pregnant individuals as poor sleepers, with 45.7% scoring above the original (>5) cut-off [2], a higher cut-off score (≥ 7) is often used for pregnant populations [120]. Finally, the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment forms [121] are brief screening tools that have been used reliably in perinatal samples [122,123].

The gold standard for any mental health diagnosis is a clinical interview. For insomnia disorder, the Structured Clinical Interview for DSM-5 (SCID-5) [124] Sleep Disorders Module, which has excellent reliability in adults in general [125], has been used reliably in pregnant populations specifically [126]. The Duke Structured Interview for Sleep Disorders [127] has also been used to screen for insomnia in pregnant samples [113]. During assessment, it is helpful to remember that pregnancy can represent a risk factor or onset of insomnia diagnosis, while symptoms and maintenance factors (such as napping and dysfunctional cognitions) have a similar presentation across the lifespan.

Treatment for insomnia during the perinatal period

The prevalence of both prenatal and postpartum insomnia highlights the need for targeted interventions and support to address the sleep-related challenges faced by parents during this critical phase of their lives. Pregnant people have historically been excluded from clinical research, including studies on insomnia treatment. Following calls for the development of interventions to treat insomnia specifically in pregnancy and the postpartum [128], a growing number of trials have been conducted on efficacy and effectiveness of psychological treatment approaches for insomnia during the perinatal period.

Although pharmacotherapy treatment for insomnia in pregnancy has been associated with improved sleep quality and reduced risk of postpartum depression [129], best practice guidelines advise against the use of most sedative sleep medications in pregnancy due to potential teratogenic effects [130]. Understandably then, pregnant individuals themselves also report a reluctance to take prescription medications due to their perception of risk for the developing fetus [131–133]. Research on treatment preferences

shows that pregnant people and their partners view cognitive behavioral therapy for insomnia (CBT-I) to be more credible and preferable compared to pharmacotherapy [134,135]. CBT-I is an evidence-based intervention that utilizes cognitive (i.e., psychoeducation, restructuring, problem-solving) and behavioral (i.e., self-monitoring, sleep restriction, stimulus control) techniques to improve sleep efficiency and quality. CBT-I is considered to be the current gold standard for treatment of insomnia among the general population [128,136–138], as it is equivalent to or outperforms medication for improving sleep, while also reducing symptoms of depression [139–144].

Emerging evidence suggests that in-person and digital CBT-I are effective for treating insomnia and improving sleep health in pregnancy [25] and the postpartum period [114,145]. For example, the Sleeping for Two five-session CBT-I adaptation for pregnancy has been delivered in an in-person group format [115] as well as an in-person and online (via videoconferencing during the COVID-19 pandemic) individual format [146]. Both formats have demonstrated effectiveness in reducing insomnia (assessed using the ISI) and improving sleep quality (assessed using the PSQI), as well as concomitant reductions in depressive symptoms, among pregnant participants [115,146,147]. The six-session digital CBT-I program Sleepio (Big Health Inc.) has also been shown to be effective for reducing insomnia (assessed using the ISI) and improving sleep quality (assessed using the PSQI), as well as decreasing anxiety and depression symptoms, among pregnant people [148–150]. Another trial adapted CBT-I into a combined format including a 1 h telephone call and up to six multimedia emails (containing audio and visual materials), with results indicating treatment effects for reducing insomnia (assessed using the ISI) and sleep disturbance (assessed using the PROMIS) at the end of pregnancy and 24 months postpartum, but not in between [80].

Mindfulness-based approaches have also shown promise for treating insomnia during the perinatal period. For example, a pilot trial of the Perinatal Understanding of Mindful Awareness for Sleep (PUMAS) intervention demonstrated reduced insomnia (assessed using the ISI) [151], by reducing cognitive arousal and sleep effort [152]. This trial also showed secondary benefits for reducing anxiety and depression, as well as improving parent-child bonding [151,153]. Similarly, secondary analysis of mindfulness based cognitive therapy for perinatal depression (MBCT-PD) demonstrated a treatment effect on improving sleep quality (assessed using the PSQI), where participants with initial worse sleep quality had greater improvement from postintervention (22–38 weeks gestation) to follow-up (3 months postpartum) [154].

Equity, diversity, and inclusivity considerations

Digital or eHealth interventions promote more equitable access for pregnant people, as they can address barriers to care including living in remote or rural areas, lack of transportation, childcare needs, and/or work schedule conflicts [155–158]. Understanding and respecting cultural differences and traditional knowledge about sleep practices during the perinatal period (such as feeding to sleep or bedsharing/co-sleeping) is crucial for developing therapeutic alliance or a trusting relationship that enables autonomous, meaningful change in psychological interventions for insomnia.

Conclusion

Sleep undergoes several changes during pregnancy and the postpartum, leading to poorer quantity and quality. Unfortunately, the perinatal period also confers increased risk for experiencing insomnia, which can have negative impacts on both parent and child health. Fortunately, treatment research has been increasingly including pregnant people in the last decade, providing much needed evidence-based psychological intervention options that can improve insomnia and have secondary benefits on mental health and family wellbeing. Further work is needed to better understand and improve care for perinatal sleep health in gender-diverse and equity seeking groups.

References

- [1] Austin M-P. Antenatal screening and early intervention for? Perinatal? Distress, depression and anxiety: where to from here? *Arch Wom Ment Health* 2004;7(1):1–6. <https://doi.org/10.1007/s00737-003-0034-4>.
- [2] Sedov ID, Cameron EE, Madigan S, Tomfohr-Madsen LM. Sleep quality during pregnancy: a meta-analysis. *Sleep Med Rev* 2018;38:168–76. <https://doi.org/10.1016/j.smrv.2017.06.005>.
- [3] Tomfohr LM, Buliga E, Letourneau NL, Campbell TS, Giesbrecht GF. Trajectories of sleep quality and associations with mood during the perinatal period. *Sleep* 2015;38(8):1237–45. <https://doi.org/10.5665/sleep.4900>.
- [4] Hertz G, Fast A, Feinsilver SH, Albertario CL, Schulman H, Fein AM. Sleep in normal late pregnancy. *Sleep* 1992;15(3):246–51. <https://doi.org/10.1093/sleep/15.3.246>.
- [5] Wilson DL, Barnes M, Ellett L, Permezel M, Jackson M, Crowe SF. Decreased sleep efficiency, increased wake after sleep onset and increased cortical arousals in late pregnancy. *Aust N Z J Obstet Gynaecol* 2011;51(1):38–46. <https://doi.org/10.1111/j.1479-828X.2010.01252.x>.
- [6] Brunner DP, Munch M, Biedermann K, Huch R, Huch A, Borbely AA. Changes in sleep and sleep electroencephalogram during pregnancy. *Sleep* 1994;17(7):576–82. <https://doi.org/10.1093/sleep/17.7.576>.

- [7] Izci-Balserak B, Keenan BT, Corbitt C, Staley B, Perlis M, Pien GW. Changes in sleep characteristics and breathing parameters during sleep in early and late pregnancy. *J Clin Sleep Med* 2018;14(7):1161–8. <https://doi.org/10.5664/jcsm.7216>.
- [8] Christian LM, Carroll JE, Teti DM, Hall MH. Maternal sleep in pregnancy and postpartum Part I: mental, physical, and interpersonal consequences. *Curr Psychiatr Rep* 2019;21(3). <https://doi.org/10.1007/s11920-019-0999-y>.
- [9] Lancel M, Faulhaber J, Holsboer F, Rupprecht R. Progesterone induces changes in sleep comparable to those of agonistic GABA_A receptor modulators. *Am J Physiol Endocrinol Metabol* 1996;271(4):E763. <https://doi.org/10.1152/ajpendo.1996.271.4.e763>.
- [10] Silvestri R, Aricò I. Sleep disorders in pregnancy. *Sleep Sci* 2019;12(3):232–9. <https://doi.org/10.5935/1984-0063.20190098>.
- [11] Freeman ME, Crissman JK, Louw GN, Butcher RL, Inskeep EK. Thermogenic action of progesterone in the rat. *Endocrinology* 1970;86(4):717–20. <https://doi.org/10.1210/endo-86-4-717>.
- [12] Oyiengo D, Louis M, Hott B, Bourjaily G. Sleep disorders in pregnancy. *Clin Chest Med* 2014;35(3):571–87. <https://doi.org/10.1016/j.ccm.2014.06.012>.
- [13] Dunbar K, Yadlapati R, Konda V. Heartburn, nausea, and vomiting during pregnancy. *Am J Gastroenterol* 2022;117(10 S):10–5. <https://doi.org/10.14309/ajg.00000000000001958>.
- [14] Fill Malfertheiner S, Seelbach-Göbel B, Costa S-D, Ernst W, Reuschel E, Zeman F, Malfertheiner P, Malfertheiner MV. Impact of gastroesophageal reflux disease symptoms on the quality of life in pregnant women: a prospective study. *Eur J Gastroenterol Hepatol* 2017;29(8):892–6. <https://doi.org/10.1097/meg.0000000000000905>.
- [15] Fujiwara Y, Arakawa T, Fass R. Gastroesophageal reflux disease and sleep disturbances. *J Gastroenterol* 2012;47(7):760–9. <https://doi.org/10.1007/s00535-012-0601-4>.
- [16] Mindell JA, Jacobson BJ. Sleep disturbances during pregnancy. *J Obstet Gynecol Neonatal Nurs* 2000;29(6):590–7. <https://doi.org/10.1111/j.1552-6909.2000.tb02072.x>.
- [17] Mindell JA, Sadeh A, Kwon R, Goh DYT. Relationship between child and maternal sleep: a developmental and cross-cultural comparison. *J Pediatr Psychol* 2015;40(7):689–96. <https://doi.org/10.1093/jpepsy/jsv008>.
- [18] Chen SJ, Shi L, Bao YP, Sun YK, Lin X, Que JY, Vitiello MV, Zhou YX, Wang YQ, Lu L. Prevalence of restless legs syndrome during pregnancy: a systematic review and meta-analysis. *Sleep Med Rev* 2018;40:43–54. <https://doi.org/10.1016/j.smrv.2017.10.003>.
- [19] Robertson NT, Turner JM, Kumar S. Pathophysiological changes associated with sleep disordered breathing and supine sleep position in pregnancy. *Sleep Med Rev* 2019;46:1–8. <https://doi.org/10.1016/j.smrv.2019.04.006>.
- [20] Louis JM, Koch MA, Reddy UM, Silver RM, Parker CB, Facco FL, Redline S, Nhan-Chang C-L, Chung JH, Pien GW, Basner RC, Grobman WA, Wing DA, Simhan HN, Haas DM, Mercer BM, Parry S, Mobley D, Benjamin C, Saade GR, Schubert FP, Zee PC. Predictors of sleep-disordered breathing in pregnancy. *Am J Obstet Gynecol* 2018;218(5):521.e1. <https://doi.org/10.1016/j.ajog.2018.01.031>.
- [21] Åkerstedt T. Psychosocial stress and impaired sleep. *Scand J Work Environ Health* 2006;32(6):493–501. <https://doi.org/10.5271/sjweh.1054>.
- [22] Hicks RA, Garcia ER. Level of stress and sleep duration. *Percept Mot Skills* 1987;64(1):44–6. <https://doi.org/10.2466/pms.1987.64.1.44>.
- [23] Dunkel Schetter C, Tanner L. Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. *Curr Opin Psychiatr* 2012;25(2):141–8. <https://doi.org/10.1097/YCO.0b013e3283503680>.
- [24] Volkovich E, Tikotzky L, Manber R. Objective and subjective sleep during pregnancy: links with depressive and anxiety symptoms. *Arch Wom Ment Health* 2016;19(1):173–81. <https://doi.org/10.1007/s00737-015-0554-8>.
- [25] Osnes RS, Roaldset JO, Follestad T, Eberhard-Gran M. Insomnia late in pregnancy is associated with perinatal anxiety: a longitudinal cohort study. *J Affect Disord* 2019;248:155–65. <https://doi.org/10.1016/j.jad.2019.01.027>.
- [26] van der Zwan JE, de Vente W, Tolvanen M, Karlsson H, Buil JM, Koot HM, Paavonen EJ, Polo-Kantola P, Huizink AC, Karlsson L. Longitudinal associations between sleep and anxiety during pregnancy, and the moderating effect of resilience, using parallel process latent growth curve models. *Sleep Med* 2017;40:63–8. <https://doi.org/10.1016/j.sleep.2017.08.023>.
- [27] Mindell JA, Cook RA, Nikolovski J. Sleep patterns and sleep disturbances across pregnancy. *Sleep Med* 2015;16(4):483–8. <https://doi.org/10.1016/j.sleep.2014.12.006>.
- [28] el Founti Khsim I, Rodríguez MM, Riquelme Gallego B, Caparros-Gonzalez RA, Amezcuá-Prieto C. Risk factors for post-traumatic stress disorder after Childbirth: a systematic review. *Diagnostics* 2022;12(11):2598. <https://doi.org/10.3390/diagnostics12112598>.
- [29] Christian LM, Carroll JE, Porter K, Hall MH. Sleep quality across pregnancy and postpartum: effects of parity and race. *Sleep Health* 2019;5(4):327–34. <https://doi.org/10.1016/j.slehd.2019.03.005>.
- [30] Silva-perez LJ, Gonzalez-Cardenas N, Surani S, Etindele Sosso FA, Surani SR. Socioeconomic status in pregnant women and sleep quality during pregnancy. *Cureus* 2019. <https://doi.org/10.7759/cureus.6183>.
- [31] Lucchini M, O'Brien LM, Kahn LG, Brennan PA, Baron KG, Knapp EA, Lugo-Candelas C, Shuffrey L, Dunietz GL, Zhu Y, Wright RJ, Wright RO, Duarte C, Karagas MR, Ngai P, O'Connor TG, Herbstman JB, Dioni S, Singh AM, Alcantara C, Fifer WP, Elliott AJ, Jacobson LP, Parker CB, Alshawabkeh AN, Ownby D. Racial/ethnic disparities in subjective sleep duration, sleep quality, and sleep disturbances during pregnancy: an ECHO study. *Sleep* 2022;45(9). <https://doi.org/10.1093/sleep/zsac075>.
- [32] Rioux C, Weedon S, London-Nadeau K, Paré A, Juster RP, Roos LE, et al. Gender-inclusive writing for epidemiological research on pregnancy. *J Epidemiol Community Health* 2022;76(8):823–7. <https://doi.org/10.1136/jech-2022-219172>. e0255799.
- [33] Knittel A, Sufrin C. Maternal health equity and justice for pregnant women who experience incarceration. *JAMA Netw Open* 2020;3(8):2013096.
- [34] Okun ML, Lac A. Postpartum insomnia and poor sleep quality are longitudinally predictive of postpartum mood symptoms. *Psychosom Med* 2023;85.
- [35] Gay CL, Lee KA, Lee SY. Sleep patterns and fatigue in new mothers and fathers. *Biol Res Nurs* 2004;5(4):311–8. <https://doi.org/10.1177/1099800403262142>.
- [36] Hunter LP, Rychnovsky JD, Yount SM. A selective review of maternal sleep characteristics in the postpartum period. *J Obstet*

- Gynecol Neonatal Nurs 2009;38(1):60–8. <https://doi.org/10.1111/j.1552-6909.2008.00309.x>.
- [37] Horibe K, Isa T, Matsuda N, Murata S, Tsuboi Y, Okumura M, Kawaharada R, Kogaki M, Uchida K, Nakatsuka K, Ono R. Association between sleep disturbance and low back and pelvic pain in 4-month postpartum women: a cross-sectional study. Eur Spine J 2021;30(10):2983–8. <https://doi.org/10.1007/s00586-021-06847-8>.
- [38] Lee KA, McEnany G, Zaffke ME. REM sleep and mood state in childbearing women: sleepy or weepy? Sleep 2000;23(7):877–85. <https://doi.org/10.1093/sleep/23.7.1b>.
- [39] Giallo R, Rose N, Vittorino R. Fatigue, wellbeing and parenting in mothers of infants and toddlers with sleep problems. J Reprod Infant Psychol 2011;29(3):236–49. <https://doi.org/10.1080/02646838.2011.593030>.
- [40] Sivertsen B, Hysing M, Dørheim SK, Eberhard-Gran M. Trajectories of maternal sleep problems before and after childbirth: a longitudinal population-based study. BMC Pregnancy Childbirth 2015;15(1). <https://doi.org/10.1186/s12884-015-0577-1>.
- [41] Bhati S, Richards K. A systematic review of the relationship between postpartum sleep disturbance and postpartum depression. J Obstet Gynecol Neonatal Nurs 2015;44(3):350–7. <https://doi.org/10.1111/1552-6909.12562>.
- [42] Gillespie SL, Mitchell AM, Kowalsky JM, Christian LM. Maternal parity and perinatal cortisol adaptation: the role of pregnancy-specific distress and implications for postpartum mood. Psychoneuroendocrinology 2018;97:86–93. <https://doi.org/10.1016/j.psyneuen.2018.07.008>.
- [43] Kennedy HP, Gardiner A, Gay C, Lee KA. Negotiating sleep: a qualitative study of new mothers. J Perinat Neonatal Nurs 2007;21(2):114–22. <https://doi.org/10.1097/01.JPN.0000270628.51122.1d>.
- [44] Di Blasio P, Camisasca E, Miragoli S. Childbirth related post-traumatic stress symptoms and maternal sleep difficulties: associations with parenting stress. Front Psychol 2018;9:2103. <https://doi.org/10.3389/fpsyg.2018.02103>.
- [45] Liu Y. Postpartum depression and postpartum post-traumatic stress disorder: prevalence and associated factors. BMC Psychiatr 2021;21(1):1–11.
- [46] Lebel V, Feeley N, Robins S, Stremler R. Factors influencing mothers' quality of sleep during their infants' NICU Hospitalization. Behav Sleep Med 2022;20(5):610–21. <https://doi.org/10.1080/15402002.2021.1971985>.
- [47] Pollock MA, Amankwaa LC, Amankwaa AA. First-time fathers and stressors in the postpartum period. J Perinat Educ 2005;14(2):19–25. <https://doi.org/10.1624/105812405X44682>.
- [48] Shorey S, Dennis C-L, Bridge S, Chong YS, Holroyd E, He H-G. First-time fathers' postnatal experiences and support needs: a descriptive qualitative study. J Adv Nurs 2017;73(12):2987–96. <https://doi.org/10.1111/jan.13349>.
- [49] Baldwin S, Malone M, Sandall J, Bick D. A qualitative exploratory study of UK first-time fathers' experiences, mental health and wellbeing needs during their transition to fatherhood. BMJ Open 2019;9(9):e030792. <https://doi.org/10.1136/bmjopen-2019-030792>.
- [50] Insana SP, Garfield CF, Montgomery-Downs HE. A mixed-method examination of maternal and paternal nocturnal care-giving. J Pediatr Health Care 2014;28(4):313–21. <https://doi.org/10.1016/j.pedhc.2013.07.016>.
- [51] Horwitz A, Bar-Shachar Y, Ran-Peled D, Finkelstein O, Ben-Zion H, Bar-Kalifa E, Meiri G, Tikotzky L. Sleep of mothers, fathers, and infants: a longitudinal study from pregnancy through 12 months. Sleep 2023;46(9). <https://doi.org/10.1093/sleep/zsad029>.
- [52] Saxbe DE, Schetter CD, Guardino CM, Ramey SL, Shalowitz MU, Thorp J, Vance M. Sleep quality predicts persistence of parental postpartum depressive symptoms and transmission of depressive symptoms from mothers to fathers. Ann Behav Med 2016;50(6):862–75. <https://doi.org/10.1007/s12160-016-9815-7>.
- [53] Cattarius BG, Schlarb AA. How the sleep of couples changes from pregnancy to three months postpartum. Nat Sci Sleep 2021;13:251–61. <https://doi.org/10.2147/NSS.S259072>.
- [54] Chhabra J, Li W, McDermott B. Predictive factors for depression and anxiety in men during the perinatal period: a mixed methods study. Am J Mens Health 2022;16(1):155798832210794. <https://doi.org/10.1177/15579883221079489>.
- [55] Da Costa D, Danieli C, Abrahamowicz M, Dasgupta K, Sewitch M, Lowenstein I, Zelkowitz P. A prospective study of postnatal depressive symptoms and associated risk factors in first-time fathers. J Affect Disord 2019;249:371–7. <https://doi.org/10.1016/j.jad.2019.02.033>.
- [56] Ngai FW, Xie YJ. Sleep and depression in couples during the transition to parenthood. Behav Sleep Med 2023;22. <https://doi.org/10.1080/15402002.2023.2255327>.
- [57] Insana SP, Montgomery-Downs HE. Sleep and sleepiness among first-time postpartum parents: a field- and laboratory-based multi-method assessment. Dev Psychobiol 2013;55(4):361–72. <https://doi.org/10.1002/dev.21040>.
- [58] Lo BK, Kang AW, Haneuse S, Yu X, Ash TV, Redline S, Taveras EM, Davison KK. Changes in fathers' body mass index, sleep, and diet from prebirth to 12 months postbirth: exploring the moderating roles of parenthood experience and coparenting support. Ann Behav Med 2021;55(12):1211–9. <https://doi.org/10.1093/abm/kaab013>.
- [59] Thomas KA, Foreman SW. Infant sleep and feeding pattern: effects on maternal sleep. J Midwifery Wom Health 2005;50(5):399–404. <https://doi.org/10.1016/j.jmwh.2005.04.010>.
- [60] Cameron EE, Sedov ID, Tomfohr-Madsen LM. Prevalence of paternal depression in pregnancy and the postpartum: an updated meta-analysis. J Affect Disord 2016;206:189–203. <https://doi.org/10.1016/j.jad.2016.07.044>.
- [61] Leiferman JA, Farewell CV, Jewell J, Lacy R, Walls J, Harnke B, Paulson JF. Anxiety among fathers during the prenatal and postpartum period: a meta-analysis. J Psychosom Obstet Gynecol 2021;42(2):152–61. <https://doi.org/10.1080/0167482X.2021.1885025>.
- [62] Divine A, Blanchard C, Benoit C, Downs DS, Rhodes RE. The influence of sleep and movement on mental health and life satisfaction during the transition to parenthood. Sleep Health 2022;8(5):475–83. <https://doi.org/10.1016/j.slehd.2022.06.013>.
- [63] Paavonen EJ, Saarenpää-Heikkilä O, Pölkki P, Kylliäinen A, Porkka-Heiskanen T, Paunio T. Maternal and paternal sleep during pregnancy in the child-sleep birth cohort. Sleep Med 2017;29:47–56. <https://doi.org/10.1016/j.sleep.2016.09.011>.
- [64] Wynter K, Francis LM, Fletcher R, McBride N, Dowse E, Wilson N, Di Manno L, Teague S, Macdonald JA. Sleep, mental health and wellbeing among fathers of infants up to one year postpartum: a scoping review. Midwifery 2020;88:102738. <https://doi.org/10.1016/j.midw.2020.102738>.

- [65] Lee AM, Keung Lam S, Mun Lau SMS, Chong CSY, Chui HW, Fong DYT. Prevalence, course, and risk factors for antenatal anxiety and depression. *Obstet Gynecol* 2007;110(5):1102–12. <https://doi.org/10.1097/01.aog.0000287065.59491.70>.
- [66] American Psychiatric Association, Diagnostic and statistical manual of mental disorders. 5th ed. American Psychiatric Pub; 2013. p. 2013.
- [67] Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. *Psychiatr Clin* 1987;10(4):541–53. [https://doi.org/10.1016/s0193-953x\(18\)30532-x](https://doi.org/10.1016/s0193-953x(18)30532-x).
- [68] Sedov ID, Anderson NJ, Dhillon AK, Tomfohr-Madsen LM. Insomnia symptoms during pregnancy: a meta-analysis. *J Sleep Res* 2021;30(1). <https://doi.org/10.1111/jsr.13207>.
- [69] Sedov ID, Tomfohr-Madsen LM. Trajectories of insomnia symptoms and associations with mood and anxiety from early pregnancy to the postpartum. *Behav Sleep Med* 2021;19(3):395–406. <https://doi.org/10.1080/15402002.2020.1771339>.
- [70] Okun ML, Lac A. Postpartum insomnia and poor sleep quality are longitudinally predictive of postpartum mood symptoms. *Psychosom Med* 2023;85(8):736–43. <https://doi.org/10.1097/PSY.0000000000001234>.
- [71] Miller EH. Women and insomnia. *Clin Cornerstone* 2004;6(1):S6. [https://doi.org/10.1016/S1098-3597\(04\)80015-2](https://doi.org/10.1016/S1098-3597(04)80015-2).
- [72] Nodine PM, Matthews EE. Common sleep disorders: management strategies and pregnancy outcomes. *J Midwifery Wom Health* 2013;58(4):368–77. <https://doi.org/10.1111/jmwh.12004>.
- [73] Swanson LM, Kalmbach DA, Raglan GB, O'Brien LM. Perinatal insomnia and mental health: a review of recent literature. *Curr Psychiatry Rep* 2020;22(12). <https://doi.org/10.1007/s11920-020-01198-5>.
- [74] Nowakowski S, Meers J, Heimbach E. Sleep and women's health. *Sleep Med Rev* 2013;4:2013.
- [75] Okun ML. Sleep in pregnancy and the postpartum. The Encyclopedia of sleep. 2. United States: American Press; 2013. p. 674–9.
- [76] Zheng X, Zhu Z, Chen J, He J, Zhu Y, Zhang L, Qu F. Efficacy of cognitive behavioural therapy for insomnia or sleep disturbance in pregnant women: a systematic review ad meta-analysis. *J Sleep Res* 2023;32(2). <https://doi.org/10.1111/jsr.13808>.
- [77] Georgiou N, Fasoulakis Z, Theodora M, Pappas VA, Papamanolis V, Kalagasisidou S, Blontzos N, Kambas NJ, Kontomanolis EN. Association of pregestational maternal sleeping disorders and preeclampsia: a retrospective cohort study and review of the literature. *Cureus* 2019. <https://doi.org/10.7759/cureus.4338>.
- [78] Yang Q, Borges MC, Sanderson E, Magnus MC, Kilpi F, Collings PJ, Soares AL, West J, Magnus P, Wright J, Häberg SE, Tilling K, Lawlor DA, Stock SJ. Associations between insomnia and pregnancy and perinatal outcomes: evidence from mendelian randomization and multivariable regression analyses. *PLoS Med* 2022;19(9):e1004090. <https://doi.org/10.1371/journal.pmed.1004090>.
- [79] Lee KA, Gay CL. Sleep in late pregnancy predicts length of labor and type of delivery. *Am J Obstet Gynecol* 2004;191(6):2041–6. <https://doi.org/10.1016/j.ajog.2004.05.086>.
- [80] Lucena L, Tufik S, Hachul H. Sleep quality in the end of pregnancy and its relevance in labor. *Arch Gynecol Obstet* 2018;298(4):843–4. <https://doi.org/10.1007/s00404-018-4876-4>.
- [81] Okun ML, Schetter CD, Glynn LM. Poor sleep quality is associated with preterm birth. *Sleep* 2011;34(11):1493–8. <https://doi.org/10.5665/sleep.1384>.
- [82] Blair LM, Porter K, Leblebicioglu B, Christian LM. Poor sleep quality and associated inflammation predict preterm birth: heightened risk among African Americans. *Sleep* 2015;38(8):1259–67. <https://doi.org/10.5665/sleep.4904>.
- [83] Tomfohr-Madsen L, Cameron EE, Dunkel Schetter C, Campbell T, O'Beirne M, Letourneau N, Giesbrecht GF. Pregnancy anxiety and preterm birth: the moderating role of sleep. *Health Psychol* 2019;38(11):1025–35. <https://doi.org/10.1037/he0000792>.
- [84] Arcangeli T, Thilaganathan B, Hooper R, Khan KS, Bhide A. Neurodevelopmental delay in small babies at term: a systematic review. *Ultrasound Obstet Gynecol* 2012;40(3):267–75. <https://doi.org/10.1002/uog.11112>.
- [85] González-Mesa E, Cuena-Marín C, Suárez-Arana M, Tripiana-Serrano B, Ibrahim-Díez N, Gonzalez-Cazorla A, Blasco-Alonso M. Poor sleep quality is associated with perinatal depression. A systematic review of last decade scientific literature and meta-analysis. *J Perinat Med* 2019;47(7):689–703. <https://doi.org/10.1515/jpm-2019-0214>.
- [86] Yu Y, Li M, Pu L, Wang S, Wu J, Ruan L, Jiang S, Wang Z, Jiang W. Sleep was associated with depression and anxiety status during pregnancy: a prospective longitudinal study. *Arch Wom Ment Health* 2017;20(5):695–701. <https://doi.org/10.1007/s00737-017-0754-5>.
- [87] Okun ML, Mancuso RA, Hobel CJ, Schetter CD, Coussons-Read M. Poor sleep quality increases symptoms of depression and anxiety in postpartum women. *J Behav Med* 2018;41(5):703–10. <https://doi.org/10.1007/s10865-018-9950-7>.
- [88] Creti L, Libman E, Rizzo D, Fichten CS, Bailes S, Tran DL, et al. Sleep in the postpartum: characteristics of first-time, healthy mothers. *Sleep Disord* 2017;1:1–10. <https://doi.org/10.1155/2017/8520358>.
- [89] Tikotzky L. Postpartum maternal sleep, maternal depressive symptoms and self-perceived mother-infant emotional relationship. *Behav Sleep Med* 2016;14(1):5–22. <https://doi.org/10.1080/15402002.2014.940111>.
- [90] Krystal AD. Depression and insomnia in women. *Clin Cornerstone* 2004;6(1):S19. [https://doi.org/10.1016/S1098-3597\(04\)80022-X](https://doi.org/10.1016/S1098-3597(04)80022-X).
- [91] Beardselee WR, Versage EM, Gladstone TRG. Children of affectively ill parents: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatr* 1998;37(11):1134–41. <https://doi.org/10.1097/00004583-19981100-00012>.
- [92] Field T. Postpartum depression effects on early interactions, parenting, and safety practices: a review. *Infant Behav Dev* 2010;33(1):1–6. <https://doi.org/10.1016/j.infbeh.2009.10.005>.
- [93] Kindle AM. Insomnia during pregnancy and severe maternal morbidity in the United States: nationally representative data from. *Sleep* 2006;45(10):2006.
- [94] Palagini L, Cipollone G, Masci I, Novi M, Caruso D, Kalmbach DA, Drake CL. Stress-related sleep reactivity is associated with insomnia, psychopathology and suicidality in pregnant women: preliminary results. *Sleep Med* 2019;56:145–50. <https://doi.org/10.1016/j.sleep.2019.01.009>.
- [95] O'Leary K, Bylsma LM, Rottenberg J. Why might poor sleep quality lead to depression? A role for emotion regulation. *Cognit Emot* 2017;31(8):1698–706. <https://doi.org/10.1080/0269931.2016.1247035>.

- [96] Palagini L, Moretto U, Dell'Osso L, Carney C. Sleep-related cognitive processes, arousal, and emotion dysregulation in insomnia disorder: the role of insomnia-specific rumination. *Sleep Med* 2017;30:97–104. <https://doi.org/10.1016/j.sleep.2016.11.004>.
- [97] Harvey AG. A cognitive model of insomnia. *Behav Res Ther* 2002;40(8):869–93. [https://doi.org/10.1016/s0005-7967\(01\)00061-4](https://doi.org/10.1016/s0005-7967(01)00061-4).
- [98] Vafapoor H, Zakeri A, Hatamian P, Bagheri A. Correlation of sleep quality with emotional regulation and repetitive negative thoughts: a causal model in pregnant women. *J Kerman Univ Med Sci* 2018;22(3):e81747. <https://doi.org/10.5812/jkums.81747>.
- [99] Rehbein E, Kogler L, Kotikalapudi R, Sattler A, Krylova M, Kagan KO, Sundström-Poromaa I, Derntl B. Pregnancy and brain architecture: associations with hormones, cognition and affect. *J Neuroendocrinol* 2022;34(2). <https://doi.org/10.1111/jne.13066>.
- [100] Rutherford HJV, Wallace NS, Laurent HK, Mayes LC. Emotion regulation in parenthood. *Dev Rev* 2015;36:1–14. <https://doi.org/10.1016/j.dr.2014.12.008>.
- [101] Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol* 2005;106(5):1071–83. <https://doi.org/10.1097/01.AOG.0000183597.31630.db>.
- [102] Kahn M, Sheppes G, Sadeh A. Sleep and emotions: bidirectional links and underlying mechanisms. *Int J Psychophysiol* 2013;89(2):218–28. <https://doi.org/10.1016/j.ijpsycho.2013.05.010>.
- [103] Maghami M, Shariatipanahi SP, Habibi D, Heidari-Beni M, Badihian N, Hosseini M, Kelishadi R. Sleep disorders during pregnancy and postpartum depression: a systematic review and meta-analysis. *Int J Dev Neurosci* 2021;81(6):469–78. <https://doi.org/10.1002/jdn.10118>.
- [104] Okun ML. Sleep and postpartum depression. *Curr Opin Psychiatr* 2015;28(6):490–6. <https://doi.org/10.1097/YCO.0000000000000206>.
- [105] Gueron-Sela N, Shahar G, Volkovich E, Tikotzky L. Prenatal maternal sleep and trajectories of postpartum depression and anxiety symptoms. *J Sleep Res* 2021;30(4). <https://doi.org/10.1111/jsr.13258>.
- [106] Tomfohr-Madsen L, Rioux C, MacKinnon A, Silang K, Roos L, Lebel C, Giesbrecht GF. Sleep and mental health in pregnancy during COVID-19: a parallel process growth model. *Sleep Health* 2022;8(5):484–90. <https://doi.org/10.1016/j.slehd.2022.05.011>.
- [107] Cunningham JEA, Shapiro CM. Cognitive Behavioural Therapy for Insomnia (CBT-I) to treat depression: a systematic review. *J Psychosom Res* 2018;106:1–12. <https://doi.org/10.1016/j.jpsychores.2017.12.012>.
- [108] Baglioni C, Riemann D. Is chronic insomnia a precursor to major depression? Epidemiological and biological findings. *Curr Psychiatr Rep* 2012;14(5):511–8. <https://doi.org/10.1007/s11920-012-0308-5>.
- [109] Osnes RS, Eberhard-Gran M, Follestad T, Kallestad H, Morken G, Roaldset JO. Mid-pregnancy insomnia is associated with concurrent and postpartum maternal anxiety and obsessive-compulsive symptoms: a prospective cohort study. *J Affect Disord* 2020;266:319–26. <https://doi.org/10.1016/j.jad.2020.01.140>.
- [110] Coussement C, Heeren A. Sleep problems as a transdiagnostic hub bridging impaired attention control, generalized anxiety, and depression. *J Affect Disord* 2022;296:305–8. <https://doi.org/10.1016/j.jad.2021.09.092>.
- [111] Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34(5):601–8. <https://doi.org/10.1093/sleep/34.5.601>.
- [112] Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med* 2001;2(4):297–307. [https://doi.org/10.1016/S1389-9457\(00\)00065-4](https://doi.org/10.1016/S1389-9457(00)00065-4).
- [113] Manber R. Cognitive behavioral therapy for prenatal insomnia: a randomized controlled trial. *Obstet Gynecol* 2019;133(5):2019.
- [114] Swanson LM, Flynn H, Adams-Mundy JD, Armitage R, Arnedt JT. An open pilot of cognitive-behavioral therapy for insomnia in women with postpartum depression. *Behav Sleep Med* 2013;11(4):297–307. <https://doi.org/10.1080/15402002.2012.683902>.
- [115] Tomfohr-Madsen LM, Clayborne ZM, Rouleau CR, Campbell TS. Sleeping for two: an open-pilot study of cognitive behavioral therapy for insomnia in pregnancy. *Behav Sleep Med* 2017;15(5):377–93. <https://doi.org/10.1080/15402002.2016.1141769>.
- [116] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatr Res* 1989;28(2):193–213. [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4).
- [117] Qiu C, Gelaye B, Zhong Q-Y, Enquobahrie DA, Frederick IO, Williams MA. Construct validity and factor structure of the Pittsburgh Sleep Quality Index among pregnant women in a Pacific-Northwest cohort. *Sleep Breath* 2016;20(1):293–301. <https://doi.org/10.1007/s11325-016-1313-4>.
- [118] Skouteris H, Wertheim EH, Germano C, Paxton SJ, Milgrom J. Assessing sleep during pregnancy. A study across two time points examining the Pittsburgh sleep quality index and associations with depressive symptoms. *Womens Health Issues* 2009;19(1):45–51. <https://doi.org/10.1016/j.whi.2008.10.004>.
- [119] Zhong QY, Gelaye B, Sánchez SE, Williams MA. Psychometric properties of the Pittsburgh sleep quality index (PSQI) in a cohort of Peruvian pregnant women. *J Clin Sleep Med* 2015;11(8):869–77. <https://doi.org/10.5664/jcsm.4936>.
- [120] Okun ML, Hanusa BH, Hall M, Wisner KL. Sleep complaints in late pregnancy and the recurrence of postpartum depression. *Behav Sleep Med* 2009;7(2):106–17. <https://doi.org/10.1080/15402000902762394>.
- [121] Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, et al. Development of short forms from the PROMIST™ sleep disturbance and sleep-related impairment item banks. *Behav Sleep Med* 2012;10(1):6–24. <https://doi.org/10.1080/15402002.2012.636266>.
- [122] Mersky JP, Lee CTP, Gilbert RM, Goyal D. Prevalence and correlates of maternal and infant sleep problems in a low-income US sample. *Matern Child Health J* 2020;24(2):196–203. <https://doi.org/10.1007/s10995-019-02852-y>.
- [123] Giesbrecht GF, Bagshawe M, Sloten Mvan, MacKinnon AL, Dhillon A, Wouw Mvan de, Vaghéh-Mehraban E, Rojas L, Cattani D, Lebel C, Tomfohr-Madsen L. Protocol for the pregnancy during the COVID-19 pandemic (PdP) study: a longitudinal cohort study of mental health among pregnant Canadians during the COVID-19 pandemic and developmental outcomes in their children. *JMIR Res Protoc* 2021;10(4):e25407. <https://doi.org/10.2196/25407>.
- [124] First MB, Williams JB, Karg RS, Spitzer RL. User's guide for the SCID-5-CV structured clinical interview for DSM-5® disorders: clinical version. American Psychiatric Publishing, Inc; 2016.

- [125] Taylor DJ, Wilkerson AK, Pruiksma KE, Williams JM, Ruggero CJ, Hale W, Mintz J, Organek KM, Nicholson KL, Litz BT, Young-McCaughan S, Dondanville KA, Borah EV, Brundige A, Peterson AL. Reliability of the structured clinical interview for DSM-5 sleep disorders module. *J Clin Sleep Med* 2018;14(3):459–64. <https://doi.org/10.5664/jcsm.7000>.
- [126] MacKinnon AL, Madsen JW, Dhillon A, Keys E, Giesbrecht GF, Williamson T, et al. Sleeping for two: study protocol for a randomized controlled trial of cognitive behavioral therapy for insomnia in pregnant women. *BMC Trials* 2021;22:532. <https://doi.org/10.1186/s13063-021-05498-w>.
- [127] Edinger J, Kirby A, Lineberger M, Loiselle M, Wohlgemuth W, Means M. The Duke structured interview for sleep disorders. Durham, NC: Duke University Medical Center; 2004.
- [128] Sharkey KM. Time to treat problematic sleep disturbance in perinatal women. *Behav Sleep Med* 2013;11(4):308–10. <https://doi.org/10.1080/15402002.2013.823789>.
- [129] Khazaie H, Ghadami MR, Knight DC, Emamian F, Tahmasian M. Insomnia treatment in the third trimester of pregnancy reduces postpartum depression symptoms: a randomized clinical trial. *Psychiatr Res* 2013;210(3):901–5. <https://doi.org/10.1016/j.psychres.2013.08.017>.
- [130] Abbott SM, Attarian H, Zee PC. Sleep disorders in perinatal women. *Best Pract Res Clin Obstet Gynaecol* 2014;28(1):159–68. <https://doi.org/10.1016/j.bpobgyn.2013.09.003>.
- [131] Dimidjian S, Goodman SH. Preferences and attitudes toward approaches to depression relapse/recurrence prevention among pregnant women. *Behav Res Ther* 2014;54(1):7–11. <https://doi.org/10.1016/j.brat.2013.11.008>.
- [132] Arch JJ. Cognitive behavioral therapy and pharmacotherapy for anxiety: treatment preferences and credibility among pregnant and non-pregnant women. *Behav Res Ther* 2014;52(1):53–60. <https://doi.org/10.1016/j.brat.2013.11.003>.
- [133] Denton LK, Creeley CE, Stavola B, Hall K, Foltz BD. An analysis of online pregnancy message boards: mother-to-mother advice on medication use. *Women Birth* 2020;33(1):e48. <https://doi.org/10.1016/j.wombi.2018.12.003>.
- [134] Sedov ID, Goodman SH, Tomfohr-Madsen LM. Insomnia treatment preferences during pregnancy. *J Obstet Gynecol Neonatal Nurs* 2017;46(3):e95. <https://doi.org/10.1016/j.jogn.2017.01.005>.
- [135] Sedov I, Madsen JW, Goodman SH, Tomfohr-Madsen LM. Couples' treatment preferences for insomnia experienced during pregnancy. *Fam Syst Health* 2019;37(1):46–55. <https://doi.org/10.1037/fsh0000391>.
- [136] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd. Darien, IL: American Academy of Sleep Medicine; 2014.
- [137] O'Brien EM, Boland EM. CBT-I is an efficacious, first-line treatment for insomnia: where we need to go from here. A commentary on the application of Tolin's criteria to cognitive behavioral therapy for insomnia. *Clin Psychol Sci Pract* 2020;27(4). <https://doi.org/10.1111/cpsp.12370>.
- [138] Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Fam Pract* 2012;13. <https://doi.org/10.1186/1471-2296-13-40>.
- [139] Okajima I, Komada Y, Inoue Y. A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. *Sleep Biol Rhythms* 2011;9(1):24–34. <https://doi.org/10.1111/j.1479-8425.2010.00481.x>.
- [140] Blom K, Hanna TT, Wiklund T, Danlycke E, Forssén M, Söderström A, Johansson R, Hesser H, Jernelöv S, Lindefors N, Andersson G, Kaldo V. Internet-vs. group-delivered cognitive behavior therapy for insomnia: a randomized controlled non-inferiority trial. *Behav Res Ther* 2015;70:47–55. <https://doi.org/10.1016/j.brat.2015.05.002>.
- [141] Manber R, Bernert RA, Suh S, Nowakowski S, Siebern AT, Ong JC. CBT for insomnia in patients with high and low depressive symptom severity: adherence and clinical outcomes. *Focus* 2014;12(1):90–8. <https://doi.org/10.1176/appi.focus.12.1.90>.
- [142] Manber R, Edinger JD, Gress JL, San Pedro-Salcedo MG, Kuo TF, Kalista T. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep* 2008;31(4):489–95. <https://doi.org/10.1093/sleep/31.4.489>.
- [143] Tomfohr-Madsen L, Madsen JW, Bonneville D, Virani S, Plourde V, Barlow KM, Owen Yeates K, Brooks BL. A pilot randomized controlled trial of cognitive-behavioral therapy for insomnia in adolescents with persistent postconcussion symptoms. *J Head Trauma Rehabil* 2020;35(2):E103. <https://doi.org/10.1097/htr.0000000000000504>.
- [144] Mitchell LJ, Bisdounis L, Ballesio A, Omlin X, Kyle SD. The impact of cognitive behavioural therapy for insomnia on objective sleep parameters: a meta-analysis and systematic review. *Sleep Med Rev* 2019;47:90–102. <https://doi.org/10.1016/j.smrv.2019.06.002>.
- [145] Manber R, Bei B, Suh S, Simpson N, Rangel E, Sit A, Lyell DJ. Randomized controlled trial of cognitive behavioral therapy for perinatal insomnia: postpartum outcomes. *J Clin Sleep Med* 2023;19(8):1411–9. <https://doi.org/10.5664/jcsm.10572>.
- [146] MacKinnon AL, Silang K, Watts D, Kaur J, Freeman M, Dewsnap K, et al. Sleeping for two: a randomized controlled trial of cognitive behavioral therapy for insomnia in pregnancy. *J Clin Sleep Med* 2025;21(2):365–76. <https://doi.org/10.5664/jcsm.11396>.
- [147] Silang K, MacKinnon A, Madsen J, Giesbrecht GF, Campbell T, Keys E, et al. Sleeping for two: a randomized controlled trial of cognitive behavioural therapy for insomnia (CBT-I) delivered in pregnancy and secondary impacts on symptoms of postpartum depression. *J Affect Disord* 2024;362:670–8. <https://doi.org/10.1016/j.jad.2024.07.117>.
- [148] Kalmbach DA, Cheng P, O'Brien LM, Swanson LM, Sangha R, Sen S, Guille C, Cuamatzi-Castelan A, Henry AL, Roth T, Drake CL. A randomized controlled trial of digital cognitive behavioral therapy for insomnia in pregnant women. *Sleep Med* 2020;72:82–92. <https://doi.org/10.1016/j.sleep.2020.03.016>.
- [149] Felder JN, Epel ES, Neuhaus J, Krystal AD, Prather AA. Randomized controlled trial of digital cognitive behavior therapy for prenatal insomnia symptoms: effects on postpartum insomnia and mental health. *Sleep* 2022;45(2). <https://doi.org/10.1093/sleep/zsab280>.
- [150] Mancinelli E, Bassi G, Gabrielli S, Saleuni S. The efficacy of digital cognitive-behavioral interventions in supporting the psychological adjustment and sleep quality of pregnant women with sub-clinical symptoms: a systematic review and meta-analysis. *Int J Environ Res Publ Health* 2022;19(15):9549. <https://doi.org/10.3390/ijerph19159549>.

- [151] Kalmbach DA, Cheng P, Reffi AN, Ong JC, Swanson LM, Fresco DM, Walch O, Seymour GM, Fellman-Couture C, Bayoneto AD, Roth T, Drake CL. Perinatal Understanding of Mindful Awareness for Sleep (PUMAS): a single-arm proof-of-concept clinical trial of a mindfulness-based intervention for DSM-5 insomnia disorder during pregnancy. *Sleep Med* 2023;108:79–89. <https://doi.org/10.1016/j.sleep.2023.05.026>.
- [152] Kalmbach DA, Cheng P, Reffi AN, Ong JC, Swanson LM, Espie CA, Seymour GM, Hirata M, Walch O, Pitts DS, Roth T, Drake CL. Reducing cognitive arousal and sleep effort alleviates insomnia and depression in pregnant women with DSM-5 insomnia disorder treated with a mindfulness sleep program. *SLEEP Advan* 2023;4(1). <https://doi.org/10.1093/sleepadvances/zpad031>.
- [153] Kalmbach DA, Reffi AN, Ong JC, Cheng P, Walch O, Pitts DS, Seymour GM, Hirata M, Roth A, Roth T, Drake CL. Preliminary evidence of psychological improvements and increased maternal-fetal attachment associated with a mindfulness sleep programme: secondary analysis of uncontrolled data in 11 pregnant women with insomnia disorder. *J Sleep Res* 2023. <https://doi.org/10.1111/jsr.14040>.
- [154] MacKinnon AL, Sedov I, Silang K, Kumari J, Giesbrecht G, Campbell T, et al. Mindfulness-based cognitive therapy in pregnancy and sleep quality: secondary analysis from a randomized controlled trial. University of Calgary; 2022. In preparation, <https://psyarxiv.com/er7p6/>.
- [155] Dennis CL, Chung-Lee L. Postpartum depression help-seeking barriers and maternal treatment preferences: a qualitative systematic review. *Birth* 2006;33(4):323–31. <https://doi.org/10.1111/j.1523-536X.2006.00130.x>.
- [156] Kim PY, Thomas JL, Wilk JE, Castro CA, Hoge CW. Stigma, barriers to care, and use of mental health services among active duty and national guard soldiers after combat. *Psychiatr Serv* 2010;61(6):582–8. <https://doi.org/10.1176/ps.2010.61.6.582>.
- [157] Flynn HA, Henshaw E, O'Mahen H, Forman J. Patient perspectives on improving the depression referral processes in obstetrics settings: a qualitative study. *Gen Hosp Psychiatr* 2010;32(1):9–16. <https://doi.org/10.1016/j.genhosppsych.2009.07.005>.
- [158] Smith MS, Lawrence V, Sadler E, Easter A. Barriers to accessing mental health services for women with perinatal mental illness: systematic review and meta-synthesis of qualitative studies in the UK. *BMJ Open* 2019;9(1). <https://doi.org/10.1136/bmjopen-2018-024803>.
- [159] Lowik A, et al. Tool# 4: Asking about & measuring participants' genders & sexes. Gender and Sex in methods & measurement-research equity toolkit. ResearchGate; 2002.

Chapter 11

Sleep in families: Dynamics, challenges, and possible solutions

Bharat Bhushan^a and Suzanne Gorovoy^b

^aDepartment of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, United States; ^bDepartment of Behavioral Sleep Medicine, University of Arizona College of Medicine, Tucson, AZ, United States

Introduction

Family dynamics and processes

Overview of family processes

Family dynamics and processes are critical components of psychological development, influencing individual behavior, emotional well-being, and social functioning. Psychologically, family dynamics refer to the patterns of interactions among family members, including communication, power structures, and roles that individuals adopt within the family unit. These dynamics are shaped by various factors, such as cultural norms, socio-economic status, and individual personalities [1,2]. Family processes involve the mechanisms through which families manage tasks like caregiving, conflict resolution, and emotional support. Effective family processes are often characterized by open communication, strong emotional bonds, and the ability to adapt to changes and stressors [3]. Dysfunctional family dynamics, such as poor communication or rigid roles, can lead to psychological issues like anxiety, depression, and behavioral problems in family members [4]. Understanding these dynamics is essential for professionals working in therapy and counseling, as interventions often focus on improving family interactions to foster healthier relationships and individual well-being.

Building on the understanding of family dynamics, it is important to consider how these interactions influence developmental outcomes across the lifespan. Family systems theory suggests that the functioning of the family has a profound impact on the psychological development of its members, particularly during critical life stages such as childhood and adolescence [5,6]. For example, positive family dynamics, characterized by warmth, support, and consistent discipline, are associated with better academic

achievement, emotional regulation, and social competence in children [7,8]. Conversely, families marked by high conflict, lack of cohesion, or inconsistent parenting practices can contribute to the development of maladaptive behaviors, such as aggression, substance abuse, and mental health disorders [9–11]. Moreover, the intergenerational transmission of these dynamics suggests that patterns of behavior and interaction are often passed down, influencing not only the immediate family members but also future generations [11]. Thus, interventions aimed at improving family dynamics can have long-term benefits, fostering resilience and promoting healthier development across generations.

Health at the family level

For health promotion to be effective, it is essential to have structural, social, and cultural conditions that support health [12]. Families play a crucial role in shaping these conditions, acting as significant influencers on an individual's health beyond what can be achieved through individual efforts alone [13,14]. By altering values, norms, and behaviors within the family, more enduring and widespread behavioral changes can be achieved [15–18]. For example, families serve as a key environment for learning health practices, through both modeling healthy behaviors and providing support for well-being and illness management, which can have lasting effects throughout life [19]. The shared environment within a household, such as access to nutritious food or exercise resources, also significantly impacts the health of family members [20,21]. However, when the shared environment is not health-promoting, coupled with shared genetics, it can increase the risk of chronic diseases among family members [22]. While genetic predispositions are traditionally seen as key

risk factors, the similarity in chronic disease patterns among spouses highlights the importance of shared environmental factors [21,23,24]. Therefore, targeting both the family unit and individuals for health promotion may be more effective than focusing on individuals alone [13].

Research on family health promotion spans multiple disciplines, including medicine, sociology, psychology, family therapy, and nursing, resulting in a diverse body of literature with varying terminology, theoretical approaches, and perspectives on the roles of family members and the health behaviors they influence. From the standpoint of family systems theory, which examines how complex family interactions shape individual behavior [25], there have been numerous theoretical adaptations to understand the influence of family on health behaviors. These adaptations are often tailored to specific health priorities and consider the different roles family members play in influencing behaviors [26,27]. Traditionally, children have been viewed as passive recipients of health influences from their parents, but recent research highlights the potential for children to act as agents of change within the family [26]. This shift suggests that the impact of family on health behaviors may be closely tied to specific roles within the family structure. The types of health behaviors influenced by family members are diverse, including areas like parental influence on children's diet and physical activity—topics that have been the focus of systematic reviews [28,29]. Other research has explored family influences on behaviors such as alcohol consumption [30] and oral hygiene [31], through mechanisms like parent-child communication, limit setting, and role modeling. Despite the breadth of research, there is a notable lack of synthesis and comparison across theories, mechanisms, and roles, which could enhance the understanding of family health promotion and support the development of more effective interventions across various health behaviors and cultural contexts.

Relevance of sleep health for family processes

Sleep health is deeply intertwined with family processes and dynamics, influencing both the emotional and physical well-being of family members. Poor sleep patterns can lead to heightened irritability, reduced patience, and impaired cognitive functioning, all of which can strain familial relationships and communication [32]. For instance, parents who suffer from inadequate sleep may have less energy to engage in positive parenting practices, such as providing emotional support or maintaining consistent discipline, which can lead to increased conflicts and behavioral issues in children [33]. Furthermore, sleep disturbances in one family member, such as a child with insomnia or a partner with sleep apnea, often affect the sleep quality of others in

the household, creating a ripple effect of stress and fatigue that can disrupt family cohesion [34]. Conversely, families that prioritize healthy sleep routines can foster a more harmonious and supportive environment, where members are better equipped to handle daily challenges and maintain strong, positive relationships [35]. Therefore, promoting good sleep health within the family is essential not only for individual health but also for the overall functioning and well-being of the family unit.

Sleep and family health

Benefits of sleep health in family processes

The benefits of maintaining good sleep health extend far beyond individual well-being, significantly enhancing family processes and relationships. When family members consistently get adequate and quality sleep, they are more likely to engage in positive interactions, demonstrating greater patience, empathy, and effective communication [36–38]. For example, well-rested parents are better equipped to model constructive conflict resolution and provide the emotional support their children need, fostering a nurturing environment that promotes healthy psychological development [39]. Additionally, children who receive sufficient sleep are more likely to exhibit better emotional regulation, which reduces the likelihood of disruptive behaviors and contributes to a calmer and more cooperative household dynamic [40]. As sleep health improves within a family, the overall atmosphere becomes more supportive and cohesive, leading to stronger familial bonds and increased resilience in facing life's challenges [41]. Thus, prioritizing sleep health is a key factor in promoting harmony and well-being within family systems.

Consequences of poor sleep health for family processes

Poor sleep health can have far-reaching negative consequences on family processes, leading to increased stress, conflict, and emotional dysregulation among family members. Sleep deprivation often results in heightened irritability and decreased tolerance, which can exacerbate conflicts between family members and reduce the ability to resolve disagreements constructively [42]. Additionally, chronic sleep loss in parents can impair their ability to provide consistent and responsive parenting, potentially leading to an increase in behavioral problems in children [43]. This can create a vicious cycle where stressed parents and misbehaving children further disrupt each other's sleep, perpetuating the problem. Moreover, when sleep-deprived, individuals may struggle with impaired cognitive functioning, making it difficult to manage daily household responsibilities effectively and increasing

overall family stress [44]. The cumulative effect of poor sleep health can weaken family bonds, decrease overall family satisfaction, and contribute to long-term relational issues. Addressing sleep health is therefore critical to maintaining a healthy, functioning family dynamic.

Sleep and emotional health in family interactions

The connection between sleep and emotional well-being is crucial and deeply influences family relationships. Sufficient sleep equips individuals with the ability to regulate their emotions, handle stress, and engage in positive social interactions [45,46]. On the contrary, lack of sleep often results in emotional instability, such as irritability and mood swings, which can place strain on familial relationships [34]. For instance, sleep-deprived parents may experience reduced patience, leading to negative interactions with their children, which can escalate conflicts and create a more stressful household environment [47,48]. Similarly, children who do not get adequate sleep may struggle with emotional regulation, affecting their ability to build and maintain healthy relationships both within the family and with their peers [40]. This reciprocal relationship between sleep deprivation and emotional challenges can create a cycle that perpetuates further sleep disturbances, ultimately impacting the entire family. Thus, prioritizing sleep health is essential for promoting emotional resilience and maintaining harmonious family dynamics.

Sleep patterns and needs across different family members

Infants and toddlers

Infant sleep needs and patterns are uniquely different from any other stage in life due to the rapid growth and developmental changes occurring during this period. Unlike older children and adults, infants require significantly more sleep—typically around 14–17 h per day in the first few months of life, though this sleep is spread across multiple short naps rather than long, continuous periods [49]. This fragmented sleep pattern is a result of their immature circadian rhythms, which take time to develop and align with the day-night cycle [50]. Moreover, the frequent sleep interruptions are driven by the need for regular feeding, as infants' small stomachs require nourishment every few hours [51]. As infants grow, their sleep gradually becomes more consolidated, but even then, the amount and structure of sleep remain markedly different from those in older children and adults. These early sleep patterns are critical, as sufficient sleep during infancy supports crucial processes like brain development, synaptic growth, and the

establishment of neural pathways that will influence cognitive and emotional functioning throughout life [52,53]. This makes the sleep patterns of infants distinctly different and vital compared to any other period in the human lifespan.

As toddlers transition from infancy, their sleep patterns undergo significant changes, characterized by a gradual consolidation of sleep into longer nighttime periods with fewer and shorter daytime naps. Typically, toddlers need about 11–14 h of sleep each day, which is crucial for their continued physical growth, cognitive development, and emotional well-being [49,54]. This period often sees the establishment of a more structured sleep schedule, with most toddlers eventually shifting from two naps a day to a single nap, generally between 12 and 18 months (Weissbluth) [55]. The transition to fewer naps, while a normal part of development, can sometimes be challenging as it requires adjustments in both the child's and the parents' routines.

Moreover, toddlers may begin to experience sleep disturbances related to increased mobility, separation anxiety, or the onset of vivid dreams, which can manifest as night awakenings or difficulties in falling asleep [56–58]. These disruptions can impact the overall sleep quality, making it essential for parents to reinforce consistent bedtime routines and create a sleep-conducive environment to support their child's sleep needs [59]. Additionally, the sleep-wake cycle during this stage is still influenced by the maturation of the circadian rhythm, which continues to develop and stabilize during early childhood, necessitating a predictable daily schedule that aligns with natural light and dark cues [50]. Addressing these evolving sleep needs with appropriate strategies is crucial for fostering healthy sleep habits that will benefit toddlers as they grow.

School-aged children

As children enter the school-age years, typically between 6 and 12 years old, their sleep patterns begin to resemble those of adults, yet they still require more sleep—generally between 9 and 12 h per night—to support their ongoing physical, cognitive, and emotional development [49,51,60]. During this stage, sleep becomes increasingly consolidated into a single long nighttime period, with most children outgrowing the need for daytime naps. However, this developmental phase also introduces new challenges related to sleep, including the influence of increased academic pressures, extracurricular activities, and social engagements, which can encroach on bedtime and lead to insufficient sleep [61,62].

Moreover, school-age children are particularly susceptible to the effects of electronic media, as the use of screens before bedtime has been shown to delay sleep onset and

reduce overall sleep duration by interfering with the production of melatonin, the hormone that regulates sleep [63,64]. This can exacerbate issues such as bedtime resistance and difficulty waking in the morning, potentially leading to daytime sleepiness and impaired academic performance [62]. Additionally, the natural progression toward later sleep and wake times in this age group often clashes with early school start times, further complicating the achievement of adequate sleep [65].

To mitigate these challenges, it is essential to establish consistent sleep routines that include a regular bedtime, limited screen use before sleep, and an environment conducive to rest, such as a dark, quiet, and cool bedroom [51,66]. Encouraging these habits during the school years lays the foundation for healthy sleep patterns that can continue into adolescence and adulthood.

Adolescents

During adolescence, sleep patterns undergo significant changes due to both biological shifts and external factors, resulting in unique sleep needs that are often unmet. Adolescents require approximately 8–10 h of sleep per night to support their rapid physical growth, emotional regulation, and cognitive development [49,65]. However, the onset of puberty triggers a biological shift known as a “sleep phase delay,” where the circadian rhythm naturally shifts to a later sleep and wake time [67]. This delay causes adolescents to feel sleepy later in the evening and can make it difficult for them to fall asleep before 11:00 p.m., even if they have early morning commitments like school [68].

Compounding this biological change are social and environmental factors, such as increased academic pressures, extracurricular activities, and the pervasive use of electronic devices, all of which can further delay sleep onset and reduce total sleep time [63,64]. The result is often chronic sleep deprivation, which is linked to a range of negative outcomes, including impaired academic performance, mood disturbances, and increased risk of mental health issues such as depression and anxiety [62,69]. Additionally, insufficient sleep during adolescence has been associated with risky behaviors, including substance use and poor decision-making, highlighting the critical need for adequate sleep during this developmental stage [65,70].

To address these challenges, it is essential to promote healthy sleep habits among adolescents, including establishing consistent sleep routines, limiting exposure to screens before bedtime, and advocating for later school start times to align with adolescents’ natural sleep patterns [62,68]. Such interventions are crucial for helping adolescents achieve the sleep they need to thrive during this pivotal period of their lives.

Parents

Parents, particularly those with young children, face unique challenges when it comes to sleep, often experiencing significant disruptions that can impact both their physical and emotional well-being. The demands of parenting, including nighttime awakenings for feeding, soothing, or responding to the needs of their children, frequently lead to fragmented sleep patterns and reduced overall sleep duration [47,51]. Research shows that parents of infants particularly experience a notable decline in sleep quality, with new mothers averaging about an hour less sleep per night compared to their preparenthood sleep patterns [71]. This sleep deprivation can accumulate over time, resulting in chronic sleep debt, which may lead to increased stress, irritability, and difficulties in cognitive functioning [72].

Moreover, the sleep needs of parents are often overshadowed by the focus on their children’s well-being, leading to a neglect of their own sleep hygiene and routines. The lack of adequate sleep can also strain marital relationships, as sleep-deprived parents may experience reduced patience and empathy, which can contribute to increased conflicts and reduced relationship satisfaction [38,73]. Additionally, the chronic nature of sleep disruption during the early years of parenting can exacerbate the risk of developing mood disorders, such as postpartum depression, particularly in mothers [74].

To address these challenges, it is crucial for parents to prioritize their own sleep health by adopting strategies such as sharing nighttime responsibilities, establishing consistent sleep schedules, and seeking social support when needed. By recognizing the importance of their own sleep, parents can enhance their capacity to manage the demands of parenting while maintaining their well-being [47,51].

Elderly family members

As individuals age, their sleep patterns often shift in notable ways, leading to challenges not only for their health but also for their relationships within the family. Elderly adults typically experience lighter, more disrupted sleep, marked by frequent night awakenings and a tendency to wake up earlier in the morning, a condition commonly known as “advanced sleep phase syndrome” [67]. This alteration is largely a result of the aging process, which affects the body’s internal clock—specifically the circadian rhythms—by diminishing the production of melatonin, the hormone essential for regulating sleep [75]. Additionally, older adults are more susceptible to sleep disturbances caused by chronic health issues such as arthritis, persistent pain, or sleep apnea, all of which become more common with age [76].

The cumulative impact of these sleep disruptions can significantly reduce both the amount and quality of sleep, leading to daytime fatigue, cognitive difficulties, and mood fluctuations [77]. These sleep-related issues can negatively affect not only the well-being of the elderly but also their participation in family life and social interactions, potentially fostering feelings of loneliness or increased reliance on family members for daily tasks [78]. Furthermore, the sleep challenges faced by older adults can add to the burden on family caregivers, who may need to provide additional support during the night or deal with the consequences of their loved one's daytime sleepiness [79].

To help older family members achieve better sleep, it is essential to promote consistent sleep routines, ensure exposure to natural light during the day, and create a sleep-friendly environment. Moreover, addressing any underlying medical conditions and minimizing potential sleep disturbances can enhance sleep quality, which in turn benefits overall health and family dynamics [75,76].

Factors influencing family sleep dynamics

Environmental factors

Environmental factors play a significant role in shaping the sleep dynamics within a family, influencing both the quality and quantity of sleep that each member experiences. Variables such as noise levels, lighting, and room temperature can significantly impact sleep patterns. For instance, excessive noise from external sources like traffic or internal household activities can lead to fragmented sleep, particularly in children, who are more sensitive to environmental disturbances [80]. Similarly, inadequate lighting, especially in the evening, can interfere with the natural circadian rhythms by suppressing melatonin production, making it difficult for family members to fall asleep [81]. Room temperature also plays a crucial role; temperatures that are too high or too low can disrupt sleep continuity, affecting overall sleep satisfaction across all age groups within the family [82,83]. Understanding and optimizing these environmental factors is essential for promoting healthier sleep habits within the household.

Behavioral factors

Behavioral factors are pivotal in influencing family sleep patterns, with the routines and habits practiced by family members playing a significant role in determining sleep quality and regularity. For example, when bedtime routines are inconsistent, it often results in irregular sleep schedules, particularly affecting young children who benefit from regularity and structure [84]. Moreover, the prevalent habit of using electronic devices before bed, common in

many families, can delay the onset of sleep. This delay is attributed to the blue light emitted from screens, which disrupts melatonin production, a key hormone in managing sleep cycles [64]. The sleep behaviors of parents also serve as an important example for their children. If parents engage in late-night activities or maintain poor sleep habits, these patterns are likely to be emulated by their children, potentially leading to widespread sleep difficulties within the family [41,85]. Thus, promoting consistent sleep routines and reducing screen time before bed are crucial steps for enhancing sleep quality for all family members.

Psychological and emotional factors

Psychological and emotional factors significantly impact sleep dynamics within families, as stress, anxiety, and emotional well-being can directly influence both the ability to fall asleep and the overall quality of sleep. High levels of stress, whether due to work, financial concerns, or interpersonal conflicts, can lead to heightened arousal and difficulty in winding down at night, resulting in delayed sleep onset and fragmented sleep patterns [86]. Anxiety, particularly in children, can manifest as bedtime resistance or night wakings, disrupting not only the child's sleep but also that of the entire family [43,57]. Moreover, the emotional climate of the household plays a critical role; families experiencing high levels of tension or conflict may struggle with sleep disturbances, as negative emotions can create an environment of unease that is not conducive to restful sleep [32]. Addressing these psychological and emotional factors through stress management techniques and fostering a supportive family environment can be essential in improving sleep outcomes for all family members.

Socioeconomic and cultural influences

Socioeconomic and cultural factors intricately weave through the fabric of family sleep dynamics, exerting profound and varied influences that can either nurture or disrupt the sleep health of its members. Families from lower socioeconomic backgrounds often face unique challenges, such as crowded living conditions, inconsistent work schedules, and limited access to healthcare, which can collectively undermine the stability of sleep routines and overall sleep quality [64]. The unpredictability of shift work, common in many lower-income households, not only disturbs the sleep of the working adults but can also disrupt the sleep patterns of children, who may struggle with irregular bedtime routines and an unpredictable home environment [87]. Cultural norms and practices further complicate this landscape, as beliefs about sleep, bedtime rituals, and co-sleeping arrangements vary widely across

cultures, shaping how families prioritize and manage sleep [50]. In some cultures, for instance, communal sleeping is a norm, fostering a sense of closeness and security but potentially leading to disturbances if one family member has sleep difficulties [88]. These socioeconomic and cultural intricacies underscore the need for a nuanced understanding of how diverse factors interplay to influence sleep within the family context, highlighting that sleep health is not merely a matter of individual habits but is deeply embedded in the broader socio-cultural and economic milieu.

Common sleep disorders that impact families

Insomnia disorder: Implications for families

Insomnia disorder, characterized by persistent difficulty in falling or staying asleep despite adequate opportunities, casts a wide-reaching shadow over family life, disrupting not only the sleep of the individual affected but also reverberating through the entire household. The implications for families are profound, as insomnia can lead to heightened irritability, decreased patience, and impaired cognitive function, which strain interpersonal relationships and disrupt daily routines [89]. For parents, insomnia often exacerbates the challenges of caregiving, as the fatigue associated with chronic sleep deprivation can reduce their capacity to provide consistent emotional support and effective discipline, potentially leading to a cycle of stress and further sleep disturbances [57,90]. Children, too, are not immune; when a parent suffers from insomnia, the resulting household tension and altered family dynamics can contribute to anxiety and sleep problems in the child, creating a feedback loop that perpetuates sleep difficulties across generations [91]. Addressing insomnia within a family context thus requires a holistic approach, one that considers the disorder's ripple effects on the family unit and emphasizes the importance of restoring both individual and familial sleep health.

Sleep apnea: Implications for families

Obstructive sleep apnea (OSA) is a persistent condition characterized by repeated blockages of the upper airway during sleep, which results in intermittent oxygen deprivation, fragmented sleep, and notable daytime impairments. The effects of OSA extend well beyond the individual, significantly affecting the entire family. Individuals with OSA often experience frequent awakenings and poor sleep quality, leading to daytime fatigue, irritability, and cognitive challenges that can strain relationships and disrupt daily family life [92]. The loud snoring and gasping sounds typical of OSA can disturb the sleep of bed

partners and other family members, contributing to widespread sleep deprivation and creating a tense, exhausted atmosphere within the home [93]. Furthermore, children in households where a parent has untreated OSA may face increased anxiety and behavioral problems, driven by the stress and disrupted routines associated with the condition [94]. These wide-ranging implications underscore the need for early diagnosis and effective management of OSA not only to enhance the affected individual's health but also to restore balance and harmony within the family.

Circadian rhythm sleep–wake disorders: Implications for families

Circadian rhythm sleep–wake disorders (CRSWDs) create distinct challenges that significantly affect family dynamics, often leading to a substantial impact on daily life and relationships within the home. These disorders arise when there is a misalignment between an individual's internal circadian rhythm and the external environment, resulting in irregular sleep patterns that can disrupt not only the affected person's sleep but also the routines and overall well-being of the entire family [95]. For example, a family member with delayed sleep–wake phase disorder may find it difficult to fall asleep until the early morning hours, leading to late wake times that conflict with the schedules of other family members, potentially causing tension and logistical complications, especially regarding shared morning activities [96]. The irregularity and unpredictability of these sleep–wake cycles can strain relationships, as partners or parents might feel frustration or concern over ongoing sleep disturbances, which can result in emotional distance or conflicts within the family [97]. Furthermore, the social and emotional isolation experienced by individuals with CRSWDs, due to their unconventional schedules, can intensify family stress, underscoring the need for a supportive and understanding family environment in managing these disorders [98]. Effectively addressing CRSWDs requires a comprehensive strategy that not only prioritizes the individual's sleep health but also considers the wider family dynamics to restore balance and harmony within the household.

Restless legs syndrome: Implications for families

Restless legs syndrome (RLS), defined by an intense urge to move the legs often coupled with uncomfortable sensations, affects not only the person experiencing it but also sends shockwaves through the family, disrupting sleep quality and daily routines. The nighttime manifestation of RLS symptoms frequently causes repeated awakenings and fragmented sleep, leading to chronic sleep deprivation that can deteriorate the physical and emotional health of the

individual [99]. This disruption often extends to bed partners and other family members, who may also suffer from disturbed sleep due to the constant leg movements or restlessness, resulting in a household atmosphere filled with fatigue and irritability [100]. The ongoing exhaustion and frustration stemming from RLS can escalate stress within the family, intensifying interpersonal tensions and potentially causing conflicts or emotional withdrawal [101]. Additionally, the unpredictable nature of RLS symptoms can make it difficult for families to maintain regular routines or participate in evening activities together, adding further strain to family dynamics. Managing RLS effectively requires a comprehensive strategy that not only addresses the symptoms but also considers the wider impact on family life, emphasizing the importance of communication, support, and adaptability within the household to lessen the disorder's effects.

Parasomnias: Implications for families

Parasomnias, which include disruptive sleep behaviors such as sleepwalking, night terrors, and confusional arousals, can significantly affect family life, often creating an atmosphere filled with tension and worry. These episodes generally occur during non-REM sleep and can be distressing for both the person experiencing them and for family members, who may be startled awake by the sudden and intense nature of these behaviors [102]. The unpredictable and sometimes severe manifestations of parasomnias can disrupt the sleep of others in the household, leading to widespread sleep deprivation, fatigue, and increased anxiety, especially among parents concerned about the safety of a child prone to such episodes [103]. The emotional impact also extends to siblings, who may feel frightened or unsettled after witnessing these events, potentially straining relationships and creating a pervasive sense of unease within the home [104]. Additionally, the constant need for vigilance and the possibility of having to intervene during these episodes can place a significant burden on caregivers, further complicating family dynamics. Addressing parasomnias within a family setting requires a comprehensive approach, incorporating safety precautions, psychological support, and, when needed, medical treatment to protect the well-being of both the affected individual and the family.

Hypersomnia disorders: Implications for families

Hypersomnia disorders, characterized by excessive daytime sleepiness and prolonged nighttime sleep, pose unique challenges not only for those affected but also for their families, often disrupting the rhythm of daily life and straining interpersonal relationships. Individuals with

hypersomnia, such as those suffering from idiopathic hypersomnia or narcolepsy, may struggle to stay awake during critical moments, leading to difficulties in maintaining employment, academic performance, and social engagements [105]. This persistent drowsiness can create a ripple effect within the household, as family members may have to compensate for the affected individual's limitations, potentially leading to feelings of frustration, resentment, or burnout [106]. The unpredictability of sudden sleep attacks, especially in narcolepsy, can induce anxiety among family members, who may feel constantly on edge, worried about the safety and well-being of their loved one [107]. Additionally, the social isolation often experienced by individuals with hypersomnia, due to their overwhelming need for sleep, can further complicate family dynamics, as it may limit participation in family activities and reduce opportunities for bonding [108]. Addressing hypersomnia disorders within a family context requires not only medical management but also robust emotional support and open communication to navigate the complex challenges these conditions present.

Interventions and strategies to improve sleep in families

Behavioral interventions in families

Sleep routines within families are fundamental to ensuring both individual well-being and harmonious family dynamics, yet they are often disrupted by a variety of factors that evolve across different stages of life. Establishing consistent sleep routines is especially critical for young children, as regular bedtimes and calming presleep rituals contribute to better sleep quality and behavior regulation, both of which influence daytime functioning and family interactions [51]. However, as children grow into adolescence, biological changes such as delayed melatonin production often push natural sleep times later, conflicting with early school start times and increasing the likelihood of fragmented sleep patterns [65]. In households where multiple family members experience sleep issues, such as parents with work-related stress or siblings with sleep disorders, maintaining a consistent routine can become exceedingly difficult, leading to a cumulative effect of sleep deprivation that strains family relationships [32]. Despite these challenges, fostering a structured sleep environment through shared routines can create a sense of stability, improving not only individual health but also promoting stronger familial bonds. Structured sleep schedules reduce conflicts surrounding bedtime and enhance emotional regulation, which is vital for maintaining a supportive family atmosphere [109,110].

Cognitive behavioral therapy for insomnia (CBT-I) has emerged as a highly effective nonpharmacological

intervention for addressing sleep disturbances within family systems, not only benefiting individuals but enhancing overall family functioning. Insomnia often presents as a complex, multifaceted issue in families, where one member's poor sleep can disrupt the routines and emotional equilibrium of the entire household [111,112]. CBT-I's structured approach, which focuses on modifying dysfunctional beliefs about sleep, establishing healthier sleep habits, and addressing maladaptive behaviors like irregular sleep schedules, can have far-reaching effects when applied within a family context [113]. For parents, CBT-I offers the tools to manage their own sleep issues, which in turn improves their mood, patience, and ability to engage positively with their children, fostering a more stable and emotionally supportive environment [35,90]. Additionally, when adolescents participate in CBT-I, it not only helps correct circadian misalignments that contribute to delayed sleep phase syndrome but also promotes greater self-regulation and reduced daytime fatigue, which can lessen tensions within the family related to school performance or mood swings [114]. Thus, integrating CBT-I into family-based interventions not only improves individual sleep but enhances communication, reduces conflict, and ultimately strengthens familial bonds.

Environmental modifications for families

Environmental modifications within the home play a critical role in improving sleep quality for all family members, often serving as an accessible and noninvasive strategy to address widespread sleep disturbances. Simple changes, such as optimizing room temperature, reducing ambient noise, and managing light exposure, can have profound effects on sleep latency and continuity [115]. A cooler bedroom environment, between 60 and 67°F, has been shown to facilitate deeper sleep by aligning with the body's natural drop in core temperature during the night [116]. Additionally, minimizing external noise, either using sound machines or acoustic insulation, helps prevent sleep fragmentation, which is particularly important for families living in urban settings [117]. Beyond physical comfort, light exposure plays a crucial role in regulating circadian rhythms. Exposure to natural light during the day, coupled with dim, warm lighting in the evening, supports melatonin production, thereby enhancing sleep onset and duration [118,119]. For children and adolescents, incorporating consistent bedtime routines alongside environmental adjustments can significantly improve sleep outcomes, reducing bedtime resistance and enhancing sleep quality [51]. By implementing these targeted environmental modifications, families can create a sleep-conducive atmosphere that fosters restorative rest and promotes overall well-being.

Educational programs for families

Educational programs aimed at improving sleep within families offer a powerful tool to address the widespread prevalence of sleep issues and their far-reaching impacts on health and well-being. These programs, designed to increase knowledge about sleep hygiene, the biology of sleep, and the effects of poor sleep, can help families cultivate healthier routines and more consistent sleep patterns. By incorporating both psychoeducation and practical strategies, such initiatives equip parents with the skills to create structured bedtime environments and reinforce consistent routines for children and adolescents, who are particularly vulnerable to erratic sleep behaviors [51]. Furthermore, these programs often emphasize the role of technology, illustrating the impact of screen time on melatonin suppression and offering guidelines for reducing evening exposure to electronic devices [64]. Family-based sleep education also helps to foster a shared understanding of the importance of sleep, reducing conflicts around bedtimes and encouraging supportive behaviors that enhance sleep quality for all family members [35,90]. When combined with community support, educational programs can even extend their reach, encouraging long-term adherence to sleep-promoting behaviors and improving overall family dynamics and well-being [120].

Medical treatments in a family context

Medical treatments for sleep disturbances in the family context require a holistic approach, addressing both the individual's needs and the broader effects on the household. Pharmacological options, such as melatonin for circadian disorders or sedatives for insomnia, must be managed cautiously, particularly in children, due to potential side effects and long-term risks [121]. Medications work best when combined with behavioral strategies and environmental changes that enhance sleep hygiene [122]. For more severe conditions like obstructive sleep apnea, CPAP therapy can improve sleep quality, but adherence, particularly in children, is often challenging [123]. Family-wide adjustments to routines are crucial when one member receives treatment, underscoring the need for family-centered care [124]. A comprehensive approach involving medical, behavioral, and educational strategies tends to produce the most effective outcomes for sleep health in families.

Conclusions and future directions

Future directions and research agenda

Future research on sleep in families must expand beyond traditional individual-centric studies to embrace a more systemic understanding of how family dynamics,

environmental factors, and socio-cultural contexts collectively influence sleep health. As families grow increasingly diverse, investigating sleep disparities across varying socioeconomic, racial, and cultural backgrounds will be essential for creating inclusive, evidence-based interventions [37]. Moreover, advancing the research agenda requires longitudinal studies that explore how sleep disturbances evolve over time within the family unit, particularly as children progress through developmental stages and parents encounter shifting work-life demands [39]. Technological advancements, such as wearable sleep monitors and home-based sleep assessments, present opportunities to capture real-time data on family sleep patterns, offering insights into the reciprocal effects of one member's sleep on another [124]. Additionally, there is a growing need to examine the intersection between sleep and mental health within family systems, identifying how chronic sleep issues may exacerbate psychological stress and emotional dysregulation across generations [125]. Future directions should also focus on integrating sleep education and interventions into primary care, school settings, and community programs to create more accessible, family-oriented solutions that promote sustainable, healthy sleep habits.

Clinical implications

The clinical implications of sleep within families are profound, as sleep disturbances not only impact individual health but ripple through the entire family system, influencing emotional regulation, cognitive functioning, and relational dynamics. Clinicians must recognize that addressing sleep in a family context requires an integrative, multilevel approach. For instance, interventions that focus solely on the individual often overlook the interconnected nature of family sleep patterns, where a child's sleep difficulties can exacerbate parental stress or contribute to sibling disturbances [32]. Family-centered sleep interventions, such as cognitive-behavioral therapy for insomnia (CBT-I) adapted for group settings, show promise in treating the systemic impacts of poor sleep by equipping families with tools to support each other's sleep hygiene and foster consistency in routines [126]. Additionally, healthcare providers must account for the unique developmental and psychosocial needs of children and adolescents, whose circadian rhythms, sleep behaviors, and screen habits often differ from adults, requiring tailored clinical approaches [65]. Integrating sleep assessments into routine family healthcare, such as pediatric visits or mental health screenings, can facilitate early detection of sleep problems and prevent long-term consequences like emotional dysregulation, cognitive impairments, and weakened immune function [35]. Thus, clinicians should adopt a holistic, family-oriented perspective, using sleep as

a key lever to improve overall family health and well-being.

Conclusions

In conclusion, sleep within the family context is a deeply intertwined and dynamic process that extends far beyond individual behaviors, influencing and being influenced by emotional, relational, and environmental factors. Understanding how family members' sleep patterns interact with one another offers critical insights into broader family health, demonstrating that sleep is not just a solitary experience but a shared one, capable of shaping the emotional climate and functioning of the entire household [37]. As research advances, it becomes increasingly clear that interventions targeting sleep must adopt a family-centered approach, addressing not only the biological and behavioral components of sleep disorders but also the relational and environmental complexities that uniquely affect families [35]. Clinicians, educators, and policy-makers must prioritize sleep health as a fundamental pillar of overall family well-being, integrating sleep assessments and interventions into routine care to promote sustainable, long-lasting improvements [125]. Ultimately, fostering healthy sleep habits within families can enhance emotional resilience, strengthen familial bonds, and provide a foundation for healthier, more harmonious lives.

References

- [1] Bowen M. Family therapy in clinical practice. New York: Jason Aronson, Inc.; 1978. <https://murraybowenarchives.org/books/family-therapy-in-clinical-practice/>.
- [2] Minuchin S. Families and family therapy. Harvard University Press; 1974.
- [3] Cox MJ, Paley B. Families as systems. Annu Rev Psychol 1997;48:243–67. <https://doi.org/10.1146/annurev.psych.48.1.243>.
- [4] Ackerman NW. Toward an integrative therapy of the family. Am J Psychiatr 1958;114:727–33. <https://doi.org/10.1176/ajp.114.8.727>.
- [5] O'Farrell P, Wilson C, Shiel G. Teachers' perceptions of the barriers to assessment of mental health in schools with implications for educational policy: a systematic review. Br J Educ Psychol 2023;93:262–82. <https://doi.org/10.1111/bjep.12553>.
- [6] Patterson J. Integrating family resilience and family stress theory. J Marriage Fam 2002;64(2):349–60.
- [7] Maccoby EE, Martin JA. Socialization in the context of the family. Parent-child interaction. New York: Wiley; 1983.
- [8] Steinberg L. We know some things: parent-adolescent relationships in retrospect and prospect. J Res Adolesc 2001;11:1–19.
- [9] McLeod E. Working with families of long term care residents. Perspectives 1991;15:7–10.
- [10] Repetti RL, Taylor SE, Seeman TE. Risky families: family social environments and the mental and physical health of offspring. Psychol Bull 2002;128:330–66.
- [11] Kerr ME, Bowen M. Family evaluation: an approach based on bowen theory. New York: W. W. Norton; 1988.

- [12] Foster C, Shilton T, Westerman L, Varney J, Bull F. World Health Organisation to develop global action plan to promote physical activity: time for action. *Br J Sports Med* 2018;52:484–5. <https://doi.org/10.1136/bjsports-2017-098070>.
- [13] Ferrer RL, Palmer R, Burge S. The family contribution to health status: a population-level estimate. *Ann Fam Med* 2005;3:102–8. <https://doi.org/10.1370/afm.266>.
- [14] McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. *Health Educ Q* 1988;15:351–77. <https://doi.org/10.1177/109019818801500401>.
- [15] Curry SJ, Wagner EH, Cheadle A, Diehr P, Koepsell T, Psaty B, McBride C. Assessment of community-level influences on individuals' attitudes about cigarette smoking, alcohol use, and consumption of dietary fat. *Am J Prev Med* 1993;9:78–84.
- [16] Jennings-Dozier K. Predicting intentions to obtain a Pap smear among African American and Latina women: testing the theory of planned behavior. *Nurs Res* 1999;48:198–205. <https://doi.org/10.1097/00006199-199907000-00002>.
- [17] Secker-Walker RH, Flynn BS, Solomon LJ, Skelly JM, Dorwaldt AL, Ashikaga T. Helping women quit smoking: results of a community intervention program. *Am J Public Health* 2000;90:940–6. <https://doi.org/10.2105/ajph.90.6.940>.
- [18] Stillman CM, Cohen J, Lehman ME, Erickson KI. Mediators of physical activity on neurocognitive function: a review at multiple levels of analysis. *Front Hum Neurosci* 2016;10:626. <https://doi.org/10.3389/fnhum.2016.00626>.
- [19] Bomar PJ. Perspectives on family health promotion. *Family and Community Health. J Health Promo Mainten* 1990;12:1–11. <https://doi.org/10.1097/00003727-199002000-00004>.
- [20] Davis SP, Northington L, Kolar K. Cultural considerations for treatment of childhood obesity. *J Cult Divers* 2000;7:128–32.
- [21] Hippisley-Cox J, Coupland C, Pringle M, Crown N, Hammersley V. Married couples' risk of same disease: cross sectional study. *Br Med J* 2002;325:636. <https://doi.org/10.1136/bmj.325.7365.636>.
- [22] Seabra AF, Mendonca DM, Goring HH, Thomis MA, Maia JA. Genetic and environmental factors in familial clustering in physical activity. *Eur J Epidemiol* 2008;23:205–11. <https://doi.org/10.1007/s10654-008-9222-x>.
- [23] Agerbo E. Risk of suicide and spouse's psychiatric illness or suicide: nested case-control study. *Br Med J* 2003;327:1025–6. <https://doi.org/10.1136/bmj.327.7422.1025>.
- [24] Sackett DL, Holland WW. Controversy in the detection of disease. *Lancet* 1975;2:357–9. [https://doi.org/10.1016/s0140-6736\(75\)92790-7](https://doi.org/10.1016/s0140-6736(75)92790-7).
- [25] Bowen M. The use of family theory in clinical practice. *Compr Psychiatry* 1966;7:345–74. [https://doi.org/10.1016/s0010-440x\(66\)80065-2](https://doi.org/10.1016/s0010-440x(66)80065-2).
- [26] Michaelson V, Pilato KA, Davison CM. Family as a health promotion setting: a scoping review of conceptual models of the health-promoting family. *PLoS One* 2021;16:e0249707. <https://doi.org/10.1371/journal.pone.0249707>.
- [27] Rhodes RE, Guerrero MD, Vanderloo LM, Barbeau K, Birken CS, Chaput JP, Faulkner G, Janssen I, Madigan S, Masse LC, McHugh TL, Perdew M, Stone K, Shelley J, Spinks N, Tamminen KA, Tomason JR, Ward H, Welsh F, Tremblay MS. Development of a consensus statement on the role of the family in the physical activity, sedentary, and sleep behaviours of children and youth. *Int J Behav Nutr Phys Activ* 2020;17:74. <https://doi.org/10.1186/s12966-020-00973-0>.
- [28] Brown HE, Atkin AJ, Panter J, Wong G, Chinapaw MJ, van Sluijs EM. Family-based interventions to increase physical activity in children: a systematic review, meta-analysis and realist synthesis. *Obes Rev* 2016;17:345–60. <https://doi.org/10.1111/obr.12362>.
- [29] Yee AZ, Lwin MO, Ho SS. The influence of parental practices on child promotive and preventive food consumption behaviors: a systematic review and meta-analysis. *Int J Behav Nutr Phys Activ* 2017;14:47. <https://doi.org/10.1186/s12966-017-0501-3>.
- [30] Hurley E, Dietrich T, Rundle-Thiele S. A systematic review of parent based programs to prevent or reduce alcohol consumption in adolescents. *BMC Public Health* 2019;19:1451. <https://doi.org/10.1186/s12889-019-7733-x>.
- [31] Castilho AR, Mialhe FL, Barbosa TS, Puppin-Rontani RM. Influence of family environment on children's oral health: a systematic review. *J Pediatr* 2013;89:116–23. <https://doi.org/10.1016/j.jpeds.2013.03.014>.
- [32] El-Sheikh M, Kelly RJ. Family functioning and children's sleep. *Child Dev Perspect* 2017;11:264–9. <https://doi.org/10.1111/cdep.12243>.
- [33] McQuillan ME, Bates JE. Parental stress and child temperament. In: Parental stress and early child development; 2017. p. 75–106. https://doi.org/10.1007/978-3-319-55376-4_4.
- [34] Troxel WM. It's more than sex: exploring the dyadic nature of sleep and implications for health. *Psychosom Med* 2010;72:578–86. <https://doi.org/10.1097/PSY.0b013e3181de7ff8>.
- [35] Meltzer LJ, Mindell JA. Systematic review and meta-analysis of behavioral interventions for pediatric insomnia. *J Pediatr Psychol* 2014;39:932–48. <https://doi.org/10.1093/jpepsy/jsu041>.
- [36] El-Sheikh M, Kelly RJ, Koss KJ, Rauer AJ. Longitudinal relations between constructive and destructive conflict and couples' sleep. *J Fam Psychol* 2015;29:349–59. <https://doi.org/10.1037/fam0000083>.
- [37] El-Sheikh M, Sadeh A. I. Sleep and development: introduction to the monograph. *Monogr Soc Res Child Dev* 2015;80:1–14. <https://doi.org/10.1111/mono.12141>.
- [38] Troxel WM, Braithwaite SR, Sandberg JG, Holt-Lunstad J. Does improving marital quality improve sleep? Results from a marital therapy trial. *Behav Sleep Med* 2017;15:330–43. <https://doi.org/10.1080/15402002.2015.1133420>.
- [39] Mindell JA, Meltzer LJ. Behavioural sleep disorders in children and adolescents. *Ann Acad Med Singapore* 2008;37:722–8.
- [40] Gregory AM, Sadeh A. Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep Med Rev* 2012;16:129–36. <https://doi.org/10.1016/j.smrv.2011.03.007>.
- [41] Buxton OM, Marcelli E. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. *Soc Sci Med* 2010;71:1027–36. <https://doi.org/10.1016/j.socscimed.2010.05.041>.
- [42] El-Sheikh M, Bagley EJ, Keiley M, Elmore-Statton L, Chen E, Buckhalt JA. Economic adversity and children's sleep problems: multiple indicators and moderation of effects. *Health Psychol* 2013;32:849–59. <https://doi.org/10.1037/a0030413>.
- [43] Meltzer LJ, Mindell JA. Sleep and sleep disorders in children and adolescents. *Psychiatr Clin* 2006;29:1059–76.

- [44] Roberts RE, Duong HT. The prospective association between sleep deprivation and depression among adolescents. *Sleep* 2014;37:239–44. <https://doi.org/10.5665/sleep.3388>.
- [45] Kahn M, Sheppes G, Sadeh A. Sleep and emotions: bidirectional links and underlying mechanisms. *Int J Psychophysiol* 2013;89:218–28. <https://doi.org/10.1016/j.ijpsycho.2013.05.010>.
- [46] Palmer CA, Alfano CA. Sleep and emotion regulation: an organizing, integrative review. *Sleep Med Rev* 2017;31:6–16. <https://doi.org/10.1016/j.smrv.2015.12.006>.
- [47] Meltzer LJ, Mindell JA. Relationship between child sleep disturbances and maternal sleep, mood, and parenting stress: a pilot study. *J Fam Psychol* 2007;21:67–73. <https://doi.org/10.1037/0893-3200.21.1.67>.
- [48] Meltzer LJ, Montgomery-Downs HE. Sleep in the family. *Pediatr Clin* 2011;58:765–74. <https://doi.org/10.1016/j.pcl.2011.03.010>.
- [49] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC, Adams Hillard PJ. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 2015;1:40–3. <https://doi.org/10.1016/j.slehd.2014.12.010>.
- [50] Jenni OG, O'Connor BB. Children's sleep: an interplay between culture and biology. *Pediatrics* 2005;115:204–16. <https://doi.org/10.1542/peds.2004-0815B>.
- [51] Mindell JA, Li AM, Sadeh A, Kwon R, Goh DY. Bedtime routines for young children: a dose-dependent association with sleep outcomes. *Sleep* 2015;38:717–22. <https://doi.org/10.5665/sleep.4662>.
- [52] Feldman R. Parent-infant synchrony and the construction of shared timing: physiological precursors, developmental outcomes, and risk conditions. *J Child Psychol Psychiatry* 2007;48:329–54. <https://doi.org/10.1111/j.1469-7610.2006.01701.x>.
- [53] Grigg-Damberger MM. The visual scoring of sleep in infants 0 to 2 months of age. *J Clin Sleep Med* 2016;12:429–45. <https://doi.org/10.5664/jcsm.5600>.
- [54] Mindell JA, Telofski LS, Wiegand B, Kurtz ES. A nightly bedtime routine: impact on sleep in young children and maternal mood. *Sleep* 2009;32:599–606. <https://doi.org/10.1093/sleep/32.5.599>.
- [55] Weissbluth M. Healthy sleep habits, happy child. A step-by-step program for a good night's sleep. Random House Publishing Group; 2015.
- [56] Anders TF, Eiben LA. Pediatric sleep disorders: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 1997;36:9–20. <https://doi.org/10.1097/00004583-199701000-00012>.
- [57] Meltzer LJ, Williamson AA, Mindell JA. Pediatric sleep health: it matters, and so does how we define it. *Sleep Med Rev* 2021;57:101425. <https://doi.org/10.1016/j.smrv.2021.101425>.
- [58] Mindell JA, Williamson AA. Benefits of a bedtime routine in young children: sleep, development, and beyond. *Sleep Med Rev* 2018;40:93–108. <https://doi.org/10.1016/j.smrv.2017.10.007>.
- [59] Ferber R. Solve your child's sleep problems: new, revised, and expanded. 2006.
- [60] Mindell JA, Owens J, Alves R, Bruni O, Goh DY, Hiscock H, Kohyama J, Sadeh A. Give children and adolescents the gift of a good night's sleep: a call to action. *Sleep Med* 2011;12:203–4. <https://doi.org/10.1016/j.sleep.2011.01.003>.
- [61] Iglovstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics* 2003;111:302–7. <https://doi.org/10.1542/peds.111.2.302>.
- [62] Owens J, Adolescent Sleep Working G, Committee on A.. Insufficient sleep in adolescents and young adults: an update on causes and consequences. *Pediatrics* 2014;134:e921–32. <https://doi.org/10.1542/peds.2014-1696>.
- [63] Cain N, Gradisar M. Electronic media use and sleep in school-aged children and adolescents: a review. *Sleep Med* 2010;11:735–42. <https://doi.org/10.1016/j.sleep.2010.02.006>.
- [64] Hale L, Guan S. Screen time and sleep among school-aged children and adolescents: a systematic literature review. *Sleep Med Rev* 2015;21:50–8. <https://doi.org/10.1016/j.smrv.2014.07.007>.
- [65] Carskadon MA. Sleep in adolescents: the perfect storm. *Pediatr Clin* 2011;58:637–47. <https://doi.org/10.1016/j.pcl.2011.03.003>.
- [66] Jodi A, Mindell JAO. A Clinical guide to pediatric sleep: diagnosis and management of sleep problems. *J Am Acad Child Adolescent Psychiatry* 2015;60(12).
- [67] Crowley SJ, Acebo C, Carskadon MA. Sleep, circadian rhythms, and delayed phase in adolescence. *Sleep Med* 2007;8:602–12. <https://doi.org/10.1016/j.sleep.2006.12.002>.
- [68] Wheaton AG, Chapman DP, Croft JB. School start times, sleep, behavioral, health, and academic outcomes: a review of the literature. *J Sch Health* 2016;86:363–81. <https://doi.org/10.1111/josh.12388>.
- [69] Dahl RE, Lewin DS. Pathways to adolescent health sleep regulation and behavior. *J Adolesc Health* 2002;31:175–84. [https://doi.org/10.1016/s1054-139x\(02\)00506-2](https://doi.org/10.1016/s1054-139x(02)00506-2).
- [70] Shochat T, Cohen-Zion M, Tzischinsky O. Functional consequences of inadequate sleep in adolescents: a systematic review. *Sleep Med Rev* 2014;18:75–87. <https://doi.org/10.1016/j.smrv.2013.03.005>.
- [71] Insana SP, Williams KB, Montgomery-Downs HE. Sleep disturbance and neurobehavioral performance among postpartum women. *Sleep* 2013;36:73–81. <https://doi.org/10.5665/sleep.2304>.
- [72] Hiscock H, Wake M. Infant sleep problems and postnatal depression: a community-based study. *Pediatrics* 2001;107:1317–22. <https://doi.org/10.1542/peds.107.6.1317>.
- [73] Kohn S, Eaton JL, Feroz S, Bainbridge AA, Hoolahan J, Barnett DJ. Personal disaster preparedness: an integrative review of the literature. *Disaster Med Public Health Prep* 2012;6:217–31. <https://doi.org/10.1001/dmp.2012.47>.
- [74] Bernard-Bonnin A-C. Maternal depression and child development. *Paediatr Child Health* 2004;9:575–98. <https://doi.org/10.1093/pch/9.8.575>.
- [75] Gooneratne NS, Vitiello MV. Sleep in older adults: normative changes, sleep disorders, and treatment options. *Clin Geriatr Med* 2014;30:591–627. <https://doi.org/10.1016/j.cger.2014.04.007>.
- [76] Ancoli-Israel S. Sleep and its disorders in aging populations. *Sleep Med* 2009;10(Suppl. 1):S7–11. <https://doi.org/10.1016/j.sleep.2009.07.004>.
- [77] Louise S, Foley HP, Osuch EA, De Pace JA, Murphy BA, Podolinsky NJ. An examination of potential mechanisms for exercise as a treatment for depression: a pilot study. *Mental Health and Physical Activity* 2008;1:69–73.
- [78] Vitiello VE, Booren LM, Downer JT, Williford A. Variation in children's classroom engagement throughout a day in preschool: relations to classroom and child factors. *Early Child Res Q* 2012;27:210–20. <https://doi.org/10.1016/j.ecresq.2011.08.005>.
- [79] McCurry SM, Logsdon RG, Teri L, Vitiello MV. Sleep disturbances in caregivers of persons with dementia: contributing factors

- and treatment implications. *Sleep Med Rev* 2007;11:143–53. <https://doi.org/10.1016/j.smrv.2006.09.002>.
- [80] Johnson CR, Turner KS, Foldes E, Brooks MM, Kronk R, Wiggs L. Behavioral parent training to address sleep disturbances in young children with autism spectrum disorder: a pilot trial. *Sleep Med* 2013;14:995–1004. <https://doi.org/10.1016/j.sleep.2013.05.013>.
- [81] Walker WH, 2nd, Walton JC, DeVries AC, Nelson RJ. Circadian rhythm disruption and mental health. *Transl Psychiatry* 2020;10:28. <https://doi.org/10.1038/s41398-020-0694-0>.
- [82] Smith LE, Weinman J, Yiend J, Rubin J. Psychosocial factors affecting parental report of symptoms in children: a systematic review. *Psychosom Med* 2020;82:187–96. <https://doi.org/10.1097/PSY.0000000000000767>.
- [83] Smith CE, Lee S, Allen TD, Wallace ML, Andel R, Buxton OM, Patel SR, Almeida DM. Designing work for healthy sleep: a multidimensional, latent transition approach to employee sleep health. *J Occup Health Psychol* 2024;29:409–30. <https://doi.org/10.1037/ocp0000386>.
- [84] Mindell JA, Leichman ES, DuMond C, Sadeh A. Sleep and social-emotional development in infants and toddlers. *J Clin Child Adolesc Psychol* 2017;46:236–46. <https://doi.org/10.1080/15374416.2016.1188701>.
- [85] Buxton OM, Lee S, Beverly C, Berkman LF, Moen P, Kelly EL, Hammer LB, Almeida DM. Work-family conflict and employee sleep: evidence from IT workers in the work, family and health study. *Sleep* 2016;39:1871–82. <https://doi.org/10.5665/sleep.6172>.
- [86] Akerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Sleep disturbances, work stress and work hours: a cross-sectional study. *J Psychosom Res* 2002;53:741–8. [https://doi.org/10.1016/s0022-3999\(02\)00333-1](https://doi.org/10.1016/s0022-3999(02)00333-1).
- [87] Burgard SA, Ailshire JA. Gender and time for sleep among U.S. Adults. *Am Sociol Rev* 2013;78:51–69. <https://doi.org/10.1177/0003122412472048>.
- [88] Mindell JA, Sadeh A, Kohyama J, How TH. Parental behaviors and sleep outcomes in infants and toddlers: a cross-cultural comparison. *Sleep Med* 2010;11:393–9. <https://doi.org/10.1016/j.sleep.2009.11.011>.
- [89] Harvey LA, Katalinic OM, Herbert RD, Moseley AM, Lannin NA, Schurr K. Stretch for the treatment and prevention of contracture: an abridged republication of a Cochrane Systematic Review. *J Physiother* 2017;63:67–75. <https://doi.org/10.1016/j.jphys.2017.02.014>.
- [90] Meltzer LJ, Plaufcan MR, Thomas JH, Mindell JA. Sleep problems and sleep disorders in pediatric primary care: treatment recommendations, persistence, and health care utilization. *J Clin Sleep Med* 2014;10:421–6. <https://doi.org/10.5664/jcsm.3620>.
- [91] Gregory AM, Sadeh A. Annual research review: sleep problems in childhood psychiatric disorders—a review of the latest science. *J Child Psychol Psychiatry* 2016;57:296–317. <https://doi.org/10.1111/jcpp.12469>.
- [92] Gottlieb M, Long B, Koyfman A. Approach to the agitated emergency department patient. *J Emerg Med* 2018;54:447–57. <https://doi.org/10.1016/j.jemermed.2017.12.049>.
- [93] Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pepin JL, Peppard PE, Sinha S, Tufik S, Valentine K, Malhotra A. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7:687–98. [https://doi.org/10.1016/S2213-2600\(19\)30198-5](https://doi.org/10.1016/S2213-2600(19)30198-5).
- [94] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *J Sleep Res* 2002;11:1–16. <https://doi.org/10.1046/j.j.1365-2869.2002.00289.x>.
- [95] Zhu Y, Fenik P, Zhan G, Somach R, Xin R, Veasey S. Intermittent short sleep results in lasting sleep wake disturbances and degeneration of locus coeruleus and orexinergic neurons. *Sleep* 2016;39:1601–11. <https://doi.org/10.5665/sleep.6030>.
- [96] Micic G, Lovato N, Gradišar M, Ferguson SA, Burgess HJ, Lack LC. The etiology of delayed sleep phase disorder. *Sleep Med Rev* 2016;27:29–38. <https://doi.org/10.1016/j.smrv.2015.06.004>.
- [97] Eastman CI, Gazda CJ, Burgess HJ, Crowley SJ, Fogg LF. Advancing circadian rhythms before eastward flight: a strategy to prevent or reduce jet lag. *Sleep* 2005;28:33–44. <https://doi.org/10.1093/sleep/28.1.33>.
- [98] Azahab Abu Hassan Shaari SR. A conceptual analysis of the McMaster family assessment device (FAD). *Int J Acad Res Bus Soc Sci* 2023;978–88. <https://doi.org/10.6007/IJARBSS/v13-i6/17550>.
- [99] Silber MH, Buchfuhrer MJ, Earley CJ, Koo BB, Manconi M, Winkelman JW, Scientific, Medical Advisory Board of the Restless Legs SF. The management of restless legs syndrome: an updated algorithm. *Mayo Clin Proc* 2021;96:1921–37. <https://doi.org/10.1016/j.mayocp.2020.12.026>.
- [100] Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J, Restless Legs Syndrome D., Epidemiology workshop at the National Institutes of H., International Restless Legs Syndrome Study G.. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4:101–19. [https://doi.org/10.1016/s1389-9457\(03\)00010-8](https://doi.org/10.1016/s1389-9457(03)00010-8).
- [101] Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. *Sleep Med* 2010;11:807–15. <https://doi.org/10.1016/j.sleep.2010.07.007>.
- [102] Mahowald MW, Schenck CH. The “when” and “where” of alpha-synucleinopathies: insights from REM sleep behavior disorder. *Neurology* 2018;91:435–6. <https://doi.org/10.1212/WNL.000000000000129>.
- [103] Zadra A, Desautels A, Petit D, Montplaisir J. Somnambulism: clinical aspects and pathophysiological hypotheses. *Lancet Neurol* 2013;12:285–94. [https://doi.org/10.1016/S1474-4422\(12\)70322-8](https://doi.org/10.1016/S1474-4422(12)70322-8).
- [104] Howell MJ. Parasomnias: an updated review. *Neurotherapeutics* 2012;9:753–75. <https://doi.org/10.1007/s13311-012-0143-8>.
- [105] Thorpy MJ, Billiard M. Sleepiness causes, consequences and treatment. *JAMA* 2011;308:517.
- [106] Dauvilliers Y, Zammit G, Fietze I, Mayleben D, Seboek Kinter D, Pain S, Hedner J. Daridorexant, a new dual orexin receptor antagonist to treat insomnia disorder. *Ann Neurol* 2020;87:347–56. <https://doi.org/10.1002/ana.25680>.
- [107] Mignot E, Mayleben D, Fietze I, Leger D, Zammit G, Bassetti CLA, Pain S, Kinter DS, Roth T, investigators. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-

- controlled, phase 3 trials. *Lancet Neurol* 2022;21:125–39. [https://doi.org/10.1016/S1474-4422\(21\)00436-1](https://doi.org/10.1016/S1474-4422(21)00436-1).
- [108] Inoue Y. Sleep-related eating disorder and its associated conditions. *Psychiatr Clin Neurosci* 2015;69:309–20. <https://doi.org/10.1111/pcn.12263>.
- [109] Sadeh A. The role and validity of actigraphy in sleep medicine: an update. *Sleep Med Rev* 2011;15:259–67. <https://doi.org/10.1016/j.smrv.2010.10.001>.
- [110] Sadeh A, El-Sheikh M. Xi. Sleep and development: conclusions and future directions. *Monogr Soc Res Child Dev* 2015;80:177–81. <https://doi.org/10.1111/mono.12151>.
- [111] Blake M, Waloszek JM, Schwartz O, Raniti M, Simmons JG, Blake L, Murray G, Dahl RE, Bootzin R, Dudgeon P, Trinder J, Allen NB. The SENSE study: post intervention effects of a randomized controlled trial of a cognitive-behavioral and mindfulness-based group sleep improvement intervention among at-risk adolescents. *J Consult Clin Psychol* 2016;84:1039–51. <https://doi.org/10.1037/ccp0000142>.
- [112] Blake MJ, Sheeber LB, Youssef GJ, Raniti MB, Allen NB. Systematic review and meta-analysis of adolescent cognitive-behavioral sleep interventions. *Clin Child Fam Psychol Rev* 2017;20:227–49. <https://doi.org/10.1007/s10567-017-0234-5>.
- [113] Edinger JD, Carney CE. Overcoming insomnia: a cognitive-behavioral therapy approach. 2015 [therapist guide].
- [114] Becker DF, Grilo CM. Comorbidity of mood and substance use disorders in patients with binge-eating disorder: associations with personality disorder and eating disorder pathology. *J Psychosom Res* 2015;79:159–64. <https://doi.org/10.1016/j.jpsychores.2015.01.016>.
- [115] Bion V, Lowe AS, Puthucheary Z, Montgomery H. Reducing sound and light exposure to improve sleep on the adult intensive care unit: an inclusive narrative review. *J Intensive Care Soc* 2018;19:138–46. <https://doi.org/10.1177/1751143717740803>.
- [116] Okamoto-Mizuno K, Mizuno K. Effects of thermal environment on sleep and circadian rhythm. *J Physiol Anthropol* 2012;31:14. <https://doi.org/10.1186/1880-6805-31-14>.
- [117] Basner M, Babisch W, Davis A, Brink M, Clark C, Janssen S, Stansfeld S. Auditory and non-auditory effects of noise on health. *Lancet* 2014;383:1325–32. [https://doi.org/10.1016/S0140-6736\(13\)61613-X](https://doi.org/10.1016/S0140-6736(13)61613-X).
- [118] C Cajochen MF, Weibel J. Effect of daylight LED on visual comfort, melatonin, mood, waking performance and sleep. *Light Res Technol* 2019;51:1044–62. <https://doi.org/10.1177/1477153519828419>.
- [119] Cajochen C, Frey S, Anders D, Spati J, Bues M, Pross A, Mager R, Wirz-Justice A, Stefani O. Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. *J Appl Physiol* 2011;110:1432–8. <https://doi.org/10.1152/japplphysiol.00165.2011>.
- [120] Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, American College of Cardiology/American Heart Association Task Force on Practice G., Obesity S.. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American college of cardiology/American heart association task force on practice guidelines and the obesity society. *J Am Coll Cardiol* 2014;63:2985–3023. <https://doi.org/10.1016/j.jacc.2013.11.004>.
- [121] Owens JA, Mindell JA. Pediatric insomnia. *Pediatr Clin* 2011;58:555–69. <https://doi.org/10.1016/j.pcl.2011.03.011>.
- [122] Sharma MP, Andrade C. Behavioral interventions for insomnia: theory and practice. *Indian J Psychiatry* 2012;54:359–66. <https://doi.org/10.4103/0019-5545.104825>.
- [123] Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, Schechter MS, Ward SD, Sheldon SH, Shiffman RN, Lehmann C, Spruyt K, American Academy of P. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2012;130:e714–55. <https://doi.org/10.1542/peds.2012-1672>.
- [124] Biggs BK, Tsai OM, Geske J, Lebow JR, Kumar S, Harper K, Grothe KB, Cunningham ML, Jensen TB, Clark MM. Development and initial validation of the support for healthy lifestyle (SHeL) questionnaire for adolescents. *Eat Behav* 2019;34:101310. <https://doi.org/10.1016/j.eatbeh.2019.101310>.
- [125] Becker CB, Middlemass K, Taylor B, Johnson C, Gomez F. Food insecurity and eating disorder pathology. *Int J Eat Disord* 2017;50:1031–40. <https://doi.org/10.1002/eat.22735>.
- [126] Rossman J. Cognitive-behavioral therapy for insomnia: an effective and underutilized treatment for insomnia. *Am J Lifestyle Med* 2019;13:544–7. <https://doi.org/10.1177/1559827619867677>.

This page intentionally left blank

Part III

Addressing sleep health at the community and population level

This page intentionally left blank

Chapter 12

Obstacles to overcome when improving sleep health at a societal level

Michael A. Grandner

Sleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States

Introduction

Sleep is important for overall health. Yet, achieving healthy sleep is difficult for a large number of people. This is not likely because people dislike sleep. Rather, there are obstacles to overcome that are imposed by individuals themselves and their contexts. This chapter will address some of the common real-world barriers to sleep health, conceptualizing how understanding these real-world barriers can be thought of in context, and recommendations for using this information to design and implement sleep health interventions in real-world settings.

Real-world barriers to sleep health

Lack of time

One of the most common explanations given for insufficient sleep is a lack of time. To examine this phenomenon, Basner and colleagues examined data from the American Time Use Survey (ATUS). The first study to explore these data [1] found that there was a relationship between sleep time and time spent socializing/leisure activities and traveling, such that less sleep associated with more of these activities. But the largest relationship was seen with work—clearly, it is work that Americans are trading for time to sleep. This relationship is displayed in Fig. 12.1. In a follow-up analysis [2], the authors examined the activities in the 2 h prior to bed and following getting up. Fig. 12.2 shows the results of this analysis. In examining the 2 h before bed, the activity that seems to be most likely to interfere with getting into bed is not work, though, but watching television. And in examining what gets people up, that seems to be where work comes into play—the likelihood of working in after awakening increases steadily in the first 2 h, as does travel (e.g., commute). Still, many people find it difficult to make time for sleep, and this is a key barrier for interventions.

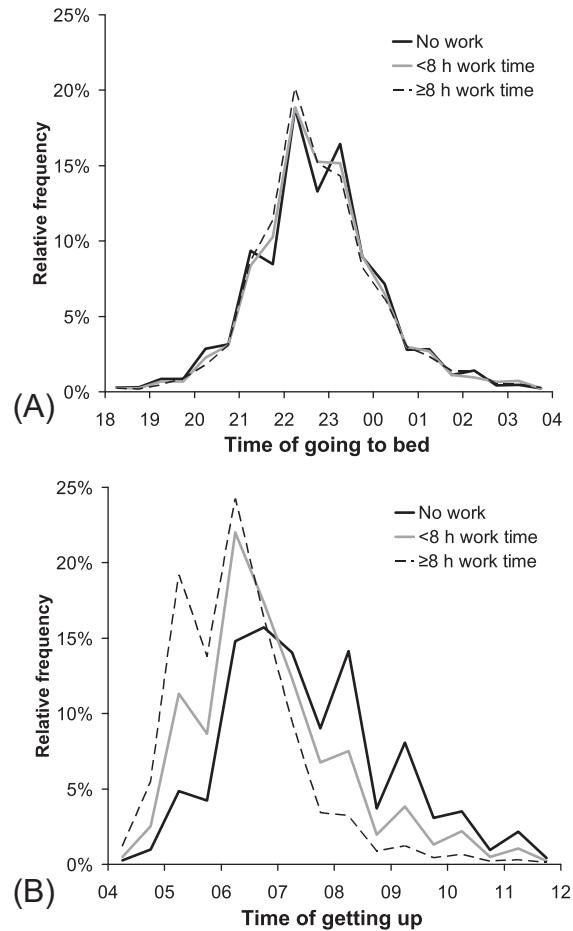


FIGURE 12.1 Panels A and B show distributions of time of going to bed (A) and time of getting up (B) for respondents who did not work (black lines, N = 9770), who worked less than 8 h (gray lines, N = 5589), and for those who worked 8 h or more (broken black lines, N = 6116). From Basner M, Fomberstein KM, Razavi FM, Banks S, William JH, Rosa RR, Dinges DF. American time use survey: sleep time and its relationship to waking activities. *Sleep* 2007;30(9):1085–95. Epub 2007/10/04. PubMed PMID: 17910380.

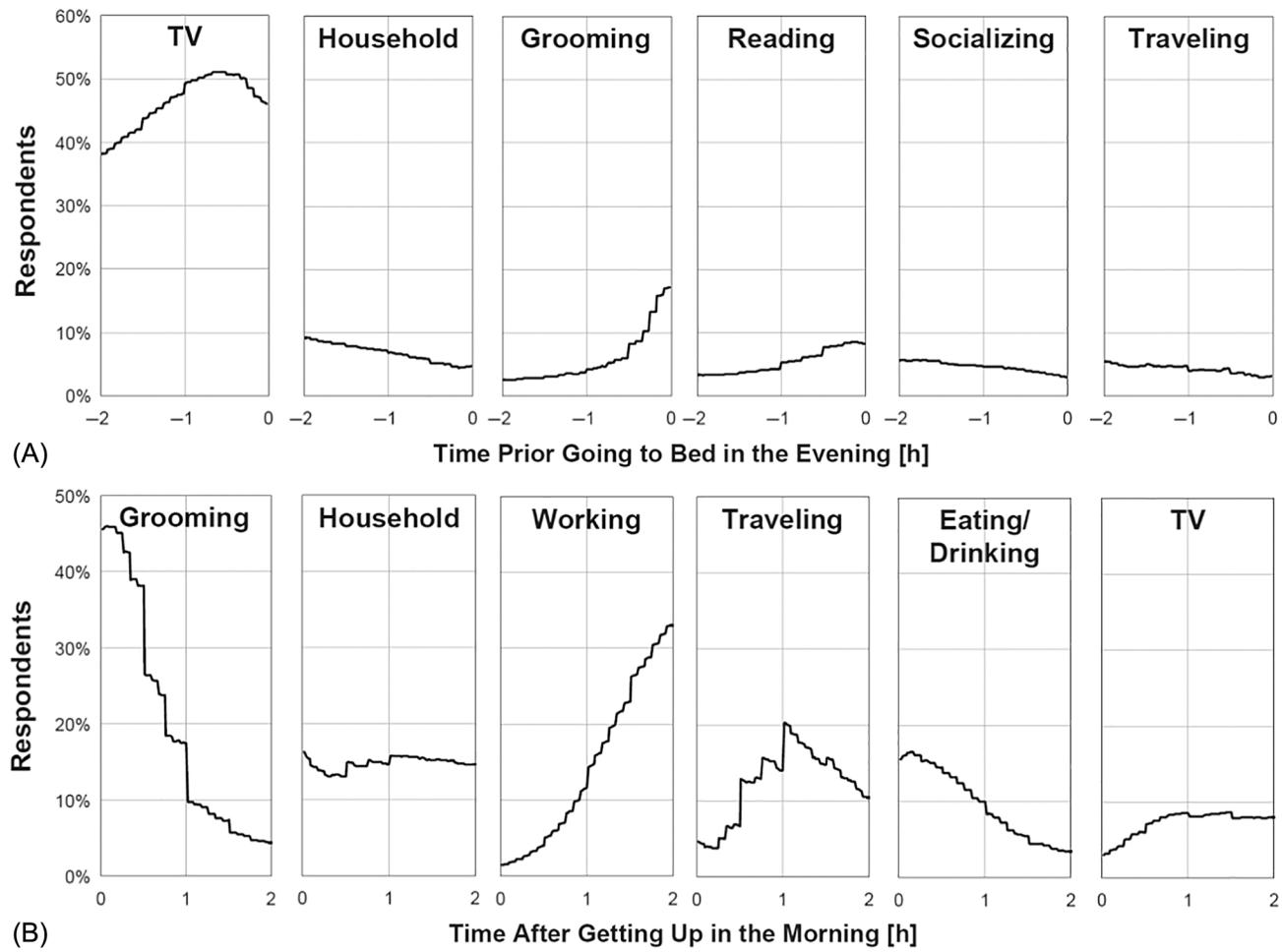


FIGURE 12.2 Activities just before and after sleep periods, from the American Time Use Survey. Panels A and B show the time course of the 6 most common waking activities in 2-h periods prior to going to bed (−2h to time of going to bed in panel A) and after getting up (time of getting up to +2h in panel B). From Basner M, Dinges DF. Dubious bargain: trading sleep for Leno and Letterman. *Sleep* 2009;32(6):747–752. Epub 2009/06/24. PubMed PMID: 19544750; PMCID: 2690561.

Social norms and beliefs

There is a general perception that sleep might be important, but it is difficult to achieve for people who are busy; this is a sentiment repeatedly echoed in the popular press but has received relatively little scientific attention. In a study by Henry and colleagues, the cultural impact of work being paramount and more important than sleep was reported by US adults [3]. In a study of a general population sample, Grandner and colleagues found that perceived social norms about the importance of sleep varied based on the outcome [4]. As depicted in Fig. 12.3, respondents generally agreed that lack of sleep could lead to cognitive/functional problems including tiredness, sleepiness, lack of energy, and memory/concentration problems. There was also general agreement that friends and family believed that lack of sleep could lead to moodiness and difficulties at work or school. The only outcomes where >40% of respondents

reported that their friends and family strongly agreed that lack of sleep could lead to that outcome were tiredness, lower energy, and daytime sleepiness. The minority of respondents agreed that their friends and family believed that lack of sleep could lead to missed days, lower sex drive, weight gain, heart disease, hypertension, diabetes, and high cholesterol. Of note, most respondents who did not agree that their friends and family believed that lack of sleep could lead to outcomes indicated that they were unsure of their friends' and family's beliefs, rather than indicating that their friends and family do not believe those things.

Physical environment

Aspects of the physical environment propose unique barriers to sleep. Since sleep requires an environment

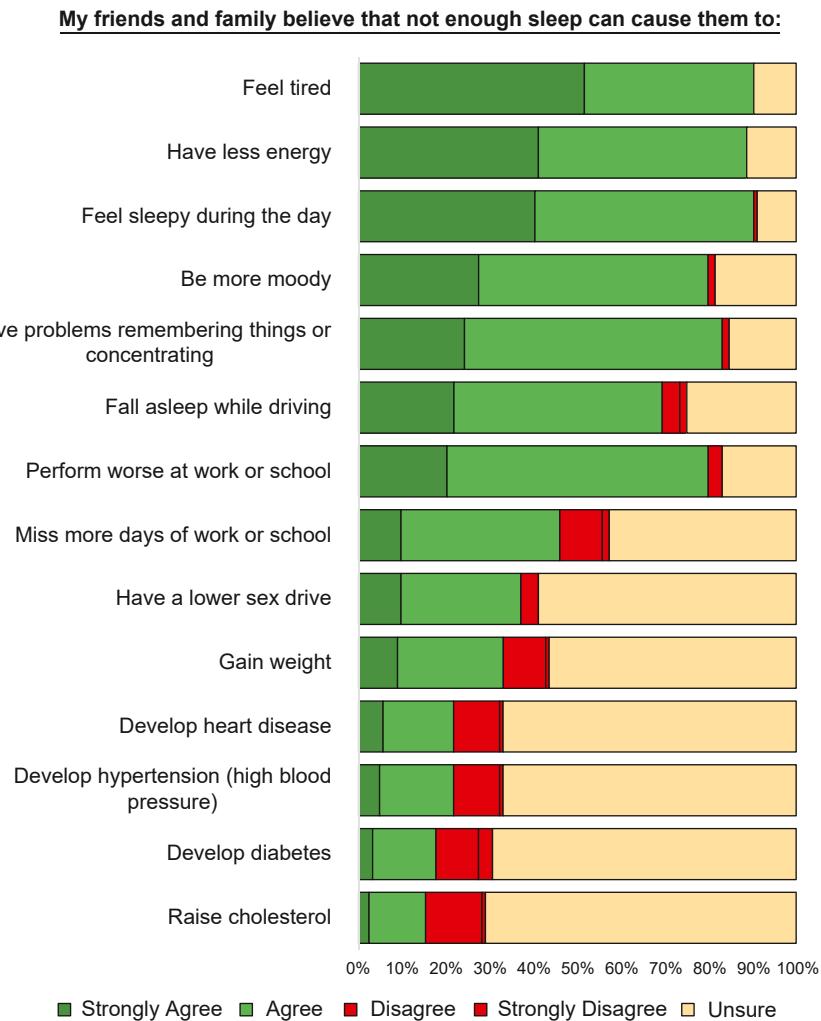


FIGURE 12.3 Perceived social norms about sleep. From Grandner MA, Jackson N, Gooneratne NS, Patel NP. The development of a questionnaire to assess sleep-related practices, beliefs, and attitudes. *Behav Sleep Med* 2014;12(2):123–142. PubMed PMID: 23514261; PMCID: 3795978.

conducive to a lack of sensory input, environments with an uncomfortable temperature level, too much or too little light, too much or too little noise, or some other aspect of the physical environment that is uncomfortable can interfere with sleep [5]. In the bedroom, this can present as environmental temperature that is too hot or too cold or contains too much light or noise. It can also be represented in an uncomfortable sleeping surface or pillows or blankets. Outside of the bedroom, barriers to sleep become apparent when aspects of the physical environment become out of the individual's control. For example, regions that experience excessive light pollution have been shown to present a unique risk for medically treated insomnia [6]. Other studies have shown that environmental noise from airplanes, traffic, and other sources can systematically interfere with sleep [7]. Addressing these aspects of the physical environment may be important ingredients of a sleep health intervention.

Health conditions and chronic pain

Chronic pain impacts approximately 1/5 of US adults [8], though this depends on age—rates ranged from 7.0% among 18–24 year olds to 33.6% among those 85 years old or older. High-impact chronic pain is estimated to impact 8% of US adults, and this also is strongly related to age, such that the least prevalence was among 18–24 year olds (1.5%) and the highest was among those 85 or older (15.8%). Chronic pain can directly interfere with sleep, causing reduced sleep duration and impaired sleep quality [9]. Other relatively common health problems can impact on sleep health as well. Sleep disorders such as sleep apnea, restless legs syndrome, and insomnia disorder are often undertreated in the population. Autoimmune and rheumatological diseases, as well as musculoskeletal and other orthopedic conditions, can also be common and impact sleep. Cardiometabolic diseases such as diabetes, obesity, and

hypertension can be reflected in poor sleep [10]. Cancer and remitted cancer are both associated with sleep difficulties [11]. Of note, nearly every domain of medical diagnosis has sleep disturbance as a common symptom either via pain/discomfort or through some other mechanism.

Substance use

Many substances that are commonly consumed in society have adverse impacts on sleep. Among these, alcohol, nicotine, caffeine, and cannabis have undergone the most study. Alcohol is consumed by the majority of US adults. It is frequently consumed as a sleep aid. Yet, alcohol can directly interfere with sleep by reducing sleep duration, increasing sleep fragmentation, and reducing sleep quality [12]. Although rates of smoking are declining, many US adults smoke. Although many people smoke to relax, and/or smoke in bed, nicotine is a stimulant. Smokers are more likely to have sleeping difficulties, especially in the beginning of the night [13,14]. Further, smoking cessation treatments also tend to be insomnogenic [15]. As cannabis use becomes legitimized in society, its effects on sleep require much more study—especially since many people are using it as a sleep aid. Existing evidence suggests that it may provide some short-term benefits in terms of sleep continuity, but this may come at a cost of impaired sleep architecture [16,17]. Further, those who regularly use cannabis are not more likely to have better sleep outcomes; rather, they frequently report worse sleep. This may indicate that although people use this substance to improve sleep, it is ineffective. Caffeine is possibly the most frequently consumed psychoactive drug in the world. Caffeine is frequently used to improve daytime functioning, and it is quite effective as a relatively safe stimulant. Yet, the effects of caffeine may last for several hours after consumption, and this may interfere with sleep [18]. These and other commonly used substances—which for many adults have become a regular part of daily life—may represent important barriers to sleep.

Distractions and on-demand culture

As the dominant culture has become one that discourages downtime and relaxation in favor of work and productivity, this has led to several widespread phenomena that are interfering with sleep. As highlighted earlier, television watching is probably the most universally common activity in the 2 h before bedtime, often leading right up until sleep [1]. Television is just one of many possible electronic distractions that people engage in the evening. For example, using mobile phones (which are actually more like handheld computers) to browse the Internet, engage with social media, communicate via messaging system, play video games, and watch videos has become an

indispensable part of the evening routines of many people. There is a growing body of evidence that the mental engagement (and distraction) that electronic devices provide may interfere with sleep just as they do so by emitting light [19]. This may reflect the cultural attitude toward constantly remaining mentally active—when not actively working or fulfilling other obligations, we keep our minds busy with these distractions. Yet, distraction is not relaxation, which is an active process of reducing physical and mental strain and tension. And this may result in extended time spent engaged in distracting activities in the hopes that they will aid in relaxation when they do not. This is evident in the practice of “binge-watching” television shows for hours rather than sleeping. This is related to the concept of “on-demand” culture, where things and experiences are available at all times, immediately. For example, whole seasons of television shows are available for bingeing at any time, day or night. Stores and especially websites are open 24 h a day, every day. In the middle of the night, in a relatively quiet town, a person can—if they so choose—watch nearly any movie or television show every recorded, shop online for everything from housewares to clothing to real estate to a new car, access nearly any book that has ever been written, immediately download and play nearly every video game ever developed, send a message to anyone that is instantly delivered, etc. It is possible that this cultural shift has provided additional opportunities for people to engage in distracting activities rather than sleeping.

Conceptualizing strategies for overcoming these barriers

Although sleep is a biological imperative, it is driven by volitional behaviors and, thus, many of the same factors that drive other health-related behaviors. Several theories of health behavior change have been developed to understand how individuals decide to engage in healthful behaviors, and these might be applicable to sleep.

The health belief model and application to sleep

The Health Belief Model has been utilized for a wide range of possible health behaviors. Briefly, the Health Belief Model conceptualizes that a person will engage in a behavior based on the following conditions:

1. Perceived susceptibility: “How vulnerable am I?”
2. Perceived severity: “Are the consequences severe?”
3. Perceived benefits: “Will taking action remove consequences?”
4. Perceived barriers: “What is preventing me from taking action?”

5. Cues to action: "Will I remember to take action?"
6. Self-efficacy: "Is taking action in my control?"

See Fig. 12.4 for a schematic of this model (reprinted from Ref. [20]). There are many ways in which this model can be applied to sleep. For example, interventions should aim to address all six components of the model. Interventions should provide education about the overall relationship of sleep to the outcomes that people care about and also how they, personally, may be at risk for those adverse outcomes. These interventions should also focus on the importance of the outcomes and place them in the context that would be relevant for daily life. For example, an intervention aimed at getting an individual to prioritize sleep should not only provide education about how sleep is relevant to outcomes that the individual is specifically interested in (e.g., weight gain, work performance, relationship quality), but that the effects are large enough to warrant action. Interventions should also address consequences of performing the action—communicate that improving sleep can produce measurable changes in the outcomes that the individual cares about. Addressing barriers is absolutely critical. As outlined above, barriers to achieving healthy sleep are often cultural, physical, and (seemingly) external. If individuals do not consider these barriers to be surmountable, the intervention will be ineffective. A thorough understanding of the barriers, and the proposed solutions to those barriers, is needed. Self-efficacy is also very important. If a person feels that they have decreased ability to get sleep, even if those barriers are removed, then the intervention will be unlikely to be effective. Finally, the health belief model notes the importance of cues to action—reminders and encouragement needed in order for the intervention to be successful. Thus, in order for change to sleep to be possible, then a broad approach needs to be undertaken that connects the individual to the outcomes that they care about, convinces

them that sleep will improve those outcomes, and facilitating that change by removing barriers, increasing self-efficacy, and providing cues to action.

The integrated behavioral model and application to sleep

The Integrated Behavioral Model arose from the Theory of Planned Behavior and Theory of Reasoned Action [21] to describe why people engage in behaviors. These are described in more detail in Chapter 14. According to the integrated behavior model, an individual needs to make a formal motivated decision (intention) to perform that behavior. That intention is thought to be the product of three separate influences:

1. Attitudes (overall cognitive and emotional perception of performing the behavior), which consist of
 - a. Experiential attitudes (emotional responses to the idea of performing the action)
 - b. Instrumental attitudes (beliefs about what would happen if the outcome is performed)
2. Subjective norms (perception of the social influences over performing the action), which consist of
 - a. Injunctive norms (beliefs about what others think an individual should do and motivation to comply with those pressures)
 - b. Descriptive norms (beliefs about what other people in an individual's social group are actually doing)
3. Personal agency (capability to actually perform the behavior, influenced by knowledge, skills, environmental constraints, etc.), which consists of
 - a. Perceived control (beliefs about whether or not an individual can actually perform the behavior in the context of constraints)
 - b. Self-efficacy (beliefs about whether or not an individual can perform a behavior well)

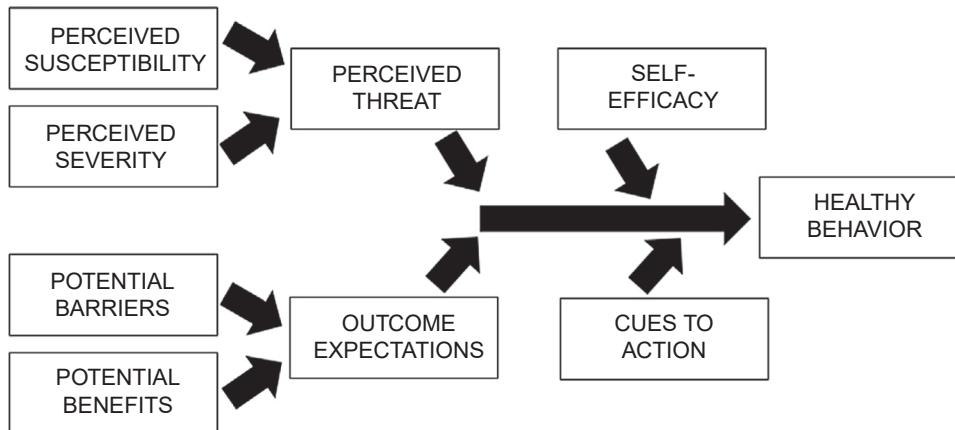


FIGURE 12.4 Health belief model. Reprinted from Grandner MA. Sleep, health, and society. *Sleep Med Clin* 2017;12(1):1–22. PubMed PMID: 28159089.

A schematic for this model is presented in Fig. 12.5. Regarding the understanding of sleep health in society, this model can help toward understanding how to build a stronger motivation for individuals to prioritize healthy sleep. According to this model, attitudes, norms, and agency all need to be addressed.

Interventions will need to focus on helping individuals to endorse helpful beliefs and attitudes about sleep. It will also necessitate that individuals generally have positive feelings about sleep—which may be difficult given the dominant culture. Norms can be addressed by better examining how the sleep of a person's (perceived) peer impacts behavior, as well as the (perceived) sleep of those to which that individual wishes to emulate. This would involve gaining a better understanding of what an individual believes their social group believes and does regarding sleep and determining the value of this information. For example, a person in a workplace where working late is prioritized over sufficient sleep will have a difficult time maintaining healthy habits no matter what positive sleep attitudes they hold. The social pressure to work late is a powerful force that will need to be addressed and not ignored. Regarding agency, this involves helping individuals feel empowered in engaging in positive sleep behaviors. When an individual has positive attitudes about sleep, perceives healthy sleep to be consistent with their

social group, and perceives themselves to have the power to influence their sleep, positive changes in society are possible.

The transtheoretical stages-of-change model

The transtheoretical model of behavior change is sometimes called the “stages of change” model because it addresses the issue of readiness for change. According to this model, behavior change depends on an individual’s readiness to engage in that healthy behavior. This is operationalized along five levels (depicted in Fig. 12.6):

1. Precontemplation (not even begun to consider change)
2. Contemplation (considered change, have not decided to act)
3. Preparation (decided to act, but have not begun)
4. Action (started to act, in early stages)
5. Maintenance (maintaining action over time)

Based on this model, an individual’s readiness to engage in a behavior exists on a spectrum, and any attempt to promote healthy behavior should be tailored to the specific stage that the individual is currently inhabiting. For example, demanding action of someone in pre-contemplation is premature. And for those in the action

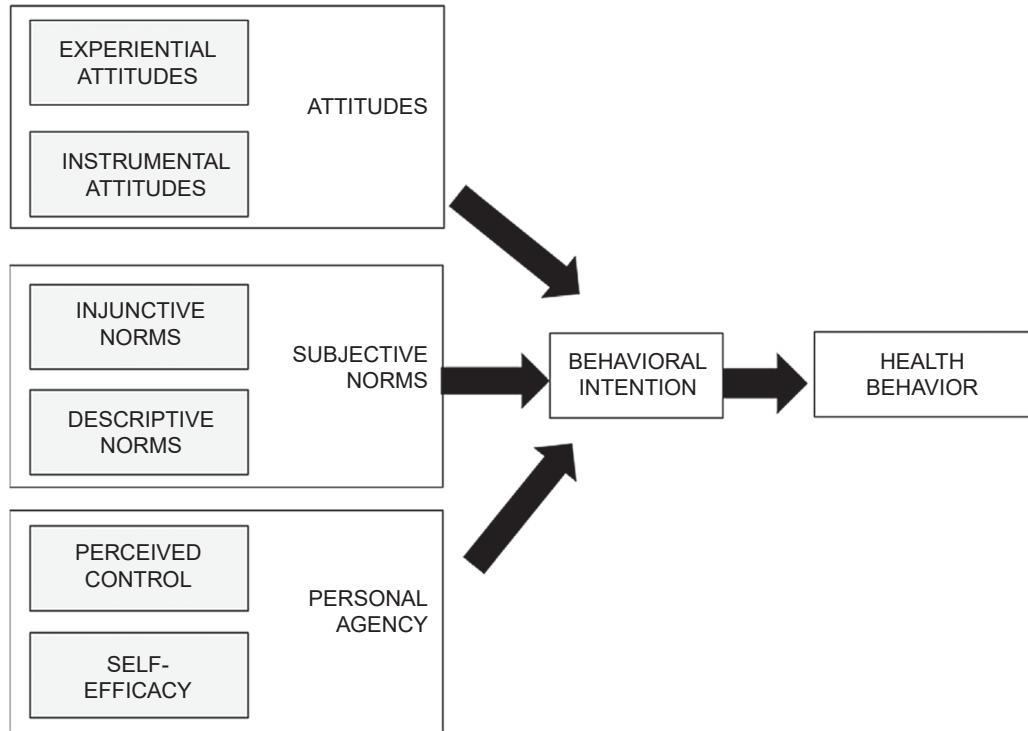


FIGURE 12.5 Integrated behavior model. Reprinted from Grandner MA. Sleep, health, and society. *Sleep Med Clin* 2017;12(1):1–22. PubMed PMID: 28159089.

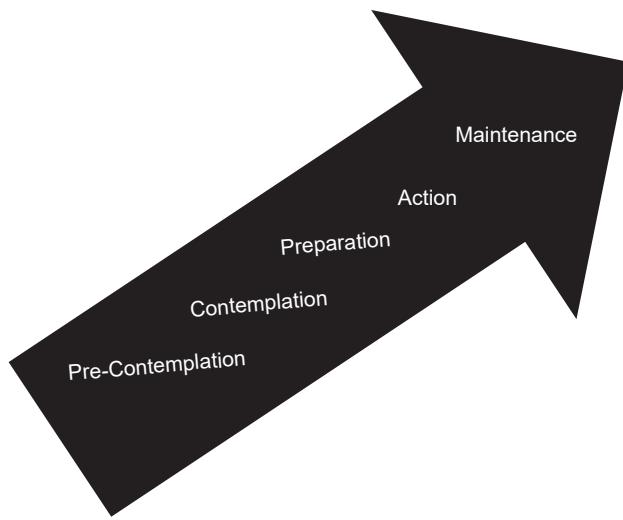


FIGURE 12.6 Transtheoretical model.

stage, relapse prevention rather than motivation to begin an action is more appropriate.

This model can help in the understanding of the role of healthy sleep in society. Many individuals are likely at the precontemplation and contemplation stages, whereas others are at other stages. Understanding this concept of readiness for change can aid in the education and provision of sleep interventions. Many interventions aim for action, but if the individual is not yet at the action stage, then the intervention will be less likely to be successful. This implies that additional efforts are needed to simply increase “contemplation” and awareness, and separate efforts need to motivate action. It also implies that efforts should also be focused on maintenance once people engage in healthy sleep behaviors, so that they are maintained.

Other health behavior models

Other health behavior models exist, and many of these are reviewed in another chapter. Taken together, they may provide insights on how sleep health interventions should be implemented in order to motivate sustained change and, eventually, better population sleep health.

Implementing sleep health programs

Addressing perceived benefits

In order for a sleep health intervention to be successful, it needs to appropriately aid the individual in perceiving benefits from improved sleep. Some suggestions include:

- Providing education on the importance of sleep for several domains of health and functioning, including

tiredness/sleepiness/fatigue, behavioral and emotional health and well-being, cardiovascular and metabolic health, immune system functioning, cognitive performance, and overall physical and mental performance. In particular, interventions should focus on the outcomes that are the most relevant to the individual. These can be specific, such as absenteeism, financial stability, etc.

- Highlighting how sleep can impact both short-term and long-term outcomes. The effects may be measurable in some outcomes very quickly and others over time. This will help reinforce that there are aspects of the person’s daily life that can be impacted quickly so that they may see benefits soon, but that longer term changes may need more sustained efforts. Still, these benefits can be expected, even if they take time.
- Demonstrating which areas of the individual’s life might be amenable to better sleep. This may provide opportunities for helping the individual see the ways that improved sleep can benefit them.
- Pointing out how their functioning is improved on days when they sleep better. This will help individuals see that benefits of better sleep are possible and that they have, in fact, already been experienced.

Addressing perceived barriers

In addition to supporting perceived benefits, interventions should address perceived barriers as well. Some suggestions include:

- Comprehensively addressing the individual’s perceived barriers to better sleep. Work with the individual to identify what all of those barriers are and develop strategies for overcoming them. These could be relatively simple or complicated, depending on the presenting problem. And some barriers may not be readily overcome (e.g., shiftwork).
- Review a chronology of a typical day or week, so that all of the barriers to healthy sleep could be identified. This can be accomplished as an interview, which would allow for follow-up questions regarding clarifying specific barriers that may be less obvious.
- Inventory which barriers are the most relevant and most likely to impede progress. Attention should be focused on those barriers that impede sleep the most.
- Develop strategies for mitigating the impact of barriers that are less amenable to change. For example, if a person’s work shift is precluding healthy sleep and this cannot be changed, perhaps fatigue countermeasures could be employed or other approaches can be taken to support healthy sleep.

Addressing social norms

Even if the individual perceives benefits to healthy sleep behaviors and perceives that the barriers are addressable, the presence of social norms about sleep is important. Some suggestions for incorporating this concept into interventions include:

- Inventory perceived social norms regarding sleep, sleep health, taking time for sleep, winding down, and other relevant concepts. This inventory should address the norms perceived across various social factors such as work, family, friends, relevant social groups, and demographic groups with which the person identified, “society,” and other groups deemed important.
- Question the degree to which unhelpful attitudes about sleep are actually held by these groups, and/or question the degree to which disagreeing with those attitudes will result in social or other adverse outcomes.
- Focus on the benefits of better sleep, and identify ways in which those benefits would be valuable according to the norms of the identified social groups. For example, if an individual believes that their workplace does not value sleep, perhaps focus on the fact that the workplace values productivity, which may be enhanced with better sleep. Thus, even in the presence of social norms that are counter to healthy sleep, other social norms may be used to support a sleep health intervention.
- Include multiple individuals in group-wide sleep health interventions and reinforce the importance of sleep from those in leadership positions. For example, if a workplace wellness program includes sleep health, then the program should reinforce the idea that all of the employees in the program are valuing sleep together, and that the company leadership also values sleep because they are supporting this program.

Addressing self-efficacy and control

There are a number of strategies that can be appropriated in order to increase an individual’s sense of control over their sleep and their sense of self-efficacy regarding taking steps to improve their sleep. Some suggestions include:

- Inventory perceived control over sleep. This can be accomplished with the Brief Index of Sleep Control (BrISC) or some other tool. Generally, any inventory should assess perceived control over sleep timing, sleep duration, and sleep quality. This may identify which aspects of sleep are seen as most problematic and should be the focus of a more intensive approach.
- Provide education about the basic functions of sleep and how basic sleep health interventions work. The

goal of this approach is to help take some of the “mystery” out of sleep and help individuals see sleep as a set of processes that they can understand (at some level) and, therefore, control.

- Interventions should focus on measurable and attainable goals. Setting goals that are too difficult to achieve (e.g., sleep 8 h a night and feel refreshed every morning) may be too difficult. And repeated, daily failure to meet those goals may lead to frustration, burnout, and giving up. Rather, interventions should focus on incremental, achievable goals (e.g., go to bed 10 min earlier tonight) that can result in a track record of successes that accumulate over time. This can reinforce a sense of mastery rather than failure.

Addressing readiness

Interventions focused on immediate action may be premature. And those struggling to maintain behaviors despite already attempting to change behavior may be left without options. Some suggestions for promoting readiness and adapting to stages of change are:

- Assess the individual’s stage of change. This would ascertain whether the person is in a stage of precontemplation, contemplation, preparation, action, or maintenance. Depending on the stage of change for sleep, interventions could be targeted.
- Individuals in the precontemplation stage should be funneled to interventions focused simply on increasing awareness. These interventions should aim to bring those individuals to the contemplation stage, whether or not they engage in behaviors yet.
- Individuals in the contemplation stage should be met with interventions aimed at achieving a behavioral intention to improve sleep and progress to the preparation stage. These interventions should aim to understand what the individual will need in order to make the decision to change their sleep.
- Individuals in the preparation stage, who are intending or planning to make a change, do not need to be convinced about the importance of sleep. Rather, interventions at this stage should focus on removing barriers and facilitating the first steps of actual action.
- Individuals at the action stage should be given all of the tools possible in order to remain successful for as long as possible. This includes a focus on the barriers and benefits, as well as maintaining focus on the issues that are most relevant to them. The goal at this stage is to turn the intervention into a habit and facilitate its maintenance.
- Individuals who have been working on their sleep for some time should be given the tools needed in order to identify problem areas, address those, and



FIGURE 12.7 Recommended elements of a sleep health intervention.

periodically reinforce their healthy practices. Dealing with lapses is important here as well. The goal at this stage is to keep individuals performing healthy sleep behaviors and preventing relapse.

Taken together, these recommendations focus on six main areas (depicted in Fig. 12.7). Interventions should include education about sleep, about the importance of sleep, and about how to make improvements to sleep. Assessment is another key component; this entails not just assessment of sleep but also assessment of the contextual factors that play a role in sleep, including social-level factors. Interventions should also include an element of facilitation—identifying and removing perceived barriers. Related to this issue is the one of control; interventions should explicitly aim to increase individuals' sense of control over their sleep and their self-efficacy regarding sleep-related behaviors. Another key element is addressing the social norms—this includes assessment but also may include strategies for mitigating unhelpful sleep-related norms. Finally, interventions should be adaptive regarding an individual's level of readiness and stage of change.

Conclusion

Real-world barriers to sleep health include intra- and interpersonal factors, as well as social and contextual factors. These can encompass a wide range of possibilities,

most prominently perceived lack of time for sleep, social norms, physical environment, health issues, substances used, and the ubiquity of distractions. These barriers and others can be conceptualized in any number of models, including the Health Belief Model, Integrated Behavior Model, and Transtheoretical Model. Using these frameworks, some recommendations for implementing sleep behavior change interventions include: (1) maximizing perceived benefits; (2) minimizing perceived barriers; (3) mitigating unhelpful social norms; (4) increasing self-efficacy and feelings of control; and (5) leveraging the concept of readiness. Future research needs to study the implementation of these approaches into existing sleep health interventions in order to evaluate which elements of sleep health interventions are most helpful and in what contexts.

References

- [1] Basner M, Fomberstein KM, Razavi FM, Banks S, William JH, Rosa RR, Dinges DF. American time use survey: sleep time and its relationship to waking activities. *Sleep* 2007;30(9):1085–95. <https://doi.org/10.1093/sleep/30.9.1085>.
- [2] Basner M, Dinges DF. Dubious bargain: trading sleep for Leno and letterman. *Sleep* 2009;32(6):747–52. <https://doi.org/10.1093/sleep/32.6.747>.
- [3] Henry D, McClellan D, Rosenthal L, Dedrick D, Gosdin M. Is sleep really for sissies? Understanding the role of work in insomnia in the

- US. Soc Sci Med 2008;66(3):715–26. <https://doi.org/10.1016/j.socscimed.2007.10.007>.
- [4] Grandner MA, Jackson N, Gooneratne NS, Patel NP. The development of a questionnaire to assess sleep-related practices, beliefs, and attitudes. Behav Sleep Med 2014;12(2):123–42. <https://doi.org/10.1080/15402002.2013.764530>.
 - [5] Pigeon WR, Grandner MA. Creating an optimal sleep environment encyclopedia of sleep. United States: Elsevier Inc.; 2013. p. 72–6. <https://doi.org/10.1016/B978-0-12-378610-4.00022-X>.
 - [6] Min JY, Min KB. Outdoor artificial nighttime light and use of hypnotic medications in older adults: a population-based cohort study. J Clin Sleep Med 2018;14(11):1903–10. <https://doi.org/10.5664/jcsm.7490>.
 - [7] Omlin S, Bauer GF, Brink M. Effects of noise from non-traffic-related ambient sources on sleep: Review of the literature of 1990–2010. Noise Health 2011;13(53):299–309. <https://doi.org/10.4103/1463-1741.82963>.
 - [8] Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, Kerns R, Korff V, Porter, Helmick L. Prevalence of chronic pain and high-impact chronic pain among adults—United States. MMWR Morb Mortal Wkly Rep 2016;67(36).
 - [9] Vitiello MV. A step toward solving the sleep/pain puzzle. Sleep 2012;35(5):593–4. <https://doi.org/10.5665/sleep.1806UnitedStates>.
 - [10] Grandner MA, Alfonso-Miller P, Fernandez-Mendoza J, Shetty S, Shenoy S, Combs D. Sleep: important considerations for the prevention of cardiovascular disease. Curr Opin Cardiol 2016;31 (5):551–65. <https://doi.org/10.1097/HCO.0000000000000324>.
 - [11] Phillips KM, Jim HS, Donovan KA, Pinder-Schenck MC, Jacobsen PB. Characteristics and correlates of sleep disturbances in cancer patients. Support Care Cancer 2012;20(2):357–65. <https://doi.org/10.1007/s00520-011-1106-z>.
 - [12] Ebrahim IO, Shapiro CM, Williams AJ, Fenwick PB. Alcohol and sleep I: effects on normal sleep. Alcohol Clin Exp Res 2013;37 (4):539–49. <https://doi.org/10.1111/acer.12006>.
 - [13] Patterson F, Grandner MA, Lozano A, Satti A, Ma G. Transitioning from adequate to inadequate sleep duration associated with higher smoking rate and greater nicotine dependence in a population sample. Addict Behav 2018;77:47–50. <https://doi.org/10.1016/j.addbeh.2017.09.011>.
 - [14] de Leeuw R, Eisenlohr-Moul T, Bertrand P. The association of smoking status with sleep disturbance, psychological functioning, and pain severity in patients with temporomandibular disorders. J Orofac Pain 2013;27(1):32–41. <https://doi.org/10.11607/jop.1040>.
 - [15] Patterson F, Grandner MA, Malone SK, Rizzo A, Davey A, Edwards DG. Sleep as a target for optimized response to smoking cessation treatment. Nicotine Tob Res 2019;21(2):139–48. <https://doi.org/10.1093/ntr/ntx236>.
 - [16] Babson KA, Boden MT, Bonn-Miller MO. The impact of perceived sleep quality and sleep efficiency/duration on cannabis use during a self-guided quit attempt. Addict Behav 2013;38(11):2707–13. <https://doi.org/10.1016/j.addbeh.2013.06.012>.
 - [17] Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Wang NY, Funderburk FR, Allen RP, David PM, Cadet JL. Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence. Sleep Med 2010;11(9):882–9. <https://doi.org/10.1016/j.sleep.2010.02.013>.
 - [18] Roehrs T, Roth T. Caffeine: sleep and daytime sleepiness. Sleep Med Rev 2008;12(2):153–62. <https://doi.org/10.1016/j.smrv.2007.07.004>.
 - [19] Weaver E, Gradisar M, Dohnt H, Lovato N, Douglas P. The effect of presleep video-game playing on adolescent sleep. J Clin Sleep Med 2010;6(2):184–9. <https://doi.org/10.5664/jcsm.27769>.
 - [20] Grandner MA. Sleep, health, and society. Sleep Med Clin 2017;12 (1):1–22. <https://doi.org/10.1016/j.jsmc.2016.10.012>.
 - [21] Montano DK. Theory of reasoned action, theory of planned behavior, and the integrated behavioral model. Jossey-Bass; 2008. p. 68–96.

Chapter 13

Screening for sleep disorders

Catherine A. McCall^{a, b} and Nathaniel F. Watson^c

^aDepartment of Pulmonary, Critical Care, and Sleep Medicine, VA Puget Sound Health Care System, Seattle, WA, United States; ^bDepartment of Psychiatry, University of Washington Sleep Medicine Center, Seattle, WA, United States; ^cDepartment of Neurology, University of Washington Sleep Medicine Center, Seattle, WA, United States

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
AIS	Athens Insomnia Scale
BMI	Body mass index
CAT	Computer-adaptive test
CPAP	Continuous positive airway pressure
DLMO	Dim light melatonin onset
EEG	Electroencephalography
ESS	Epworth Sleepiness Scale
FOSQ-30	Functional Outcomes of Sleep Questionnaire
HSAT	Home sleep apnea test
HSROC	Hierarchical summary receiver operating characteristic
ICSD	International Classification of Sleep Disorders
IRLS	International Restless Legs Syndrome Scale
IRT	Item response theory
ISI	Insomnia Severity Index
KSS	Karolinska Sleepiness Scale
MCTQ	Munich Chronotype Questionnaire
MEQ	Horne-Ostberg Morningness-Eveningness Questionnaire
MSLT	Multiple sleep latency test
MWT	Maintenance of wakefulness test
NIH	National Institutes of Health
NPV	Negative predictive value
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
PPV	Positive predictive value
PROMIS	Patient-Reported Outcomes Measurement Information System
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid eye movement
RLS	Restless legs syndrome
SD	Sleep disturbance
SRI	Sleep-related impairment
SSS	Stanford Sleepiness Scale

Introduction

An estimated 50–70 million people worldwide have chronic disorders of sleep and wakefulness [1]. The most common sleep disorders in the general population include insomnia, obstructive sleep apnea (OSA), circadian rhythm disorders, restless legs syndrome (RLS), and chronically insufficient sleep. Up to 33% of adults report difficulty with sleep onset or maintenance, with chronic insomnia affecting approximately 30 million Americans [2]. As obesity incidence increases and the population ages, the prevalence of OSA exceeds 50% in some countries, with almost 1 billion people affected worldwide [3]. Despite the high prevalence in the general population, routine screening for these disorders does not commonly occur in the primary care setting [4]. For OSA alone, between 80% and 85% of individuals with the disorder remain undiagnosed [5].

In addition to primary sleep disorders, industrialized countries face an epidemic of chronic sleep deprivation perpetuated by long work hours and commute times, early school start times, and increasing exposure to electronic devices during normal sleep hours. These societal pressures and technologies have led to increasingly later bedtimes and earlier rise times for both children and adults. In health surveys conducted by the Centers for Disease Control and Prevention, 35%–40% of US adults report sleeping < 7–8 h per night, with 15% sleeping less than 6 h [6]. In 2018, the makers of a popular consumer sleep technology (Fitbit Inc., San Francisco, CA, United States) reported an analysis of their 2017 worldwide user database indicating an average nightly sleep duration for women of 6 h and 50 min, with men averaging 6 h and 26 min [7], both substantially less than the minimum sleep duration of 7 h or more per night recommended by the American Academy of Sleep Medicine and Sleep Research Society [8].

Poor sleep is associated with numerous adverse health outcomes. Chronic insufficient sleep (<7 h per 24) has been linked with increased risk of all-cause mortality in longitudinal studies, even after controlling for age and health comorbidities [9]. In addition, chronic sleep deprivation has been associated with risk for hypertension [10], major coronary events [11], diabetes [12], poor memory, decreased concentration, slowed reaction times, motor vehicle accidents including fatal fall-asleep crashes [13], and impaired judgment [14]. Adverse health outcomes have also been well-studied in most primary sleep disorders. Untreated OSA is associated with increased risk for hypertension [15], myocardial infarction [16], stroke [17], depression [18], congestive heart failure [19], COPD [20], arrhythmias [21], type 2 diabetes [22], motor vehicle and industrial accidents [23], and overall mortality [24]. Untreated insomnia is linked to the development of depression, substance use disorders, poor quality of life, and suicide [25,26].

The costs of sleep loss and sleep disorders are estimated to be billions of dollars and are a huge economic drain at both the individual and societal levels. Recent reports indicate sleep deprivation costs the US economy \$411 billion dollars per year [27], sleep apnea \$100 billion, and insomnia \$30–100 billion [28,29]. In all three cases, most of these economic losses are due to workplace absenteeism and presenteeism, and to a lesser extent healthcare utilization costs. Excessive sleepiness is associated with industrial accidents, motor vehicle crashes, medical errors, work-related injuries, reduced academic performance, and impaired work productivity [1].

Over the past several years, increased recognition of the morbidity and mortality associated with sleep disorders has led to a rising demand for sleep medicine services. However, access to trained sleep clinicians and diagnostic testing resources is limited. Laboratory polysomnography (PSG) is considered the gold standard for the diagnostic assessment of most sleep disorders, but requires extensive resources for equipment, facilities, staffing, and interpretation of sleep data. The cost and limited availability of PSG increase wait times for diagnosis and delays in treatment. Home sleep apnea testing (HSAT) is also available as a more limited tool for detecting OSA and however still typically requires an evaluation by a sleep medicine practitioner prior to undergoing testing. An increasing need to appropriately triage high-risk individuals for further sleep evaluation underscores the need for screening tools with high-predictive validity for sleep disorders.

Various screening instruments have been developed to evaluate patients who would benefit the most from further evaluation and diagnostic testing. Screening questionnaires have been found to be an efficient and relatively simple way to identify patients at risk for sleep disorders in the primary care setting [4]. Some of these instruments assess nonspecific symptoms such as subjective sleepiness, while others

target symptoms of specific sleep disorders such as OSA. An effective screening tool is cost-effective, minimally burdensome to complete and score, and has a high sensitivity for the targeted symptoms or disorder. With the advent of mobile technology, patients are also increasingly turning to consumer sleep technologies that track sleep parameters such as timing, duration, and even sleep architecture. In the following sections, we discuss the more common screening tools that identify patients at elevated risk for sleep-related illnesses. See Table 13.1 for more information regarding each instrument, including format, scoring, and accessibility.

Sleep-disordered breathing

OSA is a sleep disorder characterized by partial or complete closure of the upper airway during sleep. Symptoms of OSA include snoring, choking during sleep, and breathing pauses associated with oxygen desaturation and/or cortical arousal. Daytime symptoms associated with this disorder include excessive sleepiness, lack of energy, morning headaches, nocturnal gastroesophageal reflux, and erectile dysfunction. Approximately 13% of men and 6% of women aged 30–70 years have an apnea-hypopnea index (AHI, a measure on polysomnography of breathing pauses or irregularity) > 15 events/h, whereas 14% of men and 5% of women have an AHI of >5 events/h with symptoms of daytime sleepiness [3]. Both of these scenarios meet criteria for obstructive sleep apnea as defined by the International Classification of Sleep Disorders [41]. The prevalence of OSA is higher in individuals with elevated body mass index (BMI), male gender, advancing age, increased neck circumference, and postmenopausal status [42,43].

Despite the increased risk conferred by signs and symptoms of OSA, subjective clinical impressions of this disorder appear to have low diagnostic sensitivity and specificity [44]. In one study of patients referred to a sleep center, a report of snoring was found to have high sensitivity (80%–90%) and low specificity (20%–50%) for the diagnosis of OSA, whereas a report of nocturnal choking or gasping was less sensitive (52%) and more specific (84%). The positive predictive value (PPV) of nocturnal choking or gasping for the diagnosis of OSA was 35%, which is greater than the PPV of morning headache, witnessed apneas, snoring, or excessive daytime sleepiness [44]. Optimal screening of patients with OSA may include a combination of signs and symptoms of OSA, including habitual snoring, witnessed apneas, large neck circumference, elevated BMI, and systemic hypertension [45]. Various screening instruments have been designed to evaluate risk for OSA by assessing these factors. Other screening tools commonly used for OSA include those assessing nonspecific symptoms such as excessive daytime sleepiness, reduced daytime function, and poor sleep quality. Screening for OSA may improve the sensitivity

TABLE 13.1 Common screening questionnaires.

Questionnaire	Symptoms measured	Timing of symptoms	Number of questions	Response options	Scoring	How to obtain
STOP-BANG [30]	Sleep-disordered breathing	No specified timing	8	Four yes/no questions plus four clinical attributes	Item responses are summed to obtain a total score. Scores range from 0 to 8. Suggested guidelines: 0–2 = low risk; 3–4 = intermediate risk; 5–8 = high risk	http://www.stopbang.ca
Berlin questionnaire [31]	Sleep-disordered breathing	No specified timing	9	Multiple choice questions in three categories: OSA symptoms, daytime sleepiness, and the presence of hypertension	Each item is given a unique score. Categories are considered “positive” with a specific number of total points. 2–3 positive categories = high risk for OSA. 0–1 positive categories = low risk for OSA	Freely available online
Epworth sleepiness scale [32]	Hypersomnolence	“Recently”; no specific timing	8	4-point Likert scale response format regarding the likelihood of falling asleep in various situations, from 0 (would never doze) to 3 (high chance of dozing)	Item responses are summed to obtain a total score. Scores range from 0 to 28. Scores of ≥ 10 indicate clinically significant hypersomnia	http://epworthsleepinessscale.com
Functional outcomes of sleep questionnaire [33]	Hypersomnolence	No specified timing	FOSQ-30: 30 FOSQ-10: 10	4-point Likert scale response format, divided into five subscales rating the current difficulty of performing various tasks due to sleepiness. Answers range from 1 (extreme difficulty) to 4 (no difficulty)	An average score is calculated for each subscale. The five subscales are totaled to produce a total score ranging from 5 to 20, with higher scores indicating better functional status. A total score < 18 indicates a clinically significant impact of sleepiness on quality of life. A change in two or more points indicates a significant change in sleep-related daily functioning	Available from the authors. Permission for use is required. Contact Terri E. Weaver, PhD, RN, University of Illinois at Chicago, teweaver@uic.edu
Stanford sleepiness scale [34]	Hypersomnolence	Current point in time	1	One item in which respondents select one of seven statements best representing their current level of sleepiness	Score is 1–7, with 1 indicating no sleepiness, and 7 indicating excessive sleepiness	Freely available online

Continued

TABLE 13.1 Common screening questionnaires.—cont'd

Questionnaire	Symptoms measured	Timing of symptoms	Number of questions	Response options	Scoring	How to obtain
Karolinska sleepiness scale [35]	Hypersomnolence	Current point in time	1	One item in which respondents select one of nine statements representing their level of alertness or sleepiness	Score is 1–9, with 7 or above indicating excessive sleepiness	A copy can be obtained from the author: Torbjörn Åkerstedt, IPM & Karolinska Institutet, Torbjorn.Akerstedt@ki.se
Insomnia severity index [36]	Insomnia	Last 2 weeks	7	5-point Likert response format ranging from 0 (none) to 4 (very severe) in two sections: Severity of insomnia, and impact of symptoms	Responses are added to determine the total score Score range is 0–28. Suggested guidelines: 0–7 = no clinically significantly insomnia; 8–14 = subthreshold insomnia; 15–21 = moderate clinical insomnia; 22–28 = severe clinical insomnia	Permission for usage can be obtained from the author: Charles M. Morin, PhD, Université Laval and Center de recherche Université, cmorin@psy.ulaval.ca
Pittsburgh sleep quality index [37]	Subjective sleep quality and insomnia	1 month	19, plus 5 additional items completed by a bed partner	Seven components: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. Items 1–4 are free entry fields for sleep timing. Remaining items have 4-point Likert scale response format with 0 indicating lowest severity/frequency, and 4 indicating greatest severity/frequency	A scoring algorithm is used to calculate each component score from 0 to 3, which are then summed to obtain a total score. Scores range from 0 to 21, with higher scores indicating worse sleep quality. A score ≥ 5 indicates poor sleep quality	Permission for usage can be obtained from the author: Daniel J. Buysse, MD, University of Pittsburgh, buyssedj@upmc.edu
Patient-reported outcomes measurement information system [38]	Sleep disturbance, sleep-related impairment	7 days	SD scale: 27; SRI scale: 16; CAT and short versions with 4, 6, and 8 items also available	5-point Likert scale response format from 1 to 5, with 5 indicating more severe sleep disturbance or impairment	A scoring algorithm converts the raw score to a standardized T-score with a mean of 50 and standard deviation of 10, with higher scores indicating greater sleep disturbance or impairment	Freely available online at: http://www.healthmeasures.net/explore-measurement-systems/promis

Horne-ostberg morningness-eveningness questionnaire [39]	Chronotype	“Recent weeks”	19	Multiple choice answers ranging from 0 to 6	Responses are added to determine the total score. Score range is 16–86, with lower scores indicating an evening chronotype and higher scores indicating a morning chronotype	Freely available online
Munich chronotype questionnaire [40]	Chronotype, circadian rhythm disorders	Last 4 weeks	Full version: 32 core version: 13	Combination of multiple choice and free entry in six sections: Personal data, sleep schedule on work days and free days, work and commute times, time spent outdoors, and frequency of stimulants		Permission for usage can be obtained from the author: Till Roenneberg, till.roenneberg@med.uni-muenchen.de
International restless legs syndrome scale [41]	Restless legs syndrome	Most recent 2 weeks	10	5-point Likert scale response format with 0 indicating no symptoms and 4 indicating greater severity or frequency of symptoms	Responses are added to determine the total score. Score range is 0–40, with higher numbers indicating more severe RLS symptoms	Permission for usage can be obtained from: Caroline Anfray, Information Resources Centre, MAPI Research Institute, canfray@mapi.fr or instdoc@mapi.fr

CAT, computer-adaptive test; OSA, obstructive sleep apnea; SD, sleep disturbance; SRI, sleep-related impairment.

and specificity of laboratory and home sleep apnea tests, and reduce overall cost by limiting expensive diagnostic studies to those who have higher pretest probability of having the disease. The following sections describe the most commonly used screening tools designed to assess sleep-disordered breathing.

STOP and STOP-BANG questionnaires

The STOP-BANG is an eight-item screening tool for OSA that consists of four yes/no questions and four clinical attributes, with a total possible score of 0–8 [31]. The tool is a simple mnemonic in which “S” stands for snoring, “T” for tiredness/fatigue, “O” for observed apneas, “P” for high blood pressure, “B” for BMI >35, “A” for age >50, “N” for neck circumference >40 cm, and “G” for male gender. This tool was originally developed as the four-item STOP questionnaire to screen for OSA in presurgical patients and was validated against the AHI recorded during overnight PSG [31]. The authors found that, of those patients with an AHI of >5 events/h, there was a higher percentage of males (57%) versus females (43%). This group was also about 10 years older, had greater BMI, and larger neck size than patients with AHI ≤5. The STOP-BANG questionnaire was then created to include these additional measures.

Since then, a number of studies have validated the effectiveness of both the STOP and the STOP-BANG for OSA screening in various populations. A systematic review and meta-regression analysis of 24 STOP questionnaire studies between 2008 and 2021 found high sensitivity for detecting OSA in both the sleep clinic (>89% for all OSA severity levels) and medical populations (86% for severe OSA), as well as high discriminative power to exclude severe OSA (negative predictive values >84%) [42].

A systematic review and meta-analysis including 17 studies with 9206 subjects validating STOP-BANG scores by polysomnographic testing concluded that in the sleep clinic population, sensitivity was 90% for detecting any OSA (defined as AHI ≥5), 94% for detecting moderate-severe OSA (defined as AHI ≥15), and 96% for detecting severe OSA (defined as AHI ≥30). However, specificity was relatively low at 49%, 34%, and 25%, respectively. The positive predictive value (PPV) was 91% for any OSA, 72% for moderate-severe OSA, and 48% for severe OSA, and the negative predictive values (NPV) were 46%, 75%, and 90%, respectively. In the sleep clinic population, the probability of severe OSA with a STOP-BANG score of 3 was 25%. With a stepwise increase in the STOP-BANG score to 4, 5, 6, and 7/8, the probability rose proportionally to 35%, 45%, 55%, and 75%, respectively [46].

The American Academy of Sleep Medicine (AASM) clinical practice guideline for the diagnostic testing of OSA notes the STOP-BANG tool demonstrates overall high sensitivity, but low specificity, for the detection of OSA in

studies validating the instrument against PSG. The findings were similar for home sleep apnea tests [47].

Berlin questionnaire

The Berlin questionnaire is an 11-item self-report measurement, divided into three categories: five questions describing snoring and witnessed apneas, four questions rating daytime sleepiness, and a yes/no question regarding the presence or absence of hypertension, scored in conjunction with the patient’s BMI (Fig. 13.1). Each category is graded as “high risk” or “low risk” for OSA based on separate criteria. The patient is considered at overall “high risk” if the patient reports having persistent (>3–4 times/week) symptoms in at least two symptom categories [32].

A meta-analysis comparing the summary sensitivity and specificity of the Berlin Questionnaire, STOP-BANG, STOP, and Epworth Sleepiness Scale (ESS) found pooled sensitivity levels of 76% for AHI ≥5, 77% for AHI ≥15, and 84% for AHI ≥30. Pooled specificity was 59% for AHI ≥5, 44% for AHI ≥15, and 38% for AHI ≥30. This was less sensitive and more specific than the STOP-BANG for all severities of OSA, but less specific than the ESS [48].

The AASM clinical practice guideline found similar results in a meta-analysis of 19 studies that evaluated the performance of the Berlin Questionnaire against PSG in various patient populations and geographic studies, finding a pooled sensitivity of 76% and pooled specificity of 45% for AHI ≥5. The authors, in addition, noted suboptimal accuracy, derived by hierarchical summary receiver operating characteristic (HSROC) curves, ranging from 56% to 70% that was progressively reduced with higher AHI thresholds [47].

Hypersomnolence

A large proportion of adults presenting to sleep clinics report symptoms of excessive daytime sleepiness. The prevalence of chronic excessive sleepiness is as high as 20% in the general population [49]. Sleepiness is associated with a wide array of sleep disorders, medical illnesses, and medication side effects. Assessing the severity of sleepiness, as opposed to fatigue, is an important aspect of diagnosis and management of sleep disorders such as OSA, idiopathic hypersomnia, and narcolepsy.

The multiple sleep latency test (MSLT) is a widely used assessment of objective sleepiness. It involves four to five sequential daytime nap opportunities, each separated by 2 h. This test is based on the premise that, given an adequate opportunity to sleep the night prior, a patient with hypersomnia will have a shorter mean sleep latency than a patient without hypersomnia. In addition, observation of two or more naps containing rapid eye movement (REM) sleep within 15 min of falling asleep is indicative of narcolepsy, a central nervous system hypersomnia disorder. The MSLT

- Category 1:**
1. Do you snore?
 - a. Yes
 - b. No
 - c. Don't know
- If you answered 'yes':
2. Your snoring is:
 - a. Slightly louder than breathing
 - b. As loud as talking
 - c. Louder than talking
 3. How often do you snore?
 - a. Almost every day
 - b. 3-4 times per week
 - c. 1-2 times per week
 - d. 1-2 times per month
 - e. Rarely or never
 4. Has your snoring ever bothered other people?
 - a. Yes
 - b. No
 - c. Don't know
 5. Has anyone noticed that you stop breathing during your sleep?
 - a. Almost every day
 - b. 3-4 times per week
 - c. 1-2 times per week
 - d. 1-2 times per month
 - e. Rarely or never
- Category 2:**
6. How often do you feel tired or fatigued after your sleep?
 - a. Almost every day
 - b. 3-4 times per week
 - c. 1-2 times per week
 - d. 1-2 times per month
 - e. Rarely or never
 7. During your waking time, do you feel tired, fatigued or not up to par?
 - a. Almost every day
 - b. 3-4 times per week
 - c. 1-2 times per week
 - d. 1-2 times per month
 - e. Rarely or never
 8. Have you ever nodded off or fallen asleep while driving a vehicle?
 - a. Yes
 - b. No
- If you answered 'yes':
9. How often does this occur?
 - a. Almost every day
 - b. 3-4 times per week
 - c. 1-2 times per week
 - d. 1-2 times per month
 - e. Rarely or never
- Category 3**
10. Do you have high blood pressure?
 - a. Yes
 - b. No
 - c. Don't know

FIGURE 13.1 Berlin questionnaire.

has a high test-retest reliability in normal subjects and is the standard method for objectively measuring daytime sleepiness despite being time-consuming and expensive. Another laboratory test that indirectly assesses sleepiness is the maintenance of wakefulness test (MWT), which measures the individual's ability to stay awake in a quiet, non-stimulating environment. Other sleepiness assessments are subjective and reviewed below.

Epworth Sleepiness Scale (ESS)

The ESS is an eight-item self-report measure assessing sleep propensity in a variety of common situations [33]. Respondents are asked, "How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?" Answer choices for each scenario range from 0 ("would never doze") to 3 ("high chance of dozing"). Responses are summed to yield a total score of 0–24, with higher scores indicating greater sleep propensity. The ESS is the most widely used tool for assessing subjective sleepiness in both research and clinical practice. Unlike other sleepiness scales such as the Stanford Sleepiness Scale, the ESS measures sleep propensity based on recall of situational tendencies to fall asleep, rather than subjective sleepiness itself.

The ESS reliability and efficacy were initially assessed in OSA patients. Fifty-four OSA patients completed the ESS before and after starting treatment with continuous positive airway pressure (CPAP). When compared to 104 medical student controls, a significant difference in baseline ESS score was observed in OSA patients before, but not after, CPAP treatment [50]. Additional evidence of validity includes a study suggesting ESS predicts narcolepsy with greater accuracy than the MSLT [51]. Since then, a number of studies have shown an association between ESS score and OSA severity using PSG or objective sleepiness using MSLT [10,52]; however other studies show no significant association [53–55].

The AASM clinical practice guideline task force reviewed studies evaluating the performance of the ESS against PSG for identifying OSA, and found a sensitivity of 27%–72%, with a specificity of 50%–76% for identifying patients with AHI ≥ 5 . When compared to home sleep apnea tests, the ESS showed low sensitivity (36%) and higher specificity (77%) for identifying OSA [47].

One challenge when evaluating ESS validity for OSA diagnosis is that sleepiness is commonly reported in OSA as fatigue and lack of energy [56,57]. Patients with moderate-to-severe OSA may report feeling unrested or tired but deny sleepiness and have a normal ESS score [57]. In addition,

some patients underestimate their own sleep propensity. One study in which both the patient and their bed partner completed the ESS, the scores completed by the partner were significantly higher than those completed by the patient. In addition, the partner and patient-partner consensus scores were both significantly correlated with the presence of OSA, whereas patient scores alone were not [58]. Physician-administered ESS scores may also be greater than patient self-reported scores. Physician-administered ESS scores also correlate better with PSG-determined AHI and oxygen desaturation indices (ODI) than those self-administered by the patient [59].

Functional outcomes of sleep questionnaire (FOSQ-30)

The FOSQ-30 is a 30-item questionnaire assessing the respondent's current difficulty performing tasks due to sleepiness, based on a Likert-type scale from 1 to 4, with a rating of 1 indicating "extreme difficulty," and 4 indicating "no difficulty." [34] The difference between "sleepy" and "tired" is clarified in the instructions. All 30 items are categorized into one of five subscales: activity level (9 items), vigilance (7 items), intimacy and sexual relationships (4 items), general productivity (8 items), and social outcomes (2 items). There is, in addition, a shorter version of the FOSQ with only 10 items.

In clinical practice and research, the FOSQ assesses sleep disorders impact on daytime function and evaluates therapeutic response. The FOSQ has good sensitivity in measuring CPAP adherence differences [60]. A score >17.9 represents the lower limit for normal sleep-related quality of life, whereas a change in two or more points indicates a clinically meaningful improvement in daily functioning [61].

Stanford Sleepiness Scale (SSS)

The Stanford Sleepiness Scale (SSS) is a simple test where patients select one of seven statements best representing their present level of perceived sleepiness [35] (Fig. 13.2). The SSS is a momentary sleepiness scale often administered repeatedly to detect sleepiness variation over the course of a day. The SSS was initially validated to predict performance deficits during acute total or short-term partial sleep deprivation [35,62]; however, it is less valid for assessing cumulative partial sleep deprivation [62] or

identifying narcolepsy [63]. The SSS has not been validated, to our knowledge, as a predictive measure for OSA.

Karolinska Sleepiness Scale (KSS)

Similar to the SSS, the Karolinska Sleepiness Scale (KSS) is a tool measuring momentary sleepiness using a nine-point Likert-type scale with possible ratings ranging from a score of 1 signifying "very alert" to 9, signifying "very sleepy, great effort to stay awake, fighting sleep." Scores of ≥ 7 are pathologic (Fig. 13.3) [64]. The original version provided labels at every other number of the scale, however studies showed a bias where subjects selected labeled numbers over unlabeled numbers. This resulted in labels being added to all numbers of the scale [65].

The KSS focuses on sleep propensity, whereas the SSS assesses levels of fatigue or boredom [66]. The KSS is validated against electroencephalography (EEG) and various performance measurements, and is most commonly used to evaluate sleepiness in drug trial participants, professional drivers, flight crews, train engineers, and oil rig workers [64,67]. The KSS varies over the diurnal cycle, and is impacted by physical activity, social interaction, and light exposure [66].

Data are limited regarding efficacy of sleepiness measures in clinical populations, including predictive value for OSA diagnosis. One study showed positive correlations between subjective sleepiness on the KSS, EEG changes indicative of sleepiness, and likelihood of errors on a 2-h monotonous driving simulator task in OSA patients treated with CPAP. After sleep restriction, OSA patients had significantly shorter safe driving times relative to controls, and underestimation of KSS-reported sleepiness level [68]. Another study with OSA patients found significantly higher baseline KSS scores in OSA patients compared with controls, but no difference in sleepiness or performance on the psychomotor vigilance task after 40 h of sustained wakefulness [69].

Insomnia and sleep quality

Insomnia is a disorder characterized by persistent difficulty with sleep initiation, sleep maintenance, sleep consolidation, and/or sleep quality. Diagnosing insomnia requires a complete history identifying medical, neurologic, psychiatric, medication, and/or substance-related causes of the

FIGURE 13.2 Stanford Sleepiness Scale.

Degree of Sleepiness	Scale Rating
Feeling active and vital, alert, wide awake	1
Functioning at a high level, but not at peak, able to concentrate	2
Relaxed, awake, not at full alertness, responsive	3
A little foggy, not at peak, let down	4
Foggy, beginning to lose interest in remaining awake, slowed down	5
Sleepy, prefer to be lying down, fighting sleep, woozy	6
Almost in reverie, sleep onset soon, lost struggle to remain awake	7

Select the one statement that best describes your sleepiness during the previous 5 minutes.

- 1. Extremely alert
- 2. Very alert
- 3. Alert
- 4. Rather alert
- 5. Neither alert nor sleepy
- 6. Some signs of sleepiness
- 7. Sleepy, but no effort to keep awake
- 8. Sleepy, some effort to keep awake
- 9. Very sleepy, great effort to keep awake, fighting sleep

FIGURE 13.3 Karolinska Sleepiness Scale.

sleep impairment. Unlike with other sleep disorders, PSG is not indicated for insomnia diagnosis, although it is necessary to rule out other sleep disorders such as OSA that may cause persistent difficulty sleeping. Screening instruments are highly predictive for insomnia because symptoms define the disorder [70]. Some instruments such as the Insomnia Severity Index (ISI) identify core symptoms of insomnia, whereas others such as the Pittsburgh Sleep Quality Index (PSQI) include additional questions on sleep quality and daytime dysfunction.

Insomnia severity index (ISI)

The ISI is a self-report instrument with seven items that characterize insomnia symptoms and the degree of concern or distress caused by those symptoms [36]. Initially developed to measure insomnia research outcomes, including clinical trials and morbidity studies, the ISI is now a commonly used insomnia screening instrument. The first three questions rate respondents' difficulty falling asleep, staying asleep, or waking up too early over the past 2 weeks, with 0 indicating "None" and four indicating "Very Severe." The last four questions rate how satisfied/dissatisfied they are with their current sleep pattern, the noticeability of their problem, how worried/distressed they are, and to what extent their sleep problem interferes with daily functioning. Each of these questions is also rated from 0 to 4, with 4 indicating greater problem severity. The total scores range from 0 to 28, with higher numbers indicating more severe insomnia.

Suggested guidelines for interpreting scores state 0–7 indicates no clinically significant insomnia, 8–14 indicates subthreshold (mild) insomnia, 15–21 indicates moderate clinical insomnia, and 22–28 indicates severe clinical insomnia. Although few studies validate these cutoffs, one community-based study found a score of ≥ 10 identified insomnia with a sensitivity of 86% and a specificity of 88%. In a clinical sample in the same study, a score reduction of 8.4 points revealed moderate insomnia improvement following treatment as rated by an independent assessor [71,72]. A study with 1670 cancer patients showed significant correlations between the ISI rating of sleep onset insomnia and PSG sleep onset latency, and ISI rating of sleep maintenance insomnia and PSG number of

nocturnal awakenings. Receiver operating characteristic analysis showed a score of 8 represents an optimal cutoff score for clinically significant insomnia, with a sensitivity of 95% and specificity of 47% [73].

A meta-analysis of 19 studies comprising 4693 participants evaluating the diagnostic accuracy of the ISI, Athens Insomnia Scale (AIS), and Pittsburgh Sleep Quality Index (PSQI) found a pooled sensitivity of 88% and specificity of 85% when compared to a diagnostic reference standard such as the International Classification of Sleep Disorders (ICSD). This was less sensitive but more specific than the PSQI for identifying individuals with insomnia [74].

Pittsburgh sleep quality index (PSQI)

The PSQI is a self-report measure of sleep quality consisting of 19 items, plus a five-item rating completed by a bed partner not included in scoring [37]. Respondents are instructed to record their typical sleep schedule and frequency of specific sleep problems over the past month on a four-point Likert-type scale, with 0 indicating lower frequency or severity, and three indicating greater frequency or severity. Unlike sleep instruments targeted to screen only for the presence of insomnia, the PSQI also includes questions on symptoms causing sleep disturbance such as snoring, nightmares, discomfort, and pain. These questions yield scores on seven subscales: subjective sleep efficiency, sleep latency, sleep duration, sleep quality, sleep disturbance, sleep medication use, and daytime dysfunction due to sleepiness. The subscale scores are added to obtain a total score ranging from 0 to 21, with higher total scores indicating poorer sleep quality.

The PSQI has high sensitivity in studies assessing insomnia screening accuracy. A meta-analysis comparing the PSQI to a diagnostic reference standard such as the International Classification of Sleep Disorders (ICSD) found a sensitivity of 94% and specificity of 76%. This was more sensitive but less specific in identifying insomnia than the ISI [74]. Studies examining other clinical populations including individuals with obstructive sleep apnea, periodic limb movement disorder, rapid eye movement sleep behavior disorder, and narcolepsy found low criterion validity for these diagnoses when compared to PSG and MSLT.

However, significant correlations were observed with symptoms of depression and anxiety in these populations [75,76]. The PSQI is useful for identifying factors contributing to insomnia, including psychiatric and medical symptoms, but requires more time to complete than shorter insomnia questionnaires.

Patient-reported outcomes measurement information system (PROMIS)

The PROMIS is a set of scales created as an NIH Roadmap initiative for improving patient-reported outcomes for a variety of symptoms, including sleep and wakefulness [38]. The scales were developed based on rigorous psychometric testing methods to provide continuous, relative values for individuals rather than categorizing disorders. There are two sleep-related item banks in this System: the Sleep Disturbance (SD) scale with 27 items, and the Sleep-Related Impairment (SRI) scale with 16 items. Questions are posed as statements with potential responses ranging from 1 to 5 for symptoms occurring within the last 7 days. Individual items can be selected from these item banks to create short forms. All of the scales are free and available in multiple “short forms” of 4, 6, and 8-item questionnaires, as well as computer-adaptive tests (CAT) that display only relevant questions based on the respondent’s prior answers. The short forms allow providers to combine questions from other domains of the PROMIS database, for example fatigue, depression, and pain. Scoring is performed using Item Response Theory (IRT), a family of statistical models linking individual questions to a theoretical underlying syndrome of sleep disturbance. Using the PROMIS scoring manual or scoring service, the respondent’s score is converted into a standardized T-score, which can be viewed relative to a mean of 50 and standard deviation of 10. Higher scores indicate greater sleep disturbance or impairment (For more information, see www.nihpromis.org).

One study investigating the validity of customized eight-item short forms for the SD and SRI item banks developed from post hoc CAT simulations found these short forms demonstrated greater measurement precision than the PSQI and ESS, although the full item banks provided greater test information [77]. A study in ambulatory cancer patients with PROMIS CAT item banks found high correlation with ISI scores, and 98% of the patients reported the screening was not burdensome [78]. We were unable to find any studies comparing the PROMIS instrument to an objective reference standard, such as PSG, for the diagnosis of a sleep disorder.

Some advantages of using the PROMIS instruments include scale-specific psychometric validity, customizability in combination with other symptom domains, and measurement power regarding an individual’s fit along a

spectrum of symptom severity. The PROMIS scales help providers follow trends in symptoms or treatment outcomes over time. The National Institutes of Health (NIH) integrates PROMIS measures into electronic health records, including Epic and Cerner. However, this instrument does not query respondents on quantitative data such as sleep timing, sleep duration, or symptoms of specific sleep disorders. Although it would help identify and track sleep-related symptoms, it does not provide the necessary screening data to quantify risk for a specific diagnosis or support PSG testing. Scoring the instrument requires time and knowledge if a scoring service is not utilized.

Circadian rhythm disorders

Although most humans sleep at night and are awake during the day, considerable inter-individual variation exists in chronotype, with extreme morning types often described as “larks” and extreme evening types described as “owls.”

Circadian rhythm sleep disorders are typically due to discrepancies between the internal circadian cycle and the external light-dark cycle. These disorders can be caused by alterations in the external cycle (e.g., shift work or jet lag), internal cycle (e.g., delayed sleep-wake phase disorder or advanced sleep-wake phase disorder), or dysfunction in the clock circuitry of the brain (e.g., irregular sleep-wake rhythm disorder). Delayed sleep-wake phase disorder typically presents as nighttime insomnia with morning hypersomnolence, whereas advanced sleep-wake phase disorder presents as evening hypersomnolence with early morning awakenings. Approximately 7%–16% of patients presenting to sleep disorders clinics with insomnia complaints are diagnosed with delayed sleep-wake phase disorder [79]. Questionnaires such as the Munich Chronotype Questionnaire (MCTQ) and the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ) may be useful to distinguish a circadian rhythm disorder from chronic insomnia by identifying the individual’s chronotype.

Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ)

The MEQ is a 19-item self-report questionnaire in which respondents report their optimal sleep and wake schedule, how they feel at various points in their current schedule, and what they would do faced with a variety of sleep scheduling scenarios [39] (Fig. 13.4). Each item has a range of possible scores from 0 to 6. The sum of the individual items ranges from 16 to 86, with lower scores corresponding to evening types or “owls,” and higher scores indicating morning types or “larks.” The MEQ has become a widely used instrument to classify circadian type in research on normal subjects and patients.

- (A)** For each question, please select the answer that best describes you by circling the point value that best indicates how you have felt in recent weeks.
1. Approximately what time would you get up if you were entirely free to plan your day?
 - [5] 5:00 AM–6:30 AM (05:00–06:30 h)
 - [4] 6:30 AM–7:45 AM (06:30–07:45 h)
 - [3] 7:45 AM–9:45 AM (07:45–09:45 h)
 - [2] 9:45 AM–11:00 AM (09:45–11:00 h)
 - [1] 11:00 AM–12 noon (11:00–12:00 h)
 2. Approximately what time would you go to bed if you were entirely free to plan your evening?
 - [5] 8:00 PM–9:00 PM (20:00–21:00 h)
 - [4] 9:00 PM–10:15 PM (21:00–22:15 h)
 - [3] 10:15 PM–12:30 AM (22:15–00:30 h)
 - [2] 12:30 AM–1:45 AM (00:30–01:45 h)
 - [1] 1:45 AM–3:00 AM (01:45–03:00 h)
 3. If you usually have to get up at a specific time in the morning, how much do you depend on an alarm clock?
 - [4] Not at all
 - [3] Slightly
 - [2] Somewhat
 - [1] Very much
 4. How easy do you find it to get up in the morning (when you are not awakened unexpectedly)?
 - [1] Very difficult
 - [2] Somewhat difficult
 - [3] Fairly easy
 - [4] Very easy
 5. How alert do you feel during the first half hour after you wake up in the morning?
 - [1] Not at all alert
 - [2] Slightly alert
 - [3] Fairly alert
 - [4] Very alert
 6. How hungry do you feel during the first half hour after you wake up?
 - [1] Not at all hungry
 - [2] Slightly hungry
 - [3] Fairly hungry
 - [4] Very hungry
 7. During the first half hour after you wake up in the morning, how do you feel?
 - [1] Very tired
 - [2] Fairly tired
 - [3] Fairly refreshed
 - [4] Very refreshed
 8. If you had no commitments the next day, what time would you go to bed compared to your usual bedtime?
 - [4] Seldom or never later
 - [3] Less than 1 hour later
 - [2] 1-2 hours later
 - [1] More than 2 hours later
 9. You have decided to do physical exercise. A friend suggests that you do this for one hour twice a week, and the best time for him is between 7-8 AM (07-08 h). Bearing in mind nothing but your own internal "clock," how do you think you would perform?
 - [4] Would be in good form
 - [3] Would be in reasonable form
 - [2] Would find it difficult
 - [1] Would find it very difficult
 10. At approximately what time in the evening do you feel tired, and, as a result, in need of sleep?
 - [5] 8:00 PM–9:00 PM (20:00–21:00 h)
 - [4] 9:00 PM–10:15 PM (21:00–22:15 h)
 - [3] 10:15 PM–12:45 AM (22:15–00:45 h)
 - [2] 12:45 AM–2:00 AM (00:45–02:00 h)
 - [1] 2:00 AM–3:00 AM (02:00–03:00 h)
 11. You want to be at your peak performance for a test that you know is going to be mentally exhausting and will last two hours. You are entirely free to plan your day. Considering only your "internal clock," which one of the four testing times would you choose?
 - [6] 8 AM–10 AM (08–10 h)
 - [4] 11 AM–1 PM (11–13 h)
 - [2] 3 PM–5 PM (15–17 h)
 - [0] 7 PM–9 PM (19–21 h)

FIGURE 13.4 Morningness-eveningness questionnaire. English version prepared by Terman M, Rifkin JB, Jacobs J, White TM (2001), New York State Psychiatric Institute, 1051 Riverside Drive, Unit 50, New York, NY, 10032.

- (B)**
12. If you got into bed at 11 PM (23 h), how tired would you be?
 - [0] Not at all tired
 - [2] A little tired
 - [3] Fairly tired
 - [5] Very tired
 13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which one of the following are you most likely to do?
 - [4] Will wake up at usual time, but will not fall back asleep
 - [3] Will wake up at usual time and will doze thereafter
 - [2] Will wake up at usual time, but will fall asleep again
 - [1] Will not wake up until later than usual
 14. One night you have to remain awake between 4-6 AM (04-06 h) in order to carry out a night watch. You have no time commitments the next day. Which one of the alternatives would suit you best?
 - [1] Would not go to bed until the watch is over
 - [2] Would take a nap before and sleep after
 - [3] Would take a good sleep before and nap after
 - [4] Would sleep only before the watch
 15. You have two hours of hard physical work. You are entirely free to plan your day. Considering only your internal "clock," which of the following times would you choose?
 - [4] 8 AM-10 AM (08-10 h)
 - [3] 11 AM-1 PM (11-13 h)
 - [2] 3 PM-5 PM (15-17 h)
 - [1] 7 PM-9 PM (19-21 h)
 16. You have decided to do physical exercise. A friend suggests that you do this for one hour twice a week. The best time for her is between 10-11 PM (22-23 h). Bearing in mind only your internal "clock," how well do you think you would perform?
 - [1] Would be in good form
 - [2] Would be in reasonable form
 - [3] Would find it difficult
 - [4] Would find it very difficult
 17. Suppose you can choose your own work hours. Assume that you work a five-hour day (including breaks), your job is interesting, and you are paid based on your performance. At approximately what time would you choose to begin?
 - [5] 5 hours starting between 4-8 AM (05-08 h)
 - [4] 5 hours starting between 8-9 AM (08-09 h)
 - [3] 5 hours starting between 9 AM-2 PM (09-14 h)
 - [2] 5 hours starting between 2-5 PM (14-17 h)
 - [1] 5 hours starting between 5 PM-4 AM (17-04 h)
 18. At approximately what time of day do you usually feel your best?
 - [5] 5-8 AM (05-08 h)
 - [4] 8-10 AM (08-10 h)
 - [3] 10 AM-5 PM (10-17 h)
 - [2] 5-10 PM (17-22 h)
 - [1] 10 PM-5 AM (22-05 h)
 19. One hears about "morning types" and "evening types." Which one of these types do you consider yourself to be?
 - [6] Definitely a morning type
 - [4] Rather more a morning type than an evening type
 - [2] Rather more an evening type than a morning type
 - [1] Definitely an evening type

Total points for all 19 questions:

FIGURE 13.4 cont'd

A review of 14 studies using the MEQ in normal subjects in comparison with an objective circadian phase marker such as core body temperature or dim light melatonin onset (DLMO) found a strong negative correlation between the MEQ score and the objective marker, indicating congruence between these measures. Four of the studies used additional measures such as actigraphy or sleep diaries and found the MEQ score correlated with the ability to adapt to night shift work, preferred exercise time, age, and characteristic circadian sleep difficulties relative to diurnal preference [80].

In clinical populations, two studies of families with familial advanced sleep-wake phase disorder showed affected family members scored significantly higher on the MEQ than unaffected members, and unaffected first-degree relatives scored higher than controls [81,82].

One criticism of the MEQ is that respondents do not report actual sleep times, nor differences between work days and free days, or circadian cues such as exposure to outdoor light [40]. The Munich Chronotype Questionnaire (MCTQ) was developed to obtain this information in addition to diurnal preferences.

Munich Chronotype Questionnaire (MCTQ)

On the MCTQ, respondents report their current sleep times, how they feel at various times of the day, and the amount of daylight exposure. They also rate themselves as one of seven chronotypes: Extreme Early, Moderate Early, Slightly Early, Normal, Slightly Late, Moderate Late, and Extreme Late [40]. Respondents are, in addition, asked to rate their chronotype at different life stages, and the chronotypes of family members. The authors of the MCTC initially developed the questionnaire to record the discrepancy between self-assessed chronotype and current sleep schedule. In their study of 500 subjects in Germany and Switzerland, they found that late chronotypes tended to accumulate considerable sleep debt during the work week, with subsequent compensation of several additional hours sleep on free days [40].

A study using both the MEQ and the MCTQ in 2481 respondents completing both questionnaires online found the midpoint sleep time on nonwork days and the self-rated chronotype on the MCTQ both correlated strongly with the chronotype based on the MEQ score. Because late chronotypes tend to have more variability in sleep times between free days and work days, the timing of mid-sleep was a better predictor of chronotype than the timing of sleep onset or wake time [83]. The midpoint sleep time on nonwork days on the MCTQ, in addition, correlates with DLMO [84].

Restless legs syndrome (RLS)

RLS, also known as Willis-Ekbom disease, is a common disorder characterized by an unpleasant sensation in the legs temporarily alleviated with movement, typically occurring at night and during rest. Up to 88% of those with RLS report at least one sleep-related symptom, with the majority reporting chronically impaired sleep consistent with insomnia [85]. RLS symptoms are exacerbated or precipitated by low ferritin levels, pregnancy, peripheral neuropathy, end-stage renal disease, and antidepressant medications [86]. Although RLS is common, the majority of sufferers go undiagnosed and untreated even after consulting a physician about their symptoms [85]. Most RLS screening instruments are brief and helpful for identifying patients at risk of disease and monitoring treatment outcomes.

International Restless Legs Syndrome Scale (IRLS)

The IRLS is a 10-item self-report questionnaire designed by the International Restless Legs Syndrome Study Group [87]. This questionnaire evaluates the severity of RLS symptoms and their impact on sleep, mood, and daily life over a 1-week period. Ratings describe RLS symptoms and

timing with each question ranging from 0 for “None” to 4 for “Very severe” or “Very often.” Total scores range from 0 to 40, with higher scores indicating greater severity and impact of RLS symptoms.

The IRLS is the most extensively used RLS severity scale for research studies. It is validated for outcome evaluation in clinical trials, and strongly correlated with measures of disease severity at baseline and after treatment [88]. Criticisms of the IRLS include the absence of questions targeting symptom timing, severity of symptoms at rest versus during activity, or the presence of symptoms in other body parts. A systematic review of RLS rating scales concludes the IRLS is validated under baseline conditions and responsive to symptom change [89].

Consumer sleep technologies

Consumer technologies designed to monitor sleep and other health-related data have become increasingly widespread and track sleep timing, duration, sleep stage, and even sleep pathology. These technologies include wearable devices, stand-alone bedside devices, and apps installed on smartphones leveraging the device’s intrinsic accelerometer function to track sleep activity. Major consumer advantages include the ability to measure sleep longitudinally in the subject’s typical sleep environment. Some technologies also measure aspects of the sleep environment itself such as temperature, light, and noise levels. The most widely used commercial sleep trackers are designed to be user-friendly, colorful, and provide immediate information about sleep and activity. Early leaders in the health care and technology consumables industry included Fitbit, Jawbone, and Garmin. In more recent years, companies such as Apple, Philips, ResMed, Nokia, and Microsoft have also entered the consumer health-tracking wearable technology space. Presently, validation research is limited on many of these devices, obviating users’ ability to substantiate their claims in both general and clinical populations.

Most consumer sleep technologies provide some type of movement detection, often based on wrist actigraphy. Additional data may include detection of heart rate, in some cases with calculation of heart rate variability. Some devices monitor sleep in a contactless manner using radiofrequency biomotion sensor technology, similar to echolocation. This device is not worn, but rather placed at the bedside. Individual device technologies use proprietary algorithms to calculate wake and sleep, in some cases categorizing sleep stage as “light sleep” or “deep sleep,” and in other cases as rapid eye movement (REM) or non-REM sleep. In recent years, devices have also begun to use more sophisticated sensors of physiologic data to calculate sleep parameters, including aspects of heart rate and respiration.

Advantages to using consumer sleep technologies include the ability for personal empowerment in tracking, viewing,

and changing sleep patterns. Consumers can assess objectively in real time the impact that behavior change has on their sleep health, increasing the probability that these healthy behaviors will become habits. Consumers are able to choose devices with appealing features and appearance, increasing the likelihood of using and gaining benefit from the device. Another potential advantage of these technologies is the ability to analyze data from all users. SleepScore Labs analyzed data from SleepScore Max and found that on average, people who sleep in a room with a temperature of 65° or lower sleep 30 min more than those sleeping in a room that is 77° or higher. In addition, they found that SleepScore Max users of any gender with obesity (BMI >30) sleep 18 min less per night than those with a normal BMI. Fitbit analyzed data from its worldwide user base (6 billion nights of data) and reported mean sleep durations by country and gender. They also found that bedtime variation between free days and workdays was inversely correlated with total mean sleep duration. Variation of 120 min was associated with approximately 30 min lower sleep duration compared with users whose bedtime varied by only 30 min [7]. In the future, data from consumer sleep technologies may be used to identify causes of short sleep duration in individual users, including sleep variation, similarly to the MCTQ.

For sleep disorder screening, the most immediate potential utility for consumer sleep technologies lies in their ability to measure sleep continuity, duration, quality, and regularity. Accurate, ecologically valid, longitudinal sleep monitoring can help in the assessment and potential treatment of insomnia, hypersomnia, circadian rhythm sleep disorders, and insufficient sleep. For insomnia sufferers, evidence exists that symptoms improve when both objective and subjective data are assessed together [90]. Of less clear benefit are device claims of accurate sleep-disordered breathing detection, although some technologies are developing this function. A device with the capability of detecting nocturnal respiratory events may be helpful for risk stratification purposes when used in conjunction with clinical data.

Downsides of consumer sleep technologies include a lack of validation and proprietary algorithms preventing assessment of how sleep stages or wake are calculated. Validation of devices against PSG exists for some devices; however, most studies validate with normal subjects devoid of sleep disorders. Fewer studies investigate validity in clinical populations. This paradigm is further limited by the rapid development and release of new versions of these technologies, which typically outpace the research timeline. As a result, available studies on devices may be applicable only to the actual device studied, and not on newer devices with revised or enhanced features. In addition, research on consumer sleep technologies is limited by variation of analytic methods. Other challenges facing consumer sleep technologies include inaccessibility to large segments of the

population due to cost, and privacy concerns regarding the use of personal data by developers.

Using screening data

A large array of screening instruments is available for identifying individuals at risk for sleep-disordered breathing. In addition to traditional paper-and-pencil questionnaires, avenues for screening have increasingly included consumer-driven technologies that provide more long-term quantitative measures of sleep duration, timing, and quality. The challenge for the primary care provider is how to utilize this potential array of information to refer high-risk patients appropriately for further evaluation and diagnostic testing.

Screening tools offer the opportunity to gather information from the patient on a variety of symptoms, including symptoms of sleep-disordered breathing, insomnia, hypersomnia, and circadian rhythm sleep disorders. They also provide the opportunity to recognize insufficient sleep, the most common cause of excessive sleepiness [49]. One strategy for using these data is to combine individual screening tools with high-predictive power for detecting specific sleep disorders such as OSA and insomnia, along with tools to detect nonspecific symptoms of excessive sleepiness. Some of the higher-sensitivity instruments, such as the STOP-BANG and the ISI, require little time for the patient to take and the clinician to score. Alternately, more comprehensive instruments such as the PSQI, that cover multiple domains of sleep, may be used as stand-alone tools for gathering basic information from which to proceed with further evaluation.

In addition, questionnaires may be used to help guide primary care providers in the types of questions to ask patients suspected of having sleep disorders. For example, use of a circadian rhythm sleep disorder screening instrument such as the MEQ or MCTQ may be given selectively to patients with unusual patterns of insomnia and hypersomnia, or for patients with sleep schedules suggesting a phase shift.

As consumer technologies continue to develop, additional screening modalities may become available to both clinicians and patients. Sleep tracking devices now boast the capability to monitor physiologic data previously unavailable outside the clinic, including movement, respiration, body position, heart rate variability, and even EEG. Devices that monitor respiratory patterns have been validated with high sensitivity. Unfortunately, technology companies do not release their algorithms to allow verification of clinical validity, and new versions of consumer technologies are released far more quickly than research studies performed to validate them. This leaves healthcare providers without the ability to evaluate the screening validity of individual sleep devices. Ultimately, the best usage of consumer sleep technologies may be in their intrauser variability, allowing the patient and their provider

to track changes in sleep over time, in conjunction with more traditional measures of sleep problems.

Over time, further collaboration between technology companies and researchers may increase the usability of technology in the clinical environment. One example is the PROMIS scales, with NIH-funded validation and integration of clinical scales into electronic medical records. These scales are completed by the patient on a tablet in clinic, using computer-adaptive testing to limit the total number of questions. Integration of sleep screening tools into consumer devices would also improve the clinical application of these devices. In the meantime, most clinical providers would benefit from using routine tools currently available today to screen for the most common sleep problems.

References

- [1] Colten HR, Altevogt, Institute of Medicine Committee on Sleep Medicine and Research. Sleep disorders and sleep deprivation: an unmet public health problem. National Academies Press; 2006.
- [2] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6(2):97–111. <https://doi.org/10.1053/smrv.2002.0186>.
- [3] Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin J-L, Peppard PE, Sinha S, Tufik S, Valentine K, Malhotra A. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7(8):687–98. [https://doi.org/10.1016/S2213-2600\(19\)30198-5](https://doi.org/10.1016/S2213-2600(19)30198-5).
- [4] Senthilvel E, Ackley D, Dasarathy J. Evaluation of sleep disorders in the primary care setting: history taking compared to questionnaires. *J Clin Sleep Med* 2011;7(1):41–8. <https://doi.org/10.5664/jcsm.28040>.
- [5] Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of obstructive sleep apnea: a population-based perspective. *Expt Rev Respir Med* 2008;2(3):349–64. <https://doi.org/10.1586/17476348.2.3.349>.
- [6] Effect of short sleep duration on daily activities—United States . Centers for Disease Control and Prevention (CDC). vol 60 (2005), 239–242.
- [7] Pogue D. What Fitbit discovered from 6 billion nights of sleep data. 2018.
- [8] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M, Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL. Joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. *Sleep* 2015;38(8):1161–83. <https://doi.org/10.5665/sleep.4886>.
- [9] Grandner MA, Hale L, Moore M, Patel NP. Mortality associated with short sleep duration: the evidence, the possible mechanisms, and the future. *Sleep Med Rev* 2010;14(3):191–203. <https://doi.org/10.1016/j.smrv.2009.07.006>.
- [10] Guo X, Zheng L, Wang J, Zhang X, Zhang X, Li J, Sun Y. Epidemiological evidence for the link between sleep duration and high blood pressure: a systematic review and meta-analysis. *Sleep Med* 2013;14(4):324–32. <https://doi.org/10.1016/j.sleep.2012.12.001>.
- [11] Barger LK, Rajaratnam SMW, Cannon CP, Lukas MA, Im KA, Goodrich EL, Czeisler CA, O'Donoghue ML. Short sleep duration, obstructive sleep apnea, shiftwork, and the risk of adverse cardiovascular events in patients after an acute coronary syndrome. *J Am Heart Assoc* 2017;6(10). <https://doi.org/10.1161/JAHA.117.006959>.
- [12] Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006;29(3):657–61. <https://doi.org/10.2337/diacare.29.03.06/dc05-0879>.
- [13] Czeisler CA, Wickwire EM, Barger LK, Dement WC, Gamble K, Hartenbaum N, Ohayon MM, Pelayo R, Phillips B, Strohl K, Tefft B, Rajaratnam SMW, Malhotra R, Whiton K, Hirshkowitz M. Sleep-deprived motor vehicle operators are unfit to drive: a multidisciplinary expert consensus statement on drowsy driving. *Sleep Health* 2016;2(2):94–9. <https://doi.org/10.1016/j.slehd.2016.04.003>.
- [14] Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res* 2003;12(1):1–12. <https://doi.org/10.1046/j.1365-2869.2003.00337.x>.
- [15] Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LKG, Amaro ACS, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD, Lorenzi-Filho G. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension* 2011;58(5):811–7. <https://doi.org/10.1161/HYPERTENSIONAHA.111.179788>.
- [16] Hung J, Whitford EG, Hillman DR, Parsons RW. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990;336(8710):261–4. [https://doi.org/10.1016/0140-6736\(90\)91799-g](https://doi.org/10.1016/0140-6736(90)91799-g).
- [17] Eric Dyken M, Bin Im K. Obstructive sleep apnea and stroke. *Chest* 2009;136(6):1668–77. <https://doi.org/10.1378/chest.08-1512>.
- [18] Gagnadoux F, Le Vaillant M, Goupid F, Pigeanne T, Chollet S, Masson P, Bizieux-Thaminy A, Humeau M-P, Meslier N. Depressive symptoms before and after long-term CPAP therapy in patients with sleep apnea. *Chest* 2014;145(5):1025–31. <https://doi.org/10.1378/chest.13-2373>.
- [19] Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Töpfer V. Sleep-disordered breathing in patients with symptomatic heart failure A contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail* 2007;9(3):251–7. <https://doi.org/10.1016/j.ejheart.2006.08.003>.
- [20] Romem A, Iacono A, McIlmoyle E, Patel KP, Reed RM, Verceles AC, Scharf SM. Obstructive sleep apnea in patients with end-stage lung disease. *J Clin Sleep Med* 2013;9(7):687–93. <https://doi.org/10.5664/jcsm.2840UnitedStates>.
- [21] Digby GC, Baranchuk A. Sleep apnea and atrial fibrillation; 2012 update. *Curr Cardiol Rev* 2012;8(4):265–72. <https://doi.org/10.2174/157340312803760811>.
- [22] Foster GD, Sanders MH, Millman R, Zammit G, Borradale KE, Newman AB, Wadden TA, Kelley D, Wing RR, Pi Sunyer FX, Darcey V, Kuna ST. Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care* 2009;32(6):1017–9. <https://doi.org/10.2337/dc08-1776UnitedStates>.
- [23] Young T, Blustein J, Finn L, Palta M. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep* 1997;20(8):608–13. <https://doi.org/10.1093/sleep/20.8.608>.
- [24] Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, et al. Epidemiology of obstructive sleep apnea in the United States. *Am J Respir Crit Care Med* 2009;179(6 Pt 1):559–66. <https://doi.org/10.1163/0003-932X-179-6-0559>.

- Shahar E, Unruh ML, Samet JM, Patel A. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;6(8). <https://doi.org/10.1371/journal.pmed.1000132>.
- [25] Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996;39(6):411–8. [https://doi.org/10.1016/0006-3223\(95\)00188-3](https://doi.org/10.1016/0006-3223(95)00188-3).
- [26] Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, Gibbons R. Time-related predictors of suicide in major affective disorder. *Am J Psychiatr* 1990;147(9):1189–94. <https://doi.org/10.1176/ajp.147.9.1189>.
- [27] Hafner S, Taylor J, Troxel CS. Why sleep matters—the economic costs of insufficient sleep: a cross-country comparative analysis. *Rand Health Q* 2016;6(4).
- [28] Wickwire EM, Shaya FT, Scharf SM. Health economics of insomnia treatments: the return on investment for a good night's sleep. *Sleep Med Rev* 2016;30:72–82. <https://doi.org/10.1016/j.smrv.2015.11.004>.
- [29] Frost S. Hidden health crisis costing America billions: under-diagnosing and undertreating obstructive sleep apnea draining healthcare system. American Academy of Sleep Medicine; 2016.
- [30] Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology* 2008;108(5):812–21. <https://doi.org/10.1097/ALN.0b013e31816d83e4>.
- [31] Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;131(7):485–91. <https://doi.org/10.7326/0003-4819-131-7-199910050-00002>.
- [32] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540–5. <https://doi.org/10.1093/sleep/14.6.540>.
- [33] Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI, Dinges DF. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20(10):835–43.
- [34] Hoddes E, Dement W, Zarcone V. The development and use of the Stanford sleepiness scale (SSS). *Psychophysiology* 1972;9.
- [35] Åkerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci* 1990;52(1–2):29–37. <https://doi.org/10.3109/00207459008994241>.
- [36] Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med* 2001;2(4):297–307. [https://doi.org/10.1016/S1389-9457\(00\)00065-4](https://doi.org/10.1016/S1389-9457(00)00065-4).
- [37] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193–213. [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4).
- [38] Buysse DJ, Yu L, Moul DE, Germain A, Stover A, Dodds NE, Johnston KL, Shablesky-Cade MA, Pilkonis PA. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep* 2010;33(6):781–92. <https://doi.org/10.1093/sleep/33.6.781>.
- [39] Horne JA, Ostberg O. A self assessment questionnaire to determine Morningness Eveningness in human circadian rhythms. *Int J Chronobiol* 1976;4(2):97–110.
- [40] Till R, Wirz-Justice A, Merrow M. Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms* 2003;18(1):80–90. <https://doi.org/10.1177/0748730402239679>.
- [41] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed, text revision. Westchester, IL: AASM; 2023.
- [42] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165(9):1217–39.
- [43] Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin sleep cohort study. *Am J Respir Crit Care Med* 2003;167(9):1181–5.
- [44] Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnea? *JAMA* 2013;310(7):731.
- [45] Flemons WW, Whitelaw WA, Brant R, Remmers JE. Likelihood ratios for a sleep apnea clinical prediction rule. *Am J Respir Crit Care Med* 1994;150(5):1279–85.
- [46] Nagappa M, Liao P, Wong J, Auckley D, Ramachandran SK, Memtsoudis S, et al. Validation of the STOP-bang questionnaire as a screening tool for obstructive sleep apnea among different populations: a systematic review and meta-analysis. *Arias-Carrion O PLoS One* 2015;10(12). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26658438>.
- [47] Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American academy of sleep medicine clinical practice guideline. *J Clin Sleep Med* 2017;13(03):479–504.
- [48] Chiu H-Y, Chen P-Y, Chuang L-P, Chen N-H, Tu Y-K, Hsieh Y-J, et al. Diagnostic accuracy of the Berlin questionnaire, STOP-BANG, STOP, and Epworth Sleepiness Scale in detecting obstructive sleep apnea: a bivariate meta-analysis. *Sleep Med Rev* 2017;36:57–70.
- [49] Guilleminault C, Brooks SN. Excessive daytime sleepiness: a challenge for the practising neurologist. *Brain* 2001;124(Pt 8):1482–91.
- [50] Johns MW. Reliability and factor analysis of the Epworth sleepiness scale. *Sleep* 1992;15(4):376–81.
- [51] Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth Sleepiness Scale: failure of the MSLT as a gold standard. *J Sleep Res* 2000;9(1):5–11.
- [52] Chervin RD, Aldrich MS, Pickett R, Guilleminault C. Comparison of the results of the Epworth Sleepiness Scale and the multiple sleep latency test. *J Psychosom Res* 1997;42(2):145–55.
- [53] Pouliot Z, Peters M, Neufeld H, Kryger MH. Using self-reported questionnaire data to prioritize OSA patients for polysomnography. *Sleep* 1997;20(3):232–6.
- [54] Chervin RD, Aldrich MS. The Epworth Sleepiness Scale may not reflect objective measures of sleepiness or sleep apnea. *Neurology* 1999;52(1):125–31.
- [55] Fong SYY, Ho CKW, Wing YK. Comparing MSLT and ESS in the measurement of excessive daytime sleepiness in obstructive sleep apnoea syndrome. *J Psychosom Res* 2005;58(1):55–60.
- [56] Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. *Chest* 2000;118(2):372–9.
- [57] He K, Kapur VK. Sleep-disordered breathing and excessive daytime sleepiness. *Sleep Med Clin* 2017;12(3):369–82.
- [58] Bonzelaar LB, Salapatas AM, Yang J, Friedman M. Validity of the Epworth Sleepiness Scale as a screening tool for obstructive sleep apnea. *Laryngoscope* 2017;127(2):525–31. <https://doi.org/10.1002/lary.26206>.

- [59] Damiani MF, Quaranta VN, Falcone VA, Gadaleta F, Maiellari M, Ranieri T, et al. The Epworth Sleepiness Scale: conventional self vs physician administration. *Chest* 2013;143(6):1569–75.
- [60] Walia HK, Thompson NR, Katzen I, Foldvary-Schaefer N, Moul DE, Mehra R. Impact of sleep-disordered breathing treatment on quality of life measures in a large clinic-based cohort. *J Clin Sleep Med* 2017;13(11):1255–63.
- [61] Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the functional outcomes of sleep questionnaire. *Sleep* 2009;32(7):915–9.
- [62] Herscovitch J, Broughton R. Sensitivity of the Stanford Sleepiness Scale to the effects of cumulative partial sleep deprivation and recovery oversleeping. *Sleep* 1981;4(1):83–91.
- [63] Valley V, Broughton R. Daytime performance deficits and physiological vigilance in untreated patients with narcolepsy-cataplexy compared to controls. *Rev Electroencephalogr Neurophysiol Clin* 1981;11(1):133–9.
- [64] Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci* 1990;52(1–2):29–37.
- [65] Baulk SD, Reyner LA, Horne JA. Driver sleepiness—evaluation of reaction time measurement as a secondary task. *Sleep* 2001;24(6):695–8.
- [66] Akerstedt T, Anund A, Axelsson J, Kecklund G. Subjective sleepiness is a sensitive indicator of insufficient sleep and impaired waking function. *J Sleep Res* 2014;23(3):240–52. <https://doi.org/10.1111/jsr.12158>.
- [67] Kaida K, Takahashi M, Akerstedt T, Nakata A, Otsuka Y, Haratani T, et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clin Neurophysiol* 2006;117(7):1574–81.
- [68] Filtness AJ, Reyner LA, Horne JA. Moderate sleep restriction in treated older male OSA participants: greater impairment during monotonous driving compared with controls. *Sleep Med* 2011;12(9):838–43.
- [69] Kkh W, Marshall NS, Grunstein RR, Dodd MJ, Rogers NL. Comparing the neurocognitive effects of 40 h sustained wakefulness in patients with untreated OSA and healthy controls. *J Sleep Res* 2008;17(3):322–30. <https://doi.org/10.1111/j.1365-2869.2008.00665.x>.
- [70] Littner M, Hirshkowitz M, Kramer M, Kopen S, Anderson WM, Bailey D, et al. Practice parameters for using polysomnography to evaluate insomnia: an update. *Sleep* 2003;26(6):754–60.
- [71] Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34(5):601–8.
- [72] Gagnon C, Belanger L, Ivers H, Morin CM. Validation of the insomnia severity index in primary care. *J Am Board Fam Med* 2013;26(6):701–10.
- [73] Savard M-H, Savard J, Simard S, Ivers H. Empirical validation of the insomnia severity index in cancer patients. *Psychooncology* 2005;14(6):429–41. <https://doi.org/10.1002/pon.860>.
- [74] Chiu H-Y, Chang L-Y, Hsieh Y-J, Tsai P-S. A meta-analysis of diagnostic accuracy of three screening tools for insomnia. *J Psychosom Res* 2016;87:85–92.
- [75] Wells RD, Day RC, Carney RM, Freedland KE, Duntley SP. Depression predicts self-reported sleep quality in patients with obstructive sleep apnea. *Psychosom Med* 2004;66(5):692–7.
- [76] Nishiyama T, Mizuno T, Kojima M, Suzuki S, Kitajima T, Ando KB, et al. Criterion validity of the Pittsburgh sleep quality index and Epworth sleepiness scale for the diagnosis of sleep disorders. *Sleep Med* 2014;15(4):422–9.
- [77] Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, et al. Development of short forms from the PROMISTM sleep disturbance and sleep-related impairment item banks. *Behav Sleep Med* 2012;10(1):6–24.
- [78] Leung YW, Brown C, Cosio AP, Dobriyal A, Malik N, Pat V, et al. Feasibility and diagnostic accuracy of the Patient-Reported Outcomes Measurement Information System (PROMIS) item banks for routine surveillance of sleep and fatigue problems in ambulatory cancer care. *Cancer* 2016;122(18):2906–17. <https://doi.org/10.1002/cncr.30134>.
- [79] Weitzman ED, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement W, et al. Delayed sleep phase syndrome. A chronobiological disorder with sleep-onset insomnia. *Arch Gen Psychiatry* 1981;38(7):737–46.
- [80] Sack RL, Ackley D, Auger RR, Carskadon MA, Wright KP, Vitiello MV, et al. Circadian rhythm sleep disorders: part I, basic principles, shift work and jet lag disorders. An American Academy of Sleep Medicine review. *Sleep* 2007;30(11):1460–83.
- [81] Jones CR, Campbell SS, Zone SE, Cooper F, DeSano A, Murphy PJ, et al. Familial advanced sleep-phase syndrome: a short-period circadian rhythm variant in humans. *Nat Med* 1999;5(9):1062–5.
- [82] Satoh K, Mishima K, Inoue Y, Ebisawa T, Shimizu T. Two pedigrees of familial advanced sleep phase syndrome in Japan. *Sleep* 2003;26(4):416–7.
- [83] Zavada A, Gordijn MCM, Beersma DGM, Daan S, Roenneberg T. Comparison of the Munich chronotype questionnaire with the horne-ostberg's morningness-eveningness score. *Chronobiol Int* 2005;22(2):267–78.
- [84] Kitamura S, Hida A, Aritake S, Higuchi S, Enomoto M, Kato M, et al. Validity of the Japanese version of the Munich chronotype questionnaire. *Chronobiol Int* 2014;31(7):845–50. Available from: <http://www.tandfonline.com/doi/full/10.3109/07420528.2014.914035>.
- [85] Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med* 2004;5(3):237–46.
- [86] Becker PM, Novak M. Diagnosis, comorbidities, and management of restless legs syndrome. *Curr Med Res Opin* 2014;30(8):1441–60.
- [87] Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al., International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med* 2003;4(2):121–32.
- [88] Allen R, Oertel W, Walters A, Benes H, Schollmayer E, Grieger F, et al. Relation of the International restless legs syndrome study group rating scale with the Clinical global impression severity scale, the restless legs syndrome 6-item questionnaire, and the restless legs syndrome-quality of life questionnaire. *Sleep Med* 2013;14(12):1375–80.
- [89] Walters AS, Frauscher B, Allen R, Benes H, Chaudhuri KR, Garcia-Borreguero D, et al. Review of severity rating scales for restless legs syndrome: critique and recommendations. *Mov Disord Clin Pract* 2014;1(4):317–24. <https://doi.org/10.1002/mdc3.12088>.
- [90] Tang NKY, Harvey AG. Altering misperception of sleep in insomnia: behavioral experiment versus verbal feedback. *J Consult Clin Psychol* 2006;74(4):767–76.

This page intentionally left blank

Chapter 14

Sleep hygiene and the prevention of chronic insomnia

Jason G. Ellis, Sarah F. Allen and Pamela Alfonso-Miller

Northumbria Sleep Research Laboratory, Northumbria University, Newcastle, United Kingdom

Sleep hygiene

What is sleep hygiene?

One of the main difficulties when several things are lumped together under one overarching term is standardization. As such, asking one person what they consider sleep hygiene to entail is likely to result in a different set of rules or techniques compared to another individuals' list [1]. As you will come to see, this can create challenges and confusion for the sleep researcher, the clinician, and indeed the public. Hauri developed the first set of "sleep hygiene" recommendations in the late 1970s with the specific aim of helping patient's manage their insomnia [2]. The original list contained 10 items ranging from not going to bed hungry, regularizing wake times and avoiding caffeine in the evening, to sound attenuating the bedroom and making sure the bedroom is not too warm (see Table 14.1). While based on the available evidence at the time, in addition to Hauri's own clinical observations, the original list has been modified extensively over the years, including by Hauri himself, as more information became available [3–8]. Where some recommendations appear to have been removed and new ones added (see Table 14.1), there are, however, a few recommendations which appear in the majority of definitions, namely, exercise, limiting caffeine, avoiding alcohol, and having a snack before bedtime.

There also appears to be some overlap between some of the recommendations outlined as "sleep hygiene" by some authors and what others might consider elements from other components of traditional cognitive behavioral therapy for insomnia (CBT-I). For example; leaving the bed if not awake, only using the bed for sleep, and avoiding napping during the day are commonly contained within some definitions of sleep hygiene while also being aspects of stimulus control instructions [9]. Similarly, decreasing time in bed is generally associated with sleep restriction

[10], as is, albeit more implicitly, keeping a regular sleep/wake schedule. Not actively trying to sleep and keeping a worry list are also commonly included in sleep hygiene instructions but also encompass the cognitive components of CBT-I [11,12]. The challenge, however, is when these elements are packaged as sleep hygiene instructions; these latter items do not represent the full instructions for stimulus control, sleep restriction, or cognitive therapy, respectively. Are they, therefore, likely to be as effective as the full instructions? Moreover, an individual who has been exposed to these brief instructions is likely to be more resistant to full CBT-I because they have "been there and done that before". So, the question remains; are these items aspects of sleep hygiene, or not? For the purpose of this chapter, we will take a psycho-educational approach and explore only those recommendations that do not overlap with other components of traditional CBT-I—namely, exercise, caffeine, alcohol, food and liquid intake, nicotine, the bedroom environment, and clockwatching. So, what are the specific recommendations for each and how do these elements impact on sleep? In terms of the first part of this question, for most aspects, there are no standardized specific recommendations, but more general guidelines, which again, vary from definition to definition [13].

Exercise

Broadly, there are two recommendations associated with exercise in the context of sleep hygiene—i) exercise is good for sleep and should be encouraged, especially outside in natural daylight but ii) exercise too close to bedtime is detrimental to sleep and should be discouraged. The benefits of both acute and regular exercise on sleep have been documented in numerous studies including children, adolescents, and older adults, with and without sleep difficulties [14,15]. These benefits appear to include

TABLE 14.1 Published definitions of sleep hygiene.

Recommendations:	Author(s)						
	Hauri(1977)	Schoicketet et al (1988)	Hauri (1992)	Hauri (1993)	Guillemainault et al. (1995)	Friedman et al. (2000)	Perlis et al. (2005)
Environmental							
Eliminate bedroom noise							
Regulate temperature of bedroom							
Eliminate clocks from the bedroom							
Make bedroom comfortable							
Sleep/wake schedule							
Eliminate napping							
Decrease time in bed							
Regular bed/wake times							
Positive things to do in the evening							
Undertake relaxing activities							
Exercise							
Make worry list							
Hot bath							
Eat a light snack							
Limit liquid intake							
Decrease or avoid smoking							
Limit or avoid caffeine							
Avoid Alcohol							
Sleep/wake behaviours							
Don't try to sleep							
Leave bed if awake							
Use the bedroom only for sleep							
Avoid use of sleeping pills							

increases in slow-wave sleep and total sleep time; reductions in sleep latencies and time awake after sleep onset and a slight delay; and minimal reductions in REM sleep [16]. That said, a recent review points to several moderators underpinning these relationships, including sex, age, type of exercise, baseline physical activity levels, and even the timing of the exercise [17]. In terms of exercising in the evening, the general consensus is that exercising too close to bedtime could disrupt the circadian system, elevate body core temperature, and/or create a form of physiological arousal—each of which could be detrimental to sleep [18]. A recent study, however, suggests otherwise, finding that evening exercise, at least within 4 h of bedtime, was not associated with poorer sleep [19]. While it appears that exercise, in general, is good for sleep, the detrimental impact of evening exercise on sleep is less clear.

Caffeine

It is widely believed that caffeine can have a negative impact on sleep [20]. In fact, acute caffeine administration has been used as an analogous model for sleep disruption and disturbance in several studies [21,22]. In these instances, a dose of caffeine before bedtime results in a

prolonged sleep latency, decreased total sleep time, and reductions in slow-wave sleep, usually in a dose-response manner [23]. The general rule relating to caffeine, with respect to sleep hygiene, is that it should be avoided after midday, although it is unclear where the timing for this rule came from. There is experimental evidence that caffeine administration 6 h before bed can negatively impact on sleep [24]. Outside the laboratory, however, the impact of caffeine on sleep is less clear with one large survey finding caffeine consumption of up to seven to eight cups per day was unrelated to self-reported levels of sleep duration and daytime somnolence, although more than eight cups per day was associated with a reduction in total sleep time [25]. Further, another study showed caffeine was unrelated to insomnia severity once anxiety and race/ethnicity were controlled for [26]. Individual differences may play a part in explaining the inconsistencies as it has been shown that the adenosine A_{2A} receptor gene may influence the relationship between caffeine and sleep [27]. That said, public awareness of the effects of caffeine on sleep might also explain why experimental studies using caffeine show an impact on sleep, but naturalistic studies tend to find only a limited relationship [28], especially in those who are already experiencing sleep problems.

Alcohol

Like caffeine, alcohol is widely recognized to negatively impact on sleep. The main issue in this context is alcohol is a sedative and as such can be an appealing hypnotic [29]. The review by Ebrahim and colleagues [30] suggests that although alcohol results in a reduction in sleep-onset latency and a more consolidated first half sleep, it is also associated with an increase in disrupted and fragmented sleep in the second half of the sleep period, largely due to the increase in body temperature in order to sweat it out. Moreover, where low and moderate doses show little effect on REM sleep, high doses can significantly reduce REM, especially in the first half of the night. The recommendation regarding alcohol is that it should be avoided in the evening and certainly not to be used as a sleep aid. With regard to the first point, however, as the effects of alcohol on sleep appear to be dose dependent, should alcohol be avoided altogether? Will that dissuade an individual from complying? As for the latter recommendation, considering that insomnia has been shown to be a significant risk factor for the development of alcohol problems [31] due to increasing tolerance to its sleep-promoting effects, it makes sense to suggest alcohol not be used as a sleep aid.

Food and liquid intake

While there is a considerable literature on the impact of sleep deprivation on hunger and food intake, there is surprisingly little information on the impact of hunger or being over sated on how an individual sleeps. The story appears to be similar for liquid intake. The general recommendation is that an individual should not go to sleep hungry or eat a heavy meal before bed and should minimize liquid intake in the evening (2–3 h before bedtime). Certainly these recommendations make physiological sense as trying to sleep is going to be more challenging if the individual is digesting a heavy meal, especially if the meal contained high levels of spice or fat. Additionally, going to bed hungry is likely to increase the chances of a blood sugar drop in the night, waking the individual. Excessive liquid during the evening is likely to increase nocturnal awakenings with the need to use the bathroom at night. The impact of which is likely to be more so for older adults [32]. These rules aside, it is important to account for individual and circumstantial (e.g., illnesses characterized by dehydration) differences in the timing and amount of food and liquid intake.

Nicotine

As with alcohol, the general recommendation is that nicotine should be avoided close to bedtime. Nicotine is a stimulant and as such has the capacity to disrupt sleep [33].

Jaehne and colleagues [33] reviewed the literature regarding nicotine and sleep and from the nine human studies that met criteria they found that smokers had double the risk of developing sleep disturbances, compared to nonsmokers. Additionally, from their review of polysomnography studies, smokers tend to demonstrate longer sleep-onset latencies, reduced SWS, and a longer REM latency compared to nonsmokers [33]. Where this would suggest curtailment or even cessation of nicotine would be good for sleep, a challenge here is the impact of withdrawal on sleep, which can begin 6 h following abstinence and last for 3 weeks or longer [34]. Nicotine abstinence has been consistently shown to relate to subjectively and objectively defined poor sleep [33]. As such it appears that a balance between abstinence and cessation needs to be struck. Passive smoking is also negatively related to sleep [35]. Sabanayagam and Shankar [36] found that while tobacco users had a two-fold increase in risk of insufficient sleep compared to nontobacco users, second-hand smoke exposure was associated with insufficient sleep among nonsmokers.

Bedroom environment

The general rule with regard to the sleep environment is ensuring that it should be cool, dark, quiet, and comfortable and more recently, free from electronics. Having a hot bedroom or an uncomfortable bed was independently associated with reports of nonrestorative sleep in one large pan-European study [37]. Environmental modifications such as blackout blinds, eye masks, earplugs, new mattresses, and the use of suitable bedding and sleepwear are encouraged under this recommendation.

Bedroom temperature—Both excessively hot and cold environments can negatively influence sleep. Above 71°F/21.6°C has been shown to disrupt sleep, as has below 41°F/5°C [38,39]. The National Sleep Foundation [40] suggests between 60°F/15.6°C and 67°F/19.4°C is ideal.

Bedroom light—Light is likely to wake the individual earlier than desired or prevent the individual from sleeping due to its influence on the circadian system and the suppression of melatonin. Indoor lighting as low as <500 Lux has been shown to suppress melatonin [41]. In one study participants exposed to <200 Lux for five consecutive days showed a later melatonin onset and a shortened melatonin duration (90 min) compared to those who were exposed to dim light <3 Lux [42].

Bedroom noise—Of all the bedroom environmental factors, noise has been the most studied [43]. The findings are clear in that excessive noise disrupts sleep, and subsequent daytime performance, even if the individual does not recall awakening during the night [43]. The World Health Organization suggests nighttime noise should be below 40 dB [44]. That said, there are individual

differences in noise tolerance with one study demonstrating that 15 dB was sufficient to wake one individual, whereas for another, it took 100 dB [45].

Bedroom comfort—A comfortable sleep environment could mean very different things to different people. For some, this may include specific elements regarding the bed itself—good bedding, a supportive mattress, the number, and density of pillows. There is little evidence for these factors making a specific impact on sleep in general, however, as personal preference is likely to be key [46]. That said, one study has demonstrated poorer sleep outcomes when sleeping on a hard surface compared to a softer one [47]. Irrespective of the definition of bedroom comfort, it stands to reason that if the bedroom environment is not perceived as comfortable, achieving sleep can be problematic.

Removal of electronics

Although not included explicitly in the original sleep hygiene recommendations, presumably due to historical reasons, recently the impact of electronics in the bedroom, and use close to bedtime, in relation to sleep has become a focus of attention [48]. The review by Cain and Gradisar [49] showed that the most consistent aspects of sleep disturbed were a delayed bedtime and reduced total sleep time. Similarly, Hale and Guan's review of 67 studies showed similar findings for screen use with 90% of those studies showing adverse sleep outcomes [50]. The question remains as to the relative contribution of the blue light emitted from these devices and the cognitive arousal that using these devices can have on sleep [51]. As such it would appear that removing electronics would be the advisable thing to do but this may be resisted, especially in younger populations.

Clockwatching

The general recommendation is that clocks are not good in the bedroom and should be removed or, at the least, not be visible. The rationale is that if an individual is awake in bed (either at bedtime or during the night), they are likely to check the clock and calculate; (i) how long they have been asleep/awake and (ii) how long they have left before they need to get up. This is likely to provoke an anxious response, prolonging sleep initiation/reinitiation, resulting in further clockwatching and a vicious cycle of checking anxiety. Surprisingly, there is very little empirical data on the impact of clockwatching on sleep. From the data that do exist, however, it appears that monitoring the clock increases presleep worry whether an individual has insomnia or not [52]. That said, people with insomnia do tend to demonstrate an attentional bias toward clocks [53] so would be more likely to gravitate toward them if awake in bed.

Measuring sleep hygiene

In the majority of cases, sleep hygiene information is gathered as part of a routine clinical interview (see Morin [54] for a good example). There are, however, three scales that specifically measure sleep hygiene—the Sleep Hygiene Awareness and Practice Scale [55], the Sleep Hygiene Self Test [56], and the Sleep Hygiene Index [57]. Additionally, there are at least two that are more developmentally focused—the Childrens' Sleep Hygiene Scale [58] and the Adolescent Sleep Hygiene Scale [59]. Again, as with the recommendations on sleep hygiene, there is no consensus between the scales as to what does and what does not constitute sleep hygiene. As such, comparing the results from studies is challenging.

Do people with insomnia have poorer sleep hygiene than normal sleepers?

Several studies have examined levels of sleep hygiene in individuals with insomnia, comparative to controls. The results are mixed, both in terms of overall findings and the influence of individual recommendations. People with insomnia were more likely to smoke and drink alcohol before bed, compared to their normally sleeping counterparts, in one study [60]. Interestingly, in the same study caffeine consumption did not differ between the groups [60]. This latter finding contradicts an earlier study whereby levels of caffeine consumption were significantly higher in those with insomnia compared to normal sleepers [55]. Further, in an Internet-based study in the USA, Gellis and Lichstein [61] found that poor sleepers engaged in poorer sleep hygiene practices; specifically, they reported sleeping in environments perceived to be uncomfortable, in terms of temperature and noise, compared to good sleepers. Another study found people with insomnia were more likely to smoke within 5 minutes of bedtime, drink more alcohol in general, use alcohol to sleep, and consume alcohol within 30 min of bedtime, compared to controls. Despite this evidence, others have found no significant differences between people with insomnia and normal sleepers on a range of sleep hygiene behaviors [62]. For example, in Harvey's study on individuals with sleep-onset insomnia, she observed no differences on several sleep hygiene measures including; bedroom noise, mattress comfort, general alcohol use, and caffeine, alcohol, and nicotine use close to bedtime [62].

As such, it appears there is no real consistent pattern of sleep hygiene behaviors that can be linked to insomnia. Whether this inconsistency speaks to different behaviors being measured or to actual inconsistencies within different populations is difficult to ascertain. Another issue is causality—is it the case that any differences observed between those with insomnia and those without are a consequence of having insomnia? Alternatively, if poor sleep hygiene can

cause insomnia, then it could reasonably be assumed that knowledge of sleep hygiene would relate to behavior.

With respect to the latter question, Brown and colleagues [1] found that knowledge of sleep hygiene rules was associated with sleep hygiene practices in college students, which in turn was related to sleep quality. Conversely, however, Voinescu and Szentagotai-Tarar [63] found that moderate to low levels of sleep hygiene awareness were unrelated to sleep quality. As such it is unclear as to whether insomnia is related to poor sleep hygiene practices. Another issue exists here in terms of the differences in what is measured. Although the terms poor sleep and insomnia have been extensively used in the literature, they could be considered distinct constructs in that poor sleep is generally defined within the context of a particular study whereas insomnia tends to have to meet certain diagnostic criteria.

What is the role of sleep hygiene in the management of insomnia?

The premise here is that if poor sleep hygiene can cause insomnia then the reverse would also be applicable—that is, correcting poor sleep hygiene can fix insomnia. This supposition is implied in the International Classification of Sleep Disorders (ICSD), which had, in its first and second iterations (ICSD [64]; ICSD-2 [65]) a specific subtype of insomnia labeled “Inadequate Sleep Hygiene” (it is still included in the ICSD-3 but as a variant form of insomnia). Under the old ICSD framework, it was suggested that there were 11 contributors to inadequate sleep hygiene. However, as we saw in the last section, the findings of an association between poor sleep hygiene and insomnia are quite mixed. One study, which examined diagnoses according to the ICSD, DSM, and ICD, found inadequate sleep hygiene was the primary diagnosis in only 6.2% of 257 patients although it was a very commonly ascribed as a secondary diagnosis—34.2% [66]. Further, a review of the literature by Reynolds and Kupfer [67] concluded that “inadequate sleep hygiene” was unlikely to be a primary cause of insomnia but rather should be seen as an exacerbating factor. The American Academy of Sleep Medicine (AASM) summarized the data from sleep hygiene studies and concluded that there is insufficient evidence to suggest that sleep hygiene is an effective stand-alone therapy for insomnia (AASM [68,69]). A more recent meta-analytic comparison of 15 studies, which employed sleep hygiene interventions, concurs with the AASMs position [70]. They found the effect sizes from the sleep hygiene interventions were similar to those observed for psychological placebo interventions for insomnia. Interestingly, although comparable treatment improvements were observed for a sleep hygiene intervention compared to meditation and stimulus control in one study, participants rated the sleep hygiene intervention less favorably [71].

Due to this accumulated knowledge and lack of consistency in findings, over time, sleep hygiene, in its broadest form, has three main functions today; (i) serving as an “active control” in insomnia intervention trials, (ii) as one aspect of the psycho-educational component in CBT-I, and (iii) as an alternative to pharmacotherapy in primary care [72]. In the latter case, despite the belief that sleep hygiene has limited value by those providing it (i.e., General Practitioners).

So, is there a role for sleep hygiene in sleep medicine and practice, beyond insomnia?

If sleep hygiene is not recommended as a stand-alone therapy for chronic insomnia, does it have a part to play elsewhere in the arena of sleep? One suggestion is that it be used as part of a broader public health campaign with the aim of increasing overall sleep health [73]. Only recently has the concept of sleep health been defined [74,75] with the premise that improvements can be made, in terms of sleep for those without sleep problems. Further that improvements in sleep health will have an impact on overall health and well-being. In line with that suggestion, an interesting study by Barber, Grawitch, and Munz [76] found that those with poorer sleep hygiene were at risk of poorer work performance due to its presumed impact on the after-work recovery process. Herein lies a further consideration, however: If someone has poor sleep hygiene but considers himself or herself an average or even good sleeper, are they going to change their sleep habits and rituals? This is an important consideration both for those with poorer sleep health and those with insomnia, one which has only recently been suggested; understanding and utilizing health behavior theory in the context of improving sleep health [77]. Here the authors provide an overview and examples whereby health belief models (taking account of attitudes and norms, perceived benefits and barriers, health beliefs, self-efficacy, etc.) have been introduced into sleep health interventions, demonstrating the potential for increased uptake and adherence. As yet, however, these models have not been systematically employed in the arena of sleep health or a preventative public health campaign [73].

Moving beyond utilizing sleep hygiene at a whole population level, recent research outside insomnia has examined the role of sleep hygiene within specific vulnerable populations where it may serve a protective factor against poor sleep (e.g., elite athletes, university students, children with ADHD, and hospitalized patients), with mixed results [78–81]. In this vein, one recent review highlighted a significant discordance between sleep hygiene recommendations and fatigue management interventions in shift workers suggesting that specific sleep hygiene recommendations should be tailored to the population which they are intended to serve [82].

The prevention of chronic insomnia

In order to outline a preventative agenda for any disorder, let alone insomnia, we must first understand its etiology. Only by knowing how and why it occurs, as well as how it evolves or changes over time, can we start to determine how and when to intervene. Intervening too early may be detrimental in that we may be altering/affecting what may be a normal biological process, whereas intervening too late is also likely to be as detrimental, if not more so, and prolong suffering. This level of understanding of a disorder can be achieved using several methods. For example, both descriptive and analytic epidemiological studies are likely to give us an insight into which individuals are most likely to be affected by the disorder and when in their lifespan they are most likely to be at risk. Unfortunately there is limited empirical data on the development of insomnia, with sufficient sensitivity, to understand its early progression [83]. That said, there is one suggestion, outlined in several of the models of insomnia, as to what initiates insomnia.

Etiological models of insomnia

The most widely regarded model of the etiology of insomnia comes from Spielman [84,85]. Spielman proposed that insomnia occurs as a combination of two factors—predisposing factors and precipitating events, respectively. Where predisposing characteristics, such as personality factors, demographic factors, or biologic traits, are not sufficient to give someone insomnia on their own, a triggering event occurs (precipitant) which then pushes the individual over a threshold, into insomnia. This phase is termed “acute” or “short term” insomnia. Further, Spielman suggests that perpetuating factors (behaviors the individual with insomnia engages in to manage their initial insomnia—such as going to bed early, napping, staying in bed in the morning) start during this acute phase and gain momentum as the insomnia progresses (Fig. 14.1).

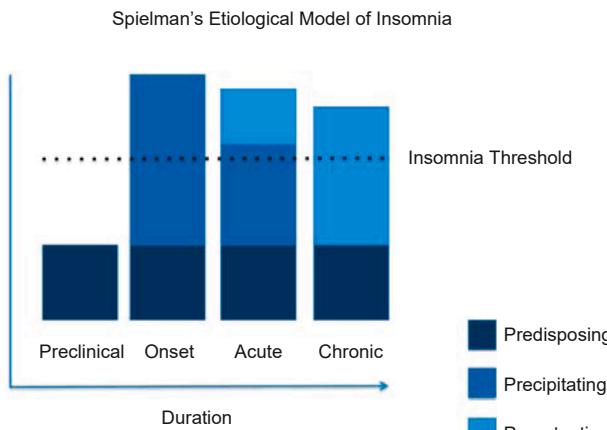


FIGURE 14.1 The 3 P etiological model of insomnia.

Although the model gives a starting point of what factors may be involved in the etiology of insomnia, and their relative contributions over time, what the model does not tell us is when insomnia becomes insomnia. Without that knowledge it is difficult to determine when best to intervene. Several other models followed Spielman's (e.g., Perlis and colleagues [86] Espie [11]; Harvey [12]; Buysse and colleagues [87]) and central to all is the concept of a precipitating event and the beginning of perpetuating factors during the acute phase (although later models emphasized cognitive as well as behavioral perpetuating factors) but none as yet have provided a duration element to their respective model.

What we know about acute insomnia?

Up to one-third (31%–36%) of the population will suffer from acute insomnia (i.e., up to 3 months) in a given year and between 7.9% and 9.5% of adults report having acute insomnia at any given time, with 51.2% of them reporting it as a first episode [88,89]. The duration criterion used in this study was based upon the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 [90]) and International Classification of Sleep Disorders (ICSD-3 [91]) definitions for Insomnia Disorder. That said, the genesis of that timeline in both classification systems has never been explicated although this has recently been questioned [92,93]. Those with acute insomnia differ from normal sleepers in both subjective and objective sleep characteristics. Those with acute insomnia report longer sleep latencies, more awakenings during the night, longer periods of nocturnal wakefulness, and lower sleep efficiencies compared to normal sleepers [93]. Further, actigraphically defined sleep fragmentation is higher in those with acute insomnia, relative to normal sleepers, as is polysomnographically defined light sleep (N2) with lower amounts of slow wave sleep [94,95]. Further, in support of Spielman, it appears that those with acute insomnia do engage in both cognitive and behavioral activities that can perpetuate insomnia in a similar manner to those with chronic insomnia (i.e., worrying about sleep, becoming preoccupied with sleep, spending more time in bed) [96–98]. That said, it appears that engagement with sleep extension, a central focus within most models of insomnia, does not routinely occur in the context of acute insomnia but rather a failure to self-restrict time in bed occurs [99].

Can we prevent acute insomnia from becoming chronic?

There is currently only one intervention that has attempted to circumvent the transition from acute to chronic insomnia [100]. Based on the assumption that acute insomnia should be easier to manage during the acute phase due to

perpetuating factors being in their infancy [93] and the relative success of brief variants of CBT-I (e.g., Refs. [101,102]), the intervention – termed the “one shot” involves a single 60–70 min treatment session and an accompanying pamphlet. Five relatively small studies have been undertaken on the “one shot” [100,103–106]. The first, a randomized controlled trial in a community sample of adults demonstrated a significant improvement in insomnia symptoms 1 month following the intervention. Furthermore, the 1-month remission rate was 60% compared to 15% in the control group [100]. Interestingly, at 3 months postintervention the remission rate in this group had increased to 73%. The second study aimed to determine whether the intervention could be delivered in groups, which it could although group treatment impacts negatively on adherence, and in that instance, the overall remission rate at 1 month was 72% [103]. The third study aimed to use the intervention in a male prison setting due to the high levels of insomnia in this population [104,107]. The remission rate in this study was similar to that observed in the second trial (73%). In these final two studies, significant reductions in anxiety and depression symptomology were also observed [103,104]. The third study used the one-shot in the context of adolescents presenting with anxiety and/or depression [105], and the final study used just the pamphlet from the one-shot, due to research mentioned earlier suggesting sleep extension may not be a facet in the trajectory from acute to chronic insomnia [99], as a buffer in the face of the stress caused by COVID [106]. While the study demonstrated significant reductions in anxiety and depressive symptoms as well as improvements in sleep for those with acute insomnia, no specific benefits were observed in those who were normal sleepers over a 3-month period [106].

Identifying those at risk

While there have been, albeit small, advances in the arena of acute insomnia, there is even less work aimed at primary prevention. One avenue that has not, until recently, been systematically explored is determining individuals’ who may be vulnerable to insomnia (i.e., Spielman’s predisposing factors). Where previous research has tended to characterize personality characteristics and other presumed predisposing factors in those who already have insomnia, Drake and colleagues created the Ford Insomnia Response to Stress Test (FIRST [108]). The FIRST is a brief self-report scale that asks the likelihood that an individual would lose sleep over several stressful situations. Several studies have been undertaken using the FIRST, and it appears to be a good indicator of a first episode of insomnia [109] in addition to having a strong genetic component [110]. Importantly, recent research using the FIRST has demonstrated that the first episode of insomnia sensitizes

the sleep system making the individual vulnerable to insomnia again in the future, as well as depression and anxiety, and that scores on the FIRST are a significant predictor of who will or will not develop acute insomnia during a life stressor [111,112].

Conclusions

Sleep hygiene is clearly a complex area in terms of defining and evidencing the specific recommendations. While there have been significant levels of investigation for some aspects (e.g., alcohol, caffeine, bedroom noise), there has been very little in other areas (e.g., clockwatching, food and liquid intake). While each aspect of sleep hygiene has the potential to influence sleep, these data have not translated well in terms of both differentiating those with insomnia from normal sleepers and in the management of insomnia. It is plausible to assume that lay knowledge of sleep hygiene, especially in those with insomnia who are more likely to seek out this information, and self-motivated behavioral change may be responsible for this lack of association between sleep hygiene and poor sleep [113–115]. Although the existing evidence base would suggest a limited role for sleep hygiene in the management of chronic insomnia, beyond a psycho-education component within CBT-I, an alternative perspective is proposed. That sleep hygiene should still be routinely assessed in all sleep disturbed patients but any corresponding advice should be tailored specifically to what the patient has not yet tried or adopted successfully. This recommendation is to account for individual differences in tolerability and vulnerability to insomnia based upon specific aspects of sleep hygiene. Furthermore, with the advent of sleep health as a concept and recent moves toward a more preventative approach to sleep medicine, sleep hygiene may still have a role to play alongside briefer forms of CBT-I. When considering the costs and consequences of chronic insomnia, prevention is clearly the way forward, preferably at a public health level.

References

- [1] Brown FC, Buboltz Jr WC, Soper B. Relationship of sleep hygiene awareness, sleep hygiene practices, and sleep quality in university students. *Behav Med* 2002;28(1):33–8.
- [2] Hauri P. The sleep disorders. Kalamazoo. Upjohn Company; 1977.
- [3] Schoicket SL, Bertelson AD, Lacks P. Is sleep hygiene a sufficient treatment for sleep-maintenance insomnia? *Behav Ther* 1988;19(2):183–90.
- [4] Hauri P. Sleep hygiene, relaxation therapy, and cognitive interventions. In: Hauri PJ, editor. Case studies in insomnia. New York: Plenum Press; 1992.
- [5] Hauri PJ. Consulting about insomnia: a method and some preliminary data. *Sleep* 1993;16(4):344–50.

- [6] Guilleminault C, Clark A, Labanowski M, Pelayo R, Claman D. Nondrug treatment trials in psychophysiologic insomnia. *Arch Intern Med* 1995;155:838–44.
- [7] Friedman L, Benson K, Noda A, Zarcone V, Wicks DA, O’Connell K, Yesavage JA. An actigraphic comparison of sleep restriction and sleep hygiene treatments for insomnia in older adults. *J Geriatr Psychiatr Neurol* 2000;13(1):17–27.
- [8] Perlis ML, Jungquist C, Smith MT, Posner D. Cognitive behavioral treatment of insomnia: a session-by-session guidevol. 1. Springer Science & Business Media; 2006.
- [9] Bootzin RR. Stimulus control treatment for insomnia. Proceedings of the American Psychological Association 1972;7:395–6.
- [10] Spielman AJ, Sasaki P, Thorpy MJ. Treatment of chronic insomnia by restriction of time in bed. *Sleep* 1987;10(1):45–56.
- [11] Espie CA. Insomnia: conceptual issues in the development, persistence, and treatment of sleep disorder in adults. *Annu Rev Psychol* 2002;53(1):215–43.
- [12] Harvey AG. A cognitive model of insomnia. *Behav Res Ther* 2002;40(8):869–93.
- [13] Stepanski EJ, Wyatt JK. Use of sleep hygiene in the treatment of insomnia. *Sleep Med Rev* 2003;7(3):215–25.
- [14] Lang C, Kalak N, Brand S, Holsboer-Trachsler E, Pühse U, Gerber M. The relationship between physical activity and sleep from mid adolescence to early adulthood. A systematic review of methodological approaches and meta-analysis. *Sleep Med Rev* 2016;28:32–45.
- [15] Hartescu I, Morgan K, Stevenson CD. Increased physical activity improves sleep and mood outcomes in inactive people with insomnia: a randomized controlled trial. *J Sleep Res* 2015;24(5):526–34.
- [16] Driver HS, Taylor SR. Exercise and sleep. *Sleep Med Rev* 2000;4 (4):387–402.
- [17] Kredlow MA, Capozzoli MC, Hearon BA, Calkins AW, Otto MW. The effects of physical activity on sleep: a meta-analytic review. *J Behav Med* 2015;38(3):427–49.
- [18] Morin CM, Hauri PJ, Espie CA, Spielman AJ, Buysse DJ, Bootzin RR. Nonpharmacologic treatment of chronic insomnia. *Sleep* 1999;22(8):1134–56.
- [19] Buman MP, Phillips BA, Youngstedt SD, Kline CE, Hirshkowitz M. Does nighttime exercise really disturb sleep? Results from the 2013 national sleep foundation sleep in America poll. *Sleep Med* 2014;15(7):755–61.
- [20] Landolt HP, Werth E, Borbély AA, Dijk DJ. Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res* 1995;675(1–2):67–74.
- [21] Bonnet MH, Arand DL. Caffeine use as a model of acute and chronic insomnia. *Sleep* 1992;15(6):526–36.
- [22] Paterson LM, Wilson SJ, Nutt DJ, Huston PH, Ivarsson M. A translational, caffeine-induced model of onset insomnia in rats and healthy volunteers. *Psychopharmacology* 2007;191(4):943–50.
- [23] Roehrs T, Roth T. Caffeine: sleep and daytime sleepiness. *Sleep Med Rev* 2008;12(2):153–62.
- [24] Drake C, Roehrs T, Shambroom J, Roth T. Caffeine effects on sleep taken 0, 3, or 6 hours before going to bed. *J Clin Sleep Med* 2013;9(11):1195–200.
- [25] Sanchez-Ortuno M, Moore N, Taillard J, Valtat C, Leger D, Bioulac B, Philip P. Sleep duration and caffeine consumption in a French middle-aged working population. *Sleep Med* 2005;6(3):247–51.
- [26] Chaudhary NS, Grandner MA, Jackson NJ, Chakravorty S. Caffeine consumption, insomnia, and sleep duration: results from a nationally representative sample. *Nutrition* 2016;32(11):1193–9.
- [27] Retey JV, Adam M, Khatami R, Luhmann UFO, Jung HH, Berger W, Landolt HP. A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. *Clin Pharmacol Therapeut* 2007;81 (5):692–8.
- [28] Kerpershoek ML, Antypa N, Van den Berg JF. Evening use of caffeine moderates the relationship between caffeine consumption and subjective sleep quality in students. *J Sleep Res* 2018;e12670.
- [29] Thakkar MM, Sharma R, Sahota P. Alcohol disrupts sleep homeostasis. *Alcohol* 2015;49(4):299–310.
- [30] Ebrahim IO, Shapiro CM, Williams AJ, Fenwick PB. Alcohol and sleep I: effects on normal sleep. *Alcohol Clin Exp Res* 2013;37 (4):539–49.
- [31] Roehrs T, Roth T. Insomnia as a path to alcoholism: tolerance development and dose escalation. *Sleep* 2018;41.
- [32] Morin CM, Mimeaule V, Gagné A. Nonpharmacological treatment of late-life insomnia. *J Psychosom Res* 1999;46(2):103–16.
- [33] Jaehne A, Loessl B, Bárkai Z, Riemann D, Hornyak M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. *Sleep Med Rev* 2009;13(5):363–77.
- [34] Hughes JR, Higgins ST, Bickel WK. Nicotine withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. *Addiction* 1994;89(11):1461–70.
- [35] Nakata A, Takahashi M, Haratani T, Ikeda T, Hojou M, Fujioka Y, Araki S. Association of active and passive smoking with sleep disturbances and short sleep duration among Japanese working population. *Int J Behav Med* 2008;15(2):81.
- [36] Sabanayagam C, Shankar A. The association between active smoking, smokeless tobacco, second-hand smoke exposure and insufficient sleep. *Sleep Med* 2011;12(1):7–11.
- [37] Ohayon MM. Prevalence and correlates of nonrestorative sleep complaints. *Arch Intern Med* 2005;165(1):35–41.
- [38] Otto E, Kramer H, Bräuer D. Effects of increasing air temperature on heart rate, body movements, rectal temperature and electroencephalogram of sleeping subjects. *Internationales Archiv für Arbeitsmedizin* 1971;28(3):189–202.
- [39] Angus RG, Pearce DG, Buguet AG, Olsen L. Vigilance performance of men sleeping under arctic conditions. *Aviat Space Environ Med* 1979;50.
- [40] National sleep foundation. (2018). <https://www.sleep.org/articles/temperature-for-sleep/>.
- [41] Boivin DB, Duffy JF, Kronauer RE, Czeisler CA. Dose-response relationships for resetting of human circadian clock by light. *Nature* 1996;379:540–2.
- [42] Gooley JJ, Chamberlain K, Smith KA, Khalsa SBS, Rajaratnam SMW, Van Reen E, Lockley SW. Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. *J Clin Endocrinol Metabol* 2011;96 (3):E463–72.
- [43] Muzet A. Environmental noise, sleep and health. *Sleep Med Rev* 2007;11(2):135–42.
- [44] World health organization. (2018). <http://www.euro.who.int/en/health-topics/environment-and-health/noise/policy/who-night-noise-guidelines-for-europe>.

- [45] Rechtschaffen A, Hauri P, Zeitlin M. Auditory awakening thresholds in REM and NREM sleep stages. *Percept Mot Skills* 1966;22(3):927–42.
- [46] Bader GG, Engdal S. The influence of bed firmness on sleep quality. *Appl Ergon* 2000;31(5):487–97.
- [47] Kinkel HJ, Maxion H. Physiological sleep studies for the evaluation of different mattresses. *Internationale Zeitschrift fur angewandte Physiologie, einschliesslich Arbeitsphysiologie* 1970;28 (3):247–62.
- [48] Villani S. Impact of media on children and adolescents: a 10-year review of the research. *J Am Acad Child Adolesc Psychiatr* 2001;40(4):392–401.
- [49] Cain N, Gradisar M. Electronic media use and sleep in school-aged children and adolescents: a review. *Sleep Med* 2010;11(8):735–42.
- [50] Hale L, Guan S. Screen time and sleep among school-aged children and adolescents: a systematic literature review. *Sleep Med Rev* 2015;21:50–8.
- [51] Gradisar M, Wolfson AR, Harvey AG, Hale L, Rosenberg R, Czeisler CA. The sleep and technology use of Americans: findings from the national sleep foundation's 2011 sleep in America poll. *J Clin Sleep Med* 2013;9(12):1291–9.
- [52] Tang NK, Schmidt DA, Harvey AG. Sleeping with the enemy: clock monitoring in the maintenance of insomnia. *J Behav Ther Exp Psychiatr* 2007;38(1):40–55.
- [53] Woods H, Marchetti LM, Biello SM, Espie CA. The clock as a focus of selective attention in those with primary insomnia: an experimental study using a modified Posner paradigm. *Behav Res Ther* 2009;47(3):231–6.
- [54] Morin CM. Insomnia: psychological assessment and management. Guilford Press; 1993.
- [55] Lacks P, Rotert M. Knowledge and practice of sleep hygiene techniques in insomniacs and good sleepers. *Behav Res Ther* 1986;24(3):365–8.
- [56] Blake DD, Gomez MH. A scale for assessing sleep hygiene: preliminary data. *Psychol Rep* 1998;83(3_Suppl. 1):1175–8.
- [57] Mastin DF, Bryson J, Corwyn R. Assessment of sleep hygiene using the sleep hygiene index. *J Behav Med* 2006;29(3):223–7.
- [58] Harsh JR, Easley A, LeBourgeois MK. A measure of children's sleep hygiene. *Sleep* 2002;25:A316.
- [59] Storfer-Isser A, Lebourgeois MK, Harsh J, Tompsett CJ, Redline S. Psychometric properties of the adolescent sleep hygiene scale. *J Sleep Res* 2013;22(6):707–16.
- [60] Jefferson CD, Drake CL, Scofield HM, Myers E, McClure T, Roehrs T, Roth T. Sleep hygiene practices in a population-based sample of insomniacs. *Sleep* 2005;28(5):611–5.
- [61] Gellis LA, Lichstein KL. Sleep hygiene practices of good and poor sleepers in the United States: an internet-based study. *Behav Ther* 2009;40(1):1–9.
- [62] Harvey AG. Sleep hygiene and sleep-onset insomnia. *J Nerv Ment Dis* 2000;188(1):53–5.
- [63] Voineskos BJ, Szentagotai-Tatar A. Sleep hygiene awareness: its relation to sleep quality and diurnal preference. *Journal of molecular psychiatry* 2015;3(1):1.
- [64] American Sleep Disorders Association, Diagnostic Classification Steering Committee. The international classification of sleep disorders: diagnostic and coding manual. American sleep disorders association; 1990.
- [65] American Academy of Sleep Medicine. International classification of sleep disorders. *Diagnostic and coding manual*. 2005. p. 51–5.
- [66] Buysse DJ, Reynolds III CF, Kupfer DJ, Thorpy MJ, Bixler E, Manfredi R, Hauri P. Clinical diagnoses in 216 insomnia patients using the international classification of sleep disorders (ICSD), DSM-IV and ICD-10 categories: a report from the APA/NIMH DSM-IV field trial. *Sleep* 1994;17(7):630–7.
- [67] Reynolds III CF, Kupfer DJ. Subtyping DSM-III-R primary insomnia: a literature review by the DSM-IV work group on sleep disorders. *Am J Psychiatr* 1991;148(4):432.
- [68] Chesson JAL, Anderson WM, Littner M, Davila D, Hartse K, Johnson S, Rafecas J. Practice parameters for the non-pharmacologic treatment of chronic insomnia. *Sleep* 1999;22 (8):1128–33.
- [69] Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). *Sleep* 2006;29 (11):1398–414.
- [70] Chung KF, Lee CT, Yeung WF, Chan MS, Chung EWY, Lin WL. Sleep hygiene education as a treatment of insomnia: a systematic review and meta-analysis. *Fam Pract* 2017;35.
- [71] Schoicket SL, Bertelson AD, Lacks P. Is sleep hygiene a sufficient treatment for sleep-maintenance insomnia? *Behav Ther* 1988;19 (2):183–90.
- [72] Everitt H, McDermott L, Leydon G, Yules H, Baldwin D, Little P. GPs' management strategies for patients with insomnia: a survey and qualitative interview study. *Br J Gen Pract* 2014;64(619): e112–9.
- [73] Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: a review of empirical evidence. *Sleep Med Rev* 2015;22:23–36.
- [74] Buysse DJ. Sleep health: can we define it? Does it matter? *Sleep* 2014;37(1):9–17.
- [75] Knutson KL, Phelan J, Paskow MJ, Roach A, Whiton K, Langer G, Lichstein KL. The national sleep foundation's sleep health index. *Sleep Health: J Natl Sleep Found* 2017;3(4):234–40.
- [76] Barber L, Grawitch MJ, Munz DC. Are better sleepers more engaged workers? A self-regulatory approach to sleep hygiene and work engagement. *Stress Health* 2013;29(4):307–16.
- [77] Mead MP, Irish LA. Application of health behaviour theory to sleep health improvement. *J Sleep Res* 2020;29(5):e12950.
- [78] Gwyther K, Rice S, Purcell R, Pilkington V, Santesteban-Echarri O, Bailey A, Walton CC. Sleep interventions for performance, mood and sleep outcomes in athletes: a systematic review and meta-analysis. *Psychol Sport Exerc* 2022;58:102094.
- [79] McAlpine T, Mullan B, Clarke PJ. Re-considering the role of sleep hygiene behaviours in sleep: associations between sleep hygiene, perceptions and sleep. *Int J Behav Med* 2023;1–13.
- [80] Nikles J, Mitchell GK, de Miranda Araújo R, Harris T, Heussler HS, Punja S, Senior HEJ. A systematic review of the effectiveness of sleep hygiene in children with ADHD. *Psychol Health Med* 2020;25(4):497–518.
- [81] Herscher M, Mikhaylov D, Barazani S, Sastow D, Yeo I, Dunn AS, Cho HJ. A sleep hygiene intervention to improve sleep quality for hospitalized patients. *Joint Comm J Qual Patient Saf* 2021;47(6):343–6.

- [82] Shriane AE, Ferguson SA, Jay SM, Vincent GE. Sleep hygiene in shift workers: a systematic literature review. *Sleep Med Rev* 2020;53:101336.
- [83] Perlis ML, Gehrman P, Ellis JG. The natural history of insomnia: what we know, don't know, and need to know. *Sleep Med Res* 2011;2:79–88.
- [84] Spielman AJ. Assessment of insomnia. *Clin Psychol Rev* 1986;6(1):11–25.
- [85] Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. *Psychiatr Clin* 1987;10(4):541–53.
- [86] Perlis ML, Giles DE, Mendelson WB, Bootzin RR, Wyatt JK. Psychophysiological insomnia: the behavioural model and a neuropsychological perspective. *J Sleep Res* 1997;6(3):179–88.
- [87] Buysse DJ, Germain A, Hall M, Monk TH, Nofzinger EA. A neurobiological model of insomnia. *Drug Discov Today Dis Model* 2011;8(4):129–37.
- [88] Ellis JG, Perlis ML, Neale LF, Espie CA, Bastien CH. The natural history of insomnia: focus on prevalence and incidence of acute insomnia. *J Psychiatr Res* 2012;46(10):1278–85.
- [89] Perlis ML, Vargas I, Ellis JG, Grandner MA, Morales KH, Gencarelli A, Thase ME. The natural history of insomnia: the incidence of acute insomnia and subsequent progression to chronic insomnia or recovery in good sleeper subjects. *Sleep* 2020;43(6):zs299.
- [90] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.
- [91] American Academy of Sleep Medicine. International classification of sleep disorders—third edition (ICSD-3). Darien, IL: American Academy of Sleep Medicine; 2014.
- [92] Perlis ML, Pigeon WR, Grandner MA, Bishop TM, Riemann D, Ellis JG, Posner DA. Why treat insomnia? *J Prim Care Commun Health* 2021;12:21501327211014084.
- [93] Ellis JG, Gehrman P, Espie CA, Riemann D, Perlis ML. Acute insomnia: current conceptualizations and future directions. *Sleep Med Rev* 2012;16(1):5–14.
- [94] Ellis JG, Perlis ML, Bastien CH, Gardani M, Espie CA. The natural history of insomnia: acute insomnia and first-onset depression. *Sleep* 2014;37(1):97–106.
- [95] Fossion R, Rivera AL, Toledo-Roy JC, Ellis J, Angelova M. Multiscale adaptive analysis of circadian rhythms and intradaily variability: application to actigraphy time series in acute insomnia subjects. *PLoS One* 2017;12(7):e0181762.
- [96] Ellis J, Cropley M. An examination of thought control strategies employed by acute and chronic insomniacs. *Sleep Med* 2002;3(5):393–400.
- [97] Man S, Freeston M, Ellis JG, Lee DR. A pilot study investigating differences in sleep and life preoccupations in chronic and acute insomnia. *Sleep Med Res (SMR)* 2013;4(2):43–50.
- [98] Ellis JG, Perlis ML, Espie CA, Grandner MA, Bastien CH, Barclay NL, Gardani M. The natural history of insomnia: predisposing, precipitating, coping, and perpetuating factors over the early developmental course of insomnia. *Sleep* 2021;44(9):zsab095.
- [99] Perlis ML, Morales KH, Vargas I, Posner DA, Grandner MA, Muench AL, Ellis JG. The natural history of insomnia: does sleep extension differentiate between those that do and do not develop chronic insomnia? *J Sleep Res* 2021;30(5):e13342.
- [100] Ellis JG, Cushing T, Germain A. Treating acute insomnia: a randomized controlled trial of a “single-shot” of cognitive behavioral therapy for insomnia. *Sleep* 2015;38(6):971–8.
- [101] Germain A, Moul DE, Franzen PL, Miewald JM, Reynolds CF, Monk TH, Buysse DJ. Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. *J Clin Sleep Med* 2006;2(04):407–8.
- [102] Edinger JD, Sampson WS. A primary care “friendly” cognitive behavioral insomnia therapy. *Sleep* 2003;26(2):177–82.
- [103] Bouillin P, Ellwood C, Ellis JG. Group vs. Individual treatment for acute insomnia: a pilot study evaluating a “one-shot” treatment strategy. *Brain Sci* 2016;7(1):1.
- [104] Randall C, Nowakowski S, Ellis JG. Managing acute insomnia in prison: evaluation of a “one-shot” cognitive behavioral therapy for insomnia (CBT-I) intervention. *Behav Sleep Med* 2018;1:1–10.
- [105] Orchard F, Pass L, Chessell C, Moody A, Ellis J, Reynolds S. Adapting brief CBT-I for depressed adolescents: a case illustration of the sleeping better program. *Cognit Behav Pract* 2020;27(3):336–46.
- [106] Elder GJ, Santhi N, Robson AR, Alfonso-Miller P, Spiegelhalder K, Ellis JG. An online behavioural self-help intervention rapidly improves acute insomnia severity and subjective mood during the COVID-19 pandemic: a stratified randomised controlled trial. *Sleep* 2024.
- [107] Dowa LH, Kyle SD, Hassan L, Shaw J, Senior J. Prevalence, associated factors and management of insomnia in prison populations: an integrative review. *Sleep Med Rev* 2015;24:13–27.
- [108] Drake C, Richardson G, Roehrs T, Scofield H, Roth T. Vulnerability to stress-related sleep disturbance and hyperarousal. *Sleep* 2004;27(2):285–91.
- [109] Jarrin DC, Chen IY, Ivers H, Morin CM. The role of vulnerability in stress-related insomnia, social support and coping styles on incidence and persistence of insomnia. *J Sleep Res* 2014;23(6):681–8.
- [110] Drake CL, Friedman NP, Wright Jr KP, Roth T. Sleep reactivity and insomnia: genetic and environmental influences. *Sleep* 2011;34(9):1179–88.
- [111] Kalmbach DA, Pillai V, Arnedt JT, Anderson JR, Drake CL. Sleep system sensitization: evidence for changing roles of etiological factors in insomnia. *Sleep Med* 2016;21:63–9.
- [112] Walker JL, Vargas I, Drake CL, Ellis JG, Muench A, Perlis ML. The natural history of insomnia: high sleep reactivity interacts with greater life stress to predict the onset of acute insomnia. *Sleep* 2022;45(9):zsac149.
- [113] Grandner MA, Jackson N, Gooneratne NS, Patel NP. The development of a questionnaire to assess sleep-related practices, beliefs, and attitudes. *Behav Sleep Med* 2014;12(2):123–42.
- [114] Robbins R, Grandner MA, Buxton OM, Hale L, Buysse DJ, Knutson KL, Jean-Louis G. Sleep myths: an expert-led study to identify false beliefs about sleep that impinge upon population sleep health practices. *Sleep Health* 2019;5(4):409–17.
- [115] Khader WS, Fernandez FX, Seixas A, Knowlden A, Ellis J, Williams N, Grandner MA. What makes people want to make changes to their sleep? Assessment of perceived risks of insufficient sleep as a predictor of intent to improve sleep. *Sleep Health* 2021;7(1):98–104.

Chapter 15

Actigraphic sleep tracking and wearables

Michael A. Grandner^a and Mary E. Rosenberger^b

^aSleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States;

^bStanford Center on Longevity and Psychology Department, Stanford University, Stanford, CA, United States

Introduction

Human sleep is naturally recurring and easily reversible state that is characterized by reduced or absent consciousness, perceptual disengagement, immobility, and adoption of a characteristic sleeping posture. Regulation of the sleep–wake system includes both homeostatic and circadian components and is modified by genetic, physiologic, environmental, and behavioral factors (see Chapter 1 in this volume). Importantly, determining whether an individual is “asleep” can only be accomplished through indirect methods—it is typically impossible to make a direct measurement of sleep or wake, as this represents a complex output of neurologic systems that are primarily contained in the midbrain. Instead, we rely in indirect measures of sleep.

The accepted “gold-standard” measure of sleep is polysomnography, which is a combination of physiologic recording channels including electroencephalography, electromyography, electrooculography, electrocardiography, oximetry, and measures of respiration [1]. Polysomnography assesses cortical synchronization activity and can be used to discern “sleep stages,” which are distinct states that occur across the sleep period and reflect characteristically distinct brain wave patterns that themselves represent and/or correlate with other physiologic processes. Polysomnography, while considered the gold-standard, is an indirect measure of sleep and has some important limitations. Most notably, it is usually very expensive and burdensome. The expense precludes repeated assessment in large samples, and the burden on patients is such that it can itself cause changes to sleep. Because of this, polysomnography is known to interfere with sleep, is rarely recorded over several nights, and polysomnographic recordings are not well-suited to reflect habitual sleep.

Field-based measurement of sleep is different from polysomnography in that it utilizes a movement-detection

apparatus to assess patterns of mobility and immobility in order to estimate whether an individual is asleep or awake [2]. Newer wearable devices also incorporate heart-rate based measurements of sleep [3]. Although actigraphy cannot assess sleep stages, it can estimate whether an individual is awake or asleep with (typically) 1-min resolution. With this information over a whole recording period, determinations can be made regarding sleep duration and time awake (e.g., sleep latency and wake time after initial sleep onset); this can be used to calculate variables such as sleep efficiency (the ratio of time asleep to total time in bed). See Table 15.1 for a broad comparison between actigraphy and polysomnography.

Scoring algorithms

The first use of movement-based recordings to determine sleep and wake were published in 1972 [4,5] on a set of psychiatric patients. Even in this first study, with little temporal resolution or precision in movement estimation, it was clear that this method could be useful for determining sleep schedules. See Fig. 15.1 for a reproduction of the first images of 24-h actigraphy recordings.

In 1978, Kripke and colleagues would publish results of a similar study using a different device, referring to the method as “actigraphy” [6]. These initial devices used crude movement-transducers to quantify movement counts. The first studies examined the raw data outputs to score sleep versus wake [6,7], but it was soon hypothesized that this scoring could be automated. The first sleep–wake scoring algorithms were developed with the assumption that simply quantifying movement was insufficient—other factors, including the context of that movement and time of day, are also essential.

Several actigraphy scoring algorithms have been developed over the course of the past ~40 years. As actigraphic technology changed, algorithms changed as well. The first validated scoring algorithm was described by

TABLE 15.1 Comparison of actigraphy to polysomnography.

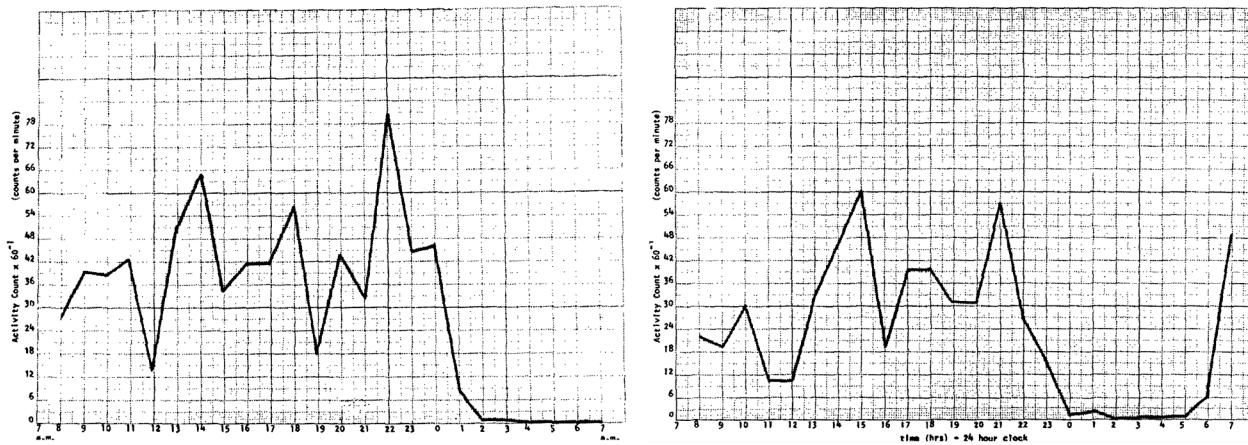
	Actigraphy	Polysomnography
Standard epoch length	1 min	30 s
Cost	Low	High
Nights typically evaluated	7–14	1–2
Captures daytime sleep	Yes	No
Channels recorded	1 or few	Many
Measures immobility	Yes	Yes
Measures reduced or absent consciousness	No	Indirectly
Measures sensory inhibition	No	Indirectly
Measures sleep-related breathing	No	Yes
Measures sleep continuity	Yes	Yes
Measures sleep timing	Yes	No
Measures sleep regularity	Yes	No
Measures sleep satisfaction	No	No

Webster and colleagues [8] and derived their algorithm against polysomnography as a gold standard. Their algorithm, which included weights of the 1-min epoch of interest, as well as the previous four epochs and subsequent two epochs for context, set the standard for future actigraphy scoring algorithms. Of note, the Webster algorithm was meant to be followed up by additional scoring rules that represented areas where the scoring algorithm often failed (such as brief apparent sleep episodes that were likely actually time awake). Overall, rate of agreement between actigraphy and polysomnography was >90%.

Subsequent attempts at developing scoring algorithms typically adopted a similar approach (weighting the epoch of interest against several previous and subsequent epochs), though the adoption of follow-up rules were often

dropped in favor of less structured hand-scoring for clear anomalies and errors. These included algorithms developed for analog motion transducers [9], analog accelerometers [10–12], and newer accelerometers that included multiaxial assessment and digital recording [13,14]. Overall, as the technology has progressed and the use of actigraphy has expanded, validation studies often included larger and more diverse samples. Still rates of agreement with polysomnography are typically around 85%–90% [2,15–17].

Of note, each of these algorithms was validated in a specific context. For example, these validation studies typically are restricted to a particular device or type of device (e.g., linear analog transducer), and it is not clear how well these algorithms will fare in other devices. There is evidence that algorithms are somewhat transferrable

**FIGURE 15.1** The first published actograms, in the paper by Foster and colleagues [4].

across devices and even movement recording modalities [8,14], but this limitation should be acknowledged. Also, these validation studies typically only compared actigraphy to polysomnography within a defined in-bed interval. Methods for using actigraphy to detect sleep during the daytime or methods to automatically determine an in-bed interval in real-world settings are often not well-validated, and therefore, caution should be taken with these approaches.

Most newer actigraphic devices use microelectromechanical systems [14,18] to record movement. These approaches, which apply nanotechnology to accelerometry and produce accelerometers that fit on a tiny microchip, often apply similar principles to traditional accelerometers, just on a smaller scale [18]. Several devices that use MEMS chips to record accelerometry for sleep detection have been validated [14], though many of these chips are optimized for physical activity measurement more than sleep.

Types of actigraph devices

The most common devices in the scientific literature include those developed by Ambulatory Monitoring, Inc. (AMI) and Mini-Mitter Inc. (later acquired by Respirationics, which was acquired by Philips) [12,13,19–24]. These devices are similar and have changed relatively little over the past several years. Several AMI devices have been validated in the scientific literature for sleep, though the ones most frequently used are the Actillume (older device) and Motionlogger (newer device). These devices, and others, are depicted in Fig. 15.2. The Actillume was an analog device with a basic accelerometer array that could capture movement in three dimensions. The Motionlogger replaced the Actillume as a digital device that was smaller and actually had a watch face. Both the Actillume and Motionlogger record environmental light with a single photometer channel, but only the Motionlogger device has a mode that can estimate off-wrist time, which is important to distinguish from on-wrist lack of movement and is also water-resistant. The device made by Mini-Mitter was the Actiwatch (also depicted in Fig. 15.2, in several iterations). The Actiwatch was similar to the Motionlogger in that it digitally recorded both movement and light and stored data in 1-min epochs. Since the manufacturer was acquired by Respirationics and then Philips, new versions of the device include the Actiwatch-2 (pictured) and the Actiwatch Spectrum (pictured). These devices similarly record movement and light; the Actiwatch-2 has a rechargeable battery and is water-resistant. The current models of the Actiwatch Spectrum are also water-resistant and also have rechargeable batteries; the added features of the Spectrum include off-wrist detection and light channels for red, green, and blue light spectra.

Several other devices have also been used with relative frequency in scientific settings, though validation of these devices is less robust. For example, the GT3X and related devices from Actigraph, Inc. (pictured in Fig. 15.2) are frequently less expensive than AMI or Philips devices, though they have been less rigorously validated [25,26]. Of note, no scoring algorithm has been developed for this device and the scoring software simply co-opts algorithms from other devices, assuming relative accuracy. Also, these devices do not contain a light channel. Other devices that have shown some degree of scientific utility include the GENEActiv [14] (made by ActivInsights), the Motion Watch [27] (made by Cambridge Neurotechnology), Fitbit devices [3,19,26,28–31] (made by Fitbit), and the Readi-band (made by Fatigue Science). These devices may be useful but are less well validated.

Other actigraphy-like devices have also emerged on the market. For example, some products are to be worn as an armband, such as the SenseWear [32] band (made by Body Media). Other devices, such as the Oura [33] (made by Oura) are to be worn as a ring on the finger. Some devices use movement recorded by the mattress using pressure-sensing technology, such as the EarlySense [34] (made by EarlySense Ltd.) device. Another device, called the SleepScore MAX (made by SleepScore, formerly the device called S + made by ResMed), uses contactless infrared technology to assess sleep-related parameters. Although it does not measure movement in a similar way, it has been used as an alternative to actigraphy for individuals who cannot tolerate a wearable and validation data for the device are relatively strong for sleep-wake detection. A portable, FDA approved, one-lead EEG sensor called the Z-machine has been validated [26,35] and used to validate other field-based measures. The validity of these devices is much less established than that of more traditional actigraphy, but this may change as more literature is published on specific devices and modalities.

It should be noted that many smartphones contain MEMS chips and many software programs (i.e., apps) attempt to leverage these for sleep-wake detection. However, these apps typically do not estimate sleep based on movement at the wrist or anywhere else on the person; rather they frequently attempt to assess movement by being placed on the mattress or otherwise near the sleeper. It should be noted that despite the apparent popularity of these apps, none has demonstrated good validity relative to validated sleep measures. For example, one very popular app was shown to be unrelated to any observed values obtained from a validated source [36].

Newer commercial wearable devices use MEMS chips in addition to heart rate sensors to improve sleep algorithmic scoring, such as the Fitbit Charge 3, the Motiv ring, and others. Heart rate measurement is relatively simple compared to other measurements during sleep, and a study

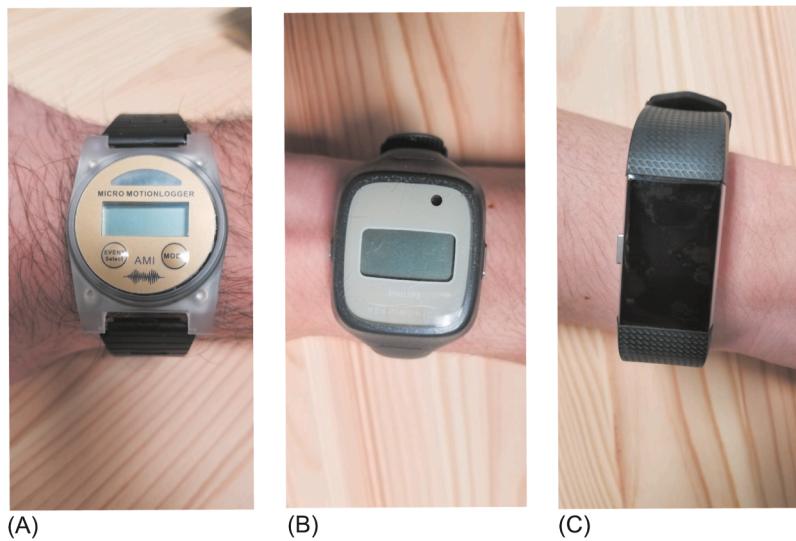


FIGURE 15.2 Images of common actigraphic devices, including the Motionlogger (A), Actiwatch Spectrum (B), and Fitbit Charge 2 (C).

of heart rate during sleep is well established [37]. Specifically heart rate variability, or the changes in time between heart beats measured as an R-R interval (referring to the EKG recording of heart rate), is specifically studied as a method for determining sleep stages [38,39]. The combination of actigraphy and heart rate measures during sleep holds promise for more accurate sleep scoring algorithms.

Limitations of actigraphy and related considerations

All measures of sleep in humans are indirect. Thus, all measures of sleep in humans are imperfect. There is no way to accurately estimate a person's sleep duration and sleep architecture over a period of days or weeks in such a way that habitual parameters can be estimated. Actigraphy may be the best and most accepted solution, but it is not without limitations.

For example, compared to polysomnography, actigraphy has relatively good sensitivity (it correctly identifies sleep most of the time), but it has relatively poor specificity (it incorrectly identifies wake much of the time). See Fig. 15.3 for an image from a paper by Marino and colleagues [15] that illustrates this based on data from a large sample of real-world adults. What this means is that, relative to polysomnography, it will identify nearly all of the sleep epochs as sleep, but it will misidentify many of the wake epochs also as sleep, thus over-estimating sleep relative to polysomnography. This pattern of findings is frequently reported in the actigraphy validation literature and is probably explained by individuals lying in bed awake immobile when they are trying to sleep. Fortunately, most people spend relatively little time immobile but awake in bed, and this measurement error is

minimized. But as the previously referenced paper by Marino and colleagues showed the more time individuals spent awake in bed not sleeping, the greater the proportion of those epochs were misidentified as sleep by actigraphy (see Fig. 15.4). Fig. 15.4 shows that although there is a strong relationship between actigraph and polysomnographic wake time after sleep onset, there is a systematic increase in underestimation as wake time after sleep onset increases beyond about 30 min. Therefore, actigraphy may be relatively accurate overall, but it is typically better at detecting sleep than wake and thus may overestimate sleep, especially when individuals spend excessive time in bed awake.

It should be noted that these studies, by design, have clearly identified in-bed intervals (defined by the time hooked up to polysomnography). Real-world implementation of actigraphy, which records over days, typically lacks this defined period in bed. Although this issue applies to nighttime sleep, it is unclear how it applies to daytime sleep. Since actigraphy algorithms typically identify many periods of brief sleep during the day, it may overestimate sleep out of bed, compared to what polysomnography would presumably record. Also of note, sleep diary is known to overestimate sleep compared to polysomnography, especially in people without insomnia. Actigraphy, though, does not approximate sleep diary in this way. It is typically a better approximation of objective sleep recorded with polysomnography than it is an approximation of self-reported sleep recorded by sleep diary. Therefore, it will appear to underestimate sleep, compared to sleep diary.

Another limitation of actigraphy is that its utility in sleep disorders is different than in individuals without sleep disorders. Of note, actigraphy can be quite useful for

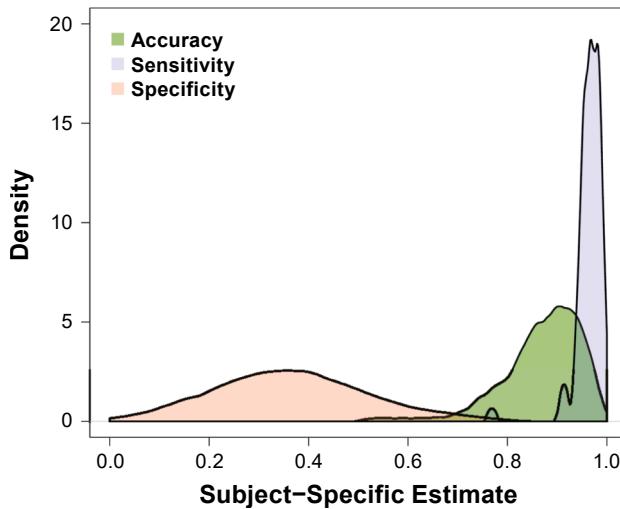


FIGURE 15.3 Sensitivity, specificity, and overall accuracy of actigraphy devices in the study by Marino and colleagues [15].

measuring sleep in insomnia patients, being relatively accurate at estimating sleep duration, sleep timing, sleep efficiency, wake after sleep onset, and other parameters. Yet, it has been shown to be relatively inaccurate regarding sleep latency, as this is likely when individuals are most likely to be awake but immobile [22]. For sleep apnea, actigraphy can often assess sleep characteristics, but the frequent movements associated with arousals may interfere with the device's accuracy [16,40–42].

Children move more during the night, especially boys. Therefore, scoring rules for actigraphy in children may need to be different and may need to vary by developmental stage. Many previous studies have validated actigraphy for pediatric populations including infants [43–47], children [19,43,48], and adolescents [19,32,40,49,50]. Especially since parent reports are unreliable and child reports of sleep are also unreliable, a method for accurately representing sleep is imperative. In this case, actigraphy is a useful option, but caution should be used in scoring in order to ensure accuracy. Additionally, sleep changes throughout the lifespan, and therefore scoring algorithms in adult populations may need modifications for specific physiological conditions, such as pregnancy [51] and in older adults [11].

A critical issue with actigraphic sleep assessment is that many sleep parameters require the estimation of values in the context of being in bed and trying to sleep. For example, sleep efficiency is based on total time in bed, and sleep latency represents the amount of time elapsed between when the person goes to bed and when they fall asleep. Therefore, knowing when a person is in bed is important for actigraphic data to be useful for characterizing sleep. Yet, actigraphic devices cannot sense when an individual is in bed. When scoring actigraphic sleep, most

software packages have proprietary methods for estimating the time a person enters and leaves the bed. These intervals are critical for determining sleep parameters in actigraphy, as illustrated in Fig. 15.5. In Fig. 15.5, a typical night is depicted, where the software estimated an in-bed interval based on movement that is clearly incorrect. The software estimate that the person was in bed where indicated in blue (the darker blue reflects the estimated interval where the individual was mostly asleep). The black lines represent movement, and the broken red line at the bottom indicates estimated sleep versus wake. The software estimated an in-bed interval from approximately 5:30 p.m. until approximately 8:00 a.m. Yet, based on the movement patterns, it is likely that the individual did not get into bed until about 11:30 p.m. Thus, rather than 14.5 h in bed, the individual likely spent about 8.5 h in bed. There is currently no validated algorithm for choosing these in-bed intervals in the software. Hand-scoring approaches have been the gold-standard [7,52], and many scorers use a combination of experience, sleep diary data, and data from the light channel (on/off) to determine the interval in which to look for sleep [2]. Along these lines, detecting time in bed for naps is similarly (and more) difficult.

Another key issue with actigraphy is that many of the most well-established devices (e.g., Actiwatch and Motionlogger) download data directly into a computer. Because of this, data loss and/or device failure is not known until the device is downloaded at the end of the assessment period. This is in contrast to devices that use Bluetooth connectivity to a mobile phone device, which can provide updates into the cloud, allowing for more prospective and/or active monitoring of data to better identify problems.

Identifying sleep stages with actigraphy

Movement-based sleep estimation is unable to distinguish between sleep stages. Scientific-grade devices that assess sleep using actigraphy should not (and typically do not) claim to be able to estimate sleep architecture or depth in any way. Yet, several commercially available devices have claimed this ability, despite available data.

There is one exception to this, in that a group led by Roenneberg [53] has characterized what they describe as "Locomotor Inactivity During Sleep" (LIDS), which is a way to characterize actigraphic recordings in more detail in such a way that may discern sleep stages. Fig. 15.6 shows some of the data from the first study of LIDS, showing a rough approximation of sleep cycles with cycling LIDS. Of note, this is still controversial, and the methods for using LIDS have not been well-characterized.

One way in which actigraphic devices have been used to relatively accurately predict sleep stages is through the use of an additional physiologic channel (typically heart

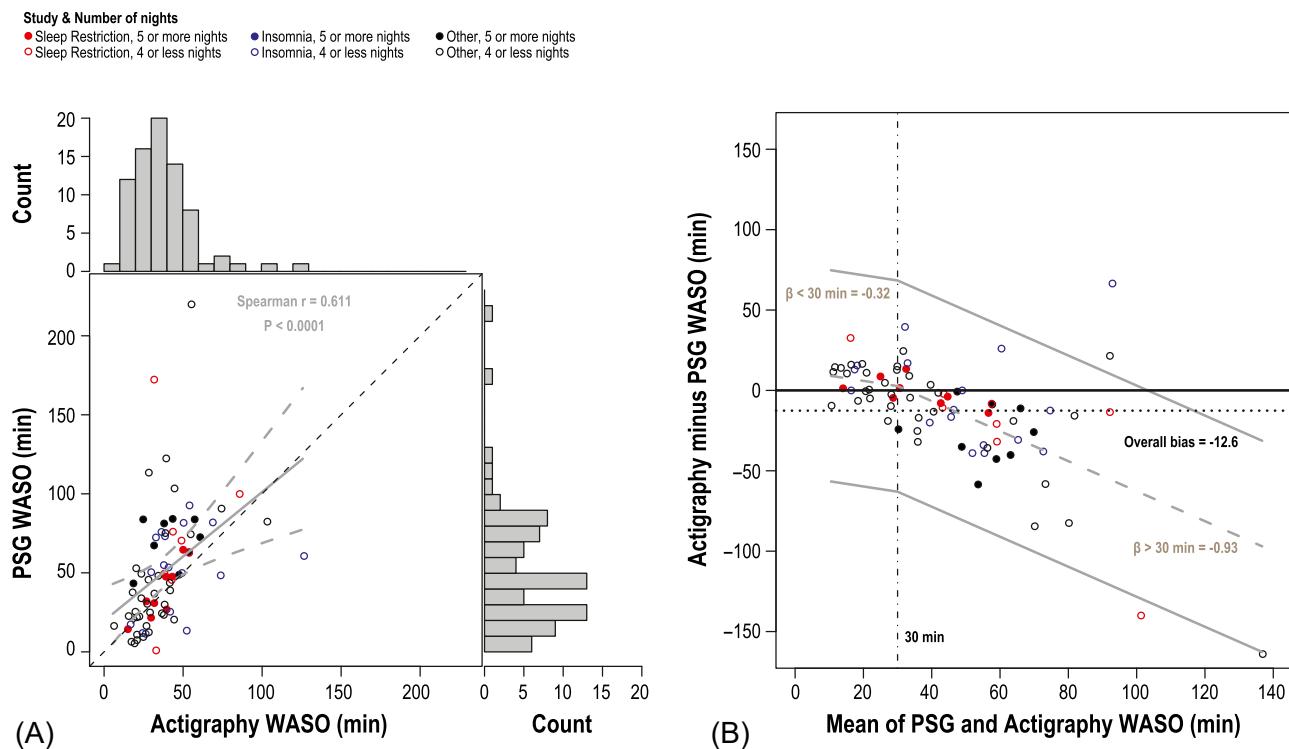


FIGURE 15.4 Underestimation of wake after sleep onset (WASO) by actigraphy, as a function of increasing polysomnographic WASO. (A) PSG WASO vs. actigraphy WASO scatterplot and their corresponding histograms. The dashed black line is the 45-degree line. The solid gray line is the line of best fit and the gray dashed lines are the confidence band of the line of best fit. (B) Bland-Altman plot of individual differences between actigraphy and PSG for WASO. The solid black horizontal line at zero denotes the scenario when no bias is present. The dashed gray line represents the best line of agreement based on the linear spline regression model describing mean change in bias over average WASO and the solid gray lines are the 95% limits of agreement. The dotted black line represents the overall mean bias. *From Marino M, Li Y, Rueschman MN, et al. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. Sleep 2013;36(11):1747–1755.*

rate). The WatchPAT (Itamar Medical) is a wrist-worn device that is used to screen for sleep apnea and includes an actigraphy channel, as well as a channel for peripheral arterial tone. Using this additional data, the device has been shown to relatively accurately distinguish between sleep stages [54,55]. Another device that uses a second channel to approximate sleep stages is Fitbit, who validated their devices which use a combination of accelerometry and optical plethysmography to get a measure of continuous heart rate [3]. This validation study showed that by combining channels, the devices were able to achieve 94.6% sensitivity (comparable to other devices) and specificity of 69.3% (which is higher than that typically seen for devices that use movement alone). Less accuracy

was seen for “light” sleep (stage N1 and N2 combined, 69.2%), “deep” sleep (stage N3, 62.4%), and REM sleep (71.6%) individually, though these values should be taken in context relative to the benefits of a repeatable and inexpensive recording. Of note, these values are similar to those seen for WatchPAT.

The paper by Beattie and colleagues further notes that the device was more accurate for some sleep patterns than others [3]. Fig. 15.7 depicts examples of where the device’s native scoring algorithm was most accurate and least accurate and a typical record. This suggests that these types of devices may be more accurate for some people than others. Further work is needed to better model these discrepancies and improve accuracy.

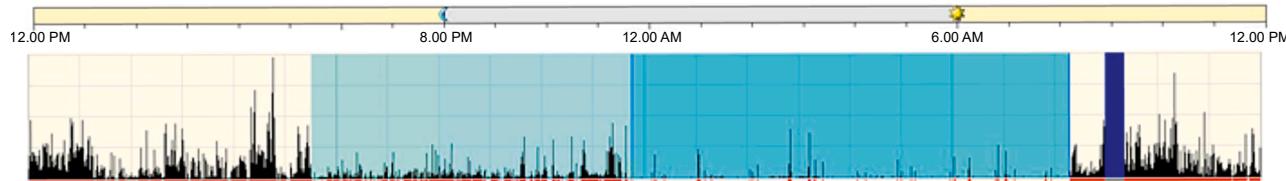


FIGURE 15.5 A typical 24-h actigraphic recording.

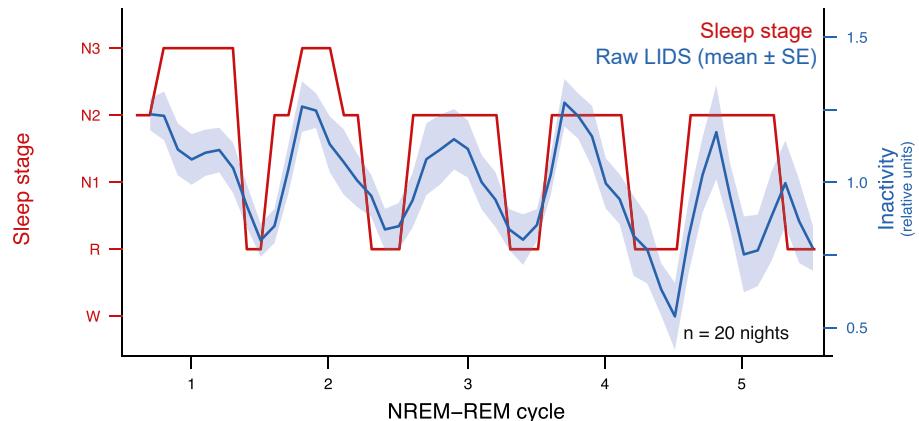


FIGURE 15.6 Approximation of locomotor activity during sleep (LIDS) values relative to sleep stages. *From the paper by Winnebeck EC, Fischer D, Leise T, Roenneberg T. Dynamics and ultradian structure of human sleep in real life. Curr Biol 2018;28(1):49–59 [e45].*

The OURA ring has also undergone validation for sleep stages [33]. Similar to the other devices, the combination of movement and heart rate data yields sensitivity (95.5%) that is generally comparable to scientific-grade devices and specificity (48.1%) that is generally better than devices that use movement alone. The relative accuracy for “light” sleep (64.6%), “deep” sleep (50.9%), and REM sleep (61.4%) are comparable to Fitbit and other similar devices.

The SleepScore MAX device, mentioned above as a contactless infrared device that assesses sleep, has also been validated for sleep staging based on the signals it collects that relate to respiration and heart rate data.

Despite the existence of validation data for these devices, sleep staging using these methods is still not endorsed by any organization or guidelines as accurate. Future guidelines may wish to take these into account, though.

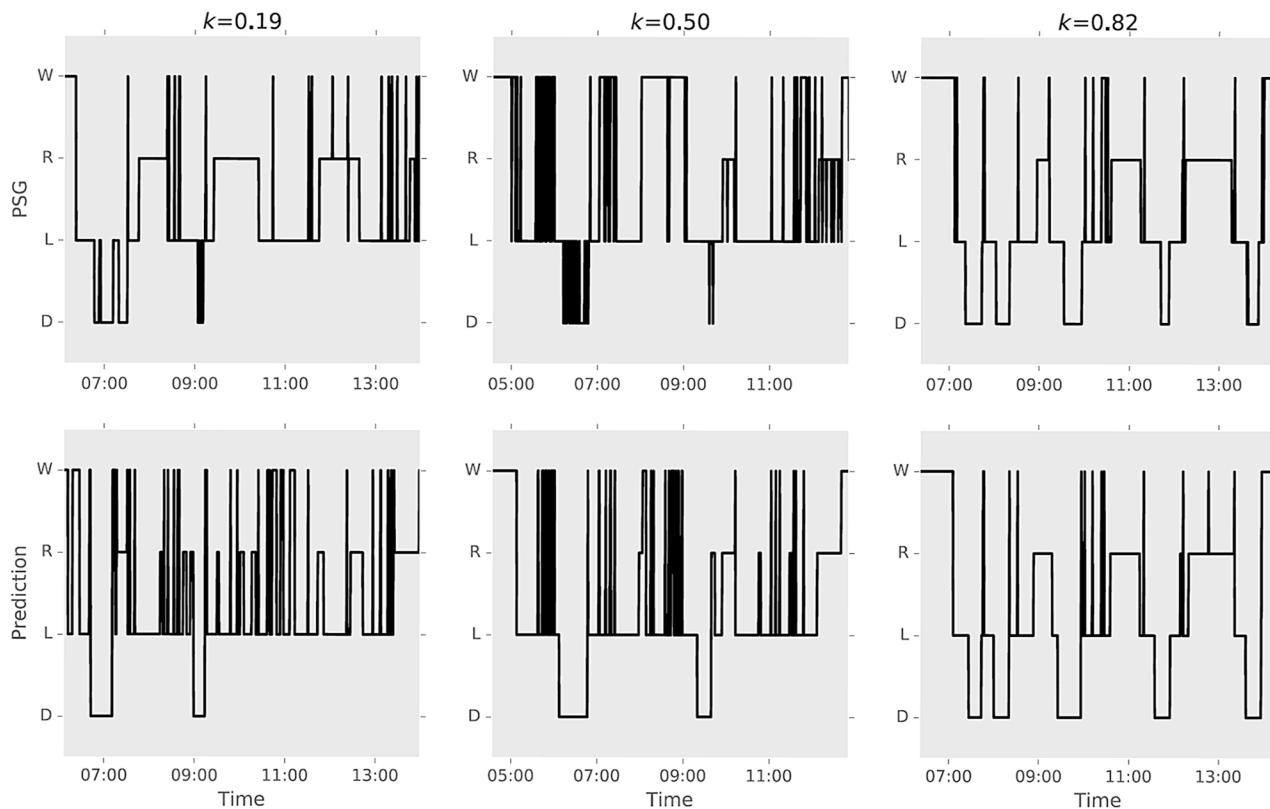


FIGURE 15.7 A comparison of hypnograms for which the Fitbit device accurately represented sleep, compared to hypnograms for which it was less accurate. *From Beattie Z, Pantelopoulos A, Ghoreyshi A, Oyang Y, Statan A, Heneghan C. Estimation of sleep stages using cardiac and accelerometer data from a wrist-worn device. Sleep 2017;40(Abstract Supplement):A26.*

Other considerations

There are a number of additional factors that should be considered when using actigraphy to record sleep:

1. *Type of movement recording.* Devices use single-axis or multiaxis recording for omnidirectional recording. In addition, some devices may use MEMS chips for accelerometry. These considerations may play a role in deciding which device is best for a situation.
2. *Recording modes.* Most actigraphic devices record in one (or more) of three recording modes. Zero-crossing mode (ZCM) is akin to a movement count approach, where each time a movement is recorded above a threshold is registered as a count, with more counts representing greater movement. Time above threshold (TAT) refers to the sum of time above a set threshold representing movement versus nonmovement. This approach is similar to ZCM but includes a time element, so it can not only capture frequency but duration of movement as well. Proportional integral mode (PIM) is the most sophisticated and uses a calculation of area under the curve for all movement recordings to most accurately represent movement. In studies comparing modes, PIM has been shown to be superior [11,56], though many older algorithms are based on ZCM because older devices recorded movement counts only.
3. *Ability to assess whether the device is off wrist.* Many devices do not have the ability to discern whether the device is off wrist; this can lead to difficulties in scoring. Off-wrist time will often be recorded as no movement and will likely be mis-scored as sleep. Therefore, if a device cannot automatically tell when it is off-wrist, hand scoring is needed to delete these instances from the record so that scoring does not incorporate these missing values as sleep.
4. *Assessment of brief changes in activity level.* Different devices quantify activity in different ways. This applies to epoch length (which should be 30 or 60 s, in line with validation studies), as well as sampling within epochs. For example, a large, quick movement surrounded by stillness may be more likely to reflect sleep than a smaller but more sustained movement. As technology changes and greater resolution of sampling within epochs becomes available, approaches to handling these sorts of movements may refine scoring.
5. *Dynamic range.* Actigraphic devices use piezoelectric materials, which convert pressure changes due to acceleration into changes in voltage. These materials are often ceramic or crystal in nature, but piezoelectric materials have varying properties. This may lead to different dynamic ranges across devices—ranges that dictate the precision of the types of pressure changes to elicit accurately recorded changes in voltage. For example, some materials may be more accurate for larger types of movements but not as accurate for smaller movements. For this reason, devices optimized for sleep are often not optimized for physical activity and vice versa.
6. *Frequency response and output deviation.* This refers to the reliability of the output voltage change recorded in the presence of movement. Some devices have very narrow ranges, such that voltage changes consistently reflect acceleration changes. Other devices may allow for more deviations, such that a single movement can produce a range of outputs that may or may not accurately reflect that movement.
7. *High and low frequency limit.* All devices have high and low limits regarding what types of activities are accurately recorded. Measurements above and below these thresholds are clipped. For sleep recording, lower thresholds are preferred, since sleep assessment requires resolution in the context of little or no movement.
8. *Noise.* All electrical systems contain noise, as do all measurements. This source of error, especially when it reflects background noise that can lead an epoch to be mis-scored as sleep or wake, can create difficulties with scoring. Devices should be evaluated relative to their noise levels.
9. *Temperature sensitivity and range.* Accelerometers measure changes in voltage output from piezoelectric materials as a result of a force of acceleration acting on a mass that interacts with the piezoelectric element. As temperatures change, density of matter changes, and this may impact voltage measurements as the density of the space around the mass expands and contracts, for example. This is especially important for MEMS chips, where a very small change in density and pressure can cause a proportionately large change in recordings. Devices should be evaluated relative to their ability to record across temperature ranges.

Scientific guidelines

Guidelines for the conduct of actigraphy have been recently published by the Society of Behavioral Sleep Medicine [2]. This guideline document outlines key considerations for those interested in using actigraphy for sleep research. In particular, this document outlines suggestions for actigraphs regarding their accelerometers (omnidirectional and/or triaxial measurements are required, recording modes other than ZCM are recommended, and epoch lengths should be 30 or 60 s, though some newer devices can make use of the raw recordings), appearance (appropriate to the population and intended use), event markers (which are recommended to increase

precision of hand scoring), light sensors (recommended to aid in hand scoring), battery type (life of 3 days is required and 2 weeks is recommended), data storage (nonvolatile memory is recommended), and customer support (required). In addition, guidelines are provided regarding data collection, recording of ambient light, integration of rating scales, inclusion of patient instructions, device placement, and use of event markers, and other techniques for gaining peripheral information to assist in scoring. Further, this document discusses three instances where data should be considered invalid: device removal (mentioned earlier), artifacts or abnormal data (i.e., suspected device malfunction), or artifacts of parenting (in pediatrics; e.g., rocking a sleeping infant). For use in research, the SBSM guidelines and other documents outline the importance of considering several key issues, including making sure scoring algorithms are appropriate and defining the major sleep period, which can be difficult and particularly error-prone using automatic methods.

When evaluating devices for use in research, all of the above issues should be considered. This includes specifications of the device and software as well as plans for implementation. For example, some external indicator of time in bed should be applied, including a sleep diary or event marker. Automated scoring of sleep periods and sleep/wake determinations should be supplemented by hand scoring to eliminate anomalies and/or device malfunctions. In evaluating specific devices, in addition to specifications, validation data should be critically evaluated. Validation by an independent research group is preferred over internal efforts, so that any appearances of conflict of interest are addressed. Whether internal or independent, characteristics of the validation study should be evaluated as well. For example, sample size should be large enough and representativeness of the sample should be adequate to the use case being considered. Some validation studies compare to overnight polysomnography as a gold standard, while others compare against other previously validated actigraphic devices. Either or both of these approaches may be appropriate, depending on the intended use of the device. For example, when using sleep measurement as a diagnostic tool, polysomnography is still the accepted method, and all devices intended for diagnostic use will need to be similarly accurate, but devices used as population surveillance and public health could be validated in the field.

Validation studies should not rely on correlation coefficients. Ideally kappa scores, Bland-Altman plots, and other statistics should be employed. In particular, values should examine epoch-by-epoch agreement across modalities, reporting values for sensitivity (number of sleep epochs identified by the gold standard that were also identified as sleep epochs by the study device), specificity (number of wake epochs identified by the gold standard that were also identified as wake epochs by the study

device), and overall rate of agreement (number of epochs for which the gold standard and study device agreed). Regarding sleep, since most evaluation periods will primarily consist of sleep, a high rate of agreement can be maintained even in the case of poor specificity. For example, if a sample achieves 90% sleep efficiency, and a device scores every epoch as sleep without even employing an algorithm; they would obtain a 90% rate of agreement, 100% sensitivity, and 0% specificity. Thus, a high rate of agreement does not alone suggest an accurate device.

Evaluating commercially available sleep trackers

Commercially available sleep trackers are widely used with relatively little validation in independent laboratories, but their popularity and effect on user behavior make these devices extremely important in a public health context. With all new technology, it is important to keep previous work in this area in mind when evaluating new devices. For example, if the Society for Behavioral Sleep Medicine does not recommend the use of actigraphy for sleep-staging, then claims of sleep-staging from commercial motion-based devices should not be trusted until validation is provided in a peer-reviewed scientific journal. Unfortunately, scientific guidelines are rarely taken into account with commercial device development and independent validation is very late if available at all.

There are several ways to demonstrate the accuracy of commercial sleep devices. An optimal validation cycle would include: *First*, a comparison to polysomnography in a laboratory setting; *second*, a comparison to validated field-based sleep measures; and *third*, validation for specific populations (such as older adults or teens). Devices should undergo this process in order to be considered validated. Unfortunately, objective scientific validation is well behind evaluating technology at the pace in which new technology is introduced to the public. In general, the quality of the data and the consumer usability of the devices are in opposition.

It should be noted that insufficient validation does not imply that a device is inaccurate; rather, it implies that the accuracy is undetermined. There are several ways in which devices are insufficiently validated. First, device manufacturers may not sufficiently determine that the electrical output of the device in question is consistent with what would be expected (e.g., that the apparatus is functioning properly). Second, manufacturers may not sufficiently determine that the electrical output is encoded, recorded, and processed in a way that is consistent with the intended function of the device. Third, device manufacturers may not sufficiently determine that the scoring is consistent with what would be expected (e.g., what is typically referred to as validation). Fourth, devices may not be tested

in the field in addition to a laboratory setting, in order to characterize their performance under real-world conditions. Completing all of these steps would be ideal. It is possible that a product could be deemed minimally sufficient if it meets some if not all of these criteria.

According to market reports [57], smart sleep tracking is expected to grow over the next 5 years, with companies such as Samsung, Philips, Nokia, Fitbit, Emfit, Garmin, ResMed, Sleepace, and Apple, Inc., all interested in sleep measurement. There have even been sleep sensors, which are completely housed under the bed's leg, which can measure heart rate, respiratory rate, and body movements [58]. In bed, sensors differ from the traditional wearable devices but rely on the same estimation of sleep from body movement and physiological measures. Validation of any of these devices usually relies on one or no studies published on their ability to measure sleep. Despite this limitation, sleep measurement using devices is probably better than the large-scale questionnaires that measure sleep in sleep epidemiology.

Conclusions

Sleep tracking is rooted in a long history of actigraphic sleep recording across days and weeks. Actigraphy is a technique for measuring sleep using movement at the wrist (and sometimes hip), and mathematically predicting the likelihood that an individual is awake or asleep based on the pattern of movement. This approach is well-validated, and there are a number of devices that have been shown to reliably and validly assess sleep, with some limitations and caveats that should be noted. Newer devices that include other channels such as heart rate can improve the detection of sleep and even offer a limited but useful estimation of sleep architecture. Devices, including commercial devices, should be used in the context of the limitations of the measurement approach, and data should be interpreted in that context. Commercially available devices are often changing and rarely provide validation data and thus should not be used for diagnosis and treatment of sleep-related disorders, but their use is limited to simple measurement in a healthy population.

References

- [1] Collop NA. Polysomnography, sleep: a comprehensive handbook. 2006. p. 973.
- [2] Ancoli-Israel S, Martin JL, Blackwell T, Buenaver L, Liu L, Meltzer LJ, Sadeh A, Spira AP, Taylor DJ. The SBSM guide to actigraphy monitoring: clinical and research applications. *Behav Sleep Med* 2015;13:S4. <https://doi.org/10.1080/15402002.2015.1046356>.
- [3] Beattie Z, Oyang Y, Statan A, Ghoreyshi A, Pantelopoulos A, Russell A, Heneghan C. Estimation of sleep stages in a healthy adult population from optical plethysmography and accelerometer signals. *Physiol Meas* 2017;38(11):1968–79. <https://doi.org/10.1088/1361-6579/aa9047>.
- [4] Foster FG, Kupfer D, Weiss G, Lipponen V, McPartland R, Delgado J. Mobility recording and cycle research in neuropsychiatry. *J Interdiscip Cycle Res* 2008;3(1):61–72. <https://doi.org/10.1080/09291017209359298>.
- [5] Kupfer DJ, Detre TP, Foster G, Tucker GJ, Delgado J. The application of delgado's telemetric mobility recorder for human studies. *Behav Biol* 1972;7(4):585–90. [https://doi.org/10.1016/S0091-6773\(72\)80220-7](https://doi.org/10.1016/S0091-6773(72)80220-7).
- [6] Kripke DF, Mullaney DJ, Messin S, Wyborne VG. Wrist actigraphic measures of sleep and rhythms. *Electroencephalogr Clin Neurophysiol* 1978;44(5):674–6. [https://doi.org/10.1016/0013-4694\(78\)90133-5](https://doi.org/10.1016/0013-4694(78)90133-5).
- [7] Mullaney DJ, Kripke DF, Messin S. Wrist-actigraphic estimation of sleep time. *Sleep* 1980;3(1):83–92. <https://doi.org/10.1093/sleep/3.1.83>.
- [8] Webster JB, Kripke DF, Messin S, Mullaney DJ, Wyborne VG. An activity-based sleep monitor system for ambulatory use. *Sleep* 1982;5(4):389–99. <https://doi.org/10.1093/sleep/5.4.389>.
- [9] Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. *Sleep* 1992;15(5):461–9. <https://doi.org/10.1093/sleep/15.5.461>.
- [10] Jean-Louis G, Kripke DF, Ancoli-Israel S, Klauber MR, Sepulveda RS. Sleep duration, illumination, and activity patterns in a population sample: effects of gender and ethnicity. *Biol Psychiatry* 2000;47(10):921–7. [https://doi.org/10.1016/S0006-3223\(99\)00169-9](https://doi.org/10.1016/S0006-3223(99)00169-9).
- [11] Jean-Louis G, Kripke DF, Cole RJ, Assmus JD, Langer RD. Sleep detection with an accelerometer actigraph: comparisons with polysomnography. *Physiol Behav* 2001;72(1–2):21–8. [https://doi.org/10.1016/S0031-9384\(00\)00355-3](https://doi.org/10.1016/S0031-9384(00)00355-3).
- [12] Jean-Louis G, Kripke DF, Mason WJ, Elliott JA, Youngstedt SD. Sleep estimation from wrist movement quantified by different actigraphic modalities. *J Neurosci Methods* 2001;105(2):185–91. [https://doi.org/10.1016/S0165-0270\(00\)00364-2](https://doi.org/10.1016/S0165-0270(00)00364-2).
- [13] Kripke DF, Hahn EK, Grizas AP, Wadiak KH, Loving RT, Poceta JS, Shadan FF, Cronin JW, Kline LE. Wrist actigraphic scoring for sleep laboratory patients: algorithm development. *J Sleep Res* 2010;19(4):612–9. <https://doi.org/10.1111/j.1365-2869.2010.00835.x>.
- [14] te Lindert BHW, Van Someren EJW. Sleep estimates using microelectromechanical systems (MEMS). *Sleep* 2013;36(5):781–9. <https://doi.org/10.5665/sleep.2648>.
- [15] Marino M, Li Y, Rueschman MN, Winkelman JW, Ellenbogen JM, Solet JM, Dulin H, Berkman LF, Buxton OM. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. *Sleep* 2013;36(11):1747–55. <https://doi.org/10.5665/sleep.3142UnitedStates>.
- [16] Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. *Sleep* 2003;26(3):342–92. <https://doi.org/10.1093/sleep/26.3.342>.
- [17] Blackwell T, Ancoli-Israel S, Gehrmann PR, Schneider JL, Pedula KL, Stone KL. Actigraphy scoring reliability in the study of osteoporotic fractures. *Sleep* 2005;28(12):1599–605. <https://doi.org/10.1093/sleep/28.12.1599>.
- [18] Stein GJ. Some recent developments in acceleration sensors. *Meas Sci Rev* 2001;1:183.

- [19] Meltzer LJ, Hiruma LS, Avis K, Montgomery-Downs H, Valentini J. Comparison of a commercial accelerometer with polysomnography and actigraphy in children and adolescents. *Sleep* 2015;38(8):1323–30. <https://doi.org/10.5665/sleep.4918>.
- [20] Rupp TL, Balkin TJ. Comparison of Motionlogger Watch and Actiwatch actigraphs to polysomnography for sleep/wake estimation in healthy young adults. *Behav Res Methods* 2011;43(4):1152–60. <https://doi.org/10.3758/s13428-011-0098-4>.
- [21] Terrill PI, Mason DG, Wilson SJ. Australia Development of a continuous multisite accelerometry system for studying movements during sleep. In: Annual International Conference of the IEEE Engineering in Medicine and Biology Society, vol. 10. EMBC; 2010. p. 6150–3. <https://doi.org/10.1109/IEMBS.2010.5627780>.
- [22] Lichstein KL, Stone KC, Donaldson J, Nau SD, Soeffing JP, Murray D, Lester KW, Aguillard RN. Actigraphy validation with insomnia. *Sleep* 2006;29(2):232–9.
- [23] Paquet J, Kawinska A, Carrier J. Wake detection capacity of actigraphy during sleep. *Sleep* 2007;30(10):1362–9. <https://doi.org/10.1093/sleep/30.10.1362>.
- [24] Weiss AR, Johnson NL, Berger NA, Redline S. Validity of activity-based devices to estimate sleep. *J Clin Sleep Med* 2010;6(4):336–42. <https://doi.org/10.5664/jcsm.27874>.
- [25] Full KM, Kerr J, Grandner MA, Malhotra A, Moran K, Godbole S, Natarajan L, Soler X. Validation of a physical activity accelerometer device worn on the hip and wrist against polysomnography. *Sleep Health* 2018;4(2):209–16. <https://doi.org/10.1016/j.slehd.2017.12.007>.
- [26] Rosenberger ME, Buman MP, Haskell WL, McConnell MV, Carstensen LL. Twenty-four hours of sleep, sedentary behavior, and physical activity with nine wearable devices. *Med Sci Sports Exerc* 2016;48(3):457–65. <https://doi.org/10.1249/MSS.0000000000000778>.
- [27] Landry GJ, Falck RS, Beets MW, Liu-Ambrose T. Measuring physical activity in older adults: calibrating cut-points for the MotionWatch 8. *Front Aging Neurosci* 2015;7. <https://doi.org/10.3389/fnagi.2015.00165>.
- [28] Baroni A, Bruzzese JM, Di Bartolo CA, Shatkin JP. Fitbit Flex: an unreliable device for longitudinal sleep measures in a non-clinical population. *Sleep Breath* 2016;20(2):853–4. <https://doi.org/10.1007/s11325-015-1271-2>.
- [29] de Zambotti M, Baker FC, Willoughby AR, Godino JG, Wing D, Patrick K, Colrain IM. Measures of sleep and cardiac functioning during sleep using a multi-sensory commercially-available wristband in adolescents. *Physiol Behav* 2016;158:143–9. <https://doi.org/10.1016/j.physbeh.2016.03.006>.
- [30] Mantua J, Gravel N, Spencer R. Reliability of sleep measures from four personal health monitoring devices compared to research-based actigraphy and polysomnography. *Sensors* 2016;16(5):646. <https://doi.org/10.3390/s16050646>.
- [31] Montgomery-Downs HE, Insana SP, Bond JA. Movement toward a novel activity monitoring device. *Sleep Breath* 2012;16(3):913–7. <https://doi.org/10.1007/s11325-011-0585-y>.
- [32] Roane BM, Van Reen E, Hart CN, Wing R, Carskadon MA. Estimating sleep from multisensory armband measurements: validity and reliability in teens. *J Sleep Res* 2015;24(6):714–21. <https://doi.org/10.1111/jsr.12317>.
- [33] de Zambotti M, Rosas L, Colrain IM, Baker FC. The sleep of the ring: comparison of the ŌURA sleep tracker against polysomnography. *Behav Sleep Med* 2017;17(2):124–36. <https://doi.org/10.1080/15402002.2017.1300587>.
- [34] Tal A, Shinari Z, Shaki D, Codish S, Goldbart A. Validation of contact-free sleep monitoring device with comparison to polysomnography. *J Clin Sleep Med* 2017;13(03):517–22. <https://doi.org/10.5664/jcsm.6514>.
- [35] Kaplan RF, Wang Y, Loparo KA, Kelly MR, Bootzin RR. Performance evaluation of an automated single-channel sleep-wake detection algorithm. *Nat Sci Sleep* 2014;6:113–22. <https://doi.org/10.2147/NSS.S71159>.
- [36] Patel P, Kim JY, Brooks LJ. Accuracy of a smartphone application in estimating sleep in children. *Sleep Breath* 2017;21(2):505–11. <https://doi.org/10.1007/s11325-016-1425-x>.
- [37] Snyder F, Hobson JA, Morrison DF, Goldfrank F. Changes in respiration, heart rate, and systolic blood pressure in human sleep. *J Appl Physiol* 1964;19:417–22. <https://doi.org/10.1152/jappl.1964.19.3.417>.
- [38] Otzenberger H, Gronfier C, Simon C, Charloux A, Ehrhart J, Piquard F, Brandenberger G. Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. *Am J Physiol Heart Circ Physiol* 1998;275(3):H946. <https://doi.org/10.1152/ajpheart.1998.275.3.h946>.
- [39] Bušek P, Vaňková J, Opavský J, Salinger J, Nevšímalová S. Spectral analysis of heart rate variability in sleep. *Physiol Res* 2005;54(4):369–76.
- [40] Johnson NL, Kirchner HL, Rosen CL, Storfer-Isser A, Cartar LN, Ancoli-Israel S, Emancipator JL, Kibler AM, Redline S. Sleep estimation using wrist actigraphy in adolescents with and without sleep disordered breathing: a comparison of three data modes. *Sleep* 2007;30(7):899–905. <https://doi.org/10.1093/sleep/30.7.899>.
- [41] Morgenthaler T, Alessi C, Friedman L, Owens J, Kapur V, Boehlecke B, Brown T, Chesson A, Coleman J, Lee-Chiong T, Jeffrey P, Todd J, Swick. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep* 2007;30(4):519–29. <https://doi.org/10.1093/sleep/30.4.519>.
- [42] Littner M, Kushida CA, Anderson WMD, Bailey D, Berry RB, Davila DG, Hirshkowitz M, Kapen S, Kramer M, Loube D, Wise M, Johnson SF. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. *Sleep* 2003;26(3):337–41. <https://doi.org/10.1093/sleep/26.3.337>.
- [43] Galland BC, Kennedy GJ, Mitchell EA, Taylor BJ. Algorithms for using an activity-based accelerometer for identification of infant sleep-wake states during nap studies. *Sleep Med* 2012;13(6):743–51. <https://doi.org/10.1016/j.sleep.2012.01.018>.
- [44] Scher A. Continuity and change in infants' sleep from 8 to 14 months: a longitudinal actigraphy study. *Infant Behav Dev* 2012;35(4):870–5. <https://doi.org/10.1016/j.infbeh.2012.07.013>.
- [45] Shinohara H, Kodama H. Relationship between duration of crying/fussy behavior and actigraphic sleep measures in early infancy. *Early Hum Dev* 2012;88(11):847–52. <https://doi.org/10.1016/j.earlhundev.2012.06.005>.
- [46] Tikotzky L, De Marcus G, Har-Toov J, Dollberg S, Bar-Haim Y, Sadeh A. Sleep and physical growth in infants during the first 6 months. *J Sleep Res* 2010;19(1-Part-I):103–10. <https://doi.org/10.1111/j.1365-2869.2009.00772.x>.
- [47] Tsai SY, Thomas KA. Actigraphy as a measure of activity and sleep for infants: a methodologic study. *Arch Pediatr Adolesc Med* 2010;164(11):1071–2. <https://doi.org/10.1001/archpediatrics.2010.208Taiwan>.
- [48] Meltzer LJ, Westin AML. A comparison of actigraphy scoring rules used in pediatric research. *Sleep Med* 2011;12(8):793–6. <https://doi.org/10.1016/j.sleep.2011.03.011>.

- [49] Arora T, Broglia E, Pushpakumar D, Lodhi T, Taheri S, Xia Y. An investigation into the strength of the association and agreement levels between subjective and objective sleep duration in adolescents. *PLoS One* 2013;8(8). <https://doi.org/10.1371/journal.pone.0072406>.
- [50] Short MA, Gradisar M, Lack LC, Wright H, Carskadon MA. The discrepancy between actigraphic and sleep diary measures of sleep in adolescents. *Sleep Med* 2012;13(4):378–84. <https://doi.org/10.1016/j.sleep.2011.11.005>.
- [51] Zhu B, Calvo RS, Wu L, Simon L, Shah K, Piano M, Khain U, Izci-Balserak B. Objective sleep in pregnant women: a comparison of actigraphy and polysomnography. *Sleep Health* 2018;4(5):390–6. <https://doi.org/10.1016/j.slehd.2018.07.011>.
- [52] Sadeh A, Hauri PJ, Kripke DF, Lavie P. The role of actigraphy in the evaluation of sleep disorders. *Sleep* 1995;18(4):288–302. <https://doi.org/10.1093/sleep/18.4.288>.
- [53] Charlotte Winnebeck E, Fischer D, Leise T, Roenneberg T. Dynamics and ultradian structure of human sleep in real life. *Curr Biol* 2018;28(1):49. <https://doi.org/10.1016/j.cub.2017.11.063>.
- [54] Hedner J, White DP, Malhotra A, Herscovici S, Pittman SD, Zou D, Grote L, Pillar G. Sleep staging based on autonomic signals: a multi-center validation study. *J Clin Sleep Med* 2011;7(3):301–6. <https://doi.org/10.5664/JCSM.1078Sweden>.
- [55] Lee SH, Choi JH, Kim EJ, Kim YS, Choi J, Kim TH, Kwon SY, Lee HM, Lee SH, Shin C. Validation study of portable device for the diagnosis of obstructive sleep apnea according to the new AASM scoring criteria: watch-PAT 100. *Acta Otolaryngol* 2010;130(7):838–43. <https://doi.org/10.3109/00016480903431139>.
- [56] Blackwell T, Ancoli-Israel S, Redline S, Stone KL. Factors that may influence the classification of sleep-wake by wrist actigraphy: the MrOS sleep study. *J Clin Sleep Med* 2011;7(4):357–67. <https://doi.org/10.5664/JCSM.1190UnitedStates>.
- [57] Smart sleep tracking device market: global demand analysis & opportunity outlook 2024. 2018.
- [58] Brink M, Müller CH, Schierz C. Contact-free measurement of heart rate, respiration rate, and body movements during sleep. *Behav Res Methods* 2006;3:511–21. <https://doi.org/10.3758/BF03192806>.

Chapter 16

Screen use, sleep, and circadian disruption

David A. Reichenberger^a, Cynthia K. Snyder^b and Anne-Marie Chang^c

^aOregon Institute of Occupational Health Sciences, Oregon Health & Science University, Portland, OR, United States; ^bSchool of Nursing and Allied Health, St. Joseph's University, Lancaster, PA, United States; ^cDepartment of Biobehavioral Health, Pennsylvania State University, University Park, MA, United States

Acronyms/abbreviations

CPU central processing unit

GPU graphics processing unit

IBM International Business Machines Corporation

ipRGC intrinsically photosensitive retinal ganglion cell

LED light-emitting diode

SCN suprachiasmatic nucleus

Screen use is ubiquitous in modern society. People of all ages actively engage with personal electronic devices while walking, during transit, and throughout daily life. About 95% of adolescents own and use personal devices everyday [1,2]. Among young adults, approximately 96% own a smartphone, 77% own a desktop or laptop computer, and more than half own a tablet [3]. Unfortunately, it is common among people of all ages in the United States to use their personal devices in the bedroom before and after lights out [4,5]. The convenience of personal devices confers many benefits to modern life, yet the benefits do not always outweigh the consequences when used during the evening. Evening use of personal devices has the potential to negatively affect sleep patterns and circadian rhythmicity, ultimately curtailing sleep [4,6–9] and contributing to the public health concern of insufficient sleep [10].

Importance of sleep for health

Sleep is vital for health. The National Sleep Foundation recommends a regular sleep duration of 8–10 h for adolescents (14–17 years), 7–9 h for adults (18–64 years), and 7–8 h for older adults (65 years and older) [11]. However, nearly 75% of high school students and about 28% of

adults obtain less than the recommended minimum amount of sleep [10]. One of the Healthy People 2030 goals for disease prevention and health promotion of all people includes increasing the proportion of the population who obtain the minimum amount of sleep in a 24-hour period [10].

Sleep undergirds physical, psychological, emotional, and developmental functions. Although sleep may be considered an unconscious state, whereby the body seems unresponsive to the external environment, sleep is a time of rest and renewal for the body. For children and adolescents, sleep is a necessity for growth and development [12]. Sleep and circadian rhythms drive the timed release of hormones, such as growth hormone, parathyroid hormone, prolactin, and cortisol [13] and the hormonal control of appetite regulation for satiety and hunger via secretion of leptin and suppression of ghrelin [12]. The immune system is strengthened by peak fluctuations of circulating cytokines and naïve T cells during the sleep cycle [13]. The glymphatic system circulates cerebral spinal fluid throughout the brain to clear accumulated toxins and cellular debris and to maintain tissue homeostasis [14,15]. Other physiological processes during sleep repair muscle and other tissues [16] as well as maintain the circadian variability of body temperature [17], heart rate [18], and blood pressure [19]. Furthermore, sleep is necessary for short-term memory consolidation, protection of memories, and reestablishment of the chronology of daily life [20]. Cognitive function [21], learning [22], and decision-making ability [23] are additionally enhanced during the sleep cycle. Insufficient or poor-quality sleep as a consequence of screen use undermines the body's systems for growth and repair.

Two-process model of sleep physiology

Sleep is regulated by a two-process mechanism: the sleep-dependent sleep–wake homeostat (process S) and the sleep-independent circadian oscillator (process C) [24]. These processes work in tandem to regulate sleep. The sleep–wake homeostatic process is a compensatory brain mechanism and is a function of sleep and wake homeostasis. Borbély proposed that the longer one is awake, the longer the period of sleep that follows. The state of wakefulness produces pressure to fall asleep that becomes stronger with the duration of time awake and dissipates during sleep.

The circadian process is a cyclic rhythmic process independent of the sleep cycle occurring approximately every 24 h, with the propensity for sleep corresponding with the lowest body temperature [24]. Process C is regulated by two suprachiasmatic nuclei (SCN) located within the anterior hypothalamus [25]. Light enters the eyes through the retina and is transmitted by intrinsically photosensitive retinal ganglion cells (ipRGC), then relayed via a nonvisual retinal hypothalamic tract to the SCN [26]. The SCN regulates circadian body processes, such as sleep, to maintain a 24-hour cycle. The ipRGC neurons are highly sensitive to light cues, especially short wavelength light that is enriched in light-emitting electronic devices, and mediate the nonimage forming circadian responses to these cues that serve to entrain the body's biological rhythms [27,28].

One such rhythm is the release of melatonin, a hormone secreted by the pineal gland. Melatonin release is inhibited by natural and artificial light and has a circadian pattern that reflects this. Melatonin levels are normally low during the day, rise prior to sleep and improve sleep propensity, and dip during morning light cues [25,29–31]. Melatonin suppression and phase resetting, or shifting, of the melatonin rhythm are two examples of nonimage forming circadian responses to light. Full-spectrum light, even of moderately low intensity, can suppress melatonin levels and shift the timing of its cycle; however, short wavelength

light in the blue-green range induces greater suppression and phase shifts [32]. The human eye is sensitive to wavelengths in the range of 390–720 nm of full-spectrum light (see Fig. 16.1). The peak sensitivity for the visual system (mediated by the rod and cone photoreceptors) occurs at 555 nm [33], whereas the peak sensitivity for circadian responses to light is at shorter wavelengths (~460–500 nm) and is mediated by the ipRGC photoreceptors [34].

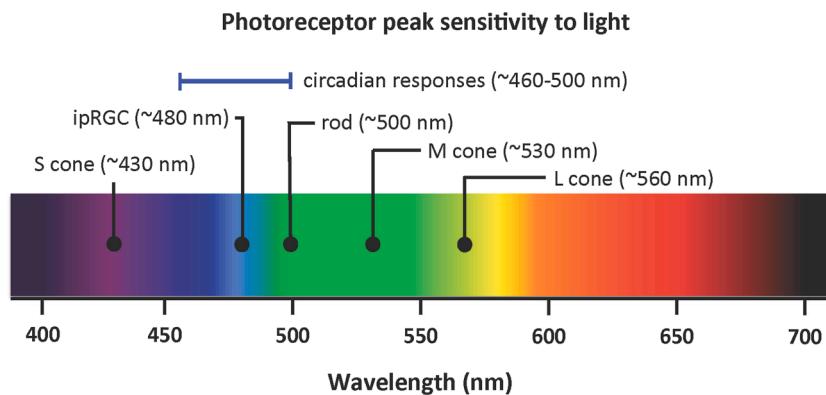
Another factor modulating the effects of light on the circadian system is the timing of the exposure. Light in the early part of the biological day (early to mid-morning) shifts circadian rhythms (e.g., melatonin release, sleep propensity, etc.) to an earlier phase, and light exposure at the end of the day (evening to early night) delays circadian phase [29,31,35]. Considering that personal devices (e.g., smartphones, tablets) predominantly emit shorter wavelength light, there may be multiple circadian pathways and interactions through which evening or nighttime screen use negatively affects sleep.

The regulation of sleep by processes S and C is balanced between the oft-opposing pressure for the sleep or wake state. For example, sleep drive (i.e., greater levels of circulating adenosine) accumulates with longer duration of wake, increasing throughout the waking day and reaching a peak at sleep onset. By contrast, the circadian system increases its drive for alertness throughout the day until reaching maximal levels in the late evening (an hour or two before bedtime). After this peak, the circadian process decreases its drive for alertness, and coinciding darkness signals the secretion of melatonin, a sleep-promoting hormone. Perturbations to either process can result in altered sleep propensity and/or timing.

Contextual factors influencing screen use and sleep behavior

Other factors can influence sleep behavior, such as socio-demographic factors and neighborhood and community

FIGURE 16.1 Peak spectral sensitivity of photoreceptors and circadian responses to light. Photoreceptors of the visual system exhibit peak sensitivities to specific wavelengths: Rods (~500 nm), S cones (short wavelength; ~430 nm), M cones (medium wavelength; ~530 nm), and L cones (long wavelength; ~560 nm). Intrinsically photosensitive retinal ganglion cells (ipRGC) have a peak spectral sensitivity of ~480 nm, which is within the range of circadian responses to light (~460–500 nm), and mediate the nonimage forming circadian responses (e.g., melatonin suppression, phase resetting).



factors. Age and gender influence sleep patterns in epidemiologic studies of children and adolescents [36] as well as adults [37]. Parents reported increased sleep insufficiency of children and adolescents with increasing age in the National Survey of Children's Health [36]. Some children as young as 6 years of age obtained insufficient sleep, and the highest levels of sleep insufficiency were among the older adolescents. Among adults surveyed in the Behavioral Risk Factor Surveillance System, young adults reported the highest levels of insufficient sleep and older adults reported the lowest levels [37].

Children and adolescents in single-parent homes were more likely to report sleep insufficiency; however, increasing income level and educational level were associated with more sleep insufficiency among all age groups [36,37]. Black/African-American and Hispanic/Latino children and adolescents were more likely to obtain insufficient sleep [36], whereas Black/African-American, Hispanic/Latino, and Asian adults were less likely to report sleep insufficiency [37]. Perceptions of environmental safety within neighborhoods may additionally affect sleep sufficiency, with increasing sleep insufficiency observed in communities where neighbors did not watch out for other children within the neighborhood [36].

Contextual factors have also been shown to affect behaviors related to screen use. Engagement with screen use near bedtime is prevalent, including watching videos, using social media, messaging, and playing video games [1,5,38]. Among adolescents, 98% engage in text messaging before bedtime, and 70% engage in sending messages after lights out [39]. Emerging adults are heavy users of multiple social media platforms, including YouTube, TikTok, Snapchat, Instagram, Discord, Facebook, and Pinterest [5], with 94% using at least one of these platforms, with declining usage with increasing age [40]. High school and college students, especially female students, are more likely to use mobile phones near and after bedtime [41–45], while male students spend more time playing video games [43,46]. Female students are also more likely to take their smartphone to bed [42] and send messages at night [47].

Emergence of modern screen use

The origin of smartphones dates back to the early 1990s with the advent of the IBM Simon device. Simon was a large, cumbersome, and costly mobile device that provided mobile phone services, information management, and fax capabilities within the confines of the device [48]. From there, mobile technology evolved quickly, first into proto-smartphones such as the PalmPilot personal digital assistant and business-oriented BlackBerry, and later into more sophisticated devices with additional features. Then, the advent of the Apple iPhone smartphone in 2007

revolutionized mobile technology. In addition to mobile phone services and text messaging, Apple's consumer touchscreen device was capable of web-browsing, video games, music playing, photography, and other novel applications. Combined with the increasing availability of wireless services within the home setting, smartphones and other portable light-emitting devices became widely available, adopted, and used in most households [49]. Mobile technology was further enhanced by tablet computing with the release of the Apple iPad in 2010 [50], which provided similar features of a smartphone but with a larger screen.

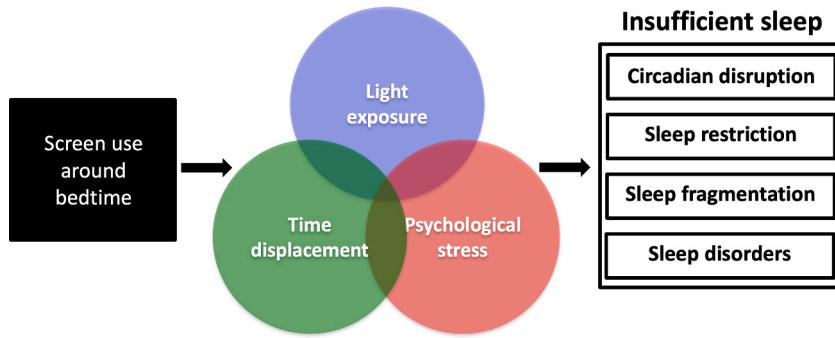
Handheld portable gaming devices emerged in the early 1980s with Nintendo's Game & Watch series of handheld games and later the Nintendo Game Boy and Sega Game Gear handheld video game consoles [51]. Like the evolution of mobile phone technology, handheld gaming systems developed from large, clunky designs with backlit liquid-crystal displays to sleeker designs with improved color and graphics, light-emitting diode (LED) screens, touchscreen technology, and the ability to play with others via wireless communication [51]. The Nintendo Switch and Valve Steam Deck are the latest in portable gaming systems, combining advanced central (CPU) and graphics (GPU) processing units, improved memory, and high-resolution touchscreens to be able to play most modern video game releases. Both systems are capable of outputting to a television or monitor or being played in handheld mode.

Electronic book-readers (e-readers) emerged in the late 1990s with the release of the NuvoMedia Rocket eBook reader [52]. Like other devices with screens, e-readers evolved over time. In the mid-2000s, Sony introduced the first dedicated e-readers with an electronic ink (e-ink) screen to mimic the reading experience of a physical book. E-ink devices were later popularized with the debut of the Amazon Kindle line in 2007 [52]. Since then, e-readers have diverged into tablets of all sizes with either e-ink screens or traditional LED screens, and ebooks are now available for download on most personal devices, irrespective of whether the device is a dedicated e-reader.

Mechanisms through which screen use affects sleep

Evening use of devices with screens is common among all age groups. It is common practice for smartphones and other personal devices to be taken to the bedroom and used near bedtime and during the night, especially among adolescents and young adults [4,5]. Adolescents and adults frequently access social media, send and receive messages, play video games, or make phone calls during this time. They may also use the devices for schoolwork, work-related purposes, or to access email or the news prior to

FIGURE 16.2 Schematic of potential mechanisms through which screen use near bedtime may lead to insufficient sleep. Exposure to light (particularly short wavelength “blue light”), time displacement, and psychological stress and/or arousal may act separately or in combination to alter multiple dimensions of sleep.



turning in for the night. Moreover, smartphones are often used as an alarm for morning awakenings. Proposed mechanisms through which device use may impact sleep include artificial light exposure, time displacement, and psychological stimulation and/or stress by media content [6–9,53] (see Fig. 16.2).

Exposure to artificial light. Light is a potent biological and behavioral stimulator of alertness. In addition to the brightness of light, exposure to visible light in the short wavelength range (i.e., blue-green light) has a greater effect on alertness than longer wavelength light exposure [54]. Personal devices frequently have LED screens that are rich in bright short wavelength blue light [55]. Artificial light from these devices at night can undermine sleep by disrupting the body’s circadian rhythm and restricting the opportunity for sleep. Considering the impact of artificial light at night on sleep health, the American Medical Association has issued recommendations for further research and interventions aimed at minimizing circadian disruption [56].

Time displacement. One day on earth has a finite number of hours. Activities such as employment, academics, leisure, personal hygiene, and sleep occupy many of these hours. Time spent on one activity precludes and displaces time available for another activity. Contemporary personal device use is able to fill the day with many screen-based activities, often at the expense of sleep. Moreover, the ubiquity and convenience of personal devices make them frequent bedpartners, which—when used prior to or after bedtime—may cause sleep restriction, deprivation, or fragmentation. Even if the device is not actively used throughout the night, personal devices often project visual or auditory alerts that signal incoming messages, phone calls, social media activity, and other notifications at any time.

Psychological stimulation and stress by media content. Social media, video games, and video-watching are popular activities among children, adolescents, and adults. However, engagement with social media [57,58], playing video games [59], and watching videos [57] before bed and after lights out may expose the individual to media content

that can induce emotional arousal or psychological stress. Social media provides instant access to their network of friends and family, but this benefit also heightens social comparison, fear of missing out on the activities of others, and awareness of the stressful events among friends and around the world [60].

Comparisons of playing violent and nonviolent video games in the evening have been primarily conducted among adolescents. One study compared duration of violent video gaming among experienced adolescent gamers prior to bedtime [61]. Players in the 50-minute session were not satisfied with the length of the gaming session and desired to continue gameplay. The 150-minute session was associated with shorter sleep time, lower sleep efficiency, and mildly increased sleep latency. Violent and nonviolent video gaming was additionally compared between a short session of less than 1 hour and a longer session of greater than 3 hours among adolescents [62]. Violent video gaming increased stress at bedtime and worsened sleep quality in both sessions.

There is some evidence related to differences in type of media exposure and the effects on sleep outcomes. For example, one study compared adolescents either playing a video game or watching a documentary for 50 min [59]. Playing video games was associated with cognitive alertness and longer sleep onset latency, whereas watching the documentary was not, and some participants even fell asleep before the session was over. Another study revealed that all participants self-selected later bedtimes regardless of video gameplay difficulty [108]. Finally, other studies found that higher volumes of video game playing were associated with later sleep timing [63], greater fatigue, more symptoms of insomnia, and worse sleep quality [64]. Each hour of time spent playing video games was associated with a 31% increase in risk of poor sleep [64].

Personal devices are commonly used to access social media. Engagement with social media in the evening may induce emotional arousal in adolescents and young adults [57,58,65]. In adolescents, nighttime use of social media led to poor sleep quality, increased anxiety and depression,

and lower self-esteem [65]. Social media-related stress, especially among female adolescents, was predictive of daytime sleepiness [58]. More recent studies have found that the experience of fear of missing out or the pressure to immediately respond to notifications [66] have been associated with late-night social media use and presleep cognitive arousal, which delayed sleep timing and shortened sleep duration [67,68].

The impact of screen use on sleep

Evening use of devices with screens may expose individuals to bright, alerting light, displace time intended for sleep, and induce psychological stress. Consequently, such effects can modulate healthy sleep patterns leading to insufficient sleep through circadian disruption, sleep restriction, fragmentation, and disorders.

Circadian disruption. Circadian disruption by exposure to artificial light at night is reported in multiple studies of device use near bedtime in both adolescents [69–72] and adults [55,73–76]. Suppression of the hormone melatonin and delayed circadian timing were observed in a group of healthy young adults after exposure to a 4-hour period of reading from an e-reader at maximum brightness prior to bedtime, compared to reading the print copy of a book over the same period in a crossover study [73]. Similarly, later melatonin release was observed in a group of adult men following 150 min of video gaming on a conventional smartphone compared to on a blue light-suppressed LED device [55].

Exposure to varying light conditions during the day and early evening produced effects on melatonin suppression. One study examined the effects of LED screens among a group of male adolescents who wore either blue light-blocking glasses or glasses with clear lenses [71]. Melatonin was suppressed while wearing glasses with clear lenses, whereas wearing blue light-blocking glasses attenuated the suppression of melatonin. [71]. Another study of adults observed that exposure to bright light for a period of 6.5 h prior to a 2-hour exposure to a self-luminous tablet or print book attenuated the melatonin suppression before bedtime [76].

Differences in melatonin suppression among studies suggest there may be a dose response to evening artificial light exposure and melatonin levels. One study evaluated a 30-minute exposure to reading from an iPad in bed in a group of young adults, compared to reading a print book, and found no difference in melatonin levels [75]. In another study, adolescents were exposed for 1 hour to either unfiltered screen light or screen light that was filtered using the *flux* application before bed [70]. Neither condition showed significant effects on sleep onset latency or sleep architecture. Screen exposure before bedtime that

lasted less than 2 hours did not have an effect on circadian disruption [70,75].

Sleep restriction. Time spent on screen-based activities on personal devices restricts the amount of time available for sleep, depriving individuals of necessary sleep. Systematic reviews and meta-analysis consistently find that screen use among children, adolescents, and adults is associated with later sleep timing, inadequate sleep duration, worse sleep quality, and excessive daytime sleepiness [7,77–80]. Moreover, engagement with personal devices near bedtime has been associated with delayed bedtimes, earlier waketimes, shorter sleep duration, and worse sleep quality [45–47,63,81–90]. These activities may include late-night device use [86,91,92], nighttime messaging [88], engagement with social media [57,63,93,94], and excessive video gaming [63,64,93–98]. Simply sleeping *near* a personal device has been associated with delayed bedtime [42] and nighttime awakenings [4,81] among adolescents.

Sleep fragmentation. Sleep fragmentation may be caused by screen use at night, either from an individual's personal device or that of another household member, such as spouse, roommate, or child. Studies among adolescents [4,42,81,84,85,99–101] and adults [92] using mobile phones at night report frequent night awakenings from smartphone activity related to messages or incoming phone calls as a consequence of taking the device to bed or accessing the device during the night. Increased prevalence of insomnia complaints was associated with screen use at bedtime among German adolescents [102]. In an online survey of adults, up to 75% of adults reported being awakened by a phone, either by their own device or that of another person, at least once a month [92]. Most participants reported messages rather than calls as the source of the disturbance. Additionally, the severity of next-day tiredness was dependent upon the time of awakening from phone alerts. Messages sent or received immediately after lights out had less effect on sleep disturbance and next-day tiredness [92].

One study evaluated the late-night use of smartphones for work-related purposes and the effects on workday outcomes [91]. Increased engagement with personal devices resulted in shorter sleep duration and impaired work engagement the next day. Another study of adults using smartphones at night showed delayed sleep onset and sleep loss [92]. Younger adults were more likely to use smartphones at night and were more likely to have shorter sleep duration and increased tiredness than older adults. Symptoms of depression, anxiety, and stress were additionally associated with nighttime use of smartphones [92]. Poor moderation of nighttime smartphone use was associated with later bedtime, poorer academic performance, and poorer sleep quality in a sample of undergraduate college students [86].

Among a sample of college students, text messaging at night was predictive of sleep disturbance and increased frequency of messaging, awareness of nighttime smartphone notifications, and compulsion to check the smartphone at night was associated with reduced self-reported sleep quality [88]. In a nationally representative sample of young adults (19–32 years of age), there was an association between social media use and sleep disturbance, with median time spent on social media of about 1 hour per day [57]. The frequency of social media use had a greater effect on sleep disturbance than the volume of social media use. In a study of video gaming among a sample of adults, each hour spent playing video games was associated with later bedtime and waketime, longer time to fall asleep, and poorer sleep quality [64]. Emerging adults who perceived video game playing to be a lower risk tended to stay up later playing video games than those who perceived a higher risk of consequences, both with and without availability of a clock to monitor time [98].

Sleep disorders. Insomnia is the most commonly reported sleep disorder associated with excessive use of media at night in adults. University students [103] and adults in general [104,105] who engaged in smartphone use after lights out tended to experience insomnia, fatigue, poor sleep quality, and daytime tiredness. Case studies of young adults in the military reported that video gaming 30–60 h per week, in addition to full-time work responsibilities, was associated with significant insomnia and daytime tiredness [106]. Reduction in time spent playing video games mitigated these negative sleep symptoms. Among adolescents, playing more than 2 hours of video games before bedtime was associated with shortened sleep duration and increased daytime sleepiness [107]. Viewing emotionally charged or disturbing content on social media platforms, such as Facebook and YouTube, in the bedroom setting resulted in emotional and psychological arousal, insomnia, and short sleep duration in adults [57]. Social media stress related to engagement with social media near bedtime was associated with increased sleep-onset latency and daytime sleepiness among female adolescents [58].

Screen use may be an epiphénoménon of insomnia

Presently, most research focuses on the direction that nighttime screen use undermines subsequent sleep. However, the reverse hypothesis—that nighttime screen use is an epiphénoménon of insomnia—should be considered [45,83]. It is possible that individuals who experience insomnia and other sleep difficulties during the night turn to screen use when they are unable to sleep. There is currently a lack of empirical studies to evaluate this phenomenon, and future research should address this potential gap.

Conclusion

Mobile technology has rapidly evolved over the last several decades, and handheld personal devices are now ubiquitous and used by people of all ages. Personal devices are a modern convenience, and their screens offer a portal for unlimited communication, news, games, art, and music, but there is a dark side to the illuminating glow of a screen. Using the device in the evening, especially near bedtime, can have a negative effect on healthy sleep. Many studies have identified relationships between greater screen use and worse sleep outcomes, but the majority of studies are cross-sectional and do not establish causality. More research is needed with longitudinal design to assess causality and to identify predictors, moderators, and mediators of the relationship between screen use and sleep health outcomes. Health education, especially among younger, more vulnerable age groups, is needed to apprise the public of the detrimental effects of evening and nighttime screen use. Intervention studies to evaluate strategies to reduce effects of screen use are needed to expand the state of the science. Finally, advocacy for healthy screen use, especially among children and adolescents, is needed to guard the health of future generations.

References

- [1] Rideout V, Robb MB. The common sense census: media use by tweens and teens. In: Common sense media. San Francisco, CA: Common Sense Media; 2019.
- [2] Pew Research Center. Teens, social media and technology 2022. 2022.
- [3] Pew Research Center. Mobile fact sheet. 2021.
- [4] Gradisar M, Wolfson AR, Harvey AG, Hale L, Rosenberg R, Czeisler CA. The sleep and technology use of Americans: findings from the national sleep foundation's 2011 sleep in America poll. *J Clin Sleep Med* 2013;09(12):1291–9.
- [5] Radesky JS, Weeks HM, Schaller AS, Robb MB, Mann S, Lenhart A. Constant companion: a week in the life of a young person's smartphone use. Common Sense Media; 2023.
- [6] Borger JN, Huber R, Ghosh A. Capturing sleep–wake cycles by using day-to-day smartphone touchscreen interactions. *NPJ Digit Med* July 29, 2019;2(1):1–8.
- [7] Hale L, Guan S. Screen time and sleep among school-aged children and adolescents: a systematic literature review. *Sleep Med Rev* 2015;21:50–8.
- [8] Lemola S, Perkins-Gloor N, Brand S, Dewald-Kaufmann JF, Grob A. Adolescents' electronic media use at night, sleep disturbance, and depressive symptoms in the smartphone age. *J Youth Adolesc* February 1, 2015;44(2):405–18.
- [9] Li X, Buxton OM, Lee S, Chang AM, Berger LM, Hale L. Sleep mediates the association between adolescent screen time and depressive symptoms. *Sleep Med* May 1, 2019;57:51–60.
- [10] Office of Disease Prevention and Health Promotion. Healthy people 2030. Sleep 2022. <https://health.gov/healthypeople/objectives-and-data/browse-objectives/sleep>.

- [11] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's updated sleep duration recommendations: final report. *Sleep Health J Natl Sleep Found.* 2015;1(4):233–43.
- [12] Leproult R, Van Cauter E. Role of sleep and sleep loss in hormonal release and metabolism. *Endocr Dev* 2010;17:11–21.
- [13] Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. *Ann N Y Acad Sci* 2010;1193(1):48–59.
- [14] Eugene AR, Masiak J. The neuroprotective aspects of sleep. *MEDtube Sci* March 2015;3(1):35–40.
- [15] Jessen NA, Munk ASF, Lundgaard I, Nedergaard M. The glymphatic system: a beginner's guide. *Neurochem Res* December 1, 2015;40(12):2583–99.
- [16] Oswald I. Sleep as a restorative process: human clues. In: McConnell PS, Boer GJ, Romijn HJ, Van De Poll NE, Corner MA, editors. *Progress in brain research* [internet]. Elsevier; 1980. p. 279–88. Available from: <https://www.sciencedirect.com/science/article/pii/S0079612308600692>.
- [17] Czeisler CA, Zimmerman JC, Ronda JM, Moore-Ede MC, Weitzman ED. Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. *Sleep* 1980;2(3):329–46.
- [18] Vandewalle G, Middleton B, Rajaratnam SMW, Stone BM, Thorleifsdottir B, Arendt J, et al. Robust circadian rhythm in heart rate and its variability: influence of exogenous melatonin and photoperiod. *J Sleep Res* 2007;16(2):148–55.
- [19] Douma LG, Gumz ML. Circadian clock-mediated regulation of blood pressure. *Free Radic Biol Med* May 1, 2018;119:108–14.
- [20] Stickgold R, Walker MP. Sleep-dependent memory consolidation and reconsolidation. *Sleep Med* June 2007;8(4):331–43.
- [21] Dahl RE. The impact of inadequate sleep on children's daytime cognitive function. *Semin Pediatr Neurol* March 1996;3(1):44–50.
- [22] Wolfson AR, Carskadon MA. Understanding adolescent's sleep patterns and school performance: a critical appraisal. *Sleep Med Rev* January 1, 2003;7(6):491–506.
- [23] Harrison Y, Horne JA. The impact of sleep deprivation on decision making: a review. *J Exp Psychol Appl* 2000;6(3):236–49.
- [24] Borbély AA. A two process model of sleep regulation. *Hum Neurobiol* 1982;1(3):195–204.
- [25] Potter GDM, Skene DJ, Arendt J, Cade JE, Grant PJ, Hardie LJ. Circadian rhythm and sleep disruption: causes, metabolic consequences, and countermeasures. *Endocr Rev* December 1, 2016;37(6):584–608.
- [26] Moore RY, Speth JC, Card JP. The retinohypothalamic tract originates from a distinct subset of retinal ganglion cells. *J Comp Neurol* February 13, 1995;352(3):351–66.
- [27] Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* February 8, 2002;295(5557):1070–3.
- [28] Hattar S, Liao HW, Takao M, Berson DM, Yau KW. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* February 8, 2002;295(5557):1065–70.
- [29] Burešová M, Dvoráková M, Zvolensky P, Illnerová H. Early morning bright light phase advances the human circadian pacemaker within one day. *Neurosci Lett* January 1991;121(1–2):47–50.
- [30] Kräuchi K, Cajochen C, Wirz-Justice A. A relationship between heat loss and sleepiness: effects of postural change and melatonin administration. *J Appl Physiol* July 1997;83(1):134–9.
- [31] Morita T, Tokura H, Wakamura T, Park SJ, Teramoto Y. Effects of the morning irradiation of light with different wavelengths on the behavior of core temperature and melatonin in humans. *Appl Hum Sci J Physiol Anthropol* 1997;16(3):103–5.
- [32] Lockley SW, Brainard GC, Czeisler CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. *J Clin Endocrinol Metab* September 2003;88(9):4502–5.
- [33] Gross H, Blechinger F, Achtner B. Human eye. In: *Handbook of optical systems* [internet]. John Wiley & Sons, Ltd; 2008. p. 1–87. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/9783527699247.ch1>.
- [34] Hatori M, Panda S. The emerging roles of melanopsin in behavioral adaptation to light. *Trends Mol Med* October 1, 2010;16(10):435–46.
- [35] Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol* June 15, 2003;549(Pt 3):945–52.
- [36] Hawkins SS, Takeuchi DT. Social determinants of inadequate sleep in US children and adolescents. *Publ Health* September 1, 2016;138:119–26.
- [37] Grandner MA, Jackson NJ, Izci-Balserak B, Gallagher RA, Murray-Bachmann R, Williams NJ, et al. Social and behavioral determinants of perceived insufficient sleep. *Front Neurol* [Internet] 2015. <https://www.frontiersin.org/articles/10.3389/fneur.2015.00112>.
- [38] Rideout V, Peebles A, Mann S, Robb MB. Common sense census: media use by tweens and teens. In: *Common sense media*. San Francisco, CA: Common Sense Media; 2021.
- [39] Troxel WM, Hunter G, Scharf D. Say "GDNT": frequency of adolescent texting at night. *Sleep Health* December 1, 2015;1(4):300–3.
- [40] Pew Research Center. Social media use in 2018. 2018.
- [41] Bruni O, Sette S, Fontanesi L, Baiocco R, Laghi F, Baumgartner E. Technology use and sleep quality in preadolescence and adolescence. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med* December 15, 2015;11(12):1433–41.
- [42] Falbe J, Davison KK, Franckle RL, Ganter C, Gortmaker SG, Smith L, et al. Sleep duration, restfulness, and screens in the sleep environment. *Pediatrics* 2015;135(2):e367–75.
- [43] King DL, Delfabbro PH, Zwaans T, Kaptsis D. Sleep interference effects of pathological electronic media use during adolescence. *Int J Men Health Addict* February 1, 2014;12(1):21–35.
- [44] Kubiszewski V, Fontaine R, Rusch E, Hazouard E. Association between electronic media use and sleep habits: an eight-day follow-up study. *Int J Adolesc Youth* July 3, 2014;19(3):395–407.
- [45] Munezawa T, Kaneita Y, Osaki Y, Kanda H, Minowa M, Suzuki K, et al. The association between use of mobile phones after lights out and sleep disturbances among Japanese adolescents: a nationwide cross-sectional survey. *Sleep* August 1, 2011;34(8):1013–20.
- [46] Hysing M, Pallesen S, Stormark KM, Jakobsen R, Lundervold AJ, Sivertsen B. Sleep and use of electronic devices in adolescence: results from a large population-based study. *BMJ Open* January 1, 2015;5(1):e006748.
- [47] Grover K, Pecor K, Malkowski M, Kang L, Machado S, Lulla R, et al. Effects of instant messaging on school performance in adolescents. *J Child Neurol* June 2016;31(7):850–7.

- [48] Dainow E. A concise history of computers, smartphones and the internet. Ernie Dainow; 2017.
- [49] Pew Research Center. The smartphone difference. 2015.
- [50] Arthur C. The history of smartphones: timeline, vol 24. The Guardian [Internet]; 2012. Available from: <https://www.theguardian.com/technology/2012/jan/24/smartphones-timeline>.
- [51] Lambie R. Den of geek. The evolution of handheld video gaming in 17 consoles. 2017. Available from: <https://www.denofgeek.com/games/the-evolution-of-handheld-video-gaming-in-17-consoles/>.
- [52] Bartram M. The history of eBooks from 1930's "readies" to today's GPO eBook services. 2014. Available from: <https://govbooktalk.gpo.gov/2014/03/10/the-history-of-ebooks-from-1930s-readies-to-todays-gpo-ebook-services/>.
- [53] LeBourgeois MK, Hale L, Chang AM, Akacem LD, Montgomery-Downs HE, Buxton OM. Digital media and sleep in childhood and adolescence. *Pediatrics* 2017;140(Suppl. 2):S92–6.
- [54] Cajochen C. Alerting effects of light. *Sleep Med Rev* December 1, 2007;11(6):453–64.
- [55] Heo JY, Kim K, Fava M, Mischoulon D, Papakostas GI, Kim MJ, et al. Effects of smartphone use with and without blue light at night in healthy adults: a randomized, double-blind, cross-over, placebo-controlled comparison. *J Psychiatr Res* April 1, 2017;87:61–70.
- [56] Stevens RG, Brainard GC, Blask DE, Lockley SW, Motta ME. Adverse health effects of nighttime lighting: comments on American medical association policy statement. *Am J Prev Med* September 1, 2013;45(3):343–6.
- [57] Levenson JC, Shensa A, Sidani JE, Colditz JB, Primack BA. The association between social media use and sleep disturbance among young adults. *Prev Med* April 2016;85:36–41.
- [58] van der Schuur WA, Baumgartner SE, Sumter SR. Social media use, social media stress, and sleep: examining cross-sectional and longitudinal relationships in adolescents. *Health Commun* April 2019;34(5):552–9.
- [59] Weaver E, Gradisar M, Dohnt H, Lovato N, Douglas P. The effect of presleep video-game playing on adolescent sleep. *J Clin Sleep Med* April 2010;6(2):184–9.
- [60] Hampton K, Rainie L, Lu W, Shin I, Purcell K. Social media and the cost of caring. 2015.
- [61] King DL, Gradisar M, Drummond A, Lovato N, Wessel J, Micic G, et al. The impact of prolonged violent video-gaming on adolescent sleep: an experimental study. *J Sleep Res* April 2013;22(2):137–43.
- [62] Ivarsson M, Anderson M, Åkerstedt T, Lindblad F. The effect of violent and nonviolent video games on heart rate variability, sleep, and emotions in adolescents with different violent gaming habits. *Psychosom Med* 2013;75(4):390–6.
- [63] Reichenberger DA, Master L, Mathew GM, Snyder CK, Buxton OM, Hale L, et al. Interactive screen-based activities predict worse actigraphic sleep health that night among adolescents. *J Adolesc Health* December 13, 2023. <https://www.sciencedirect.com/science/article/pii/S1054139X2300558X>.
- [64] Exelmans L, Van den Bulck J. Sleep quality is negatively related to video gaming volume in adults. *J Sleep Res* April 2015;24(2):189–96.
- [65] Woods HC, Scott H. #Sleepyteens: social media use in adolescence is associated with poor sleep quality, anxiety, depression and low self-esteem. *J Adolesc* August 1, 2016;51:41–9.
- [66] Almeida F, Marques DR, Gomes AA. A preliminary study on the association between social media at night and sleep quality: the relevance of FOMO, cognitive pre-sleep arousal, and maladaptive cognitive emotion regulation. *Scand J Psychol* April 2023;64(2):123–32.
- [67] Rogers AP, Barber LK. Addressing FoMO and telepressure among university students: could a technology intervention help with social media use and sleep disruption? *Comput Hum Behav* April 1, 2019;93:192–9.
- [68] Scott H, Woods HC. Fear of missing out and sleep: cognitive behavioural factors in adolescents' nighttime social media use. *J Adolesc* October 2018;68:61–5.
- [69] Figueiro M, Overington D. Self-luminous devices and melatonin suppression in adolescents. *Light Res Technol* December 1, 2016;48(8):966–75.
- [70] Heath M, Sutherland C, Bartel K, Gradisar M, Williamson P, Lovato N, et al. Does one hour of bright or short-wavelength filtered tablet screenlight have a meaningful effect on adolescents' pre-bedtime alertness, sleep, and daytime functioning? *Chronobiol Int* May 2014;31(4):496–505.
- [71] van der Lely S, Frey S, Garbazza C, Wirz-Justice A, Jenni OG, Steiner R, et al. Blue blocker glasses as a countermeasure for alerting effects of evening light-emitting diode screen exposure in male teenagers. *J Adolesc Health* January 1, 2015;56(1):113–9.
- [72] Wood B, Rea MS, Plitnick B, Figueiro MG. Light level and duration of exposure determine the impact of self-luminous tablets on melatonin suppression. *Appl Ergon* March 1, 2013;44(2):237–40.
- [73] Chang AM, Aeschbach D, Duffy JF, Czeisler CA. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. *Proc Natl Acad Sci* January 27, 2015;112(4):1232–7.
- [74] Green A, Cohen-Zion M, Haim A, Dagan Y. Comparing the response to acute and chronic exposure to short wavelength lighting emitted from computer screens. *Chronobiol Int* January 2018;35(1):90–100.
- [75] Grønli J, Byrkjedal IK, Bjørvatn B, Nødtvedt Ø, Hamre B, Pallesen S. Reading from an iPad or from a book in bed: the impact on human sleep. A randomized controlled crossover trial. *Sleep Med* May 1, 2016;21:86–92.
- [76] Rångtell FH, Ekstrand E, Rapp L, Lagermalm A, Liethof L, Búcaro MO, et al. Two hours of evening reading on a self-luminous tablet vs. reading a physical book does not alter sleep after daytime bright light exposure. *Sleep Med* July 2016;23:111–8.
- [77] Bartel KA, Gradisar M, Williamson P. Protective and risk factors for adolescent sleep: a meta-analytic review. *Sleep Med Rev* June 1, 2015;21:72–85.
- [78] Brautsch LAS, Lund L, Andersen MM, Jennum PJ, Folker AP, Andersen S. Digital media use and sleep in late adolescence and young adulthood: a systematic review. *Sleep Med Rev* December 2022;31:101742.
- [79] Carter B, Rees P, Hale L, Bhattacharjee D, Paradkar MS. Association between portable screen-based media device access or use and sleep outcomes: a systematic review and meta-analysis. *JAMA Pediatr* 2016;170(12):1202–8.
- [80] Hale L, Kirschen GW, LeBourgeois MK, Gradisar M, Garrison MM, Montgomery-Downs H, et al. Youth screen media habits and sleep: sleep-friendly screen-behavior recommendations

- for clinicians, educators, and parents. *Child Adolesc Psychiatr Clin N Am* April 2018;27(2):229–45.
- [81] Arora T, Broglia E, Thomas GN, Taheri S. Associations between specific technologies and adolescent sleep quantity, sleep quality, and parasomnias. *Sleep Med* 2014;15(2):240–7.
- [82] Bartel KA, Williamson P, van Maanen A, Cassoff J, Meijer AM, Oort F, et al. Protective and risk factors associated with adolescent sleep: findings from Australia, Canada, and The Netherlands. *Sleep Med* 2016;26:97–103.
- [83] Fossum IN, Nordnes LT, Storemark SS, Bjorvatn B, Pallesen S. The association between use of electronic media in bed before going to sleep and insomnia symptoms, daytime sleepiness, morningness, and chronotype. *Behav Sleep Med* September 3, 2014;12(5):343–57.
- [84] Garmy P, Ward TM. Sleep habits and nighttime texting among adolescents. *J Sch Nurs* April 2018;34(2):121–7.
- [85] Johansson AEE, Petrisko MA, Chasens ER. Adolescent sleep and the impact of technology use before sleep on daytime function. *J Pediatr Nurs* September 1, 2016;31(5):498–504.
- [86] Li J, Lepp A, Barkley JE. Locus of control and cell phone use: implications for sleep quality, academic performance, and subjective well-being. *Comput Hum Behav* November 1, 2015;52:450–7.
- [87] Mireku MO, Barker MM, Mutz J, Dumontheil I, Thomas MSC, Röösli M, et al. Night-time screen-based media device use and adolescents' sleep and health-related quality of life. *Environ Int* March 1, 2019;124:66–78.
- [88] Murdock KK, Horissian M, Crichlow-Ball C. Emerging adults' text message use and sleep characteristics: a multimethod, naturalistic study. *Behav Sleep Med* May 4, 2017;15(3):228–41.
- [89] Nosetti L, Lonati I, Marelli S, Salsone M, Sforza M, Castelnovo A, et al. Impact of pre-sleep habits on adolescent sleep: an Italian population-based study. *Sleep Med* 2021;81:300–6.
- [90] Rosen L, Carrier LM, Miller A, Rokkum J, Ruiz A. Sleeping with technology: cognitive, affective, and technology usage predictors of sleep problems among college students. *Sleep Health* March 2016;2(1):49–56.
- [91] Lanaj K, Johnson RE, Barnes CM. Beginning the workday yet already depleted? Consequences of late-night smartphone use and sleep. *Organ Behav Hum Decis Process* May 1, 2014;124(1):11–23.
- [92] Saling LL, Haire M. Are you awake? Mobile phone use after lights out. *Comput Hum Behav* November 1, 2016;64:932–7.
- [93] Galland BC, de Wilde T, Taylor RW, Smith C. Sleep and pre-bedtime activities in New Zealand adolescents: differences by ethnicity. *Sleep Health* February 1, 2020;6(1):23–31.
- [94] Perrault AA, Bayer L, Peuvrier M, Afyouni A, Ghisletta P, Brockmann C, et al. Reducing the use of screen electronic devices in the evening is associated with improved sleep and daytime vigilance in adolescents. *Sleep* 2019;42(9):zs125.
- [95] Hisler G, Twenge JM, Krizan Z. Associations between screen time and short sleep duration among adolescents varies by media type: evidence from a cohort study. *Sleep Med* February 1, 2020;66:92–102.
- [96] Khan A, Burton NW. Electronic games, television, and psychological wellbeing of adolescents: mediating role of sleep and physical activity. *Int J Env Res Public Health* August 23, 2021;18(16).
- [97] Pillion M, Gradisar M, Bartel K, Whittall H, Kahn M. What's "app"-ning to adolescent sleep? Links between device, app use, and sleep outcomes. *Sleep Med* December 1, 2022;100:174–82.
- [98] Reynolds CM, Gradisar M, Kar K, Perry A, Wolfe J, Short MA. Adolescents who perceive fewer consequences of risk-taking choose to switch off games later at night. *Acta Paediatr Int J Paediatr* 2015;104(5):e222–7.
- [99] Adachi-Mejia AM, Edwards PM, Gilbert-Diamond D, Greenough GP, Olson AL. TXT me I'm only sleeping: adolescents with mobile phones in their bedroom. *Fam Commun Health* December 2014;37(4):252.
- [100] Fobian AD, Avis K, Schwab DC. The impact of media use on adolescent sleep efficiency. *J Dev Behav Pediatr JDBP* January 2016;37(1):9–14.
- [101] Schoeni A, Roser K, Röösli M. Symptoms and cognitive functions in adolescents in relation to mobile phone use during night. *PLoS One* July 29, 2015;10(7):e0133528.
- [102] Lange K, Cohrs S, Skarupke C, Gorke M, Szagun B, Schlack R. Electronic media use and insomnia complaints in German adolescents: gender differences in use patterns and sleep problems. *J Neural Transm* February 2017;124:S79–87.
- [103] Zarghami M, Khalilian A, Setareh J, Salehpour G. The impact of using cell phones after light-out on sleep quality, headache, tiredness, and distractibility among students of a university in north of Iran. *Iran J Psychiatry Behav Sci* December 2015;9(4):e2010.
- [104] Exelmans L, Van den Bulck J. Bedtime mobile phone use and sleep in adults. *Soc Sci Med* January 1, 2016;148:93–101.
- [105] Rod NH, Dissing AS, Clark A, Gerds TA, Lund R. Overnight smartphone use: a new public health challenge? A novel study design based on high-resolution smartphone data. *PLoS One* October 16, 2018;13(10):e0204811.
- [106] Eickhoff E, Yung K, Davis DL, Bishop F, Klam WP, Doan AP. Excessive video game use, sleep deprivation, and poor work performance among us marines treated in a military mental health clinic: a case series. *Mil Med* July 2015;180(7):E839–43.
- [107] Brunetti VC, O'Loughlin EK, O'Loughlin J, Constantin E, Pigeon É. Screen and nonscreen sedentary behavior and sleep in adolescents. *Sleep Health* December 2016;2(4):335–40.
- [108] Smith LJ, King DL, Richardson C, Roane BM, Gradisar M. Mechanisms influencing older adolescents' bedtimes during videogaming: the roles of game difficulty and flow. *Sleep Med* November 2017;39:70–6.

This page intentionally left blank

Chapter 17

Behavior change models and theories

Adam Knowlden^a and Sarah Flora^b

^aThe University of Alabama, Health Science, Tuscaloosa, AL, United States; ^bUniversity of Alabama, Tuscaloosa, AL, United States

List of abbreviations

CBT	Cognitive behavioral therapy
CBT-I	Cognitive Behavioral Therapy-Insomnia
HBM	Health belief model
IBM	Integrated behavioral model
MGDB	Model of goal-directed behavior
MI	Motivational interviewing
SCT	Social cognitive theory
SNT	Social network theory
TACT	Target, action, context, and time
TMB	Time management behavior
TPB	Theory of planned behavior
TRA	Theory of reasoned action
TTM	Transtheoretical model

Foundation of theory for behavior change

Conceptually, theory is grounded in the discipline of *epistemology*: the study of knowledge [1]. Theories can be conceptualized as *structural*, *functional*, and *dynamic* [1]. From a *structural* perspective, theories comprise a set of abstract concepts, systematically organized into a logical and causal progression. *Functionally*, theories need to demonstrate that a specific cause, or set of causes, produces a specific effect(s). From the perspective of behavior change, a theory must demonstrate that a hypothesized set of constructs is linked to a specified behavioral outcome. Such a theory would elucidate the relationship between the set of variables, and the conditions under which these relationships do or do not occur [2]. The advancement of a theory is tied closely to its ability to demonstrate causation. Causation is the foundation of empiricism, and, in this regard, theories are *dynamic* entities that can be subjected to scientific scrutiny [1].

Given their dynamic nature, theories serve a functional role in predicting, interpreting, and explaining phenomena of interest. *Concepts* are the building blocks of a theory [3].

Constructs are concepts that are explicitly defined and causally ordered into a theoretical framework. To subject a theory to empirical testing, its constructs must be operationalized into quantifiable, measurable variables. *Operationalization* is the process of tailoring and quantifying constructs from a theory or model to the purpose of the intervention or program [3]. Operationalized constructs with a range of possible quantitative outcomes are classified as *variables* [3].

Closely related to the concept of a theory is that of a *model*. Although the terms “theory” and “model” are often used interchangeably, there are subtle differences between the two. *Models* are scaled representations of reality [4]. Depending on a model’s comprehensiveness, it may contain multiple theories. For example, the social-ecological approach (covered later in this chapter) is comprised of multiple layers; each layer potentially including a variety of behavioral and/or environmental theories. Typically, models are conceptual and comprehensive. While models may not be at the level of specificity of a theory, they must be rooted in rationality. In the field of public health, *logic models* are often used during the program planning stage to illustrate the processes applied during intervention implementation [5].

Like the term model and theory, the terms intervention and program, while often used interchangeably, have subtle distinctions between them. Behavior change *interventions* are systematically planned and organized activities carried out over time to accomplish specific behavior-related goals and objectives [6]. Alternatively, behavior change *programs* may consist of a set or series of behavior change interventions [6]. For example, a community-based, public health program designed to improve sleep behaviors may include a mass media campaign, a mobile phone sleep tracking application, and interactive telephone health counseling sessions. Combined, this set of interventions would be considered a behavior change program. During the planning stages of

the program, a logic model may be conceptualized to show how available community resources will be utilized to maximize the practicality, robustness, and feasibility of the program. Furthermore, the specific intervention activities may be rooted in an evidence-based behavior change theory. To evaluate the program scientifically, the constructs of the behavior change theory could then be measured using a valid and reliable instrument at pretest and posttest. Assuming significant behavior change occurred, the intervention team could link the improvements in sleep behavior to the specific theoretical constructs targeted by the program. During this process, the team could determine which constructs were responsible for the most behavior change. If the program were replicated, those constructs responsible for the greatest change could be emphasized more, potentially leading to more robust programs in the future.

Utility of theory for changing health behaviors

Historically, health was contextualized as the relative absence or presence of physical ailment. However, in 1946, the World Health Organization (WHO) published a new, holistic definition of health which stated “health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity [7].” In 1986, WHO expanded upon this definition, stating health is “a resource for everyday life, not the objective of living [8].” From these definitions, several proprieties of health emerge [6]. *First*, health extends beyond the mere presence or absence of physical disease and includes quality of life factors such as an individual’s social, emotional, spiritual, environmental, occupational, intellectual, and physical well-being. As such, sleep health can include both the increased risk of chronic disease associated with long-term sleep deprivation and acute effects of sleep deprivation such as stymied emotional regulation. *Second*, the various dimensions of health overlap and influence one another to various degrees. Sleep, for example, influences both physical and mental health outcomes [9]. *Third*, health cannot not be categorized as a static state of being but instead is a dynamic condition of the human organism. For example, an individual may acquire consistent sleep quality regularly; yet they may occasionally experience periods of acute insomnia. *Fourth*, health should be considered a resource for living rather than an end unto itself. In Western culture, sleep is often considered an expendable behavior. Individuals may believe they will experience more opportunities in their lives if they deprive themselves of adequate sleep when, in fact, research indicates quality of life is significantly improved when a consistent, healthy sleep pattern is adopted and maintained.

To improve health, it is necessary to change behaviors. *Behaviors* are overt actions that consist of a measurable frequency, intensity, and duration. In the context of sleep, sleep behavior may be defined as obtaining 7–9 h of sleep (duration) every night (frequency) while experiencing all sleep stages (intensity). *Health behaviors* are actions undertaken by individuals to maintain, restore, or improve health. To apply theory for measurement purposes, the targeted health behavior must be operationally defined. The theory of planned behavior (described later in this chapter), for example, requires any given behavior be defined in terms of its relevant target, action, context, and time (TACT).

There are multiple benefits of incorporating theory into sleep health programs and interventions. *First*, theory can assist in specifying measurable program outcomes. Primarily, this occurs through the operationalization of theory, which will be detailed later in this chapter. Once operationalized, theory can be used to test scientific hypotheses or to evaluate program objectives. *Second*, theory can guide best practices for actualizing behavior change. For example, the theoretical construct of self-efficacy can be increased by [1]: breaking a complex behavior down into small steps [2]; reducing stress associated with behavior change [3]; applying verbal reinforcement; and [4] including role models into the intervention activities. *Third*, theory can assist in optimizing the timing of an intervention. For example, the transtheoretical model can categorize individuals into stages of readiness for behavior change. An individual in the contemplation stage of behavior change may require a different type of intervention relative to an individual in the action stage. *Fourth*, theory can assist in selecting the right mix of strategies. Once operationalized, a theory can be modeled and the relative importance of the various constructs of a theory can be ascertained (e.g., beta weights in a regression model). Modeling of theory can inform which constructs should receive the most emphasis when implementing an intervention. This approach lends itself to ideal intervention dosage, efficient allocation of resources, and a greater likelihood of behavior change. *Fifth*, theory can aid in replication. If the constructs of a theory are measured in valid and reliable ways, researchers can conduct scoping reviews, systematic reviews, and meta-analyses to help advance theory-based research. *Sixth*, theory can enhance communication among professionals. For example, a consensus on a definition of self-efficacy among sleep researchers can streamline research presentations and publications.

Causation in behavior change theories

Perhaps, the foremost advantage of applying theory to behavior change interventions is theory’s capacity to

empirically examine causal relationships between constructs. Incorporation of theory into an intervention should be set up such that causation can be evaluated as part of the intervention. For example, a theory-based intervention for changing sleep behaviors must be able to demonstrate the causal connection between the constructs of theory and any observed changes in the targeted sleep behavior. The capacity to ascertain causation primarily lies in the design of the intervention (e.g., randomized control trial design), random selection and assignment, as well as operationalization and measurement of the targeted theoretical constructs.

In 1965, Sir Austin Bradford Hill published, “The Environment and Disease: Association or Causation?” [10]. In his publication, Hill outlined nine criteria for evaluating the causal connection between variables. These criteria, known as *Hill’s Criteria of Causation*, form the basis of modern epidemiological research. Hill’s criteria were a consequence of his work in the British Doctor’s Study, often considered the first definitive publication demonstrating a causal link between smoking and lung cancer [11]. Hill’s criteria originate in the axioms of causation delineated by the philosopher, David Hume (1711–76) [12]. Hume argued that causality can never be proven. Rather, causation is ultimately a judgment call based on the interpretation of the available evidence. In applying this principle, for example, the American Academy of Sleep Medicine may review all available evidence about a treatment option and make judgment calls about causation. While Hill’s criteria cannot prove causation, they can assist in ruling out explanations outside of a causal relationship. Incorporation of Hill’s criteria into intervention design maximizes the utility of theory for advancing evidence-based treatment approaches.

The first criterion of causation that Hill described is the *strength of association*. The strength of association between two or more variables describes the magnitude of their relationship. For example, when evaluating a data set, a researcher may find a strong association between short sleep and high levels of stress. This may provide a clue that a causal connection exists between these variables; however, when considering strength of association, it is important to keep in mind the often-cited mantra that “correlation does not equal causation.” It is entirely possible for two variables to be strongly associated yet have no causal connection. It is also possible that a confounding, mediating, or moderating variable is influencing the strength of the association. All three of these types of variables have the potential to produce biased results. *Confounding variables* are external influences that change the relationship between two variables. The greatest risk of confounding variables is failure to collect data on the confounder and thus not being able to explain the anomalous results. A *mediating variable* creates an indirect

effect between the independent and dependent variables. When present, the path between the two hypothesized causally connected variables is partially explained by a third variable. A *moderating variable* creates an interaction effect. When present, two variables may share no relationship unless in the presence of the moderating variable. Measurement of theory as part of a behavior change intervention requires careful consideration of these variable types. To avoid these issues, it is best to conduct a thorough operationalization process (discussed later in this chapter). Even if the behavior change program is limited in such a way that collecting data related to all possible confounding/mediating/moderating variables is not feasible, thorough formative research and pilot studies may assist in explaining those variables most likely to be the most important to measure as well as provide a context for any anomalous results.

Hill’s second criterion of causation is *consistency*. Consistency is built upon the scientific axiom of repeatability. In other words, if a causal relationship exists between variables, evidence of the relationship must be demonstrated consistently even if tested by different researchers at different locations and at different times. Importantly, use of theory for changing sleep outcomes must have a thorough methods section so that other researchers can independently test the theory for gauging consistency. The third criterion of causation is *temporality*. Often considered the only necessary criterion of causation, demonstrating a causal relationship requires the cause to precede the effect. Typically, temporality is assessed using a pretest–posttest design whereby researchers can demonstrate changes in a theoretical construct led to changes in the targeted behavior. The fourth criterion is the *dose–response relationship*. This criterion dictates that an increase in dose will lead to an increase in the response. Often, the dose-response relationship between a theorized cause and effect is illustrated using a dose-response curve. The fifth criterion is *coherence*. The hypothesized causal connection should be consistent with existing theory and knowledge. Similarly, the association should be plausible with currently accepted pathological processes (the sixth criterion). *Specificity*, the seventh criterion, is confirmed when a single cause produces a specific effect. In terms of behavior change, this is considered the weakest criterion as most behaviors are the consequence of multiple causes. The eighth criterion is *experimental evidence*. If it can be shown that a condition was prevented or ameliorated by an appropriate experimental treatment/intervention, it lends evidence to a causal connection. In judging whether a reported association is causal, it is necessary to determine the extent to which researchers have taken *alternative explanations* (ninth criterion) into account and have effectively ruled out such alternate explanations (e.g., controlled for bias).

Hill's criteria serve to provide the foundation for the composition of a quality theory. First, theory must be causally *predictive*. Predictability entails that a given theory be testable and therefore amenable to hypothesis testing. Second, theory must be *measurable*. Measurability allows researchers to gauge consistency and determine if a given health outcome can be changed through the manipulation of a theory's constructs (experimental evidence). Furthermore, it can assist in determining the amount of change to a construct required to elicit meaningful change (dose-response). Third, a quality theory must be *generalizable*. Although health behavior theories can be tailored for specific uses and demographics, the core constructs of a theory should hold true for most populations (consistency). Fourth, a theory must be *practical*. From a health behavior perspective, practicality is important in two ways. The first is parsimony. The principle of parsimony states that an optimal theory will explain the greatest amount of variability using the smallest number of constructs. Interventions seeking to change health behaviors are inevitably constrained by time and resources. Although a theory comprised of a large ensemble of constructs may improve the theory's predictive capacity, such a theory may not be practical to implement from an intervention perspective. Often, a balance between what is ideal and what is practical must be identified. Secondly, practically requires that a theory's constructs be modifiable. For a theory to have utility, there must be established methods of changing a theory's constructs (e.g., increasing self-efficacy, discussed later in this chapter).

Types of theories

While there are numerous ways to categorize behavior change theories, perhaps the two most common are whether the theory is targeting a level of influence (socio-ecological approach) or whether the theory attempts to explain a behavior (continuum or stage theories) [5]. From the socio-ecological perspective, the health behavior of individuals is shaped in part by the social context in which they exist. Social-ecological approaches apply a system's perspective to model the upstream and downstream environmental and behavioral factors that influence a given behavior [13]. McLeroy, Bibeau, Steckler, and Glanz have defined five socio-ecological levels of influence on behavior [1]: intrapersonal factors [2]; interpersonal factors [3]; institutional or organizational factors [4]; community factors; and [5] public policy factors.

In this context, the intrapersonal level of the socio-ecological approach primarily focuses on factors such as knowledge, emotions, beliefs, experiences, motivation, skills, and behavior. The interpersonal level examines a

person's immediate social context and seeks to determine how social interactions influence health outcomes. Behavior change theories at the interpersonal level explain the influence of social environments on an individual's behaviors. People's attitudes about health and their health behaviors do not exist in isolation; they affect, and are affected by, the attitudes and behaviors of others. The more proximal any two individuals are the greater role this social context will have on their health behaviors. Furthermore, this influence will have a reciprocal effect on those individuals that make up their social environment. The organizational level considers how one's workplace environment impacts a given health outcome. For example, an individual may desire to change a health behavior, but if their employer does not provide access to health insurance, it may prohibit their ability to actualize behavior change. The community level explores how settings, such as schools, workplaces, and neighborhoods, in which social relationships occur influence health outcomes. Finally, the policy level seeks to understand how policies and social climates influence health outcomes. Simons-Morton et al. [14] included two additional levels of socio-ecological influence on behavior [6]: the physical environment and [7] culture [14]. The socio-ecological model posits that personal health behaviors are shaped by multiple levels of influence. Therefore, a central tenant of the socio-ecological approach is that interventions must target multiple levels of influence to create sustainable changes in health behaviors. Fig. 17.1 illustrates a social-ecological model of sleep and health.

Theories can also be categorized by the causal chain they use to explain behavior. *Continuum theories* seek to identify variables that influence a behavior and quantify them to predict the likelihood of behavior change. *Stage theories* comprise an ordered set of categories by which individuals can be classified according to their progress in behavior change. Stage theories also identify factors that will induce movement from one category of behavior change to the next. Weinstein, Rothman, and Sutton [15] have identified four characteristics of stage theories [1]: a categorical system to define the stages of change [2]; an ordering of the stages of change [3]; identification of the common barriers to change which may prevent people from transition to the next stage; and [4] identification of the different barriers to change facing people in different stages. For the purposes of this chapter, the behavior change theories presented will be organized by the level of influence they are designed to target and whether they can constitute a continuum or stage theory. While there are numerous models and theories of behavior change, the ones presented in this chapter are some of the most frequently applied theories cited in the literature.

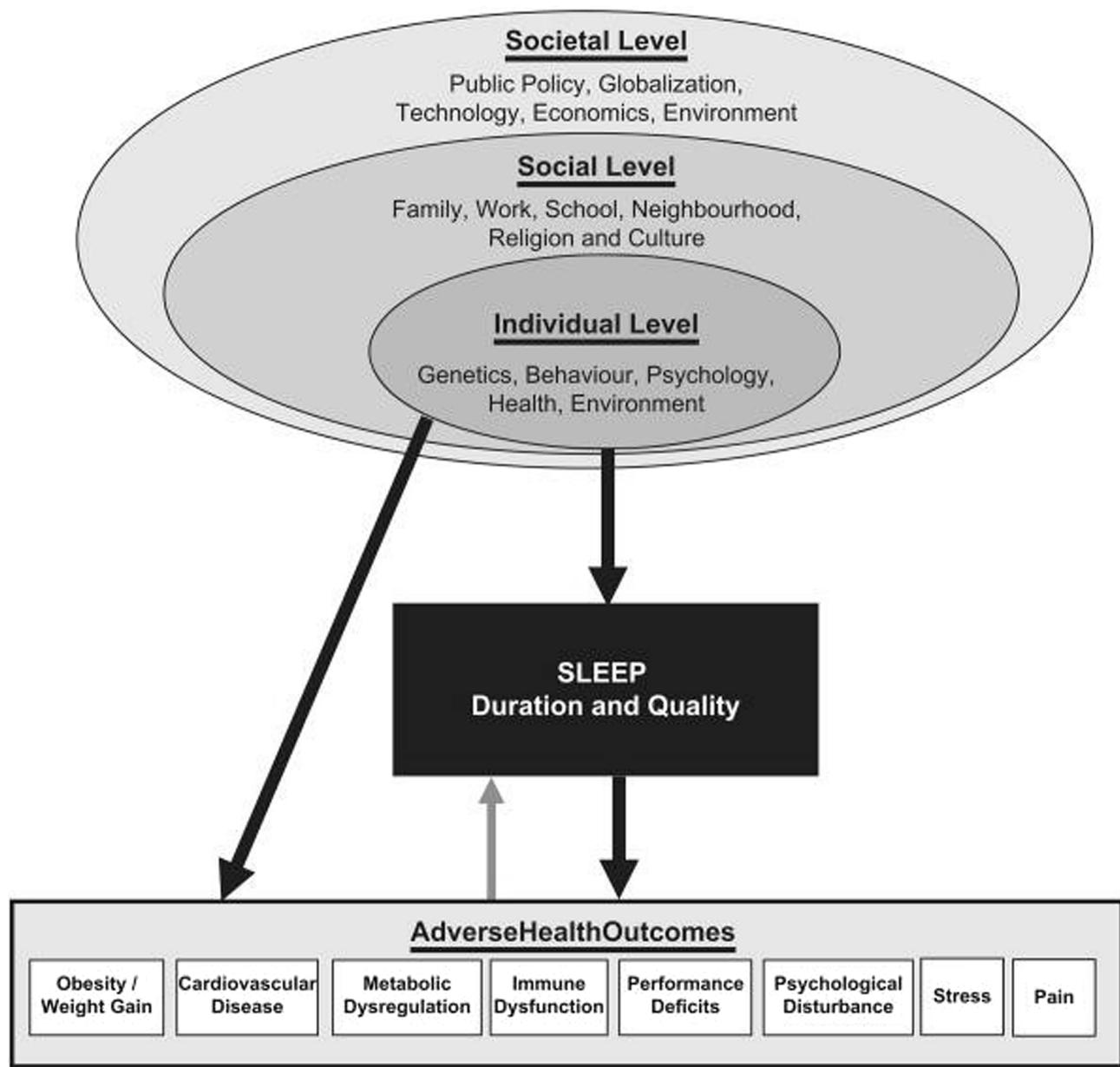


FIGURE 17.1 Socio-ecological model of sleep and health. Adapted from Grandner et al. (2010c). Reprinted by permission of Taylor and Francis.

Intrapersonal theories

Health belief model

Continuum theory

The *health belief model* (HBM) is a value-expectancy framework. Value-expectancy theories attempt to explain how an individual's behaviors are influenced by the expectancy that an action will be followed by certain consequences. In this context, the HBM seeks to predict and explain the cognitions individuals employ when engaging in a specific health behavior. Developed in the 1950s to understand why individuals were not utilizing free, mobile,

tuberculosis screening services [16], the HBM is considered one of the first theories of health behavior [17]. It hypothesizes that health-related behaviors depend on the simultaneous occurrence of three classes of factors [1]: sufficient motivation [2]; the belief that one is susceptible to the deleterious outcomes of a health problem [3]; the belief that a certain behavior would be beneficial in reducing the perceived threat and that the action can be initiated at an acceptable cost.

The HBM was originally comprised of five theoretical constructs. *Perceived susceptibility* describes an individual's subjective risk of procurement of a negative

health outcome. *Perceived severity* describes the subjective extent of harm incurred through the engagement of a behavior. Often, perceived susceptibility and perceived severity are combined into the construct of *perceived threat*. *Perceived benefits* encompass the personal advantages of engaging in a given behavior. *Perceived barriers* include the subjective and objective costs of adopting a behavior. *Cues to action* include the cognitive triggers that motivate a given behavior. In recent years, the construct of self-efficacy has become central to the HBM. *Self-efficacy* is an individual's confidence to engage in a specific behavior and is the sixth construct of the HBM.

Application

The HBM may be a useful model for researchers seeking to predict the negative health outcomes from poor sleep. Knowlden et al. [18] specified an HBM model to measure and predict the sleep behavior of employed college students. This cross-sectional study found the HBM explained 34% of the variance in sleep behavior, with perceived severity, perceived barriers, cues to action, and self-efficacy identified as significant predictors. Fig. 17.2 illustrates the final HBM with standardized regression weights. In this study, self-efficacy was identified as the strongest predictor of adequate sleep. Fig. 17.2 illustrates the final model from this study.

Theory of reasoned action and the theory of planned behavior

Continuum theory

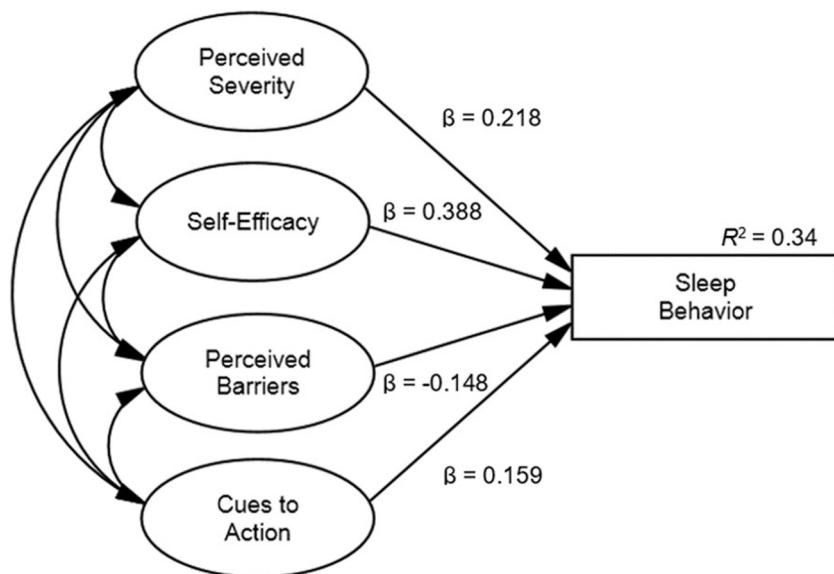
The *theory of reasoned action* (TRA) and the *theory of planned behavior* (TPB) [19] assist in predicting the

complex nature of health behaviors [20]. As value-expectancy theories, the TRA and TPB assume that altering domain-specific beliefs can assist in modifying unhealthy behaviors. Both models posit that behavior is purposeful and results from defined cognitive processes that arise as individuals assess their environment [21]. The TRA and the TPB define *behavior* as an observable action delineated in terms of its TACT [22]. According to these theories, *behavioral intention* is the most immediate antecedent of behavior. *Behavioral intention* is described as an individual's readiness to perform a specific behavior [23]. Conceptually, the constructs of the TRA and the TPB are considered independent predictors of intention.

Theory of reasoned action

The constructs of the TRA predict volitional behaviors, that is, behaviors that are intentional and explicitly under the control of the individual. The TRA postulates that behavioral intention is the function of two factors: attitude toward the behavior and subjective norm. The construct of *attitude toward the behavior* refers to the overall feeling of like or dislike toward a given behavior. Attitude is shaped by *behavioral beliefs*, which reflect an individual's disposition toward performing a specific behavior, and *outcome evaluations*, which refer to the value an individual associates with engaging in a behavior. In addition to attitudes, the TRA hypothesizes that *subjective norms* are a salient determinant of behavioral intentions. The subjective norm construct is comprised of *normative beliefs* and *motivation to comply*. Normative beliefs are an individual's perception about how referent others would like them to act regarding an explicit behavior. Motivation to comply, in turn, is the

FIGURE 17.2 Health belief structural model illustrating standardized regression weights for the sample of employed undergraduate college students ($n = 188$). Reprinted by permission of Wolters Kluwer Health, Inc.



degree to which an individual is willing to act in accordance with the referent group.

Theory of planned behavior

Although the TRA is a strong predictor of volitional behavior [24], it is unable to account for behaviors that are beyond the complete control of the individual. To compensate, Ajzen [23] proposed the addition of the *perceived behavioral control* construct. Perceived behavioral control is divided into two components: *control beliefs* and *perceived power*. Control beliefs describe beliefs related to external and internal factors that can impede or promote the performance of a behavior. Perceived power is the perception of ease or difficulty an individual ascribes to a behavior. Additionally, Ajzen [23] posited that to the extent to which perceived behavioral control was reflective of actual behavioral control, perceived behavioral control combined with intention, could serve as a direct predictor of behavior. The addition of this construct led to the evolution of the TRA into its modern form of the TPB.

Application

The TRA and TPB may be useful models for researchers seeking to understand the behavioral intentions that underlie sleep behavior. Knowlden et al. [25] operationalized the TPB to predict the sleep intentions and behaviors of undergraduate college students. Their results found each of the three predictors regressed on behavioral intention were deemed significant: perceived behavioral control ($\beta = 0.457$, $P < .001$), subjective norm ($\beta = 0.179$, $P = .003$), and attitude toward the behavior ($\beta = 0.231$, $P < .001$). Collectively, the predictors produced an R^2_{adjusted} value of 0.362 ($P < .001$), suggesting the model accounted for 36.2% of the variance in the behavioral intention to obtain adequate sleep in the sample of participants. Behavioral intention was identified as a significant predictor of sleep behavior ($P < .001$), explaining 18.5% of the variance of the participants' sleep behavior. To the best of the author's knowledge, this was the first study to operationalize a behavior change model for predicting sleep behaviors.

Integrated behavior, goal-directed behavior, and time management behavior models

The TPB has been extended to incorporate additional variables hypothesized to strengthen the intention-behavior connection. The advantage of extended models is that they offer further context for explaining behavior change through their inclusion of relevant constructs beyond those of the base TPB framework. The difficulty of testing extended models is due to the many constructs required to fully operationalize an extended framework. In addition to extended models of the TPB, the behavior-intention

framework is useful in predicting various behavioral outcomes. As sleep behavior change model research evolves, the intention-behavior approach may become more prominent. An apparent advantage of the intention-behavior approach is these models retain the parsimonious nature of the core TPB framework without necessarily denigrating the TPB's predictive potential.

Integrated behavior model

An extension of TPB, the Integrated Behavior Model (IBM) [26], applies concepts from multiple theories to account for the automatic and subconscious processes that influence behavior. To do so, IBM uses constructs from the TPB to account for intentional actions that influence behavior. In addition, it includes four additional constructs intended to measure automatic processes that influence behavior [1]: knowledge and skills to perform the behavior [2], salience of the behavior [3], environmental constraints, and [4] habit. The model permits the inclusion of background factors, such as demographics, which may influence the behavior under investigation.

Application

Robbins et al. [27] operationalized IBM to investigate cognitive factors hypothesized to influence college students' intentions to engage in healthy sleep. Their analysis identified indirect measures of attitude, perceived control, and descriptive norms as significant in predicting sleep-related intentions ($\beta = 0.32$, 0.25 , 0.16) and behavior ($\beta = 0.26$, 0.25 , 0.12), respectively ($P < 0.001$). Their conceptualization of the model highlights the ability of IBM to provide a cognitive context for developing sleep health interventions.

The model of goal-directed behavior

The model of goal-directed behavior (MGDB) is an extension of Ajzen's TPB [23,28,29]. Hypothetically, additional constructs can be included along with the primary TPB constructs to improve the TPB's predictive and behavior change capacity. The MGDB is one such theory that attempts to incorporate this feature of the TPB. The MGDB posits behavioral desires, a motivational state of mind in which reasons to act are formed, are a direct determinant of behavioral intentions. These behavioral desires mediate the effects of attitudes toward a behavior (evaluation of the behavior), perceived behavioral control (self-efficacy assessments), subjective norms (perceptions of social pressures), and anticipated emotions (prefactuals posited to influence desires to perform a behavior) on behavioral intentions. According to the MGDB, the standard predictors of TPB (attitudes, perceived behavioral control, and subjective norms) are not directly related to behavioral intentions, but indirectly through behavioral

desires. The MGDB posits that anticipated emotions, both positive and negative, predict behavioral desires along with the standard TPB variables.

Application

The MGDB may be useful for researchers who seek to understand the role affect plays in explaining sleep behavior. Knowlden et al. [30] tested an MGDB-based theoretical framework for its capacity to measure and predict the sleep desires, intentions, and behavior of employed college students. Significant paths were identified between attitude toward the behavior, positive emotions, and negative emotions for behavioral desires ($R^2 = 0.654$). Direct paths were identified between perceived behavioral control and behavioral desires for behavioral intentions ($R^2 = 0.513$). Finally, direct paths were identified between perceived behavioral control and behavioral intentions for sleep behavior ($R^2 = 0.464$).

Time management behavior model

The TMB model includes three latent constructs, *setting goals and priorities*, *mechanics of time management*, and *preference for organization*, hypothesized to predict *perceived control of time*. Similar to the *perceived behavioral control* construct from the TPB, *perceived control of time* may act as a proxy for predicting behavior.

Application

Knowlden et al. [31] found Macan's Time Management Behavior (TMB) [32] model was a significant predictor of sleep quality ($R^2 = 0.196$). While further testing is required to gauge the full extent of time management's capacity to predict sleep behaviors, models that actualize the behavioral intentions pathways appear promising.

The transtheoretical model

Stage theory

The *transtheoretical model* (TTM) focuses on explaining how individuals and populations progress toward the adoption and maintenance of health behavior change [33]. The TTM, sometimes called the *stages of change model*, was developed in 1977 by James Prochaska and Carlo DiClemente after completing a comparative analysis of therapy systems as well as a critical review of therapy outcome studies. The core constructs of the TTM include the stages of change, the process of change, decisional balance, self-efficacy, and temptation. The stage construct is comprised of categories of change along a continuum of readiness to change problematic behavior. The first stage of change is *precontemplation*. During this stage, the person is not considering changing their behavior [34]. The second stage of change is *contemplation* in which the person is

considering change within the next 6 months. Following contemplation, a person enters the *preparation* stage in which the person is actively planning for change in the near future. During the *action* stage, the person has made meaningful change leading into *maintenance* in which a person has maintained this change for an extended period. During the *termination* stage, the person has no temptation to revert to their prior behavior and has reached maximum self-efficacy. Aside from the *maintenance* stage, each stage is susceptible to relapse, that is, reverting to a previous stage of change.

The second primary construct of the TTM is *processes of change* [34]. These processes are the activities people utilize to progress through the stages of change. The 10 processes of change include [1] consciousness raising which involves raising awareness about the causes, consequences, and cures for a particular problem [2]; dramatic relief which focuses on enhancing emotional arousal about the behavior and the relief that can come from changing it [3]; environmental re-evaluation which explains how the behavior impacts a persona's proximal social and physical environment and how changing it would benefit the environment [4]; self-evaluation which includes assessment of one's self-image if they employed the new behavior [5]; self-liberation which is a person's belief that they can change and make a commitment to act on the change [6]; counter-conditioning which entails learning a new healthy behavior to replace the old, unhealthy behaviors [7]; reinforcement management which includes applying reinforcements and punishments for taking steps toward behavior change [8]; stimulus control which requires modification of one's environment to increase cues for a healthy behavior and decrease cues for unhealthy behavior [9]; helping relationships which includes seeking relationships that will reinforce adherence to the new behavior [10]; and social liberation which includes realizing social norms are changing in the direction of supporting the healthy behavior change.

Research studies have found certain processes are more useful at specific stages of change. The processes of consciousness raising, dramatic relief, and environmental re-evaluation are typically used to help individuals progress from the precontemplation to the contemplation stage. The process of self-evaluation can assist in progression from contemplation to preparation, while the process of self-liberation can assist in progression from preparation to action. The final four processes—counterconditioning, stimulus control, helping relationships, and reinforcement management—can help individuals progress from action to maintenance.

The construct of *decisional balance* includes the pros and cons associated with behavior change [35]. Characteristically, the pros of healthy behavior are low during the initial stages of change and increase as the individual

progresses through the stages of change. If the pros of the behavior change outweigh the cons, it is more likely the change in behavior will transpire. The fourth construct of the TTM is *self-efficacy* which is the confidence to perform a specific behavior [36]. Increase in self-efficacy is incremental until 100% self-efficacy is reached. The final construct is *temptation*, which is the converse of self-efficacy. Temptation reflects the urges to revert to an unhealthy behavior when in a difficult situation such as being under emotional distress, social situations, and cravings [37]. Temptation decreases as the individual moves through the stages of change and progresses toward termination.

The TTM not only includes five core constructs but is based on five critical assumptions [1]: no single theory can account for all the complexities of behavior change [2]; behavior change is a process that progresses over time through a sequence of stages of change [3]; stages of change are both stable and open to change in the same way behavioral risk factors are stable and open to change [4]; most at-risk populations are not prepared for action; therefore, traditional action-oriented behavior changes programs. Determining a population's current stage of change helps identify the optimal intervention for the population [5]; specific processes should be emphasized at specific stages to optimize behavior change efficacy.

Application

The TTM can be useful to understand the current stage of change toward sleep health in which intervention participants currently reside. Based on such results, different intervention strategies can be applied. Using data from an online health risk assessment (HRA) survey completed by participants of the Kansas State employee wellness program, Hui and Grandner found poor sleep quality was associated with an increased likelihood of contemplation, preparation, and action [38]. However, the likelihood of maintenance of healthy behavior was generally lower.

Behavior change theories and behavioral therapies

Motivational Interviewing

Although motivational interviewing (MI) [39] was not developed from a specific behavior change theory, it closely aligns with principles of self-determination theory [40]. Self-determination theory hypothesizes that human beings are proactive organisms whose intrinsic motivations can either be promoted or impeded based on the social context in which they are embedded. The primary role of a therapist using MI is to create a safe and supportive environment where clients can express their ambivalence and resistance to behavior change. Once the client-therapist relationship develops, practitioners of MI incorporate

behavior change techniques apropos to supporting intrinsic motivation, often incorporating constructs from the TTM. For example, the therapist may use the TTM-based construct of decisional balance to help their client identify the pros and cons associated with their desired behavior change, and then work with them to develop a customized change plan.

Application

MI has been used as a therapeutic technique to improve CPAP compliance. Crosby et al. [41] conducted a systematic review and meta-analysis of clinical trials comparing MI against standard care for its efficacy in augmenting CPAP compliance. Their results found MI had a small-to-moderate effect on CPAP compliance in first-time users at 1, 2, and 3 months upon beginning CPAP. However, they found a similar number of trials showed comparable effects between MI and standard care. Rapelli et al. [42] conducted a scoping review examining the effectiveness of MI and Motivational Enhancement Therapy for CPAP adherence among novel users. Their review found motivation-based interventions were more effective than usual care/educational programs at increasing CPAP adherence. However, they noted most treatment effects were short-term and decreased over time. They cited a lack of details surrounding [1] training of healthcare professionals delivering MI [2]; intervention content, such as motivational strategies employed [3]; assessment of intervention fidelity; and [4] theoretical foundations explaining the outcome variability they observed. Overall, MI appears promising for improving short-term compliance for first-time CPAP users. However, it has been suggested MI has higher rates of success in those resistant to behavior change [42], which does not necessarily describe novel CPAP patients. Thus, MI may prove more effective when incorporated into behavior change interventions that address sleep hygiene in populations resistant to modifying their unhealthy sleep behaviors.

Cognitive behavior therapy

Cognitive behavioral therapy (CBT) is an evidence-based psychotherapy that capitalizes on the relationship between thoughts, emotions, and behaviors. CBT recognizes that automatic thoughts, cognitive distortions, and underlying beliefs shape an individual's emotional states and that these processes can lead to dysfunctional behaviors [43]. CBT has been used to treat various mental conditions, including insomnia. From a treatment perspective, CBT-I incorporates two core therapeutic modalities [11,44]: Stimulus control therapy: Grounded in operant conditioning, stimulus control seeks to decrease conditional arousal (e.g., lying awake in bed while trying to sleep) by strengthening the pairing of the bed/bedroom environment

to sleep [2]. Sleep restriction therapy capitalizes on the homeostatic drive for sleep by limiting the sleep opportunity window to match the individual's sleep ability, eventually leading to improved sleep efficiency. CBT-I incorporates two adjunctive components [1]: Cognitive therapy: modification of negative thoughts around sleep that promote anxiety and perpetuate insomnia [2]; sleep hygiene: adopting lifestyle factors and creating environmental conditions conducive to a healthy sleep/wake cycle.

Application

From a sleep perspective, CBT has primarily been used to treat insomnia (CBT-I) in various populations. A systematic review and meta-analysis conducted by Mitchell et al. [45] suggested that CBT-I appears more effective in improving subjective domains of sleep compared to objective domains of sleep. An additional review of CBT-I by Zachariae et al. [46] found that CBT-I delivered over the Internet (eCBT-I) was as efficacious as face-to-face CBT-I at improving multiple subjective and objective sleep parameters. Future research may seek to combine the strengths of behavior change theories and behavioral therapies to increase treatment-seeking motivations. For example, as noted by Fishbein and Ajzen [47], fundamentally, CBT is designed to capitalize on pre-existing intentions, not necessarily to increase or change intentions. In this context, a combined TPB/CBT-I intervention could be used to Ref. [1] increase behavioral intentions for insomnia treatment seeking behaviors using constructs of the TPB and then [2] use CBT-I or eCBT-I to provide a means to actualize any newly formed intentions.

Interpersonal theories

Social cognitive theory

Continuum theory

Social cognitive theory (SCT) [36] operates on the premise of reciprocal determinism; a causal model that assumes behaviors are influenced by triadic reciprocal causation between personal (e.g., cognition, affect), behavioral (e.g., behavioral patterns, biological traits), and environmental factors (e.g., social dynamics). Several constructs influence these factors. The *reinforcement* construct can be direct, such as a physician who provides verbal feedback to a patient. Reinforcement can also occur vicariously, by observing the actions of others. Reinforcement can also be self-induced. Self-reinforcement would pertain to an individual who keeps records of their behaviors and sets up a system of rewards based on whether they accomplished their self-set behavioral objectives.

For an individual to undergo a behavior, they must understand the behavior and have the *behavioral capacity*

to perform it. Closely aligned to behavioral capacity is the construct of *expectations*. *Outcome expectations* refer to an individual's perception of the likely outcomes that would ensue because of engaging in the behavior. *Outcome expectancies*, in turn, refer to the value a person places on the probable outcomes resulting from performing that behavior. The construct of *self-control* or *self-regulation* includes setting goals and developing plans to accomplish a behavior. Bandura identified six methods for achieving self-regulation [1]: self-monitoring of one's behavior [2]; setting both short and long-term goals [3]; obtaining feedback on the behavior and how it can be improved [4]; self-reinforcement or rewarding one's self [5]; self-instructing [6]; and obtaining social support [48].

Likely, the most popular construct in all of behavior change theories is the staple of SCT; namely, the construct of *self-efficacy*. *Self-efficacy* is the confidence to perform a specific behavior. Self-efficacy includes the capacity to overcome barriers one may face in executing a specific behavior. Individuals become self-efficacious toward a behavior in four main ways [1]: personal mastery of a task, which can be achieved by breaking a complex task down into smaller steps [2]; vivacious learning, such as observing a credible and relatable role model carry out the behavior [3]; persuasion or re-assurance, even in the face of behavioral relapse [4]; and emotional arousal, such as reducing emotional stress that comes from adopting a new behavior.

Application

Due to its core construct of self-efficacy, SCT will perhaps have the most utility for researchers seeking to include skill acquisition as a component of an intervention. Baron, Berg, Czajkowski, Smith, Gunn, and Jones [49] investigated individual differences in the daily associations between CPAP use and improvements in the effect and sleepiness of patients beginning CPAP. They found those with greater treatment self-efficacy and moderate outcome expectancies reported stronger daily benefits from CPAP. In terms of general sleep behavior, Knowlden, Robbins, and Grandner [50] tested the capacity of Bandura's social cognitive model of health behavior to account for variance in fruit and vegetable consumption, moderate physical activity, and sleep behavior in overweight and obese men. In this study, self-efficacy had the greatest total effect on sleep behavior ($\beta_{\text{total}} = 0.406$). Self-efficacy also had a significant indirect ($\beta_{\text{indirect}} = 0.194$) effect on sleep behavior through its influence on outcome expectations ($\beta_{\text{direct}} = 0.265$), socio-structural factors ($\beta_{\text{direct}} = 0.679$), and goals ($\beta_{\text{direct}} = 0.700$). Fig. 17.3 illustrates the final SCT structural model of sleep behavior with standardized regression weights.

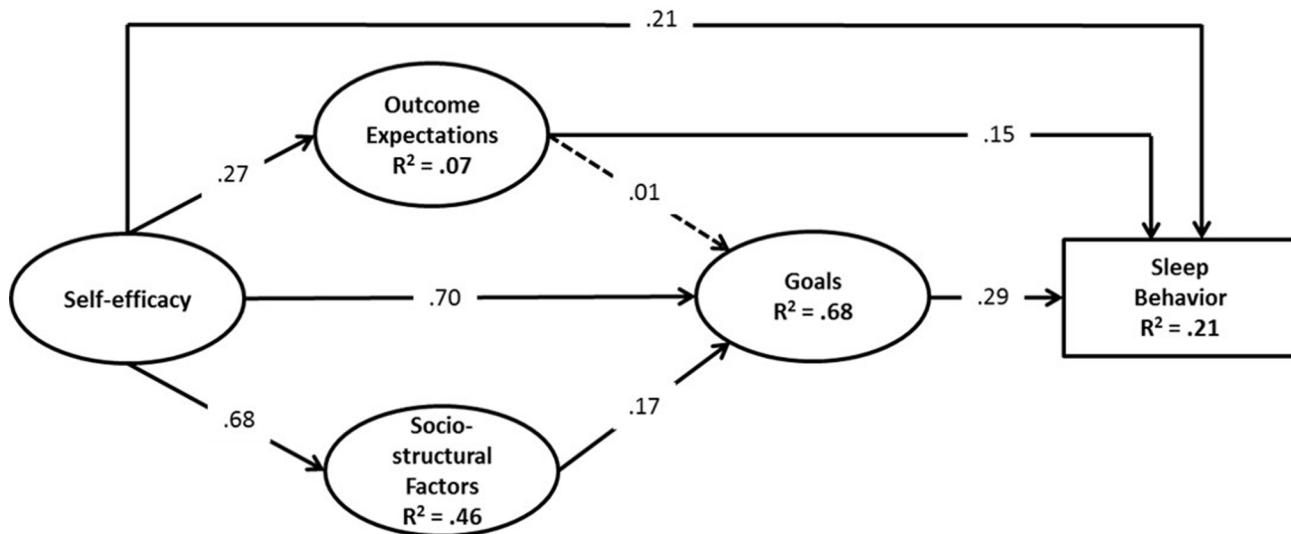


FIGURE 17.3 Social cognitive theory model of sleep behavior ($N = 303$). Filled-in lines represent significant direct pathways; dotted lines represent non-significant pathways ($p > 0.05$). Direct model pathways reported as standardized beta coefficients while squared multiple correlations are presented in bold text. Reprinted with permission of the authors.

Social network theory

Continuum theory

Social network theory (SNT) refers to the web of social relationships that surround people and includes the structural characteristics of that web [51]. Social epidemiological observational studies have documented the positive effects that support networks have on health outcomes. However, due to the lack of intervention studies using SNT, some experts caution that social networks do not constitute a theory, but rather a set of concepts that describe the processes, functions, and structure(s) of social relationships [52]. In considering the influence of a network, the following must be assessed to understand the role of the network on a given health behavior [1]: centrality versus marginality (how much involvement does the person have on the network?) [2]; reciprocity of relationships (are relationships one-way or two way?) [3]; complexity and intensity of relationships [4]; homogeneity or heterogeneity of those existing within the network [5]; subgroups within the network; and [6] communication patterns in the network (how is information transmitted?). While it is known that social networks impact health status, specifics of who in the network is impacted and to what extent the impact influences health behavior outcomes is unknown.

Application

While there are no known studies applying SNT to sleep, in the field of health promotion, social networks play an integral role in interpersonal-level interventions. Robbins

et al. [53] implemented a sleep health education intervention tailored to African American populations. The recruitment strategy for their intervention relied heavily upon social networks. For example, the team developed relationships with local community and faith-based organizations as well as barber shops and churches. They also assembled a community steering committee, comprised of community stakeholders, patients, and health advocates to provide feedback on the content of the intervention. Researchers seeking to increase awareness about sleep health, recruit participants, or design interventions may wish to incorporate SNT.

Community level theories

Diffusion theory

Stage theory

Diffusion theory provides a framework to understand how innovations, such as new ideas or behaviors, spread across various channels in a population or community [54]. In this context, there are three types of innovations. Incremental innovations represent a relatively small improvement over previous ideas or products. Distinctive innovations reflect significant improvement but do not rely on any new technology or approach. Breakthrough innovations are based on a new approach or new technology. Similar to the transtheoretical model, diffusion theory hypothesizes that populations go through stages of change when assimilating innovations. Rogers has outlined the following five stages [1]: acquiring knowledge of the innovation [2]; persuasion or attitudes about the innovation [3]; decision about

whether to adopt or reject the innovation [4]; implementation of the innovation; and [5] confirmation or ongoing use of the innovation.

The diffusion of an innovation in a population can be represented by the standard bell-curve. *Innovators*, representing approximately 2%–3% of a given population, are the individuals who are the first to adopt an innovation. Innovators are characterized as risk takers and adventurous. *Early adopters*, which represent approximately 14% of a given population, are those who accept an innovation early on. Early adopters are characterized as respected opinion leaders. *Early majority* are characterized as being ahead of the average and comprise approximately 34% of a given population. *Late majority* (34%) are skeptical and will wait until most people in a social system have adopted the innovation. *Laggards*, which represent about 16% of the population, are not interested in the innovation and will be the last to adopt the innovation if they do at all. Because diffusions transpire over time, the rate of adoption can be plotted against time. In doing so, the rate of adoption can be modeled as an S-shaped curve.

In terms of promoting diffusion into a system, it is important to identify population characteristics. Homophily, or similarity among groups (e.g., culture), can speed the diffusion of an innovation. Additionally, the identification of physical and virtual social networks used by the population can be leveraged to hasten the speed at which an innovation is adopted. When working in communities, identifying change agents and opinion leaders is crucial. These individuals can be considered gatekeepers to innovations, and their favorable perspective of an innovation can assist in its permeation through a social system. Diffusions can also be promoted using such strategies as *social marketing*. Social marketing is the application of commercial marketing techniques to promote beneficial behaviors. Social marketing methods such as audience segmentation can be used to develop messages targeted to specific groups.

Application

Although no current sleep health interventions have directly applied diffusion theory, sleep researchers are increasingly incorporating consumer sleep technology into their interventions. Mobile phones and wearable devices have diffused into the marketplace at a rapid pace. In 2018, the American Academy of Sleep Medicine released a position statement regarding consumer sleep technologies [55]. In brief, they indicated that consumer sleep technology can be useful as a tool to bolster patient–clinician interaction when used as part of a clinical evaluation. They did note, however, that the general lack of validation, access to algorithms, and Food and Drug Administration oversight limits their current applicability. To evaluate the effectiveness of the diffusion framework for sleep behavior interventions, Knowlden et al. [56]

recommended recruiting and matching participants according to their stage of innovation adoption, similar to matching participants by their current TTM stage of change. Matching participants this way could allow for greater intervention customization while increasing prescription adherence.

Behavioral economics

Continuum theory

In recent years, the potential application of economic theory to behavior change has received greater attention. *Economics* is a social science concerned with the description and analysis of the production, distribution, and consumption of goods and services. Standard economic theory describes how people should behave when acting in their own best interests. It considers individuals to be acting as purely rational agents. Under this model, if an individual fails to acquire sufficient duration of sleep, it is assumed decision is best for them, and they have thought through all the costs and benefits of this action. However, behaviors are not completely rational actions. When considering whether to engage in a particular action, factors such as emotions, heuristics, and present-tense biases help inform the behavioral decision-making process. *Behavioral economics* operates under the assumption that individuals often act irrationally; however, they do so in predictable ways. Experts have suggested that behavioral economics can be applied to move individuals towards environments that can motivate healthier choices [57].

Behavioral economic approaches seek to overcome three key biases that often factor into the behavioral decision-making process [58]. The first is *present-tense bias*. Often, individuals overemphasize immediate benefits relative to long-term costs. For example, an individual may drive all night to arrive at a destination in a timelier manner. While this may provide a more immediate convenience to the individual, their decision does not factor in the long-term costs of a potential accident due to drowsy driving. *Visceral factors* also tend to bias behavioral decision-making. Cues or stimuli in the social or physical environment may override rational decision making. Visceral factors tend to be characterized by a direct hedonic impact (usually deleterious) and the relative desirability of other related actions. A final bias that behavioral economics attempts to address is *status quo bias*. People tend to adhere to the current or default option. If a person has always voluntarily restricted their sleep throughout the week and engaged in oversleeping on the weekends, they are more likely to maintain the status quo, even if a healthier behavior, such as consistent sleep/wake schedule is available. In considering these biases, behavioral economics suggests both unconscious and nonrational forces influence people's behaviors and may partly explain why simply informing individuals about, for example, their need for adequate sleep does not always result in behavior change.

Application

Behavioral economics may assist researchers seeking to influence the commonly held belief in Western cultures that sleep is an expendable resource. Although no current behavioral economic interventions have been implemented in the realm of sleep health, Malone, Ziporyn, and Buttenheim [59] suggested four behavioral economics strategies for individuals and communities seeking to address school start time policies. Their first recommendation is to offer later start times as the default option. They also recommend promoting social norms using success stories. To counter omission bias, the researchers recommend visually depicting deleterious outcomes related to early school start times such as poorer test scores and automobile accidents related to drowsy driving. Finally, they recommend increasing messaging salience. One method they recommend is to color code those districts with later start times in school publications and websites to better inform community stakeholders.

Measurement of models and theories for behavior change interventions

Empirical evaluation of theory-based, behavior change programs requires measurement of the theoretical constructs targeted by the intervention. Often, researchers will state that an intervention is theory-based, yet they do not conduct measurements of the theoretical constructs used in the intervention. Failure to measure theoretical constructs makes it impossible to scientifically assess hypothesized causal connections between the applied theory and the intervention results. If, for example, operationalization, does not occur other researchers cannot apply the same methods to gauge consistency, an essential criterion for the assessment of causation (see Hill's Criteria).

Application of theoretical frameworks for behavior change interventions involves three steps: (a) explicit operationalization of the theoretical constructs, (b) actuation of the theoretical constructs for intervention application, and (c) measurement of the theoretical constructs at pre- and postintervention to ascertain whether the theoretical constructs indeed improved. For example, if self-efficacy for obtaining 8 h of sleep is targeted by an intervention, self-efficacy should be measured both before and after the intervention to determine if self-efficacy increased. Instruments for measuring theory-based interventions are developed through psychometric modeling. Validated theoretical models can provide detailed insight into the dynamics that underlie behavior change. The following section will provide a framework for incorporation of instruments for measuring theoretical constructs.

Step 1: Define purpose of instrument

The first step in developing an instrument (instrumentation) is to *define its purpose*. If the purpose is not explicitly defined, there is a risk the instrument will not be relevant for the study. The purpose of the instrument should align with the study's research questions and hypotheses.

Step 2: Identify objects of interest

An object of interest is any factor or determinant that is theoretically connected to the behavior. Objects of interest should be grounded in the literature (e.g., correlates, predictors, descriptive epidemiological studies). Sometimes, objects of interest are not well known or understood. In such a case, formative qualitative research may be required (e.g., grounded theory). The socio-ecological approach can be used to identify objects of interest at all levels of influence.

Step 3: Constitutively define objects of interest

For this step, the standardized, universal definitions of the object of interest should be considered. At this point, the research team may opt to use a theoretical framework to guide the objects of interest they will measure. For example, if the research team decides the TPB will best address their research questions, they will need to define each TPB construct. For instance, the universal definition of attitude toward the behavior from the TPB is "the degree to which performance of the behavior is positively or negatively valued." Once each object of interest is defined, the objects of interest must be prioritized in terms of their ability to evaluate the research questions and hypotheses. It is unlikely that each object of interest will become part of the instrument. In the field of health education and promotion, for example, Golden et al. found fewer than 10% of interventions incorporated the socio-ecological approach as the foundation of their interventions [60]. Even if an intrapersonal level theoretical framework is used for the study, it is possible that not all constructs from the theory will be measured. For example, the SCT includes approximately 10 constructs. This is a relatively large number of constructs. Based on time and resources, it may not be feasible to include the full set of constructs. As an aside, one reason the TPB is popular, is its parsimonious composition. However, even if the instrument will only seek to measure a select number of objects of interest, it is still important to identify all objects. Doing so may help account for unexplained variance in the theoretical model. For example, if the TPB is used to model sleep behavior and it is found the model only accounts for 30% variance in the outcome variable. The remaining 70%

variance could be attributed to objects of interest that were not measured.

Step 4: Operationally define objects of interest

Operationalization requires two main features [1]: tailoring of objects for the need of the research [2] and assigning numerical values to the objects for measurement purposes. The following example demonstrates the translation of the universal definitions of sleep behavior and attitude toward the behavior into operational definitions of these objects.

- *Universal definition:* A behavior is an overt human action, conscious or unconscious, with measurable frequency, duration, and intensity. Behavior from the vantage point of the TPB is defined in terms of the target, action, context, and time (TACT) principle.
- *Operational definition:* For the purposes of this program, adequate sleep behavior is defined as adults receiving 7–9 h of continuous sleep in a 24-hour period. Applying the TACT principle, adequate sleep behavior is defined as adults (target) achieving 7–9 h (time) of sleep (action) every 24 h (context). The sleep behavior variable will be assessed through self-report.
- *Universal definition:* Attitude toward a behavior is the degree to which performance of the behavior is positively or negatively valued.
- *Operational definition:* For the purpose of this study, attitude toward the behavior of obtaining adequate sleep is operationally defined as the individual's overall feeling of like or dislike toward obtaining adequate sleep behavior. A total of six items will be used to measure this construct. Seven-point semantic differential scale will be used to measure each item. A score of 6–42 is possible for this construct. The mean of the item scores will be calculated to provide an overall attitude score. A higher score is indicative of a more positive attitude toward the behavior.

Step 5: Review previously developed instruments

For example, if the researcher conducts a TPB-based sleep program for college students, they may want to use the instrument developed by Knowlden et al. [25]. In such a case, this previously developed instrument may be an optimal fit. If the research team opts to use a previously validated instrument for their intervention, they must carefully consider the original purpose of the instrument, and the demographics that were sampled. Instruments developed with different demographics, literacy levels, online delivery versus paper-and-pencil administration, etc., may impact measurement accuracy. When adopting previously developed instruments, it is also important to

consider the psychometrics and limitations of the methods applied during the original instrumentation process. For example, if the instrument has weak internal consistency, it may not introduce bias into the measurement process. If the data collected for instrumentation was from non-probability samples, the validity of the findings may not be generalizable (external validity).

Researchers can search research databases for instruments that may fit the needs of their interventions. Popular research databases include Medical Literature Analysis and Retrieval System Online (MEDLINE) & PubMed, Education Resources Information Center (ERIC), Cumulative Index to Nursing and Allied Health CINAHL, and Google Scholar. Some questions researchers may wish to address when considering whether to use a previously validated instrument include [1]: Was the instrument developed with similar demographics? [2] How did the researchers go about conducting the process of instrumentation? [3] Does the instrument have adequate psychometric properties (reliability/validity)?

Step 6: Develop an original instrument

If no previously developed instrument meets the needs of the study, the researchers may need to develop an original instrument. It is important to note that if the research team opts to develop an original instrument, it is likely to add considerable time and resources to the research study. Therefore, it may be beneficial to use a previously developed instrument, even if it will not provide the highest degree of measurement precision. This will be largely determined by the resources available to the research team and the need for measurement precision.

Step 7: Select appropriate scales

For this step, consider the level of measurement (e.g., nominal, ordinal, interval, and/or ratio) used to evaluate the study hypotheses. Ratio-level variables provide the most precision and allow for a wide range of statistical tests. However, ratio-level variables are not always possible. Furthermore, higher levels of measurement are limited by how the data are collected. For example, the precision of the ratio-level data can vary if self-report (indirect monitoring) is used as opposed to accelerometers (direct monitoring) collecting ratio-level data on sleep. It is often best to remember that there is no perfect method of measurement. Researchers operate within a range of confidence.

In terms of selecting scales, some theories provide guidance on the type of scale that should be applied. For example, the developer of the TPB, Icek Ajzen, recommends the use of semantic differential scales to measure TPB constructs [23]. If no recommendation exists, the

literature can also help inform which scale the researchers should use. For example, the research team may look at five different research papers describing the development of questionnaires using SCT. Based on the psychometric properties of the papers or some other feature, such as similarity in the type of behavior, the researchers may opt for one type of scale over another. In considering the type of scale for questionnaires, it is often advisable to maintain, as much as possible, the same type of scale throughout the questionnaire. For example, if Likert-type scales are selected, strive to use Likert-type scales throughout as opposed to integrating multiple types of scales. Multiple scales can increase questionnaire complexity and lead to participant bias.

Step 8: Develop items

One item should be developed corresponding to each property of a construct. Items must be clear and only tap one attribute of a construct. When a concept has been reduced to a variable, the scale of measurement chosen, and the items developed, the instrument is also called a questionnaire. Paper-and-pencil questionnaires are the conventional method of delivery. Web-based questionnaires are becoming more popular. Each medium of questionnaire delivery possesses inherent strengths and limitations. Developing items is a tedious, iterative process. It is a skill that requires time and experience to develop. A good first step is to examine items that have already been developed and tested. It might be possible to slightly alter such items. A common paradox for researchers is developing items that fully tap into a construct while simultaneously seeking to minimize participant burden. If too many items are present, it can increase participant burden and introduce bias (e.g., acquiescence bias). One method for accomplishing this is separating “need to know” information from “nice to know” information. Every item on a questionnaire should answer something the researcher needs to know to test their hypotheses. If an item is not directly linked to the study hypotheses, it is likely “nice to know” information.

Step 9: Prepare a draft instrument

Directions are important in any instrument. They should be optimum in length and easy to understand. The instrument should have clear guidance about scoring: how each item will be scored, how different subscales will be scored, whether there will be one scorer or more, what will be the range of scores, and what high and low scores mean (develop a code book). The instrument should have a clean, organized, professional layout. Developing an appealing hard copy or online questionnaire layout can take

considerable time. Online questionnaires are compatible with many interfaces and are smartphone accessible, allowing participants to complete the questionnaire when it is convenient for them. Participants can also save their answers and return to them later.

Step 10: Test for readability

Health literacy is a topic of growing importance in public health. Health literacy is conceptualized as an individual’s ability to obtain, process, and comprehend health information to make informed health decisions [61]. Readability metrics can serve as a starting point for gauging health literacy. Readability scores are based on the number of syllables in words and should be a beginning point for gauging health literacy. There are numerous readability metrics available. Two such examples are the Flesch Reading Ease and Flesch-Kincaid Grading tests. Reading ease between 60 and 70 is generally good. Grade level scores coincide with U.S. Education Grade levels, for example, a level of five indicates general compatibility with fifth-grade U.S. education standards. If a questionnaire indicates a high level of literacy is required, a good first step is to simplify words with three or more syllables. Further refinement should occur through pilot testing.

Step 11: Send to panel of experts

A panel of experts is a group of individuals with sufficient expertise to gauge the properties of an instrument. A panel of experts is typically comprised of six jurors: two subject experts (including theory, if theory has been used), two experts in measurement and instrument development, and two experts of the priority population. Primarily, they will be involved in evaluating readability as well as face and content validity. Face validity contrasts operational definitions against universal definitions of the construct. Content validity subjectively assesses whether the items fully capture all the dimensions of the intended construct as operationally defined. Panel members should also evaluate the directions, layout, and readability of the questionnaire. Experts can be identified by e-mailing corresponding authors from research articles. The letter to panel members should be formal, professional, and ask for their assistance. Typically, a form for completing the evaluation of the instrument is supplied along with the questionnaire to ease juror burden. After receiving input from the first round with the panel of experts, changes are made, and then in the second round once again the panelists are approached to check if suggestions have been sufficiently incorporated; and add more rounds of review if necessary.

Step 12: Conduct a pilot test

This step can be conducted before or after forming the panel of experts. In this pilot test, the target population members are instructed to encircle any words they do not understand or any unclear statements. They are also timed to determine approximately how long it takes to complete the instrument in a practical setting. The pilot sample is also asked to provide any suggestions regarding improving the readability of the instrument. If possible, the pilot test should be followed with a debriefing session in which participants provide verbal feedback.

Step 13: Establish reliability and validity

Establishing reliability and validity of an instrument requires proficiency in statistics and statistical software. The following section will provide a brief overview of reliability and validity but is by no means exhaustive. Let us consider the following example to help conceptualize reliability and validity. First, let us consider that we are interested in measuring body weight for a weight loss intervention. A couple of factors may go into our methods for consistently measuring body weight. First, we may want participants to weigh themselves on an empty stomach, first thing in the morning. Second, we may want participants to place the scale on a flat surface. Third, we may want participants to use an electronic scale that is appropriately calibrated. We could say that these three properties of measuring body weight must be internally consistent to reliably capture body weight. This same idea is applied when using a collection of cohesive instrument items, or scales, to tap into a psychological construct. Internal consistency gauges how well the items gel together to tap into a construct. A common statistic to gauge internal consistency is Cronbach's alpha. Typically, values of 0.70 or higher are recommended [62].

Now, let us say that we are interested in testing the stability of our theoretical construct. We request that participants step onto the scale at the beginning of the trial. Let us assume, the pretest mean body weight of the sample is 135 lbs. At the end of the program, participants' weight is once again measured. The posttest mean bodyweight of the sample is 125 lbs. It appears the intervention worked! But we think back to many times in which we stepped onto a weighing scale. We stepped on and recorded our weight. We waited for it to recalibrate and we stepped on it again, only to find the scale produced a weight that differed by a few pounds compared to the first time we stepped on. If this is the case with an objective instrument like a scale, intangible concepts like attitude are likely more prone to measurement error. Even if consistent procedures are applied, there may be fluctuations, or measurement errors, inherent to the instrument. The less objective the

measurement tool, the more likely error will be present. For example, with body weighing scales, a cheaper bathroom scale will have less accuracy than a sophisticated electronic body weighing scale. If we do not attempt to determine if the fluctuation is reasonable, it is possible we could find changes from pretest to posttest that are due to random fluctuation as opposed to actual change attributed to the intervention. Stability reliability, then, is the degree of association between a measurement taken at one point in time against the same measurement taken at a second point in time. The method used to assess stability reliability is called the test-retest method. The statistic used to gauge the degree of association between the two measurements is called a correlation coefficient. Often, Pearson's r correlation coefficient is applied. Although, there are much more sophisticated metrics, such as intraclass correlations that can be applied. Typically, Pearson's r values of 0.70 or higher are considered adequate for gauging stability.

Validity would be, for example, the ability of the scale to measure fat loss as opposed to some other features such as water weight. There are several types of validity [62]. Construct validity is gauging whether a construct confirms an a priori theoretical framework. Methods for construct validity are complex and require advanced training (typically doctoral-level statistics classes). Two other types of validity include concurrent validity and predictive validity. Concurrent validity attempts to gauge the ability of a field-based instrument such as an accelerometer or self-report questionnaire to correlate to the current gold standard. For example, how valid are accelerometers for measuring sleep when compared to the gold standard of polysomnography. Predictive validity attempts to determine how well a set of constructs predicts an outcome of interest. For example, how accurate is the TPB for predicting sleep behavior intentions.

Limitations of behavior change theories

Although models and theories can be helpful tools in explaining and predicting health behavior change, they are not without their limitations. No single theory is useful in all situations. Additionally, each theory presented in this chapter has its inherent limitations. Continuum, value-expectancy theories tend to focus on cognitive factors but do not consider that behavior change occurs over time. Meanwhile, many theorists disagree with the way stage theories classify the process of behavior change. In addition to these limitations, behavior change theories are rarely operationalized and measured in intervention research. To improve the utility of behavior change models and theories, more interventions that can demonstrate a causal connection between theoretical constructs and behavior change are needed.

Conclusion

A range of behavior change models and theories are available to assist in the process of modifying sleep behaviors. Theories can assist in explaining why individuals do, or do not, engage in healthful sleep actions. Effective implementation of behavior change models and theories can reduce intervention costs, make more efficient use of time, and elicit greater behavioral outcomes. Models and theories can be classified into two general domains [1]: continuum theories, which seek to quantify theoretical constructs correlated to a behavior; and [2] stage theories, which attempt to classify individuals according to their progress toward permanent behavior change. To advance the efficaciousness of behavior change models and theories for improving sleep health, researchers must operationalize the theoretical constructs they apply. Poor sleep impacts a large segment of the United States and other Westernized populations. As such, an emphasis on theory-based research at the community level is greatly needed.

References

- [1] Gopnik A, Meltzoff an, Words BP. Theories. 1997.
- [2] Nutbeam, Harris E. Theory in a nutshell: a guide practitioner's guide to health promotion theory. McGraw Hill; 1999.
- [3] Glanz K, Rimer BK, Viswanath. , Health behavior and health education: theory, research, and practice. John Wiley & Sons; 2008.
- [4] D. CP, Chaplin JS, Krawiec TS, Lundin RW, Marx MH, Hillix WA. Systems and theories of psychology. Am J Psychol 1979;92(4):751. <https://doi.org/10.2307/1421805>.
- [5] McKenzie N, Thackeray R. Planning, implementing & evaluating health promotion programs. A primer; 2017.
- [6] Randall JG, McKenzie J, Seabert, Principles and foundations of health promotion and education. 2015.
- [7] World Health Organization. Constitution of the world health organization. Geneva: World Health Organization; 1948.
- [8] World Health Organization. The Ottawa Charter for health promotion [website]. Geneva: World Health Organization; 1986.
- [9] Bixler E. Sleep and society: an epidemiological perspective. Sleep Med 2009;10(1):S3. <https://doi.org/10.1016/j.sleep.2009.07.005>.
- [10] Hill AB. The environment and disease: association or causation? J R Soc Med 1965;58(5):295–300. <https://doi.org/10.1177/003591576505800503>.
- [11] Doll R, Hill AB. The mortality of doctors in relation to their smoking habits. BMJ 1954;1(4877):1451–5. <https://doi.org/10.1136/bmj.1.4877.1451>.
- [12] David Lorkowski C. Causation the internet encyclopedia.
- [13] Rimer G. Theory at a glance: a guide for health promotion practice. 2005.
- [14] Simons-Morton B, McLeroy KR, Wendel ML. Behavior theory in health promotion practice and research. Jones & Bartlett Publishers; 2012.
- [15] Weinstein ND, Rothman AJ, Sutton SR. Stage theories of health behavior: conceptual and methodological issues. Health Psychol 1998;17(3):290–9. <https://doi.org/10.1037/0278-6133.17.3.290>.
- [16] Hochbaum GM. Government Printing Office Public participation in medical screening programs: a socio-psychological study. 1958.
- [17] Rosenstock IM. Historical origins of the health belief model. Health Educ Monogr 1974;2(4):328–35. <https://doi.org/10.1177/109019817400200403>.
- [18] Adam PK, Sharma M. Health belief structural equation model predicting sleep behavior of employed college students. Fam Community Health 2014;37(4):271–8. <https://doi.org/10.1097/fch.0000000000000043>.
- [19] Ajzen I. From intentions to actions: a theory of planned behavior. Springer Science and Business Media LLC; 1985. p. 11–39. https://doi.org/10.1007/978-3-642-69746-3_2.
- [20] Casper ES. The theory of planned behavior applied to continuing education for mental health professionals. Psychiatr Serv 2007;58(10):1324–9. <https://doi.org/10.1176/ps.2007.58.10.1324>.
- [21] Fishbein M, Ajzen I, Predicting and changing behavior: the reasoned action approach. Psychology Press.
- [22] Sharma M, Romas JA. Theoretical foundations of health education and health promotion. Jones & Bartlett Publishers; 2008.
- [23] Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991;50(2):179–211. [https://doi.org/10.1016/0749-5978\(91\)90020-t](https://doi.org/10.1016/0749-5978(91)90020-t).
- [24] Madden TJ, Scholder Ellen P, Ajzen I. A comparison of the theory of planned behavior and the theory of reasoned action. Pers Soc Psychol Bull 1992;18(1):3–9. <https://doi.org/10.1177/0146167292181001>.
- [25] Knowlden AP, Sharma M, Bernard AL. A theory of planned behavior research model for predicting the sleep intentions and behaviors of undergraduate college students. J Prim Prev 2012;33(1):19–31. <https://doi.org/10.1007/s10935-012-0263-2>.
- [26] Fishbein, Bandura A, Triandis, Kanfer B, Middlestadt, Eichler. Factors influencing behavior and behavior change: final report— theorists' workshop. 1992.
- [27] Robbins R, Niederdeppe J. Using the integrative model of behavioral prediction to identify promising message strategies to promote healthy sleep behavior among college students. Health Commun 2015;30(1):26–38. <https://doi.org/10.1080/10410236.2013.835215>.
- [28] Perugini M, Bagozzi RP. The role of desires and anticipated emotions in goal-directed behaviours: broadening and deepening the theory of planned behaviour. Br J Soc Psychol 2001;40(1):79–98. <https://doi.org/10.1348/014466601164704>.
- [29] Perugini M, Conner M. Predicting and understanding behavioral volitions: the interplay between goals and behaviors. Eur J Soc Psychol 2000;30(5):705–31. [https://doi.org/10.1002/1099-0992\(200009/10\)30:5<705::aid-ejsp18>3.0.co;2-#](https://doi.org/10.1002/1099-0992(200009/10)30:5<705::aid-ejsp18>3.0.co;2-#).
- [30] Knowlden AP, Sharma M, Shewmake ME. Testing the model of goal-directed behavior for predicting sleep behaviors. Health Behav Policy Rev 2016;3(3):238–47. <https://doi.org/10.14485/HBPR.3.3.5>.
- [31] Knowlden AP, Naher S. Time management behavior structural equation model predicts global sleep quality in traditional entry university students. Am J Health Educ 2023;1–10.
- [32] Macan TH. Time management: test of a process model. J Appl Psychol 1994;79(3):381–91. <https://doi.org/10.1037/0021-9010.79.3.381>.
- [33] Prochaska JO, Norcross JC. Norcross, systems of psychotherapy: a transtheoretical analysis. Oxford University Press; 2018.

- [34] Prochaska JO. Systems of psychotherapy: a transtheoretical analysis. Dorsey Press; 1979.
- [35] Janis IL, Mann L. Decision making: a psychological analysis of conflict, choice, and commitment. Free press; 1977.
- [36] Bandura A. Social foundations of thought and action. Prentice-Hall; 1986.
- [37] Prochaska JO. Essential psychotherapies: theory and practice 403 440. Guilford Press An eclectic and integrative approach: Trans-theoretical therapy; 1995.
- [38] Hui SkA, Grandner MA. Associations between poor sleep quality and stages of change of multiple health behaviors among participants of employee wellness program. *Prev Med Rep* 2015;2:292–9. <https://doi.org/10.1016/j.pmedr.2015.04.002>.
- [39] Rollnick S, Miller WR. What is motivational interviewing? *Behav Cognit Psychother* 1995;23(4):325–34. <https://doi.org/10.1017/S135246580001643X>.
- [40] Deci EL, Ryan RM. Intrinsic motivation and self-determination in human behavior. Plenum; 1985.
- [41] Crosby ES, Spitzer EG, Kavookjian J. Motivational interviewing effects on positive airway pressure therapy (PAP) adherence: a systematic review and meta-analysis of randomized controlled trials. *Behav Sleep Med* 2023;21(4):460–87. <https://doi.org/10.1080/15402002.2022.2108033>.
- [42] Rapelli G, Pietrabissa G, Manzoni GM, Bastoni I, Scarpina F, Tovaglieri I, Perger E, Garbarino S, Fanari P, Lombardi C, Castelnuovo G. Improving CPAP adherence in adults with obstructive sleep apnea syndrome: a scoping review of motivational interventions. *Front Psychol* 2021;12. <https://doi.org/10.3389/fpsyg.2021.705364>.
- [43] Chand DPK, Huecker MR. Cognitive behavior therapy. StatPearls. StatPearls Publishing; 2023.
- [44] Уокер Д, Мионч А, Перлис МІ, Варрак А. Cognitive behavioral therapy for insomnia (CBT-I): a primer. Клиническая и специальная психология 2022;11(2):123–37. <https://doi.org/10.17759/cpsc.2022110208>.
- [45] Mitchell LJ, Bisdounis L, Ballesio A, Omlin X, Kyle SD. The impact of cognitive behavioural therapy for insomnia on objective sleep parameters: a meta-analysis and systematic review. *Sleep Med Rev* 2019;47:90–102. <https://doi.org/10.1016/j.smrv.2019.06.002>.
- [46] Zachariae R, Lyby MS, Ritterband LM, O'Toole MS. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia - a systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev* 2016;30:1–10. <https://doi.org/10.1016/j.smrv.2015.10.004>.
- [47] Fishbein M, Ajzen I. Theory-based behavior change interventions: comments on hobbis and Sutton. *J Health Psychol* 2005;10 (1):27–31. <https://doi.org/10.1177/1359105305048552>.
- [48] Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev* 1977;84(2):191–215. <https://doi.org/10.1037/0033-295x.84.2.191>.
- [49] Baron KG, Berg CA, Czajkowski LA, Smith TW, Gunn HE, Jones CR. Self-efficacy contributes to individual differences in subjective improvements using CPAP. *Sleep Breath* 2011;15 (3):599–606. <https://doi.org/10.1007/s11325-010-0409-5>.
- [50] Knowlden AP, Robbins R, Grandner M. Social cognitive models of fruit and vegetable consumption, moderate physical activity, and sleep behavior in overweight and obese men. *Health Behav Res*. 2018;1(2). <https://doi.org/10.4148/2572-1836.1011>.
- [51] Edberg M. Essentials of health behavior: social and behavioral theory in public health. 2007.
- [52] Heaney Israel BA. Health behavior and health education: theory, research, and practice 189 210 Jossey-Bass social networks and social support. 2008.
- [53] Robbins R, Allegante J, Rapoport D, Senathirajah Y, Rogers, Williams N, Cohalll, Butler M, Ogedegbe O, Louis J-. Tailored approach to sleep health education (TASHE): preliminary results for a randomized controlled trial of a web-based educational tool to promote self-efficacy for OSA diagnosis and treatment among blacks. *Sleep* 2018;41(Suppl. 1_1).
- [54] Rogers EM. Diffusion of innovations. Free Press; 2003.
- [55] Khosla S, Deak MC, Gault D, Goldstein CA, Hwang D, Kwon Y, O'Hearn D, Schutte-Rodin S, Yurcheshen M, Rosen IM, Kirsch DB, Chervin RD, Carden KA, Ramar K, Nisha Aurora R, Kristo DA, Malhotra RK, Martin JL, Olson EJ, Rosen CL, Rowley JA. Consumer sleep technology: an American academy of sleep medicine position statement. *J Clin Sleep Med* 2018;14(5):877–80. <https://doi.org/10.5664/jcsm.7128>.
- [56] Knowlden AP, Wilkerson AH, Dunlap KB, Stellefson M, Elijah OA. Systematic review of electronically delivered behavioral obesity prevention interventions targeting men. *Obes Rev* 2022;23 (9). <https://doi.org/10.1111/obr.13456>.
- [57] Bickel WK, Vuchinich. Reframing health behavior change with behavioral economics. Psychology Press; 2000.
- [58] George L. Out of control: visceral influences on behavior. *Organ Behav Hum Decis Process* 1996;65(3):272–92. <https://doi.org/10.1006/obhd.1996.0028>.
- [59] Kohl Malone S, Ziporyn T, Buttenheim AM. Applying behavioral insights to delay school start times. *Sleep Health* 2017;3(6):483–5. <https://doi.org/10.1016/j.slehd.2017.07.012>.
- [60] Golden SD, Earp JAL. Social ecological approaches to individuals and their contexts: twenty years of health education & behavior health promotion interventions. *Health Educ Behav* 2012;39 (3):364–72. <https://doi.org/10.1177/1090198111418634>.
- [61] Parker R, Ratzan SC. Health literacy: a second decade of distinction for Americans. *J Health Commun* 2010;15(2):20–33. <https://doi.org/10.1080/10810730.2010.501094>.
- [62] Polit DF, Beck CT. Nursing research: principles and methods. Lippincott Williams & Wilkins; 2004.

Part IV

Sleep and cardiometabolic health

This page intentionally left blank

Chapter 18

Insufficient sleep and obesity

Andrea M. Spaeth

Department of Kinesiology and Health, School of Arts and Sciences, Rutgers University, New Brunswick, NJ, United States

More than two-thirds of adults and one-third of children are considered to be overweight/obesity in the United States, and the prevalence rate of obesity among adults has increased from 33.7% to 39.6% in just the past decade [1]. The high prevalence of obesity and its associated diseases, such as type 2 diabetes and cardiovascular disease, have prompted calls for the evaluation of innovative approaches to decrease obesity risk and promote healthy weight management. Emerging evidence suggests that sleep plays an important role in energy balance and metabolism and that enhancing sleep may represent a novel, modifiable behavior for weight regulation in children, adolescents, and adults. Recent research has also begun to examine how sleep and circadian rhythm disorders affect energy balance regulation as well as how changes in weight status, diet, and exercise impact sleep physiology.

Sleep duration

Epidemiologic studies consistently demonstrate that habitual short sleep duration is a risk factor for obesity. Cross-sectional and longitudinal studies show that adults who report sleeping $\leq 5\text{--}6$ h/day have more adiposity, larger waist circumferences, gain more weight over time and are more likely to have obesity [2–4]. In one study of nearly 14,000 adults, short sleepers (≤ 6 h/day) were 1.0 kg/m^2 heavier and had a 2.2 cm larger waistline than sufficient sleepers (7–9 h/day) [5]. Similarly, adults who slept < 5 h a night exhibited a 16% higher prevalence of general obesity and a 9% higher prevalence of abdominal obesity compared with those who slept 7–8 h [6]. Consistent with these correlational findings, two in-laboratory experimental protocols demonstrated that healthy adults randomized to a sleep restriction condition gained more weight than those randomized to a sufficient sleep condition [7,8].

The relationship between sleep duration and obesity has also been studied in pediatric populations. Short sleep duration during infancy predicts increased risk for obesity

in preschool-aged children [9,10], and cross-sectional studies have revealed an association between short sleep duration and obesity in preschoolers, school-aged children, and teenagers [10–13]. A recent metaanalysis examining the longitudinal impact of sleep duration on weight status in children and adolescents found that short sleepers had twice the risk for becoming overweight/obese compared with sufficient sleepers [14] and, in a large cohort followed longitudinally, self-reported sleep problems in adolescence (mean age 13 years) predicted general obesity in young adulthood (mean age 20 years) [15]. Furthermore, in a counterbalanced crossover experiment, school-aged children exhibited greater weight gain when sleep was restricted by 1.5 h/night for 1 week compared with when sleep was prolonged by 1.5 h/night for 1 week [16]. Collectively, these studies provide strong support for the identification of habitual short sleep duration as a risk factor for obesity in children and adults.

Obesogenic behaviors

Modifiable behaviors that contribute to uncontrolled weight gain include (1) being sedentary/having low levels of physical activity, (2) overeating and consuming a poor diet, and (3) exhibiting a delayed meal timing pattern. Several epidemiological studies have demonstrated that sleep duration associates with physical activity levels, diet quality, and caloric intake (Fig. 18.1). Children and adolescents who habitually obtain sufficient sleep exhibit more physical activity, greater fruit/vegetable intake, lower total caloric intake (kcal/day), reduced diet energy density, less added sugar intake, and soda consumption [17–22]. Data from the UCLA Energetics Study using self-report measures of sleep duration and objective measures of energy intake (estimated based on doubly labeled water measurement of total energy expenditure) revealed that sleeping adults ≤ 6 h/night consumed approximately 50 more calories than those sleeping 7 h/night, 160 more calories than those sleeping 8 h/night and 440 more

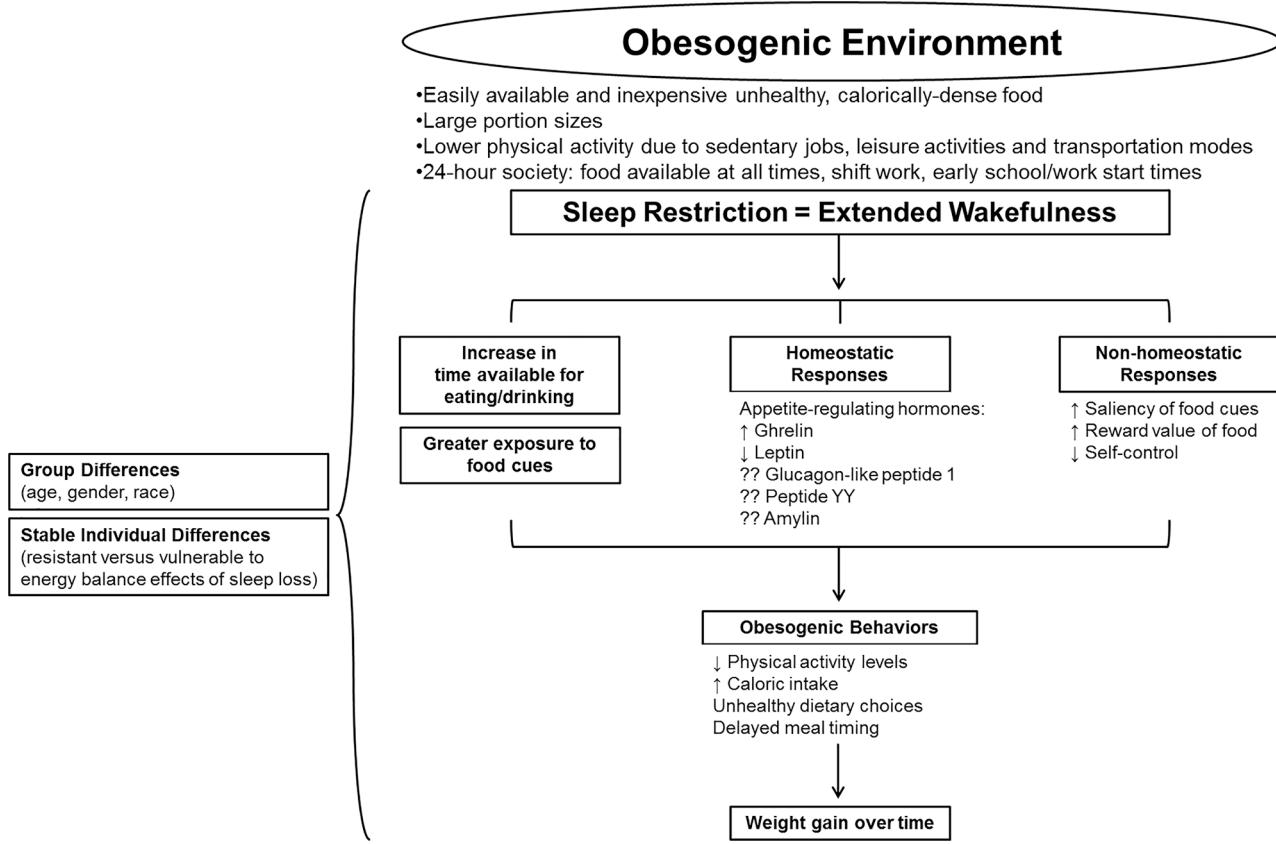


FIGURE 18.1 Relationship between sleep loss and obesity within the context of our current environment.

calories than those sleeping 9 h/night [23]. These differences in energy intake were also reflected in BMI and the prevalence of obesity (≤ 6 h: BMI 28.0, 34% obese; 7 h: BMI 25.0, 23%; 8 h: BMI 23.7, 14% obese, 9 h: BMI 24.6, 10% obese) [23].

In children [24] and adults [25] participating in experimental protocols, physical activity was lower during days following sleep restriction compared with days following sufficient sleep and this overall decrease is due to less time spent in moderate-vigorous activity. Laboratory studies in adults have also demonstrated that sleep restriction leads to increased caloric intake, more food purchases, greater consumption of snacks, increased portion sizes, and increased impulsivity in response to food cues [7,8,26–31]. For example, when given ad libitum access to food in a laboratory setting, participants consumed nearly 500 additional calories in one study [7] and nearly 300 additional calories in another study [28] during days following sleep restriction compared with days following sufficient sleep. In both studies, participants also consumed calories more frequently when sleep restricted suggesting increased snacking behavior.

Regarding macronutrient intake, some studies have shown that sleep restriction leads to increased craving and

consumption of carbohydrates [27,32], and others have observed greater consumption of fats [28,33,34]. Normal-to-overweight adolescents assigned 6.5 h TIB/night for five nights consumed foods with a higher glycemic index and more desserts/sweets than when assigned 10 h TIB/night for five nights [35]. Similarly, during an in-laboratory study, during days following sleep restriction (compared with days following sufficient sleep), adults consumed significantly more calories from these categories: (1) grains and pasta; (2) condiments; (3) desserts; (4) salty snacks; and (5) caffeine-free soda and juice but did not consume more calories from healthier food categories (meat, eggs, and fish; fruit, vegetables, and salad; milk) [33]. Therefore, although macronutrient intake findings are mixed, in general it seems that sleep restriction is associated with greater intake of unhealthy foods [36].

Delayed meal timing has also been identified as important for weight regulation. Women who were dieting and consumed the majority of calories earlier in the day lost more weight than women who consumed the majority of calories later in the day, even when total daily caloric intake was held constant [37,38]. In a cross-sectional cohort of healthy young adults (18–22 years), delayed circadian timing of food intake (calculated relative

to each participant's melatonin onset) was significantly associated with body fat percentage and body mass [39].

Recent findings suggest that sleep duration may impact meal timing. When bedtime was delayed during an in-laboratory sleep restriction protocol (five nights of 4 h TIB/night), adults consumed approximately 500 additional calories during the late-night hours when they were kept awake instead of going to bed (10:00 p.m.–04:00 a.m.) and then consumed approximately 100 fewer calories the following morning (08:00 a.m.–03:00 p.m.) [7,33]. This led to a shift such that participants consumed the majority of daily calories before 03:00 p.m. during sufficient sleep and consumed the majority of daily calories after 03:00 p.m. during sleep restriction. Furthermore, the percentage of daily calories consumed during the late-night period (10:00 p.m.–04:00 a.m.) positively associated with weight gained during the study [40]. Calories consumed during the late-night period were also higher in fat compared with calories consumed during the two earlier time periods [7]. Evening fat intake may be particularly contributory to weight gain; Baron and colleagues found that the percentage of fat consumed after 10:00 p.m. associated with greater total caloric intake and a higher BMI among adults [41].

Thus, habitual short sleep duration may lead to uncontrolled weight gain by decreasing physical activity, increasing energy intake and promoting a low-quality diet, and by shifting the timing of caloric intake. Findings suggest that behavioral interventions that simultaneously target sleep and these obesogenic behaviors may be particularly effective in promoting healthy weight management.

Potential physiological mechanisms

Laboratory studies have begun to examine possible physiological mechanisms—such as appetite-regulating hormones and changes in brain activation—underlying the relationship between sleep duration and weight gain (Fig. 18.1). Leptin, an anorexigenic hormone released from adipocytes, and ghrelin, an orexigenic hormone released from the stomach, have been the most studied appetite-regulating hormones in regards to sleep duration. Two large cross-sectional studies reported that short sleepers (5 h/night) exhibit lower leptin and higher ghrelin levels than normal sleepers (8 h/night) [42,43]. Spiegel and colleagues found that men, undergoing two nights of sleep restriction (4 h TIB/night) with controlled energy intake via an intravenous glucose infusion, exhibited increased levels of ghrelin (+28%) and decreased levels of leptin (−18%) and these neuroendocrine changes were accompanied by significant increases in self-reported ratings of hunger and appetite [32]. A recent study [44] collected blood samples from healthy men at 15–30 min intervals for

24 h on the third consecutive night of either sufficient sleep (8.5 h TIB/night) or sleep restriction (4.5 h TIB/night). Caloric intake was strictly controlled during blood sampling but was then ad libitum on the day following the fourth consecutive night of each sleep condition. Sleep restriction led to significantly higher mean 24 h ghrelin levels (ghrelin was elevated during the nocturnal period) and postprandial ghrelin levels (meal-related peaks were higher and postmeal nadirs were attenuated) compared with the sufficient sleep condition. Furthermore, peak ghrelin levels at the dinner meal predicted calories consumed from sweet snacks [44]. However, leptin and pancreatic polypeptide levels were similar across conditions [44].

Other laboratories have either not observed changes in ghrelin or leptin, or have observed increases in leptin levels [45]. Glucagon-like peptide 1 and peptide YY have also been studied in relation to changes in sleep duration in a few studies; however, results have been mixed [46]. One reason for the heterogeneity in results may be gender differences—St-Onge and colleagues [46,47] found that sleep restriction led to increased ghrelin levels in men but not in women. Another reason may be differences in protocol procedures, with some studies allowing participants ad libitum food/drink intake and others implementing dietary control. Given that most studies demonstrate an increase in the frequency of eating during sleep restriction, future studies should examine postprandial signals, such as amylin, which influence the interval length to the next meal.

In addition to these homeostatic, appetite-regulating hormones, it may be particularly important to also focus on nonhomeostatic processes (reward and limbic systems) given that laboratory studies have observed overeating during sleep loss. The amount of additional calories that adults consume when sleep restricted (~300–500 kcal) exceeds the amount of additional energy they need to maintain prolonged wakefulness (~100–150 kcal) and these calories are derived from unhealthy, palatable, more rewarding foods [7,8,28,48]. In today's obesogenic environment, there is an abundance of food cues and energy-dense foods are easily available at any time of day. Palatability and pleasantness are as equally or more powerful determinants of food intake than hunger or homeostatic drive.

Neuroimaging studies examining the effect of sleep loss on brain activation have demonstrated that participants undergoing sleep restriction display greater overall neuronal activity in response to food stimuli, particularly in areas related to reward including the putamen, nucleus accumbens, thalamus, insula, and prefrontal cortex compared with sufficient sleep [49,50]. Participants also display greater activation in the insular cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex in

response to images of healthy versus unhealthy foods during sleep restriction [50,51]. Increased activation has also been observed in regions associated with sensory/motor signaling (right paracentral lobule), inhibitory control (right inferior frontal gyrus), and reward coding and decision-making (ventral medial prefrontal cortex) [49].

Compared with normal sleep, participants undergoing total sleep deprivation exhibited increased activation in the right anterior cingulate cortex (ACC) in response to food images, and the change in activation correlated with postscan appetite ratings for pictures of high-calorie foods [52]. Conversely, in another study involving total sleep deprivation, participants displayed decreased activation in higher-order cortical evaluation regions (i.e., ACC, left lateral orbitofrontal cortex, and anterior insula) and enhanced activation in the amygdala while rating their desirability for various foods displayed in pictures [53]. Thus, in parallel to the homeostatic metabolic pathways, sleep restriction impacts both reward and control processing in response to food cues.

Maintaining a healthy weight in our obesogenic environment requires self-control and the maintenance of healthy habits, for example, eating egg whites instead of pastry for breakfast, packing a lunch instead of eating fast food, or taking a walk instead of drinking a glass of wine to destress after work. Sleep loss impairs decision-making and self-control and is associated with decreases in activity within the prefrontal cortex and thalamus—two areas that play critical roles in exerting self-control [54]. Therefore, habitually restricting sleep likely contributes to the accumulation of unhealthy choices that can lead to obesity. More research is needed to directly examine the relationship between sleep, self-control, decision-making, and weight management.

Two recent studies have used resting state functional connectivity to assess changes in network activity in response to sleep. The first focused on salience network connectivity following a night of total sleep deprivation relative to sufficient sleep [34]. In this protocol, caloric intake was ad libitum and participants were healthy adults. During total sleep deprivation, participants consumed nearly 1000 cal during the overnight period of wakefulness. Despite consuming these additional calories overnight, participants consumed a similar number of calories during the day following total sleep deprivation compared with the day following sufficient sleep. In addition, participants consumed a greater percentage of calories from fat and a smaller percentage of calories from carbohydrates during the day following total sleep deprivation compared with the day following sufficient sleep. At the neural level, one night of total sleep deprivation enhanced dorsal ACC functional connectivity with bilateral putamen and bilateral insula, which are core regions of the salience network. Moreover, dorsal ACC connectivity with these two regions

positively correlated with the percentage of calories consumed from fat and negatively correlated with the percentage of calories consumed from carbohydrates after total sleep deprivation. Thus, total sleep deprivation altered salience network functional connectivity and the increased co-activation of dorsal ACC and insula as well as dorsal ACC and putamen predicted subsequent macronutrient intake [34]. At any given moment, our sensory systems receive multiple sources of stimuli; the salience network selects which of these stimuli are relevant and deserving of our attention. Thus, sleep deprivation may alter food choices by affecting how much attention is focused on food stimuli.

The second resting-state study, a pilot investigation, focused on reward and interoception-related brain circuitry following three nights of normal (Midnight to 08:00 a.m.) or late (03:30–11:30 a.m.) sleep timing with either normal or late meal timing [55]. Resting-state functional connectivity between the insula and somatosensory cortex, the post-central gyrus and precuneus, as well as between the central opercular cortex, somatosensory cortex, and the pre-/post-central gyrus, was stronger during the late sleep schedule compared with the normal sleep schedule. As neuroimaging technology continues to advance, these studies will be critical in our understanding of the relationship between habitual short sleep duration and increased risk for obesity.

Group differences

Demographic characteristics, such as age, gender, and race, may influence the relationship between sleep duration and obesity (Fig. 18.1). Although the significant association between sleep duration and risk for obesity has been observed in nearly every age range (see summary above), there is evidence that the association between short sleep duration and body mass index (BMI) may be stronger among young (18–29 years) and middle-aged (30–64 years) adults than among older (>65 years) adults [56,57]. A longitudinal study examined 5-year change in computed tomography-derived visceral adipose tissue and subcutaneous adipose tissue in African Americans and Hispanic Americans (IRAS Family Study) [58]. Sleep duration (assessed by questionnaire and categorized as ≤5 h, 6–7 h, and ≥8 h) at baseline interacted with age to predict change in fat measures. Individuals 18–40 years who slept ≤5 h exhibited greater accumulation of visceral adipose tissue (13 cm^2) and subcutaneous adipose tissue (42 cm^2) compared with those sleeping 6–7 h. However, there was no significant association between sleep duration and fat depot change in participants older than 40 years old.

Findings related to gender differences have been mixed, with some population studies observing a stronger association between sleep duration and BMI in women [59], and

others demonstrating a stronger association in men [60,61]. In a prospective cohort study, short sleep duration was associated with weight gain and the development of obesity at 1-year follow-up in men but not in women [62]. During an in-laboratory protocol, sleep-restricted men exhibited a greater increase in daily caloric intake, consumed a greater percentage of daily calories during late-night hours (10:00 p.m.–04:00 a.m.), and gained more weight than women [7,33]. Several studies in adolescents and children have also observed stronger effects in males compared with females [63–65]; however, it is not the case in all studies.

Finally, race may also play an important role in the relationship between sleep duration and weight. African American children and adults are more likely to be short sleepers than Caucasian children and adults [66–68] and two epidemiological studies found that the association between short sleep duration and increased odds for obesity was stronger in African Americans than Caucasians [69,70]. During an in-laboratory experimental protocol, sleep-restricted African Americans gained more weight and exhibited lower resting metabolic rates compared with sleep-restricted Caucasians [7,71]. In addition, although the two groups did not differ in daily caloric intake or meal timing patterns, there were differences in macronutrient intake. African Americans consumed a lower percentage of calories from protein and a higher percentage of calories from carbohydrates [33]. Racial differences in the relationship between sleep duration and risk for obesity require more research, particularly in Hispanic and Asian populations. Although the relationship between sleep duration and BMI has also been demonstrated in these groups, whether or not the relationship is stronger compared with African Americans or Caucasians remains unknown.

In conclusion, epidemiologic and laboratory studies have indicated that younger adults, men, and African Americans may be more vulnerable to the weight-gain effect of sleep loss than older adults, women, and Caucasians, respectively. More research is needed to understand why these groups may be more susceptible and to determine if short-sleeping Hispanics or Asians are also at greater risk. This is particularly important given that African American and Hispanic minority groups exhibit higher prevalence rates of obesity as well as diseases associated with obesity (e.g., cardiovascular disease and type 2 diabetes).

Individual differences

In addition to group differences, emerging evidence suggests that there are individual differences in the way people respond to sleep loss (Fig. 18.1). Two recent in-laboratory studies examined these individual differences in detail

[40,72]. The first study examined data collected during two randomized crossover trials from 43 healthy adults and calculated the difference in objectively measured caloric intake during a sufficient sleep condition and a sleep restriction condition [72]. Large interindividual variability was observed—the change in caloric intake during sleep restriction ranged from –813 kcal (participants consumed fewer calories when sleep restricted) to 1437 kcal/day (participants consumed significantly more calories when sleep restricted).

The second study assessed caloric intake, meal timing, and weight change in a group of healthy adults who participated in two separate sleep restriction experiments in the same laboratory [40]. Participation in each experiment was separated by at least 60 days and both protocols involved two nights of sufficient sleep followed by five nights of sleep restriction. Large interindividual differences were observed for all three variables (when averaging across both experiments for each participant). Some participants experienced weight loss whereas others experienced substantial weight gain, change in caloric intake during sleep restriction ranged from –500.7 to 1178.2 kcal, and late-night caloric intake ranged from 11.9 to 1434.1 kcal. In addition to examining these interindividual differences, Spaeth and colleagues also assessed intra-individual consistency to determine if the same individuals respond the same way during two separate exposures to sleep restriction [40]. Change in weight during the protocol and change in caloric intake during sleep restriction were very consistent for men but not women. Men who gained a substantial amount of weight and increased their caloric intake to a significant degree during sleep restriction did so consistently during both exposures, suggesting they may be particularly vulnerable to the energy balance effects of sleep restriction. Conversely, men who lost or maintained weight during the protocol and did not show a substantial increase in caloric intake during sleep restriction also did so consistently during both exposures, suggesting they may be resistant to the energy balance effects of sleep restriction. Late-night caloric intake was very consistent among men and women; suggesting that some individuals are more prone to late-night eating than others. Therefore, adults who are particularly vulnerable to late-night eating and who are awake during late-night hours due to shift work or other lifestyle circumstances may be at heightened risk for weight gain.

Collectively, these findings suggest that although there are consistent group-average increases in weight, caloric intake and late-night eating during sleep restriction, there is also considerable variability between individuals. Furthermore, obtaining sufficient sleep may be particularly important for weight maintenance in individuals who are the most vulnerable. Future research is needed to identify biomarkers for predicting this vulnerability and to establish

countermeasures for helping vulnerable individuals who experience sleep loss due to shiftwork or other lifestyle factors.

Sleep timing

In addition to short sleep duration, disruptions in the timing of sleep have also been associated with increased risk for obesity; however, it can be difficult to separate the two constructs. Humans are less efficient sleepers when attempting to sleep outside of their endogenous circadian rhythm; therefore, altering the timing of sleep can also lead to shortened sleep. Four areas of research examining the relationship between sleep timing and obesity risk are chronotype, social jetlag, shift work, and delayed bedtime.

Chronotype refers to an individual's optimal timing of wakefulness and sleep. Humans exhibit a diurnal circadian rhythm (active during the day, sleep during the night) but some individuals prefer activity in the morning (larks) and exhibit an advanced (earlier) sleep period whereas others prefer activity in the evening (owls) and exhibit a delayed (later) sleep period. Age, gender, and genetic factors influence morningness versus eveningness preference. The interaction between Earth's light/dark cycle and current school/work schedules complement individuals who function best in the morning rather than in the evening. Because owls experience heightened alertness in the late evening, they often delay bedtime but still have to wake up early in the morning to accommodate school/work schedules which produces sleep restriction during the work week. There is evidence that adolescents and adults with an evening preference are at increased risk for weight gain/obesity [73–76], consume a less healthy diet [77–79], and exhibit delayed meal timing [80–82]. For example, a prospective study in college freshmen found that students characterized as evening types gained significantly more weight over an 8-week period compared with morning types [74]. Baron and colleagues found that late sleepers (sleep midpoint > 0530 h) exhibited a shorter sleep duration, consumed more calories at dinner and after 2000 h, more fast food and full-calorie soda, and had a higher BMI compared with normal sleepers (sleep midpoint < 0530 h) [41]. Finally, in a large sample of severely obese adults undergoing bariatric surgery, evening-type individuals weighed more before surgery, lost less weight after surgery, and regained more weight at follow-up [83].

Social jetlag describes a misalignment between biological and social time. For example, a person's internal clock may prefer a wake time of 07:30 a.m. but a 5 a.m. wake time is needed to fulfill personal and household tasks before attending work. Individuals with social jetlag sleep longer on "free" nights (such as weekends when work obligations do not dictate sleep timing) and exhibit large differences in sleep duration and/or the midpoint of sleep

between free and nonfree days. Many students experience social jetlag due to early school start times and many adults experience chronic social jetlag for the duration of their working career. When quantifying social jetlag as the difference in mid-sleep time between free days and workdays, Roenneberg and colleagues observed that 69% of participants experienced at least 1 h of social jetlag and that social jetlag significantly increased the probability of participants being overweight/obese [84]. Among those who were overweight/obese, social jetlag positively correlated with weight. Social jetlag has also been associated with cardiovascular risk factors, fat mass, and incidence of metabolic syndrome [85–87]. In a cross-sectional study of children aged 8–10 years, social jetlag was associated with adiposity (body fat %, fat mass, fat mass index (kg/m^2), waist to hip ratio, and body mass index (kg/m^2); with body fat increasing by 3% per 1 h of social jetlag [88].

It is unclear if short sleep during nonfree days drives these energy balance responses or the inconsistency in sleep timing between free and nonfree days. Ideally, individuals would be able to obtain adequate sleep during free and nonfree nights and thus maintain sufficient sleep duration *and* a consistent sleep schedule. However, given that school/work schedules and household/personal/social obligations influence sleep opportunity, the effects of "catching up" on sleep during free days warrant more study. One recent study found that adults who engaged in catch-up sleep on weekends exhibited a lower BMI than those who did not [89] and there is evidence that "banking sleep" (providing an extended sleep opportunity, ~10 h in bed) before engaging in sleep restriction attenuates deficits in neurobehavioral function caused by sleep loss [90].

Shift work, an essential component of our 24 h economy that requires work performed outside of the traditional 9 a.m.–5 p.m. business day, represents more extreme circadian misalignment than social jetlag. Shift work schedules often require an individual to work during the night when the circadian system is promoting sleep, and require an individual to sleep during the day when the circadian system is promoting wakefulness. Night shift workers sleep 2–4 h less per day than day shift workers and are more likely to experience excessive sleepiness. Shift workers are at increased risk for weight gain and obesity as well as diseases associated with obesity including type 2 diabetes, cardiovascular disease, and gastrointestinal disorders [87,91,92]. Interestingly, daily caloric intake does not seem to differ between shift workers and traditional day workers; however, poor diet quality, lower physical activity levels, delayed meal timing, and altered nutritional metabolism have all been observed as possible mechanisms underlying the relationship between shift work and obesity [87,91,92]. A recent metaanalysis found that the overall odds ratio of night shift work was 1.23 (95% confidence interval = 1.17–1.29) for risk of overweight/

obesity, shift workers had a higher frequency of developing abdominal obesity (odds ratio = 1.35) than other obesity types, and permanent night workers had a 29% higher risk of developing abdominal obesity than rotating shift workers (odds ratio 1.43 vs. 1.14) [93].

Experimental studies mimicking shift work schedules have shown that this type of circadian misalignment leads to decreased energy expenditure and impaired glucose metabolism, which are also likely contributors to the propensity for weight gain [94]. Research is ongoing to examine how an individual's morning/evening preference affects his/her response to shift work. For example, the relationship between night shift work and obesity may be stronger for morning types than for evening types.

Finally, when examining the relationship between bedtime and weight gain/obesity (independent from sleep duration) studies have shown that increased variability in bedtime and going to bed later is associated with unhealthy diet and higher BMI in children, adolescents, and adults [95–100]. These associations are consistent with findings from an experimental study [7]. During this protocol, adult participants experienced two nights of sufficient sleep (10 h TIB/night) followed by five nights of sleep restriction (4 h TIB/night) and sleep restriction was implemented by delaying bedtime until 04:00 a.m. Participants exhibited increased caloric intake on all days when bedtime was delayed to 04:00 a.m., including the first day of the sleep restriction phase, when participants woke up after sufficient sleep but were kept awake for 20 h (until 04:00 a.m.). Caloric intake was not increased on the last day of the sleep restriction phase, when subjects woke up after five consecutive nights of insufficient sleep but were only kept awake for 14 h and went to bed at 10:00 p.m. This pattern suggested that bedtime and/or hours of wakefulness are better predictors of daily intake than how much sleep was achieved during the preceding night [7]. The timing and variability of bedtime may be targets for improving sleep and promoting weight maintenance and this may be particularly important for low-income families where sleep habits are less stable and the risk for obesity is greater [100,101].

Sleep disorders

Sleep disorders, such as insomnia, obstructive sleep apnea (OSA), and narcolepsy, can also lead to changes in sleep duration or timing and energy balance. Insomnia occurs when an individual complains of having difficulty initiating or maintaining sleep, waking up earlier than desired and impaired daytime functioning despite having sufficient opportunities for sleep. Insomnia is highly comorbid with psychiatric disorders and is not always associated with objectively measured short sleep duration. There is a paucity of research examining the relationship between

insomnia and obesity and results have been mixed. A recent metaanalysis showed that the odds of having obesity among individuals with an insomnia diagnosis was not significantly greater than among those who did not have an insomnia diagnosis but there was a small, significant cross-sectional correlation between insomnia symptoms and BMI [102]. Longitudinal data on the association between insomnia symptoms and future incidence of obesity were inconclusive [102]. Insomnia with objectively measured short sleep duration has been associated with other markers of metabolic dysregulation (i.e., hypertension and type 2 diabetes) and insomnia symptoms have been associated with development of the metabolic syndrome [103–105]. More work is needed in this area, particularly since the primary treatment for insomnia involves decreasing sleep opportunity which may impact weight regulation via the behaviors and mechanisms described above.

OSA occurs when an individual exhibits shallow breathing or ceases to breathe during sleep; symptoms include loud snoring, gasping for air and reduced airflow during sleep and impaired daytime functioning. The most common cause of OSA is obesity. It is estimated that 50% of children and adults with obesity have OSA and studies have consistently demonstrated that weight loss improves OSA symptoms (see Refs. [106–108] for reviews on this topic). OSA is also associated with metabolic dysregulation, independent of obesity, and treatment of OSA with continuous positive airway pressure leads to improvements in daytime functioning and metabolic health [109]. Given the serious adverse cognitive and health consequences of untreated OSA, it is critical for physicians to screen for and treat OSA in patients with obesity.

Narcolepsy occurs when an individual experiences excessive sleepiness with uncontrolled need for sleep or lapses into sleep during the day and be accompanied with (Type 1) or without (Type 2) cataplexy and cerebral spinal fluid hypocretin-1 deficiency. Hypocretin (also referred to as orexin) also plays an important role in appetite, reward, and motivation. Patients with narcolepsy exhibit a higher BMI than those without narcolepsy and this association has been observed in children, adolescents, and adults [110–112]. Orexin deficiency and decreased energy expenditure have been identified as mechanisms that may underlie the relationship between narcolepsy and obesity [113–116]. Narcoleptics are also more likely to experience persistent food cravings, binge eat, and have an eating disorder [117–119].

A recent study used a behavioral paradigm to explore the effects of satiation on food choice and caloric intake in patients with narcolepsy type 1 compared with healthy matched controls [120]. First, participants were trained on a choice task to earn their preferred salty or sweet snacks. One of the snack outcomes was devalued by having participants actually consume it until they were sated.

Participants then completed the choice task again. Control participants decreased choosing the devalued snack by 14% whereas participants with narcolepsy only decreased choosing the devalued snack by 4%. Finally, when participants were given access to snacks at the end of the task, participants with narcolepsy consumed nearly four times as many calories as control participants (~400 vs. ~120 kcal). Findings suggest that individuals with narcolepsy may not experience sensory-specific satiety to the same degree as healthy individuals. In addition, as expected, healthy controls were less hungry and wanted the devalued snack less after consuming it until sated, this decrease in hunger and wanting associated with choosing the devalued snack less in the choice task. By contrast, there was no association between decreased hunger/wanting and performance on the choice task in participants with narcolepsy, suggesting that these individuals may not experience the connection between subjective experiences to the same degree as healthy individuals [120]. Thus, changes in satiety and subjective experiences may increase risk of overeating in individuals with narcolepsy.

Interestingly, recent studies have also demonstrated differences in the energy balance response to two common treatments for narcolepsy. After beginning treatment, patients using sodium oxybate (a GABA receptor agonist) lost weight (women: -2.56 kg/m^2 , men: -0.84 kg/m^2) between the first and last measurement whereas patients using modafinil (an atypical, selective dopamine transporter inhibitor) gained weight (women: $+0.57 \text{ kg/m}^2$, men: $+0.67 \text{ kg/m}^2$); the effect of drug treatment on BMI was most pronounced in those with a higher baseline BMI [121]. Future research examining weight regulation in patients with narcolepsy will not only inform clinical practice but also help elucidate the physiological role of hypocretin/orexin in both sleep and energy balance regulation.

Sleep in individuals with obesity

Poor sleep quality and excessive daytime sleepiness are frequent complaints among individuals with obesity [122,123]. Weight loss after either diet/exercise programs or bariatric surgery leads to improvements in sleep and daytime functioning [124–126]. Psychological distress may play an important role in the relationships between obesity, sleep, and daytime functioning [127]. Obese youth are more likely to report difficulties with sleep, symptoms of depression, and lower quality of life; in a cross-sectional study that was conducted in a specialized obesity clinic, degree of obesity predicted increased sleep difficulties and decreased quality-of-life scores [128]. In addition, obese children with more symptoms of depression had more sleep problems.

Few studies have objectively measured sleep in obese individuals; however, evidence suggests that excessive adiposity relates to changes in sleep architecture in children, adolescents, and adults. Sleep is comprised of rapid eye movement (REM) sleep and non-REM sleep, and non-REM sleep is further categorized as stage 1, stage 2, and slow-wave sleep (SWS). SWS duration has been negatively correlated with BMI, waist circumference, ghrelin levels, intake during an ad libitum meal, saturated fat intake, and hunger ratings [129–131] and has been positively related with fiber intake, lean body mass, and growth hormone release [132–134]. REM sleep duration has been correlated with increased hunger ratings, body fat percentage, higher BMI, and positive energy balance due to overeating [130,132,135,136]. However, other studies have shown that REM sleep duration is inversely correlated with waist circumference and BMI [129,131].

In 12 healthy normal-weight men participating in an in-laboratory study involving 2 days of caloric restriction to 10% of energy requirements followed by 2 days of ad libitum/free feeding, sleep architecture was measured by polysomnography [137]. Two days of caloric restriction significantly increased the duration of SWS and this effect was entirely reversed after ad libitum feeding. Interestingly, caloric restriction also decreased orexin levels and the change in orexin levels positively correlated with duration of SWS during caloric restriction.

Normal-weight adults exhibit higher sleep efficiency than overweight or obese individuals in young, middle-aged, and older adults [138–140]; however, results have been more mixed in children and adolescent populations [73,135,136,141,142]. More research is needed to examine differences in sleep architecture between normal, overweight, and obese individuals and assess how changes in weight and/or body composition affect subjective and objective measures of sleep.

Two eating disorders associated with increased risk for obesity are Binge Eating Disorder and Night Eating Syndrome. Although it is beyond the scope of this chapter, interested readers are referred to Ref. [143] for a review of changes in sleep (e.g., subjective measures of sleep quality as well as objective measures of sleep duration, latency, efficiency, and architecture) in these and other eating disorders.

The role of sleep in weight-loss interventions

Recent research has highlighted the importance of sleep during weight-loss interventions and assessed the efficacy of sleep extension as a behavioral modification to promoting health. In children (2–5 years) enrolled in a randomized trial to improve household routines (6-month

intervention, promoted family meals, adequate sleep, limiting TV time, and removing the TV from the child's bedroom), intervention participants exhibited increased sleep duration and decreased BMI [144]. In a sample of obese preschool-aged children enrolled in a weight management program, longer sleep duration associated with lower BMI and caloric intake posttreatment [145]. In obese adolescents attending a clinical multidisciplinary weight management program, longer weekly sleep duration at baseline predicted greater weight loss after 3 months of treatment; those who reduced their BMI by $\geq 1 \text{ kg/m}^2$ reported approximately 4 more hours of sleep/week compared with those who reduced their BMI by $<1 \text{ kg/m}^2$ [146]. Similarly, in obese adolescents participating in a summer camp-based immersion treatment program, shorter sleep duration, lower sleep quality, and more sleep debt associated with larger waist circumference and higher BMI preintervention and smaller weight reduction during the intervention [147].

Compared with adults currently enrolled in weight-loss interventions, those who successfully maintained weight loss for at least a year (National Weight Control Registry) were more likely to be a morning type, less likely to be a short sleeper ($<6 \text{ h/night}$), and reported better sleep quality [148]. Among women randomized to a weight-loss program, better subjective sleep quality and sleeping $>7 \text{ h/night}$ at baseline significantly increased the likelihood of weight-loss success [125]. Similarly, baseline sleep duration and sleep quality predicted greater fat mass loss (assessed by dual-energy X-ray absorptiometry) during a 15–24 weeks weight-loss intervention consisting of a targeted 600–700 kcal/day decrease in energy intake in overweight and obese men and women; an increase by 1 h in sleep duration at baseline was associated with a decrease of 0.7 kg in fat mass (after adjustment for covariates) [149]. Collectively, these findings suggest that sleep plays an important role in weight-loss across many age groups and types of weight-loss programs; future studies are needed to examine how sleep can be used to increase weight-loss success and what mechanisms underlie this relationship.

During an in-laboratory experimental study [150], overweight/obese women were placed on a hypocaloric diet for 14 days with either 8.5 or 5.5 h sleep opportunity each night. During the 5.5 h sleep condition, woman lost a similar amount of weight as during the 8.5 h condition; however, they lost less fat, reported greater hunger, and exhibited a higher respiratory quotient (RQ). Recently, a similar experiment was conducted outside of the laboratory; overweight or obese adults were randomized to 8-week of caloric restriction with either sufficient sleep or sleep restriction [151]. Participants were instructed to restrict daily calorie intake to 95% of their measured resting metabolic rate, and participants in the sleep

restriction group were instructed to reduce time in bed on five nights by 1 h per night and to sleep ad libitum on the other two nights during each week. Although both groups lost similar amounts of weight, lean mass, and fat mass, the proportion of total mass lost as fat was significantly less in the sleep-restricted group. Participants in the sufficient sleep condition exhibited a significant reduction in body fat percentage and RQ over the 8 weeks whereas participants in the sleep restriction condition did not. Although more work is needed in this area, these experiments demonstrate that sleep influences changes in physiology that occur during weight loss. Therefore, addressing sleep hygiene may help individuals achieve success in losing weight and maintaining a healthy weight.

Sleep extension interventions in children [152], adolescents [153], and adults [154] have been proposed for weight management and metabolic health. These interventions focus on using behavioral modification strategies (self-monitoring, goal-setting, positive reinforcement, etc.) to increase the amount of time participants set aside for sleep (time-in-bed). Preliminary data demonstrate that sleep extension decreases desire for high-calorie foods and sugar intake [155,156], improves blood pressure [157], and associates with increased insulin sensitivity in adults [158]. Thus, sleep extension interventions prove to be a promising new behavioral approach to weight management and metabolic health.

Conclusion

Habitual short sleep, due to lifestyle factors, evening chronotype, or sleep disorders, associates with an increased risk for obesity in children, adolescents, and adults. Experimental studies demonstrate that sleep restriction leads to increased daily caloric intake, greater consumption of unhealthy food and drink, and delayed meal timing as well as alterations in appetite-regulating hormones and brain activity that promote positive energy balance and weight gain over time. Addressing sleep issues with individuals who are at risk for uncontrolled weight gain or are obese will improve daytime functioning and may increase the likelihood of weight-loss success.

References

- [1] Hales CM, Fryar CD, Carroll MD, Freedman CL, Ogden. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age. *JAMA* 2007;319(16):1723–2007.
- [2] Vézina-Im L-A, Nicklas TA, Baranowski T. Associations among sleep, body mass index, waist circumference, and risk of type 2 diabetes among U.S. childbearing-age women: National Health and Nutrition Examination Survey. *J Womens Health* 2018;27(11):1400–7. <https://doi.org/10.1089/jwh.2017.6534>.
- [3] Deng H-B, Tam T, Chung-Ying Zee B, Chung RY-N, Su X, Jin L, Chan T-C, Chang L-Y, Yeoh E-K, Xiang QL. Short sleep duration

- increases metabolic impact in healthy adults: a population-based cohort study. *Sleep* 2017;40(10). <https://doi.org/10.1093/sleep/zsx130>.
- [4] Potter GDM, Cade JE, Hardie LJ, Kiechl S. Longer sleep is associated with lower BMI and favorable metabolic profiles in UK adults: findings from the National Diet and Nutrition Survey. *PLoS ONE* 2017;12(7). <https://doi.org/10.1371/journal.pone.0182195>.
- [5] Ford ES, Li C, Wheaton AG, Chapman DP, Perry GS, Croft JB. Sleep duration and body mass index and waist circumference among US adults. *Obesity* 2014;22(2):598–607. <https://doi.org/10.1002/oby.20558>.
- [6] Ogilvie RP, Redline S, Bertoni AG, Chen X, Ouyang P, Szklo M, Lutsey PL. Actigraphy measured sleep indices and adiposity: the multi-ethnic study of atherosclerosis (MESA). *Sleep* 2016;39(9):1701–8. <https://doi.org/10.5665/sleep.6096>.
- [7] Spaeth AM, Dinges DF, Goel N. Effects of experimental sleep restriction on weight gain, caloric intake, and meal timing in healthy adults. *Sleep* 2013;36(7):981–90. <https://doi.org/10.5665/sleep.2792>.
- [8] Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, Wright KP. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Natl Acad Sci USA* 2013;110(14):5695–700. <https://doi.org/10.1073/pnas.1216951110>.
- [9] Halal CSE, Matijasevich A, Howe LD, Santos IS, Barros FC, Nunes ML. Short sleep duration in the first years of life and obesity/overweight at age 4 years: a birth cohort study. *J Pediatr* 2016;168:99. <https://doi.org/10.1016/j.jpeds.2015.09.074>.
- [10] Chaput JP, Gray CE, Poitras VJ, Carson V, Gruber R, Birken CS, MacLean JE, Aubert S, Sampson M, Tremblay MS. Systematic review of the relationships between sleep duration and health indicators in the early years (0-4 years). *BMC Public Health* 2017;17. <https://doi.org/10.1186/s12889-017-4850-2>.
- [11] Katzmarzyk PT, Barreira TV, Broyles ST, Champagne CM, Chaput JP, Fogelholm M, Hu G, Johnson WD, Kuriyan R, Kurpad A, Lambert EV, Maher C, Maia J, Matsudo V, Olds T, Onywera V, Sarmiento OL, Standage M, Tremblay MS, Tudor-Locke C, Zhao P, Church TS. Relationship between lifestyle behaviors and obesity in children ages 9-11: results from a 12-country study. *Obesity* 2015;23(8):1696–702. <https://doi.org/10.1002/oby.21152>.
- [12] Mitchell JA, Rodriguez D, Schmitz KH, Audrain-McGovern J. Sleep duration and adolescent obesity. *Pediatrics* 2013;131(5). <https://doi.org/10.1542/peds.2012-2368>.
- [13] Wu Y, Gong Q, Zou Z, Li H, Zhang X. Short sleep duration and obesity among children: a systematic review and meta-analysis of prospective studies. *Obes Res Clin Pract* 2017;11(2):140–50. <https://doi.org/10.1016/j.orcp.2016.05.005>.
- [14] Fatima Y, Doi SAR, Mamun AA. Longitudinal impact of sleep on overweight and obesity in children and adolescents: a systematic review and bias-adjusted meta-analysis. *Obes Rev* 2015;16(2):137–49. <https://doi.org/10.1111/obr.12245>.
- [15] Fatima Y, Doi SAR, Al Mamun A. Sleep problems in adolescence and overweight/obesity in young adults: is there a causal link? *Sleep Health* 2018;4(2):154–9. <https://doi.org/10.1016/j.sleeh.2018.01.002>.
- [16] Hart CN, Carskadon MA, Considine RV, Fava JL, Lawton J, Raynor HA, Jelalian E, Owens J, Wing R. Changes in children's sleep duration on food intake, weight, and leptin. *Pediatrics* 2013;132(6). <https://doi.org/10.1542/peds.2013-1274>.
- [17] Bel S, Michels N, De Vriendt T, Patterson E, Cuenca-García M, Diethelm K, Gutin B, Grammatikaki E, Manios Y, Leclercq C, Ortega FB, Moreno LA, Gottrand F, Gonzalez-Gross M, Widhalm K, Kafatos A, Garaulet M, Molnar D, Kaufman JM, Gilbert CC, Hallström L, Sjöström M, Marcos A, De Henauw S, Huybrechts I. Association between self-reported sleep duration and dietary quality in European adolescents. *Br J Nutr* 2013;110(5):949–59. <https://doi.org/10.1017/S0007114512006046>.
- [18] Börnhorst C, Wijnhoven TMA, Kunešová M, Yngve A, Rito AI, Lissner L, Duleva V, Petruskiene A, Breda J. WHO European Childhood Obesity Surveillance Initiative: associations between sleep duration, screen time and food consumption frequencies. *BMC Public Health* 2015;15(1). <https://doi.org/10.1186/s12889-015-1793-3>.
- [19] Fisher A, McDonald L, van Jaarsveld CHM, Llewellyn C, Fildes A, Schrempt S, Wardle J. Sleep and energy intake in early childhood. *Int J Obes* 2014;38(7):926–9. <https://doi.org/10.1038/ijo.2014.50>.
- [20] Franckle RL, Falbe J, Gortmaker S, Ganter C, Taveras EM, Land T, Davison KK. Insufficient sleep among elementary and middle school students is linked with elevated soda consumption and other unhealthy dietary behaviors. *Prev Med* 2015;74:36–41. <https://doi.org/10.1016/j.ypmed.2015.02.007>.
- [21] Hjorth MF, Quist JS, Andersen R, Michaelsen KF, Tetens I, Astrup A, Chaput JP, Sjödin A. Change in sleep duration and proposed dietary risk factors for obesity in Danish school children. *Pediatr Obes* 2014;9(6):e156. <https://doi.org/10.1111/ijo.264>.
- [22] Weiss A, Xu F, Storfer-Isser A, Thomas A, Ivers-Landis CE, Redline S. The association of sleep duration with adolescents' fat and carbohydrate consumption. *Sleep* 2010;33(9):1201–9. <https://doi.org/10.1093/sleep/33.9.1201>.
- [23] Kjeldsen JS, Hjorth MF, Andersen R, Michaelsen KF, Tetens I, Astrup A, Chaput JP, Sjödin A. Short sleep duration and large variability in sleep duration are independently associated with dietary risk factors for obesity in Danish school children. *Int J Obes* 2014;38(1):32–9. <https://doi.org/10.1038/ijo.2013.147>.
- [24] Hart CN, Hawley N, Davey A, Carskadon M, Raynor H, Jelalian E, Owens J, Considine R, Wing RR. Effect of experimental change in children's sleep duration on television viewing and physical activity. *Pediatr Obes* 2017;12(6):462–7. <https://doi.org/10.1111/ijo.12166>.
- [25] Bromley LE, Booth JN, Kilkus JM, Imperial JG, Penev PD. Sleep restriction decreases the physical activity of adults at risk for type 2 diabetes. *Sleep* 2012;35(7):977–84. <https://doi.org/10.5665/sleep.1964>.
- [26] Chapman CD, Nilsson EK, Nilsson VC, Cedernaes J, Vogel H, Dickson SL, Broman JE, Hogenkamp PS, Schiöth HB, Benedict C. Acute sleep deprivation increases food purchasing in men. *Obesity* 2013;21(12):E555. <https://doi.org/10.1002/oby.20579>.
- [27] Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. *J Clin Endocrinol Metab* 2009;94(9):3242–50. <https://doi.org/10.1210/jc.2009-0483>.
- [28] St-Onge M-P, Roberts AL, Chen J, Kelleman M, O'Keeffe M, RoyChoudhury A, Jones PJH. Short sleep duration increases energy intakes but does not change energy expenditure in normal-

- weight individuals. *Am J Clin Nutr* 2011;94(2):410–6. <https://doi.org/10.3945/ajcn.111.013904>.
- [29] Cedernaes J, Brandell J, Ros O, Broman JE, Hogenkamp PS, Schiöth HB, Benedict C. Increased impulsivity in response to food cues after sleep loss in healthy young men. *Obesity* 2014;22(8):1786–91. <https://doi.org/10.1002/oby.20786>.
- [30] Hogenkamp PS, Nilsson E, Nilsson VC, Chapman CD, Vogel H, Lundberg LS, Zarei S, Cedernaes J, Rångtell FH, Broman JE, Dickson SL, Brunstrom JM, Benedict C, Schiöth HB. Acute sleep deprivation increases portion size and affects food choice in young men. *Psychoneuroendocrinology* 2013;38(9):1668–74. <https://doi.org/10.1016/j.psyneuen.2013.01.012>.
- [31] Calvin AD, Carter RE, Adachi T, MacEdo PG, Albuquerque FN, Van Der Walt C, Bukartyk J, Davison DE, Levine JA, Somers VK. Effects of experimental sleep restriction on caloric intake and activity energy expenditure. *Chest* 2013;144(1):79–86. <https://doi.org/10.1378/chest.12-2829>.
- [32] Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004;141(11):846–50. <https://doi.org/10.7326/0003-4819-141-11-200412070-00008>.
- [33] Spaeth AM, Dinges DF, Goel N. Sex and race differences in caloric intake during sleep restriction in healthy adults. *Am J Clin Nutr* 2014;100(2):559–66. <https://doi.org/10.3945/ajcn.114.086579>.
- [34] Fang Z, Spaeth AM, Ma N, Zhu S, Hu S, Goel N, Detre JA, Dinges DF, Rao H. Altered salience network connectivity predicts macronutrient intake after sleep deprivation. *Sci Rep* 2015;5. <https://doi.org/10.1038/srep08215>.
- [35] Beebe DW, Simon S, Summer S, Hemmer S, Strotman D, Dolan LM. Dietary intake following experimentally restricted sleep in adolescents. *Sleep* 2013;36(6):827–34. <https://doi.org/10.5665/sleep.2704>.
- [36] Capers PL, Fobian AD, Kaiser KA, Borah R, Allison DB. A systemic review and meta-analysis of randomized controlled trials of the impact of sleep duration on adiposity and components of energy balance. *Obes Rev* 2015;16(9):771–82. <https://doi.org/10.1111/obr.12296>.
- [37] Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee YC, Ordovás JM, Scheer FAJL. Timing of food intake predicts weight loss effectiveness. *Int J Obes* 2013;37(4):604–11. <https://doi.org/10.1038/ijo.2012.229>.
- [38] Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity* 2013;21(12):2504–12. <https://doi.org/10.1002/oby.20460>.
- [39] McHill AW, Phillips AJK, Czeisler CA, Keating L, Yee K, Barger LK, Garaulet M, Scheer FAJL, Klerman EB. Later circadian timing of food intake is associated with increased body fat. *Am J Clin Nutr* 2017;106(5):1213–9. <https://doi.org/10.3945/ajcn.117.161588>.
- [40] Spaeth AM, Dinges DF, Goel N. Phenotypic vulnerability of energy balance responses to sleep loss in healthy adults. *Sci Rep* 2015;5. <https://doi.org/10.1038/srep14920>.
- [41] Baron KG, Reid KJ, Kim T, Van Horn L, Attarian H, Wolfe L, Siddique J, Santostasi G, Zee PC. Circadian timing and alignment in healthy adults: associations with BMI, body fat, caloric intake and physical activity. *Int J Obes* 2017;41(2):203–9. <https://doi.org/10.1038/ijo.2016.194>.
- [42] Taheri S, Lin L, Austin D, Young T, Mignot E, Froguel P. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 2004;1(3):e62. <https://doi.org/10.1371/journal.pmed.0010062>.
- [43] Chaput JP, Després JP, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: results from the Québec family study. *Obesity* 2007;15(1):253–61. <https://doi.org/10.1038/oby.2007.512>.
- [44] Broussard JL, Kilkus JM, Delebecque F, Abraham V, Day A, Whitmore HR, Tasali E. Elevated ghrelin predicts food intake during experimental sleep restriction. *Obesity* 2016;24(1):132–8. <https://doi.org/10.1002/oby.21321>.
- [45] St-Onge MP. The role of sleep duration in the regulation of energy balance: effects on energy intakes and expenditure. *J Clin Sleep Med* 2013;9(1):73–80. <https://doi.org/10.5664/jcsm.2348>.
- [46] St-Onge M-P. Sleep-obesity relation: underlying mechanisms and consequences for treatment. *Obes Rev* 2017;18:34–9. <https://doi.org/10.1111/obr.12499>.
- [47] St-Onge MP, O'Keeffe M, Roberts AL, RoyChoudhury A, Laferrère B. Short sleep duration, glucose dysregulation and hormonal regulation of appetite in men and women. *Sleep* 2012;35(11):1503–10. <https://doi.org/10.5665/sleep.2198>.
- [48] Shechter A, Rising R, Albu JB, St-Onge MP. Experimental sleep curtailment causes wake-dependent increases in 24-h energy expenditure as measured by whole-room indirect calorimetry 1–4. *Am J Clin Nutr* 2013;98(6):1433–9. <https://doi.org/10.3945/ajcn.113.069427>.
- [49] Demos KE, Sweet LH, Hart CN, McCaffery JM, Williams SE, Mailloux KA, Trautvetter J, Owens MM, Wing RR. The effects of experimental manipulation of sleep duration on neural response to food cues. *Sleep* 2017;40(11). <https://doi.org/10.1093/sleep/zsx125>.
- [50] St-Onge MP, McReynolds A, Trivedi ZB, Roberts AL, Sy M, Hirsch J. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. *Am J Clin Nutr* 2012;95(4):818–24. <https://doi.org/10.3945/ajcn.111.027383>.
- [51] St-Onge M-P, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. *Int J Obes* 2014;38(3):411–6. <https://doi.org/10.1038/ijo.2013.114>.
- [52] Benedict C, Brooks SJ, O'Daly OG, Almèn MS, Morell A, Åberg K, Gingnell M, Schultes B, Hallschmid M, Broman JE, Larsson EM, Schiöth HB. Acute sleep deprivation enhances the brain's response to hedonic food stimuli: an fMRI study. *J Clin Endocrinol Metab* 2012;97(3):E443. <https://doi.org/10.1210/jc.2011-2759>.
- [53] Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. *Nat Commun* 2013;4. <https://doi.org/10.1038/ncomms3259>.
- [54] Pilcher JJ, Morris DM, Donnelly J, Feigl HB. Interactions between sleep habits and self-control. *Front Hum Neurosci* 2015;9(May). <https://doi.org/10.3389/fnhum.2015.00284>.
- [55] Yoncheva YN, Castellanos FX, Pizinger T, Kovtun K, St-Onge M-P. Sleep and meal-time misalignment alters functional connectivity: a pilot resting-state study. *Int J Obes* 2016;40(11):1813–6. <https://doi.org/10.1038/ijo.2016.132>.

- [56] Canning KL, Brown RE, Jamnik VK, Kuk JL. Relationship between obesity and obesity-related morbidities weakens with aging. *J Gerontol Ser A Biol Sci Med Sci* 2014;69(1):87–92. <https://doi.org/10.1093/gerona/glt026>.
- [57] Grandner MA, Schopfer EA, Sands-Lincoln M, Jackson N, Malhotra A. Relationship between sleep duration and body mass index depends on age. *Obesity* 2015;23(12):2491–8. <https://doi.org/10.1002/oby.21247>.
- [58] Hairston KG, Bryer-Ash M, Norris JM, Haffner S, Bowden DW, Wagenknecht LE. Sleep duration and five-year abdominal fat accumulation in a minority cohort: the IRAS family study. *Sleep* 2010;33(3):289–95. <https://doi.org/10.1093/sleep/33.3.289>.
- [59] St-Onge MP, Perumean-Chaney S, Desmond R, Lewis CE, Yan LL, Person SD, Allison DB. Gender differences in the association between sleep duration and body composition: the CARDIA study. *Int J Endocrinol* 2010;2010. <https://doi.org/10.1155/2010/726071>.
- [60] Meyer KA, Wall MM, Larson NI, Laska MN, Neumark-Sztainer D. Sleep duration and BMI in a sample of young adults. *Obesity* 2012;20(6):1279–87. <https://doi.org/10.1038/oby.2011.381>.
- [61] Yang TC, Matthews SA, Chen VYJ. Stochastic variability in stress, sleep duration, and sleep quality across the distribution of body mass index: insights from quantile regression. *Int J Behav Med* 2014;21(2):282–91. <https://doi.org/10.1007/s12529-013-9293-2>.
- [62] Watanabe M, Kikuchi H, Tanaka K, Takahashi M. Association of short sleep duration with weight gain and obesity at 1-year follow-up: a large-scale prospective study. *Sleep* 2010;33(2):161–7. <https://doi.org/10.1093/sleep/33.2.161>.
- [63] Araújo J, Severo M, Ramos E. Sleep duration and adiposity during adolescence. *Pediatrics* 2012;130(5). <https://doi.org/10.1542/peds.2011-1116>.
- [64] Suglia SF, Kara S, Robinson WR. Sleep duration and obesity among adolescents transitioning to adulthood: do results differ by sex? *J Pediatr* 2014;165(4):750–4. <https://doi.org/10.1016/j.jpeds.2014.06.052>.
- [65] Tatone-Tokuda Fabiola, Dubois Lise, Ramsay Timothy, Girard Manon, Touchette Evelyne, Petit Dominique, Montplaisir Jacques Y. Sex differences in the association between sleep duration, diet and body mass index: a birth cohort study. *J Sleep Res* 2012;21(4):448–60. <https://doi.org/10.1111/j.1365-2869.2011.00989.x>.
- [66] Peña MM, Rifas-Shiman SL, Gillman MW, Redline S, Taveras EM. Racial/ethnic and socio-contextual correlates of chronic sleep curtailment in childhood. *Sleep* 2016;39(9):1653–61. <https://doi.org/10.5665/sleep.6086>.
- [67] Adenekan B, Pandey A, McKenzie S, Zizi F, Casimir GJ, Jean-Louis G. Sleep in America: role of racial/ethnic differences. *Sleep Med Rev* 2013;17(4):255–62. <https://doi.org/10.1016/j.smrv.2012.07.002>.
- [68] Whinnery J, Jackson N, Rattanaumpawan P, Grandner MA. Short and long sleep duration associated with race/ethnicity, socio-demographics, and Socioeconomic position. *Sleep* 2014;37(3):601–11. <https://doi.org/10.5665/sleep.3508>.
- [69] Donat M, Brown C, Williams N, Pandey A, Racine C, McFarlane SI, Jean-Louis G. Linking sleep duration and obesity among black and white US adults. *Clin Pract* 2013;10(5):661–7. <https://doi.org/10.2217/cpr.13.47>.
- [70] Grandner MA, Chakravorty S, Perlis ML, Oliver L, Gurubhagavatula I. Habitual sleep duration associated with self-reported and objectively determined cardiometabolic risk factors. *Sleep Med* 2014;15(1):42–50. <https://doi.org/10.1016/j.sleep.2013.09.012>.
- [71] Spaeth AM, Dinges DF, Goel N. Resting metabolic rate varies by race and by sleep duration. *Obesity* 2015;23(12):2349–56. <https://doi.org/10.1002/oby.21198>.
- [72] McNeil J, St-Onge MP. Increased energy intake following sleep restriction in men and women: a one-size-fits-all conclusion? *Obesity* 2017;25(6):989–92. <https://doi.org/10.1002/oby.21831>.
- [73] Arora T, Taheri S. Associations among late chronotype, body mass index and dietary behaviors in young adolescents. *Int J Obes* 2015;39(1):39–44. <https://doi.org/10.1038/ijo.2014.157>.
- [74] Culnan E, Kloss JD, Grandner M. A prospective study of weight gain associated with chronotype among college freshmen. *Chronobiol Int* 2013;30(5):682–90. <https://doi.org/10.3109/07420528.2013.782311>.
- [75] Maukonen M, Kanerva N, Partonen T, Kronholm E, Konttinen H, Wennman H, Männistö S. The associations between chronotype, a healthy diet and obesity. *Chronobiol Int* 2016;33(8):972–81. <https://doi.org/10.1080/07420528.2016.1183022>.
- [76] Yu JH, Yun CH, Ahn JH, Suh S, Cho HJ, Lee SK, Yoo HJ, Seo JA, Kim SG, Choi KM, Baik SH, Choi DS, Shin C, Kim NH. Evening chronotype is associated with metabolic disorders and body composition in middle-aged adults. *J Clin Endocrinol Metab* 2015;100(4):1494–502. <https://doi.org/10.1210/jc.2014-3754>.
- [77] Maukonen M, Kanerva N, Partonen T, Kronholm E, Tapanainen H, Kontto J, Männistö S. Chronotype differences in timing of energy and macronutrient intakes: a population-based study in adults. *Obesity* 2017;25(3):608–15. <https://doi.org/10.1002/oby.21747>.
- [78] Mota MC, Waterhouse J, De-Souza DA, Rossato LT, Silva CM, Araújo MBJ, Tufik S, de Mello MT, Crispim CA. Association between chronotype, food intake and physical activity in medical residents. *Chronobiol Int* 2016;33(6):730–9. <https://doi.org/10.3109/07420528.2016.1167711>.
- [79] Patterson F, Malone SK, Lozano A, Grandner MA, Hanlon AL. Smoking, screen-based sedentary behavior, and diet associated with habitual sleep duration and chronotype: data from the UK biobank. *Ann Behav Med* 2016;50(5):715–26. <https://doi.org/10.1007/s12160-016-9797-5>.
- [80] Lucassen EA, Zhao X, Rother KI, Mattingly MS, Courville AB, de Jonge L, Csako G, Cizza G. Evening chronotype is associated with changes in eating behavior, more sleep apnea, and increased stress hormones in short sleeping obese individuals. *PLoS ONE* 2013;8(3). <https://doi.org/10.1371/journal.pone.0056519>.
- [81] Reutrakul S, Hood MM, Crowley SJ, Morgan MK, Teodori M, Knutson KL. The relationship between breakfast skipping, chronotype, and glycemic control in type 2 diabetes. *Chronobiol Int* 2014;31(1):64–71. <https://doi.org/10.3109/07420528.2013.821614>.
- [82] Muñoz JSG, Cañavate R, Hernández CM, Cara-Salmerón V, Morante JJH. The association among chronotype, timing of food intake and food preferences depends on body mass status. *Eur J Clin Nutr* 2017;71(6):736–42. <https://doi.org/10.1038/ejcn.2016.182>.
- [83] Ruiz-Lozano T, Vidal J, de Hollanda A, Scheer FAJL, Garaulet M, Izquierdo-Pulido M. Timing of food intake is associated with weight loss evolution in severe obese patients after bariatric

- surgery. *Clin Nutr* 2016;35(6):1308–14. <https://doi.org/10.1016/j.clnu.2016.02.007>.
- [84] Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jetlag and obesity. *Curr Biol* 2012;22(10):939–43. <https://doi.org/10.1016/j.cub.2012.03.038>.
- [85] Parsons MJ, Moffitt TE, Gregory AM, Goldman-Mellor S, Nolan PM, Poulton R, Caspi A. Social jetlag, obesity and metabolic disorder: investigation in a cohort study. *Int J Obes* 2015;39(5):842–8. <https://doi.org/10.1038/ijo.2014.201>.
- [86] Rutters F, Lemmens SG, Adam TC, Bremmer MA, Elders PJ, Nijpels G, Dekker JM. Is social jetlag associated with an adverse endocrine, behavioral, and cardiovascular risk profile? *J Biol Rhythms* 2014;29(5):377–83. <https://doi.org/10.1177/0748730414550199>.
- [87] Reutrakul S, Knutson KL. Consequences of circadian disruption on cardiometabolic health. *Sleep Med Clin* 2015;10(4):455–68. <https://doi.org/10.1016/j.jsmc.2015.07.005>.
- [88] Lee S, Castro N, Signal L, Skidmore P, Faulkner J, Lark S, Williams MA, Muller D, Harrex H. Sleep and adiposity in pre-adolescent children: the importance of social jetlag. *Child Obes* 2018;14(3):158–64. <https://doi.org/10.1089/chi.2017.0272>.
- [89] Im HJ, Baek SH, Chu MK, Yang KI, Kim WJ, Park SH, Thomas RJ, Yun CH. Association between weekend catch-up sleep and lower body mass: population-based study. *Sleep* 2017;40(7). <https://doi.org/10.1093/sleep/zsx089>.
- [90] Rupp TL, Wesensten NJ, Bliese PD, Balkin TJ. Banking sleep: realization of benefits during subsequent sleep restriction and recovery. *Sleep* 2009;32(3):311–21. <https://doi.org/10.1093/sleep/32.3.311>.
- [91] Depner CM, Stothard ER, Wright KP. Metabolic consequences of sleep and circadian disorders. *Curr Diabetes Rep* 2014;14(7). <https://doi.org/10.1007/s11892-014-0507-z>.
- [92] Laermans J, Depoortere I. Chronobesity: role of the circadian system in the obesity epidemic. *Obes Rev* 2016;17(2):108–25. <https://doi.org/10.1111/obr.12351>.
- [93] Sun M, Feng W, Wang F, Li P, Li Z, Li M, Tse G, Vlaanderen J, Vermeulen R, Tse LA. Meta-analysis on shift work and risks of specific obesity types. *Obes Rev* 2018;19(1):28–40. <https://doi.org/10.1111/obr.12621>.
- [94] Buxton OM, Cain SW, Connor O', McLaren SP, Czeisler D, Shea CA. Metabolic consequences of chronic sleep restriction combined with circadian misalignment. *Sleep* 2010;33.
- [95] Asarnow LD, McGlinchey E, Harvey AG. Evidence for a possible link between bedtime and change in body mass index. *Sleep* 2015;38(10):1523–7. <https://doi.org/10.5665/sleep.5038>.
- [96] Golley RK, Maher CA, Matricciani L, Olds TS. Sleep duration or bedtime? Exploring the association between sleep timing behaviour, diet and BMI in children and adolescents. *Int J Obes* 2013;37(4):546–51. <https://doi.org/10.1038/ijo.2012.212>.
- [97] Taylor BJ, Matthews KA, Hasler BP, Roecklein KA, Kline CE, Buysse DJ, Kravitz HM, Tiani AG, Harlow SD, Hall MH. Bedtime variability and metabolic health in midlife women: the SWAN Sleep Study. *Sleep* 2016;39(2):457–65. <https://doi.org/10.5665/sleep.5464>.
- [98] Scharf RJ, Deboer MD. Sleep timing and longitudinal weight gain in 4- and 5-year-old children. *Pediatr Obes* 2015;10(2):141–8. <https://doi.org/10.1111/ijpo.229>.
- [99] Thivel D, Isacco L, Aucouturier J, Pereira B, Lazaar N, Ratel S, Doré E, Duché P. Bedtime and sleep timing but not sleep duration are associated with eating habits in primary school children. *J Dev Behav Pediatr* 2015;36(3):158–65. <https://doi.org/10.1097/dbp.0000000000000131>.
- [100] Miller AL, Kaciroti N, Lebourgeois MK, Chen YP, Sturza J, Lumeng JC. Sleep timing moderates the concurrent sleep duration–body mass index association in low-income preschool-age children. *Acad Pediatr* 2014;14(2):207–13. <https://doi.org/10.1016/j.acap.2013.12.003>.
- [101] Appelhans BM, Fitzpatrick SL, Li H, Cail V, Waring ME, Schneider KL, Whited MC, Busch AM, Pagoto SL. The home environment and childhood obesity in low-income households: indirect effects via sleep duration and screen time. *BMC Public Health* 2014;14(1). <https://doi.org/10.1186/1471-2458-14-1160>.
- [102] Chan WS, Levensen MP, McCrae CS. A meta-analysis of associations between obesity and insomnia diagnosis and symptoms. *Sleep Med Rev* 2018;40:170–82. <https://doi.org/10.1016/j.smrv.2017.12.004>.
- [103] Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diab Care* 2009;32(11):1980–5. <https://doi.org/10.2337/dc09-0284>.
- [104] Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep* 2009;32(4):491–7. <https://doi.org/10.1093/sleep/32.4.491>.
- [105] Troxel WM, Buysse DJ, Matthews KA, Kip KE, Strollo PJ, Hall M, Drumheller O, Reis SE. Sleep symptoms predict the development of the metabolic syndrome. *Sleep* 2010;33(12):1633–40. <https://doi.org/10.1093/sleep/33.12.1633>.
- [106] Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014;383(9918):736–47. [https://doi.org/10.1016/S0140-6736\(13\)60734-5](https://doi.org/10.1016/S0140-6736(13)60734-5).
- [107] Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol* 2013;62(7):569–76. <https://doi.org/10.1016/j.jacc.2013.05.045>.
- [108] Araghi MH, Chen YF, Jagielski A, Choudhury S, Banerjee D, Hussain S, Neil Thomas G, Taheri S. Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis. *Sleep* 2013;36(10):1553–62. <https://doi.org/10.5665/sleep.3056>.
- [109] Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, Foster GD, Maislin G, Saif H, Broderick P, Chittams J, Hanlon AL, Pack AI. CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014;370(24):2265–75. <https://doi.org/10.1056/NEJMoa1306187>.
- [110] Ponziani V, Gennari M, Pizza F, Balsamo A, Bernardi F, Plazzi G. Growing up with type 1 narcolepsy: its anthropometric and endocrine features. *J Clin Sleep Med* 2016;12(12):1649–57. <https://doi.org/10.5664/jcsm.6352>.
- [111] Dahmen N, Bierbrauer J, Kasten M. Increased prevalence of obesity in narcoleptic patients and relatives. *Eur Arch Psychiatr Clin Neurosci* 2001;251(2):85–9. <https://doi.org/10.1007/s004060170057>.
- [112] Poli F, Plazzi G, Di Dalmazi G, Ribichini D, Vicennati V, Pizza F, Mignot E, Montagna P, Pasquali R, Pagotto U. Body mass index-

- independent metabolic alterations in narcolepsy with cataplexy. *Sleep* 2009;32(11):1491–7. <https://doi.org/10.1093/sleep/32.11.1491>.
- [113] Šonka K, Kemlink D, Bušková J, Pretl M, Šrůtková Z, Maurovich Horvat E, Vodička P, Poláková V, Nevšímalová S. Obesity accompanies narcolepsy with cataplexy but not narcolepsy without cataplexy. *Neuroendocrinol Lett* 2010;31(5):631–4.
- [114] Wang Z, Wu H, Stone WS, Zhuang J, Qiu L, Xu X, Wang Y, Zhao Z, Han F, Zhao Z. Body weight and basal metabolic rate in childhood narcolepsy: a longitudinal study. *Sleep Med* 2016;25:139–44. <https://doi.org/10.1016/j.sleep.2016.06.019>.
- [115] Dahmen N, Tonn P, Messroghli L, Ghezel-Ahmadi D, Engel A. Basal metabolic rate in narcoleptic patients. *Sleep* 2009;32(7):962–4.
- [116] Overeem S, Scammell TE, Lammers GJ. Hypocretin/orexin and sleep: implications for the pathophysiology and diagnosis of narcolepsy. *Curr Opin Neurol* 2002;15(6):739–45. <https://doi.org/10.1097/00019052-200212000-00013>.
- [117] Chabas D, Foulon C, Gonzalez J, Nasr M, Lyon-Caen O, Willer JC, Derenne JP, Arnulf I. Eating disorder and metabolism in narcoleptic patients. *Sleep* 2007;30(10):1267–73. <https://doi.org/10.1093/sleep/30.10.1267>.
- [118] Droogleever Fortijn HA, Swinkels S, Buitelaar J, Renier WO, Furer JW, Rijnders CA, Hodiamont PP, Overeem S. High prevalence of eating disorders in narcolepsy with cataplexy: a case-control study. *Sleep* 2008;31(3):335–41. <https://doi.org/10.1093/sleep/31.3.335>.
- [119] Dimitrova A, Fronczeck R, Van Der Ploeg J, Scammell T, Gautam S, Pascual-Leone A, Lammers GJ. Reward-seeking behavior in human narcolepsy. *J Clin Sleep Med* 2011;7(3):293–300. <https://doi.org/10.5664/JCSM.1076>.
- [120] Janke van Holst R, van der Cruijsen L, Mierlo Pvan, Jan Lammers G, Cools R, Overeem S, Aarts E. Aberrant food choices after satiation in human orexin-deficient narcolepsy type 1. *Sleep* 2016;39(11):1951–9. <https://doi.org/10.5665/sleep.6222>.
- [121] Schinkelshoek MS, Smolders IM, Donjacour CE, van der Meijden WP, van Zwet EW, Fronczeck R, Lammers GJ. Decreased body mass index during treatment with sodium oxybate in narcolepsy type 1. *J Sleep Res* 2019;28(3). <https://doi.org/10.1111/jsr.12684>.
- [122] Fatima Y, A.R. Doi S, Mamun AA. Sleep quality and obesity in young subjects: a meta-analysis. *Obes Rev* 2016;17(11):1154–66. <https://doi.org/10.1111/obr.12444>.
- [123] Rahe C, Eszter Czira M, Teismann H, Berger K. Associations between poor sleep quality and different measures of obesity. *Sleep Med* 2015;16(10):1225–8. <https://doi.org/10.1016/j.sleep.2015.05.023>.
- [124] Toor P, Kim K, Buffington CK. Sleep quality and duration before and after bariatric surgery. *Obes Surg* 2012;22(6):890–5. <https://doi.org/10.1007/s11695-011-0541-8>.
- [125] Thomson CA, Morrow KL, Flatt SW, Wertheim BC, Perfect MM, Ravia JJ, Sherwood NE, Karanja N, Rock CL. Relationship between sleep quality and quantity and weight loss in women participating in a weight-loss intervention trial. *Obesity* 2012;20(7):1419–25. <https://doi.org/10.1038/oby.2012.62>.
- [126] Fernandez-Mendoza J, Vgontzas AN, Kritikou I, Calhoun SL, Liao D, Bixler EO. Natural history of excessive daytime sleepiness: role of obesity, weight loss, depression, and sleep propensity. *Sleep* 2015;38(3):351–60. <https://doi.org/10.5665/sleep.4488>.
- [127] Vgontzas AN, Lin H-M, Papaliaga M, Calhoun S, Vela-Bueno A, Chrousos GP, Bixler EO. Short sleep duration and obesity: the role of emotional stress and sleep disturbances. *Int J Obes* 2008;32(5):801–9. <https://doi.org/10.1038/ijo.2008.4>.
- [128] Whitaker BN, Fisher PL, Jambhekar S, Com G, Razzaq S, Thompson JE, Nick TG, Ward WL. Impact of degree of obesity on sleep, quality of life, and depression in youth. *J Pediatr Health Care* 2018;32(2):e37. <https://doi.org/10.1016/j.pedhc.2017.09.008>.
- [129] Rao MN, Blackwell T, Redline S, Stefanick ML, Ancoli-Israel S, Stone KL. Association between sleep architecture and measures of body composition. *Sleep* 2009;32(4):483–90. <https://doi.org/10.1093/sleep/32.4.483>.
- [130] Rutters F, Gonnissen HK, Hursel R, Lemmens SG, Martens EA, Westerterp-Plantenga MS. Distinct associations between energy balance and the sleep characteristics slow wave sleep and rapid eye movement sleep. *Int J Obes* 2012;36(10):1346–52. <https://doi.org/10.1038/ijo.2011.250>.
- [131] Theorell-Haglöw J, Berne C, Janson C, Sahlin C, Lindberg E. Associations between short sleep duration and central obesity in women. *Sleep* 2010;33(5):593–8. <https://doi.org/10.1093/sleep/33.5.593>.
- [132] Spaeth AM, Dinges DF, Goel N. Objective measurements of energy balance are associated with sleep architecture in healthy adults. *Sleep* 2017;40(1). <https://doi.org/10.1093/sleep/zsw018>.
- [133] St-Onge MP, Roberts A, Shechter A, Choudhury AR. Fiber and saturated fat are associated with sleep arousals and slow wave sleep. *J Clin Sleep Med* 2016;12(1):19–24. <https://doi.org/10.5664/jesm.5384>.
- [134] Van Cauter E, Plat L, Scharf MB, Leproult R, Cespedes S, L’Hermite-Balériaux M, Copinschi G. Simultaneous stimulation of slow-wave sleep and growth hormone secretion by gamma-hydroxybutyrate in normal young men. *J Clin Investig* 1997;100(3):745–53. <https://doi.org/10.1172/JCI119587>.
- [135] Arun R, Pina P, Rubin D, Erichsen D. Association between sleep stages and hunger scores in 36 children. *Pediatr Obes* 2016;11(5):e9. <https://doi.org/10.1111/ijo.12064>.
- [136] Wojnar J, Brower KJ, Dopp R, Wojnar M, Emslie G, Rintelmann J, Hoffmann RF, Armitage R. Sleep and body mass index in depressed children and healthy controls. *Sleep Med* 2010;11(3):295–301. <https://doi.org/10.1016/j.sleep.2009.02.012>.
- [137] Collet TH, Van Der Klaauw AA, Henning E, Keogh JM, Suddaby D, Dachi SV, Dunbar S, Kelway S, Dickson SL, Farooqi IS, Schmid SM. The sleep/wake cycle is directly modulated by changes in energy balance. *Sleep* 2016;39(9):1691–700. <https://doi.org/10.5665/sleep.6094>.
- [138] Kahlhöfer J, Karschin J, Breusing N, Bosy-Westphal A. Relationship between actigraphy-assessed sleep quality and fat mass in college students. *Obesity* 2016;24(2):335–41. <https://doi.org/10.1002/oby.21326>.
- [139] Moraes W, Poyares D, Zalcman I, de Mello MT, Bittencourt LR, Santos-Silva R, Tufik S. Association between body mass index and sleep duration assessed by objective methods in a representative sample of the adult population. *Sleep Med* 2013;14(4):312–8. <https://doi.org/10.1016/j.sleep.2012.11.010>.
- [140] Wirth MD, Hébert JR, Hand GA, Youngstedt SD, Hurley TG, Shook RP, Paluch AE, Sui X, James SL, Blair SN. Association between actigraphic sleep metrics and body composition. *Ann*

- Epidemiol 2015;25(10):773–8. <https://doi.org/10.1016/j.annepidem.2015.05.001>.
- [141] Chamorro R, Algarín C, Garrido M, Causa L, Held C, Lozoff B, Peirano P. Night time sleep macrostructure is altered in otherwise healthy 10-year-old overweight children. *Int J Obes* 2014;38(8):1120–5. <https://doi.org/10.1038/ijo.2013.238>.
- [142] Mcneil J, Tremblay MS, Leduc G, Boyer C, Bélanger P, Leblanc AG, Borghese MM, Chaput JP. Objectively-measured sleep and its association with adiposity and physical activity in a sample of Canadian children. *J Sleep Res* 2015;24(2):131–9. <https://doi.org/10.1111/jsr.12241>.
- [143] Allison KC, Spaeth A, Hopkins CM. Sleep and eating disorders. *Curr Psychiatry Rep* 2016;18(10):92.
- [144] Haines J, McDonald J, O'Brien A, Sherry B, Bottino CJ, Schmidt ME, Taveras EM. Healthy habits, happy homes: randomized trial to improve household routines for obesity prevention among preschool-aged children. *JAMA Pediatr* 2013;167(11):1072–9. <https://doi.org/10.1001/jamapediatrics.2013.2356>.
- [145] Clifford LM, Beebe DW, Simon SL, Kuhl ES, Filigno SS, Rausch JR, Stark LJ. The association between sleep duration and weight in treatment-seeking preschoolers with obesity. *Sleep Med* 2012;13(8):1102–5. <https://doi.org/10.1016/j.sleep.2012.06.019>.
- [146] Sallinen BJ, Hassan F, Olszewski A, Maupin A, Hoban TF, Chervin RD, Woolford SJ. Longer weekly sleep duration predicts greater 3-month BMI reduction among obese adolescents attending a clinical multidisciplinary weight management program. *Obes Facts* 2013;6(3):239–46. <https://doi.org/10.1159/000351819>.
- [147] Valrie CR, Bond K, Lutes LD, Carraway M, Collier DN. Relationship of sleep quality, baseline weight status, and weight-loss responsiveness in obese adolescents in an immersion treatment program. *Sleep Med* 2015;16(3):432–4. <https://doi.org/10.1016/j.sleep.2014.11.007>.
- [148] Ross KM, Graham Thomas J, Wing RR. Successful weight loss maintenance associated with morning chronotype and better sleep quality. *J Behav Med* 2016;39(3):465–71. <https://doi.org/10.1007/s10865-015-9704-8>.
- [149] Chaput JP, Tremblay A. Sleeping habits predict the magnitude of fat loss in adults exposed to moderate caloric restriction. *Obes Facts* 2012;5(4):561–6. <https://doi.org/10.1159/000342054>.
- [150] Nedeltcheva AV, Kilkus JM, Imperial J, Schoeller DA, Penev PD. Insufficient sleep undermines dietary efforts to reduce adiposity. *Ann Intern Med* 2010;153(7):435–41. <https://doi.org/10.7326/0003-4819-153-7-201010050-00006>.
- [151] Wang X, Sparks JR, Bowyer KP, Youngstedt SD. Influence of sleep restriction on weight loss outcomes associated with caloric restriction. *Sleep* 2018;41(5). <https://doi.org/10.1093/sleep/zsy027>.
- [152] Hart CN, Hawley NL, Wing RR. Development of a behavioral sleep intervention as a novel approach for pediatric obesity in school-aged children. *Pediatr Clin* 2016;63(3):511–23. <https://doi.org/10.1016/j.pcl.2016.02.007>.
- [153] Van Dyk TR, Zhang N, Catlin PA, Cornist K, McAlister S, Whitacre C, Beebe DW. Feasibility and emotional impact of experimentally extending sleep in short-sleeping adolescents. *Sleep* 2017;40(9). <https://doi.org/10.1093/sleep/zsx123>.
- [154] Cizza G, Marincola P, Mattingly M, Williams L, Mitler M, Skarulis M, Csako G. Treatment of obesity with extension of sleep duration: a randomized, prospective, controlled trial. *Clin Trials* 2010;7(3):274–85. <https://doi.org/10.1177/1740774510368298>.
- [155] Tasali E, Chapotot F, Wroblewski K, Schoeller D. The effects of extended bedtimes on sleep duration and food desire in overweight young adults: a home-based intervention. *Appetite* 2014;80:220–4. <https://doi.org/10.1016/j.appet.2014.05.021>.
- [156] Al Khatib HK, Hall WL, Creedon A, Ooi E, Masri T, McGowan L, Harding SV, Darzi J, Pot GK. Sleep extension is a feasible lifestyle intervention in free-living adults who are habitually short sleepers: a potential strategy for decreasing intake of free sugars? A randomized controlled pilot study. *Am J Clin Nutr* 2018;107(1):43–53. <https://doi.org/10.1093/ajcn/nqx030>.
- [157] Haack M, Serrador J, Cohen D, Simpson N, Meier-Ewert H, Mullington JM. Increasing sleep duration to lower beat-to-beat blood pressure: a pilot study. *J Sleep Res* 2013;22(3):295–304. <https://doi.org/10.1111/jsr.12011>.
- [158] Leproult R, Deliens G, Gilson M, Peigneux P. Beneficial impact of sleep extension on fasting insulin sensitivity in adults with habitual sleep restriction. *Sleep* 2015;38(5):707–15. <https://doi.org/10.5665/sleep.4660>.

This page intentionally left blank

Chapter 19

Insufficient sleep and cardiovascular disease risk

Sogol Javaheri^a, Omobomi Fashanu^a and Susan Redline^{a,b}

^aBrigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; ^bBeth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

Abbreviations

ACTH	Adrenocorticotrophic hormone
CARDIA	Coronary artery risk development in young adults
chd	Coronary heart disease
CRP	C-reactive protein
IL-6	Interleukin-6
MONICA	Monitoring trends and determinants on cardiovascular disease
NHANES	National Health and Nutrition Examination Survey
PSG	Polysomnography
REGARDS	Reasons for Geographic And Racial Differences in Stroke
TNF- α	Tumor necrosis factor-alpha

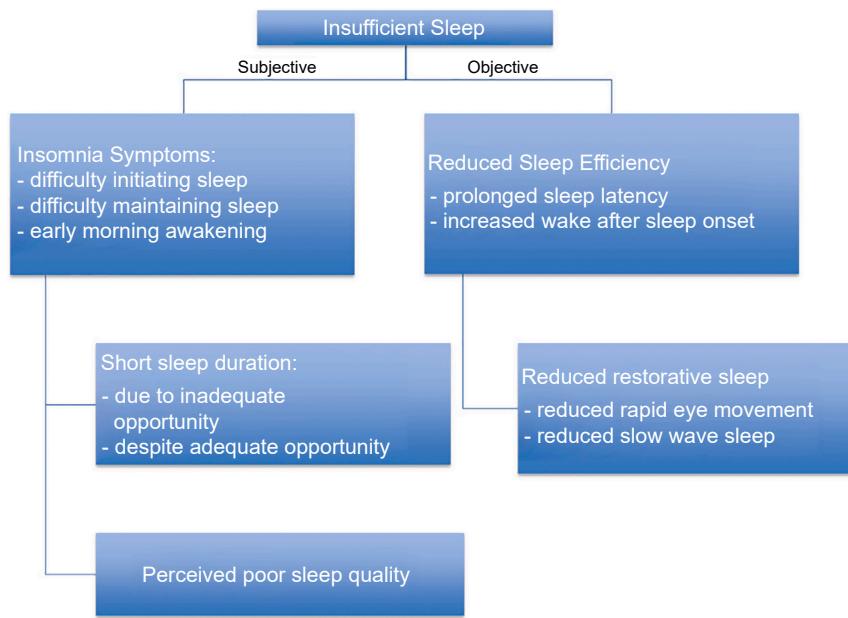
Introduction

Sleep deficiency, commonly used to represent habitual short sleep duration or reduced sleep quality, is a distinct entity yet overlaps with the clinical phenotype, insomnia. According to the National Sleep Foundation, healthy sleep duration in adults is 7–9 h each night [1]. However, elements of sleep quality may play a role in whether sleep is sufficient (see Fig. 19.1), including the continuity, depth, night to night variability, and perceived quality of sleep. Objective measurements of these aspects of sleep, made using actigraphy or polysomnography, include sleep efficiency (time spent sleeping divided by time spent in bed), wake after sleep onset, sleep latency (time to sleep onset), time and progression of sleep stages (particular time in deep, slow wave sleep, and rapid eye movement sleep), and various summary measurements of numbers and patterns of sleep–wake bouts. Subjective sleep quality is assessed using standardized questionnaires or sleep diaries assessing an individual's satisfaction with his or her sleep and includes perceived concerns falling asleep,

maintaining sleep, early awakenings, and feeling refreshed after sleep. Most large epidemiologic studies examining insufficient sleep and cardiovascular disease have used the more readily available self-reported measurements of sleep duration and quality rather than objective recordings, resulting in a relative limitation of data on the association of sleep fragmentation or depth on health outcomes.

Chronic insomnia is defined as difficulty initiating or maintaining sleep, or early morning awakening, coupled with daytime impairment, for at least 3 months' duration. An estimated 10%–20% of Americans suffer from chronic insomnia [2], the most prevalent sleep disorder in the United States, while an estimated 1/3 of Americans are considered short or insufficient sleepers. Both insomnia and insufficient sleep impair attention and can contribute to impaired cognition and increase in risk of motor vehicle and industrial accidents, reduced work productivity, and increased healthcare costs [2]. Based on results of primarily observational data, both insufficient sleep and insomnia confer increased risk of cardiovascular disease, including hypertension, coronary heart disease, heart failure, stroke, arrhythmia, and cardiovascular mortality. Further, emerging data suggest that insomnia, coupled with short sleep duration, is associated with an even stronger cardiovascular disease risk than either of these entities alone [3,4]. While there is some conflicting data on the associations between cardiovascular disease and sleep, this may in part be due to varying definitions of insomnia and insufficient sleep, an active area of interest in the sleep research community. The mechanisms by which insufficient sleep and insomnia may contribute to cardiovascular disease risk are overlapping, and future trials and experimental research are needed to further delineate the pathways linking insufficient sleep with cardiovascular disease and better define sleep-related risk factors. Throughout this

FIGURE 19.1 Subjective and objective components of sleep quality and duration that comprise the umbrella term “insufficient sleep.”



chapter, we will attempt to distinguish associations with cardiovascular risk that are related to insufficient sleep as well as with insomnia specifically. The high prevalence of these conditions and the associated risks and adverse health outcomes highlight the need for ongoing research as well as public education for improved identification and treatment in the population.

Defining insufficient sleep

Insufficient sleep may be defined as voluntary or involuntary sleep restriction. With behaviorally induced sleep deprivation, the individual has inadequate sleep due to failure to allow adequate time for sleep. Involuntary sleep restriction, however, may occur as a result of insomnia, circadian rhythm or other sleep disorders, another comorbidity, or for a variety of other reasons. Varying cut-offs are used to define insufficient sleep, most commonly ranging from <5 to <7 h. The CDC defines healthy sleep in adults at least 7 h each night based on analysis of data showing consistency of findings associating sleeping <7 h with increased risk for adverse cardio-metabolic disorders including obesity, diabetes, heart disease, and all-cause mortality. However, epidemiologic studies have found that short sleep durations, particularly <5 and < 6 h, predict higher rates of obesity or adverse cardiovascular outcomes as compared to 6 and 7 h of sleep [5–7].

Self-reported sleep duration can vary significantly compared to sleep duration measured by actigraphy or polysomnography (PSG), with correlations often <0.40 [8] and kappa values estimating the degree of agreement

across categories of short-, intermediate-, and long-sleep duration weak or modest. Therefore, extrapolating thresholds for defining sleep duration from studies using one set of measurements to other settings needs to be done very cautiously. Population-based data on other aspects of sleep deficiency and cardiovascular risk are sparse, limiting the ability to use standardized definitions for defining thresholds for prolonged sleep onset, low sleep efficiency, and poor sleep quality.

A variety of tools may be used to characterize insufficient sleep, including PSG, actigraphy, and subjective self-reporting tools such as questionnaires and sleep diaries. These tools may capture different aspects of sleep quality and provide different estimates of duration that reflect different pathophysiologic process. While polysomnography is not recommended for diagnosis of insomnia, it provides information on secondary contributors to insufficient sleep (e.g., sleep apnea, periodic limb movements) and quantifies sleep stage distributions. The latter may be particularly relevant to understanding cardiometabolic disease, given that selected reduction of slow wave sleep is associated with incident hypertension [9], obesity [10], and metabolic dysfunction [11]. However, polysomnography is more burdensome than other methods, and its general use for only one night in laboratory settings may reduce the representativeness of its estimates of sleep. Actigraphy, a watch-like device with an accelerometer to detect movement, is typically worn on the wrist for sleep estimation and can be used to depict rest-activity patterns for days to weeks in the individual’s typical environments. Various algorithms are applied to the measured activity

counts that provide estimates of 24 h sleep patterns, including average and night to night variability in sleep duration, wake after sleep onset, and sleep efficiency. However, sleep onset latency, a key feature used to gauge insomnia severity, can be difficult to estimate due to vagaries in knowing the time of “lights off” or “in-bed” timing. Compared to polysomnography, sleep may be systematically overestimated for individuals who move little or underestimated in individuals with sleep disorders or who are very active during sleep [12]. Questionnaires, including the Pittsburgh Sleep Quality Index, the Insomnia Severity Index, and the Women’s Health Initiative Insomnia Rating Scale, among others, are commonly used for evaluating insomnia in the research setting. Single-item questions on sleep duration and/or quality are also frequently used in large epidemiologic studies. These tools are generally administered at a single point in time and therefore may not reflect habitual sleep duration over time. Sleep diaries record subjective daily estimation of sleep and wake times and are considered a standard assessment of insomnia and sleep duration in clinical settings. The growing availability of electronic communication devices that can deliver research surveys provides the ability to deliver sleep diaries electronically, potentially improving compliance. Finally, questions on sleep can be asked at random and repeated intervals over time to gain information on changing sleep behaviors in real time using an approach known as ecological momentary assessment. Each of these tools ultimately captures different aspects of insomnia and insufficient sleep and poses their own challenges regarding accuracy and what specific aspect of sleep health is being measured.

Pathophysiology

The pathophysiologic mechanisms underlying the associations between insufficient sleep and insomnia with cardiovascular disease are multifactorial and, though not fully understood, are also overlapping and will be discussed together here. General mechanisms include increased sympathetic activity resulting in elevated heart rate and blood pressure [13], dysregulation of the hypothalamic-pituitary-adrenal axis [14–16], increased inflammation [17–19], impaired glucose metabolism, vascular dysfunction [20], increased atherogenesis [17,21], and obesity [22]. A prior review article on insomnia and risk of cardiovascular disease details the pathogenesis, and Fig. 19.2, modified from this review, summarizes the relationship between insufficient sleep, insomnia, and cardiovascular disease.

Compared to normal controls, human studies show that individuals with either insomnia or short sleep have elevated plasma and urine norepinephrine levels, increased heart rate and blood pressure, as well as blunted heart rate

variability [23–25]. Increased sympathetic nervous system activity, one of the primary mechanisms thought to underlie the relationship between short sleep, insomnia, and cardiovascular disease, will be further addressed in the “Insufficient sleep and blood pressure” section.

Evidence from human studies also demonstrates increased ACTH and cortisol secretion mechanisms that may lead to cardiovascular disease directly or indirectly through mediating pathways such as impaired glucose tolerance and diabetes. Elevations in C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6) have been demonstrated in short sleepers and individuals with insomnia [17,19], markers that are implicated in multiple disease processes including obesity, diabetes, and atherosclerosis, among others. A causal association between inflammation and insomnia is supported by the results of a randomized control trial assessing the effect of cognitive behavioral therapy in older adults with insomnia, finding that effective insomnia treatment and remission resulted in reductions in CRP levels [26]. Short sleep also results in diminished nitrous oxide availability, one potential pathway by which short sleep contributes to impaired endothelium-dependent vasodilation [20]. Finally, sleep loss potentiates weight gain and obesity by tilting the balance between energy intake and expenditure via increased appetite, altered eating behaviors, and reduced physical activity [27,28]. While early studies suggested that increased caloric intake resulting from effects of sleep deprivation on increasing the appetite stimulating hormone ghrelin and reducing the appetite suppressing hormone leptin [29], recent research suggests that the mechanisms may be through effects on central brain reward centers [28].

Insufficient sleep and blood pressure

Arterial blood pressure is modulated by the autonomic nervous system and baroreceptors that are in part regulated by sleep and circadian rhythm. In normotensive individuals, the typical circadian rhythm of blood pressure is characterized by a 10%–20% nocturnal decrease, a phenomenon referred to as “dipping.” This is followed by a morning surge in blood pressure. Nondipping, the absence of this nocturnal blood pressure decrease, has been observed in cardio-metabolic disorders including hypertension [30,31] and is associated with increased mortality independent of daytime blood pressure [32]. It has been hypothesized that increased sympathetic outflow, decreased baroreflex sensitivity, and a higher baroreflex set-point [13] are some mechanisms by which sleep deprivation contributes to increased blood pressure [31]. Increased inflammation [33] and vascular dysfunction [34,35] are other potential mechanisms for hypertension. Experimental studies of acute sleep deprivation in adult

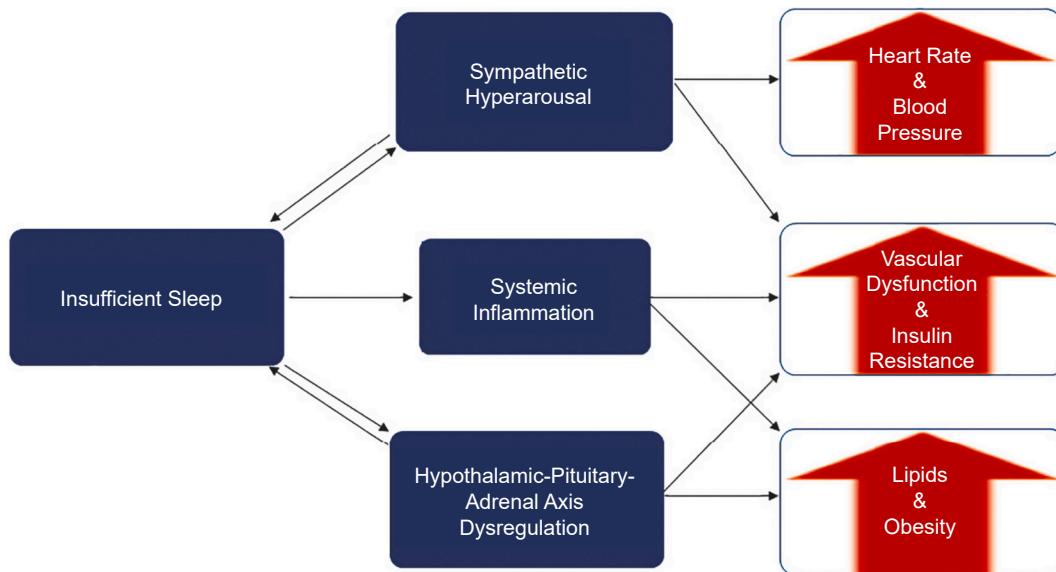


FIGURE 19.2 Flow diagram demonstrating possible pathophysiologic mechanisms underlying the relationship between insufficient sleep and cardiovascular disease.

volunteers have generally demonstrated elevations in blood pressure and heart rate [35], particularly during the night and the following morning [36]. A number of epidemiologic studies throughout the world, both cross-sectional and prospective, have also demonstrated an association between reduced sleep duration and consolidation (measured both subjectively and objectively) and elevated blood pressure or hypertension. The Coronary Artery Risk Development in Young Adults (CARDIA) sleep study, an ancillary study to the CARDIA cohort study, showed that reduced sleep duration and lower sleep efficiency maintenance measured by actigraphy predicted increased higher systolic and diastolic blood pressures cross-sectionally as well as increased odds of incident hypertension [37]. A prospective study of 1715 Korean adults aged 40–70 who were free of hypertension were followed for a median of 2.6 years and participants with <6 h self-reported sleep duration demonstrated increased odds of incident hypertension (odds ratio 1.71, 95% confidence interval 1.01–2.89) compared to normal sleepers (6–7.9 h of sleep) [38]. In the Penn State Cohort, a random, general population sample of 1741 men and women, objective short sleep duration measured by polysomnography associated with elevated blood pressure [39], and objective short sleep was estimated to partially mediate the relationship between hypertension and all-cause mortality [40].

Two prospective studies have found interactions between age and sleep duration that influence the association of short sleep with incident hypertension. A prospective

study of 3086 English men and women aged 50 and over demonstrated that self-reported short sleep was predictive of incident hypertension in men and women <60 years old but not in older people [33]. The National Health and Nutrition Examination Survey (NHANES) also found a significant interaction between age and sleep duration. They followed 4810 participants for 8–10 years for incident HTN and found that ≤5 h of self-reported short sleep was significantly associated with increased risk of incident hypertension (hazard ratio 1.51; 95% confidence interval 1.17–1.95) in younger (age 32–59 years) participants after adjusting for confounders but not in older individuals. They reported a higher percentage of patients developing hypertension who reported <7 h of sleep in their cohort compared to those with 7–8 h per night in the younger group only. They also found that obesity and diabetes were partial mediators of this association, as shown by the attenuation of associations after adding these variables to the models relating short sleep and incident HTN [41]. One of the most recent large epidemiologic studies on short sleep duration (sleep <6 h) showed an increase in the risk for elevated blood pressure by 8% (adjusted hazards ratio 1.08, confidence interval 1.04–1.13) in a population of 162,121 adult men and women free from major diseases including obesity [42]. This supports NHANES in that although obesity may be a partial mediator on the pathway between short sleep and high blood pressure, there are other underlying mechanisms independent of obesity at play.

The above findings have also been confirmed with meta-analyses that demonstrate increased risk of hypertension or elevated blood pressure in short sleepers [43], including meta-analysis restricted to prospective cohort studies [44]. Finally, short sleep and reduced sleep efficiency have also been associated with elevated blood pressure in adolescents [45,46]. The latter is of particular importance, given that confounding factors are likely to be fewer in younger generally healthy individuals compared to older individuals with multiple chronic diseases.

The insomnia literature also generally supports an association between insomnia and incident hypertension, though the data are more conflicting than that for short sleep, which may at least in part be due to the wider variation in how insomnia is defined [24]. There is also evidence that chronic insomnia coupled with objective short sleep duration is an even stronger predictor of incident hypertension than either sleep parameter alone. In the Penn State Cohort, chronic insomnia (present for at least 1 year) coupled with objective short sleep (<6 h by polysomnography) was associated with an almost fourfold increased odds of incident hypertension (odds ratio 3.75, 95% confidence interval 1.58–8.95) as compared to chronic insomnia alone (odds ratio 2.24, 95% confidence interval 1.19–4.19) [47]. A cross-sectional observational study of 255 adults with clinically diagnosed insomnia found that individuals with insomnia and <6 h sleep by polysomnography had increased prevalence of reported hypertension compared to those with ≥6 h sleep but found no significant differences in hypertension in those with insomnia and subjectively reported short sleep [48].

The associations between poorer sleep quality (reduced sleep efficiency and adverse changes in sleep architecture) and blood pressure are not as well defined as with sleep duration and insomnia. Multiple small studies demonstrate that reduced time in deeper stages of sleep (slow wave and REM sleep) as well as lower sleep efficiency are associated with blunted blood pressure dipping in healthy adults [49–51]. Poorer sleep quality may also contribute to the reduction in blood pressure dipping African-Americans experience compared to Caucasians [52]. Reduced sleep efficiency has been associated with prehypertension in adolescents in one study [45]. Ultimately, larger prospective studies are needed to further understand these associations, particularly since blunted dipping is associated with increased risk of cardiovascular mortality [53].

The evidence overwhelmingly suggests that insufficient sleep, particularly short sleep duration, increases risk of elevated blood pressure and incident hypertension, and there is also strong evidence supporting an association between insomnia and incident hypertension. To date, however, there are few published randomized control trials, and no large studies assessing whether therapies targeted at extending sleep or improving sleep may improve

blood pressure. A small randomized control study provides encouragement for future investigation. In this pilot study, 22 participants with prehypertension or stage 1 hypertension and habitual sleep duration of <7 h were randomized to receive 6-week of sleep extension or to a sleep-maintenance control group. 24 h beat to beat systolic and diastolic blood pressure was collected over a 24 h period pre and postintervention. 24 h recordings in the sleep maintenance group demonstrated large decreases in systolic (14 ± 3 mmHg) and diastolic (8 ± 3 mmHg) blood pressure from pre to postintervention. While the decrease in the sleep-maintenance group was not significant (7 ± 5 and 5 ± 4 mmHg reduction in systolic and diastolic blood pressure, respectively), the difference between groups was not significant, which may reflect a lack of power in this small sample. Larger investigations are needed to test the effect of behavioral interventions on blood pressure reduction, and this is an emerging area of interest [54]. Currently, there are trials underway evaluating cognitive behavioral therapy for insomnia and brief behavioral therapy for insomnia as a therapeutic target for lowering blood pressure.

Insufficient sleep and coronary heart disease

The effect of insufficient sleep on coronary heart disease (CHD) is more conflicting than that of insufficient sleep and blood pressure, and the relative effects of short sleep versus reduced sleep quality on incident CHD are also debated. There are no randomized control trials assessing sleep as a therapeutic target for CHD beyond treatment of obstructive sleep apnea. General mechanisms underlying a relationship between poor sleep and increased risk of CHD include increased blood pressure [55], diabetes [55], increased body mass index, and adverse alterations in markers of inflammation [56] and lipid levels [57] as already described. Mechanisms more specific to CHD include endothelial vascular dysfunction that could contribute to development and progression of atherosclerosis and subsequent acute coronary events. To this end, a study of 30 adult men demonstrated lower forearm blood flow response to intraarterial infusion of acetylcholine in short sleepers (total sleep time approximately 6 h) compared to normal sleeping controls (sleep duration of 7.7 h) as well as diminished nitrous oxide availability. Their data suggest that impaired nitrous-oxide-mediated endothelium-dependent vasodilation may be an important mechanism contributing to increased CHD risk in insufficient sleepers [20].

Overall, the largest prospective epidemiologic studies support the trend that short or insufficient sleep is associated with increased risk of CHD in both men and women [58,59], despite some smaller studies finding an association in only one sex or the other [60,61]. Additionally, some

data suggest that the combination of short sleep and disturbed sleep better predicts incident adverse CHD events compared to short sleep duration or insomnia alone [62]. We will present data from some of the largest prospective studies and discuss potential reasons for discrepancies in the literature.

The monitoring trends and determinants on cardiovascular disease (MONICA) Augsburg cohort study, a population sample of 3508 and 3388 middle aged German men and women, reported a significant association between self-reported short sleep (≤ 5 h) with incident myocardial infarction in women (hazard ratio 2.98, 95% confidence interval 1.48–6.03) but not men. They found no associations between self-reported difficulty initiating sleep or difficulty maintaining sleep and incident myocardial infarction. Participants were followed for a mean of 10 years, and health outcomes were ascertained by medical registries and death certificates. These results need to be cautiously interpreted due to the low number of incident cases (295 cases in men and 85 cases among women), particularly in those with shortest sleep duration, and while stratified analyses suggested sex differences, the test for statistical interaction between sex and sleep duration categories was not significant [61]. However, these findings suggest that there may be sex-specific variation in the effects of short sleep on cardiovascular outcomes due to different pathophysiologic manifestations of sleep deficit or responses to sleep disturbance in men compared to women and different expression of chronic inflammation in women compared to men [63].

In contrast, a smaller population-based Swedish cohort of 1870 men and women aged 45–65 found that poor sleep quality was associated with adverse cardiovascular outcomes in men rather than women and reported no relationship with short sleep in either sex. Specifically, self-reported difficulty initiating sleep, a key symptom of insomnia, was associated with increased coronary artery disease mortality in men but not women (relative risk 3.1, 95% confidence interval 1.5–6.3) [60]. Because there were fewer subjects in this study, the negative findings for short sleep and adverse cardiovascular outcomes may be related to lack of power. Alternatively, this study highlights that considering sleep duration without other information on sleep quality, particularly in small studies may inadequately characterize sleep-related stressors relevant to cardiovascular disease.

When evaluating cohort studies with larger numbers of participants, short sleep duration has a positive association with risk of CHD. For example, a large prospective study of 71,617 women aged 45–65 from the Nurse's Health Study found that ≤ 5 h self-reported sleep duration was predictive of incident CHD compared to 6 and > 7 h (relative risk 1.45, 95% confidence interval 1.1–1.92) [59].

The Whitehall II study, a large prospective study in London, England, sought to address the discrepancy of effect of insufficient sleep in men versus women as well as the relative effects of sleep duration versus sleep quality. 10,308 Men and women were evaluated for sleep duration and sleep quality using questions from the General Health Questionnaire-30 and then were followed for a mean of 15 years for development of CHD events including fatal CHD deaths, incident nonfatal myocardial infarction, or incident angina. They found no differences by sex in sleep complaints and risk of CHD, and in multivariate models, combining men and women found an increased risk of CHD events in those reporting disturbed sleep (hazard ratio 1.23, 95% confidence interval 1.07–1.43) but not self-reported short sleep (≤ 5 h as well as between 5 and 6 h). There was also some evidence of an interaction effect between short sleep and disturbed sleep, with participants with < 6 h sleep and report of low-quality sleep showing the highest hazard rate for incident CHD events (hazard ratio 1.45, 95% confidence interval 1.24–1.7) after adjusting for confounders [62]. The authors suggest that disturbances of the physiologic processes occurring during sleep, rather than the duration of sleep itself, may be driving the increased CHD risk.

A large prospective study to date examining sleep quality, sleep duration, and risk of incident CHD in 60,586 Asian adults found that < 6 h self-reported sleep duration or difficulty falling asleep/use of sleeping pills were associated with increased risk of CHD (hazard ratio 1.13, 95% confidence interval 1.04–1.23 and 1.31, 95% confidence interval 1.16–1.47, respectively) [58]. The primary weaknesses in this study were that incident CHD events were also self-reported, and sleep apnea was not accounted included as a covariate. The combined effects of sleep duration and sleep quality were not assessed.

A number of prospective observational studies have also shown an association between insomnia and risk of CHD and recurrent acute coronary syndrome [24]. The largest study collected information on subjective insomnia symptoms that impair work performance in 52,610 men and women followed for 11.4 years for first acute myocardial infarction. They found that difficulty initiating sleep, difficulty maintaining sleep, and complaint of non-restorative sleep are all associated with increased risk of acute myocardial infarction in men and women, and that difficulty initiating sleep was the sleep symptom most strongly associated with incident myocardial infarction [64]. The second largest study used data from the Taiwan National Health Insurance Research Database and matched individuals with and without insomnia ($n = 44,080$) by age, sex, and comorbidity. Individuals were followed for 10 years for acute myocardial infarction, and those with insomnia had a 68% increased risk of developing an

incident myocardial infarction (95% confidence interval 1.31–2.16) [65].

In summary, the largest prospective cohort studies report associations between reduced sleep duration and quality and risk of incident CHD [58,59], with some evidence that combining information on short sleep and poor sleep quality identify individuals at high risk for CHD [62]. The insomnia literature also supports associations between insomnia and incident CHD. Generally <5 h of sleep is more likely to be associated with risk of incident CHD events than sleep of higher durations, particularly if individuals also have reduced sleep quality. This is consistent with the insomnia literature that demonstrates insomnia coupled with objective short sleep may be a stronger predictor of adverse cardiovascular outcomes such as hypertension [47].

Insufficient sleep and heart failure

Inasmuch as insufficient sleep has been associated with hypertension and cardiovascular disease, it would seem reasonable to presume that a similar association exists with heart failure, given the common underlying mechanisms for these conditions. However, data on the association between insufficient sleep and heart failure are limited, and the relationship between heart failure and insufficient sleep is more difficult to understand given potential for bidirectionality. Heart failure may cause insufficient sleep due to symptoms such as paroxysmal nocturnal dyspnea or Cheyne Stoke Respiration, treatment with medications resulting in sleep fragmentation such as diuretics, or disease-related anxiety and depression. Subjective sleep assessments with use of standardized questionnaires in chronic heart failure patients have demonstrated difficulty initiating sleep, maintaining sleep, and shorter total sleep duration, and that heart failure patients with sleep complaints have reduced healthcare quality of life as compared to those without sleep complaints [66].

One of the few prospective studies to examine the association between self-reported sleep duration and incident heart failure, the British Regional Study, followed 3723 older men with and without pre-existing cardiovascular disease but without prevalent heart failure for approximately 9 years. Self-reported nighttime sleep duration of <6 h was associated with heart failure risk in men with preexisting cardiovascular disease. Regardless of duration of nighttime sleep, men without preexisting cardiovascular disease did not have increased risk of heart failure, although daytime napping appeared to associate with increased heart failure risk in this group [67]. Notably, obstructive sleep apnea was not assessed in this cohort, and given that daytime napping may reflect an underlying diagnosis of obstructive sleep apnea, a common sleep disorder in older men, and that obstructive sleep apnea may

be an independent risk factor for heart failure, it cannot be assumed that daytime napping was solely related to insufficient sleep in this cohort. As such, the relationship between insufficient sleep and heart failure in patients without pre-existing cardiovascular disease is not as clear.

Currently, prospective studies examining the relationship between sleep duration and incident heart failure are very limited. Some of these studies have demonstrated a lack of association between self-reported nighttime sleep duration and heart failure in the overall population [68,69]. However, it is of interest that when symptoms of sleep disturbance coexisted with reported short sleep duration, there was a demonstrable association with a composite cardiovascular disease outcome that included heart failure, though not specific to heart failure [69].

Large prospective cohort studies have demonstrated similar findings with regards to an association between self-reported insomnia symptoms (difficulty initiating, difficulty maintaining sleep and nonrestorative sleep) and increased risk of incident heart failure [70,71]. One such study was limited to a cohort of overweight middle-aged men and demonstrated that the observed relationship was independent of their established risk factors for heart failure [71]. Based on these data, insufficient sleep may potentially play a role in incident heart failure but it appears that overall sleep-related cardiovascular consequences are more pronounced in the presence of coexisting sleep symptoms. Short sleep duration appears to have a more evident impact on heart failure risk in patients with preexisting cardiovascular disease.

Insufficient sleep and stroke

Several of the changes observed with insufficient sleep are linked to mechanisms that potentiate risk factors for stroke discussed earlier such as hypertension, vascular dysfunction and inflammation.

The majority of these studies are limited by use of subjective reports of sleep duration. Short sleep (<6 h) has been associated with increased risk for stroke in several studies. The European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study followed 23,620 middle-aged men and women over 8 years and short sleepers were found to have a significantly increased risk for ischemic and hemorrhagic stroke [72]. A study of 93,175 postmenopausal women aged 50–79 years followed over 7.5 years in the Women's Health Initiative study found an association between short sleep (≤ 6 h) and ischemic stroke in subjects without preexisting cardiovascular disease or diabetes at baseline [73]. The MONICA/KORA Augsburg cohort study followed subjects aged 25–74 years over a 14-year period and found short sleep (≤ 5 h) to be significantly associated with a 2.3-fold increase in stroke in men [74]. Another study followed 5666

employed participants from the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study aged ≥ 45 years, over a 3-year period, collecting data on self-reported sleep duration and self-reported stroke symptoms. In the overall sample, short sleep duration was not associated with incident stroke symptoms in fully adjusted models, but normal weight individuals were at increased risk for stroke symptoms after stratification by BMI. The study concluded that short sleep duration (< 6 h) is prospectively associated with a fourfold increased risk of self-reported stroke symptoms in normal weight individuals after adjusting for demographics, stroke risk factors, health behaviors, and diet (hazard ratio 4.2, 95% confidence interval 1.62–10.84) [75].

On the other hand, there have also been prospective studies that have not supported these associations [76–78]. A prospective study of 9692 stroke-free participants aged 42–81 from the European Prospective Investigation into Cancer-Norfolk cohort found that long sleep but not short sleep was associated with a higher risk of stroke [78].

There are also studies that have found that short sleep is independently associated with an increased risk of stroke [79,80]. The Singapore Chinese Health Study, a cohort of 63,257 adults aged 45–74 showed that short sleep (≤ 5 h), when compared to 7 h of sleep duration was significantly associated with increased risk for ischemic and non-specified stroke mortality (but not hemorrhagic stroke) in subjects with hypertension [80].

Insomnia is also implicated as a risk factor for stroke [81]. When insomnia symptoms coexist with objective short sleep duration (defined as < 5 h on polysomnography), it represents a more severe phenotype and carries a higher risk for increased heart rate variability, hypertension, diabetes, neurocognitive impairment, and mortality when compared with insomnia with longer objective sleep [4,47,82].

A retrospective cohort study of 21,438 individuals with clinically diagnosed insomnia (with an ICD 9 diagnosis code of insomnia) and 64,314 age and sex matched non-insomniac controls taken from the Taiwan National Health Insurance Research database and tracked for 4 years, showed that individuals with insomnia have a 54% higher risk of developing stroke; this risk was highest in young adults aged 18–34 years. In addition, those with persistent insomnia had a higher 3-year cumulative incidence of stroke compared to the remission group. Patients with sleep apnea were excluded [81].

In conclusion, several large studies have established an association between short sleep and incident stroke. Mechanisms are likely similar to those relating sleep insufficiency with CHD. The coexistence of insomnia symptoms may confer a higher risk than short sleep alone [69].

Conclusions

The overall literature supports an association between insufficient sleep (whether defined as short sleep duration, reduced sleep quality, or insomnia symptoms) and incident cardiovascular disease, particularly hypertension, stroke, and CHD. Additionally, insomnia, coupled with objective short sleep duration, appears to be a high-risk phenotype with increased risk of developing incident cardiovascular disease. Mechanisms underlying the pathophysiology of this relationship, including increased sympathetic activity, cortisol dysregulation, increased inflammation, and vascular dysfunction resulting from insufficient sleep. Larger epidemiologic studies evaluating insufficient sleep and heart failure are needed to have sufficient statistical power to address this potential association. The majority of studies do not account for obstructive sleep apnea or other underlying sleep disorders that may reduce sleep duration and/or quality, and therefore, it is unclear the extent to which sleep disordered breathing may be confounding or mediating this relationship. Also, since most studies are based on self-report data, there is little known about how sleep fragmentation and sleep architecture influences cardiovascular risk. Additionally, future studies are needed assessing sleep quality/duration as a therapeutic target in modifying cardiovascular disease risk, particularly for hypertension, CHD, and stroke.

References

- [1] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC, Adams Hillard PJ. National sleep foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 2015;1(1):40–3. <https://doi.org/10.1016/j.sleb.2014.12.010>.
- [2] Buysse DJ. Insomnia. *JAMA* 2013;309(7):706–16. <https://doi.org/10.1001/jama.2013.193>.
- [3] Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Basta M, Fernández-Mendoza J, Bixler EO. Insomnia with short sleep duration and mortality: the Penn State cohort. *Sleep* 2010;33(9):1159–64. <https://doi.org/10.1093/sleep/33.9.1159>.
- [4] Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev* 2013;17(4):241–54. <https://doi.org/10.1016/j.smrv.2012.09.005>.
- [5] Xiao Q, Arem H, Moore SC, Hollenbeck AR, Matthews CE. A large prospective investigation of sleep duration, weight change, and obesity in the NIH-AARP diet and health study cohort. *Am J Epidemiol* 2013;178(11):1600–10. <https://doi.org/10.1093/aje/kwt180>.
- [6] Ogilvie RP, Redline S, Bertoni AG, Chen X, Ouyang P, Szkołko M, Lutsey PL. Actigraphy measured sleep indices and adiposity: the multi-ethnic study of atherosclerosis (MESA). *Sleep* 2016;39(9):1701–8. <https://doi.org/10.5665/sleep.6096>.

- [7] Sepahvand E, Jalali R, Mirzaei M, Kargar Jahromi M. Association between short sleep and body mass index, hypertension among acute coronary syndrome patients in coronary care unit. *Global J Health Sci* 2015;7(3):134–9. <https://doi.org/10.5539/gjhs.v7n3p134>.
- [8] Jackson CL, Patel SR, Jackson WB, Lutsey PL, Redline S. Agreement between self-reported and objectively measured sleep duration among white, black, Hispanic, and Chinese adults in the United States: multi-ethnic study of atherosclerosis. *Sleep* 2018;41(6). <https://doi.org/10.1093/sleep/zsy057>.
- [9] Javaheri S, Zhao YY, Punjabi NM, Quan SF, Gottlieb DJ, Redline S. Slow-wave sleep is associated with incident hypertension: the sleep heart health study. *Sleep* 2018;41(1). <https://doi.org/10.1093/sleep/zsx179>.
- [10] Patel SR, Hayes AL, Blackwell T, Evans DS, Ancoli-Israel S, Wing YK, Stone KL. The association between sleep patterns and obesity in older adults. *Int J Obes* 2014;38(9):1159–64. <https://doi.org/10.1038/ijo.2014.13>.
- [11] Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci USA* 2008;105(3):1044–9. <https://doi.org/10.1073/pnas.0706446105>.
- [12] Blackwell T, Paudel M, Redline S, Ancoli-Israel S, Stone KL. A novel approach using actigraphy to quantify the level of disruption of sleep by in-home polysomnography: the MrOS Sleep Study: sleep disruption by polysomnography. *Sleep Med* 2017;32:97–104. <https://doi.org/10.1016/j.sleep.2016.11.019>.
- [13] Ogawa Y, Kanbayashi T, Saito Y, Takahashi Y, Kitajima T, Takahashi K, Hishikawa Y, Shimizu T. Total sleep deprivation elevates blood pressure through arterial baroreflex resetting: a study with microneurographic technique. *Sleep* 2003;26(8):986–9. <https://doi.org/10.1093/sleep/26.8.986>.
- [14] Castro-Diehl C, Roux AVD, Redline S, Seeman T, Shrager SE, Shea S. Association of sleep duration and quality with alterations in the hypothalamic-pituitary adrenocortical axis: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Clin Endocrinol Metabol* 2015;100(8):3149–58. <https://doi.org/10.1210/jc.2015-1198>.
- [15] Foam S, Simpson N, Nemeth E, Scott-Sutherland J, Gautam S, Haack M. Sleep characteristics as predictor variables of stress systems markers in insomnia disorder. *J Sleep Res* 2015;24(3):296–304. <https://doi.org/10.1111/jsr.12259>.
- [16] Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab* 2001;86(8):3787–94. <https://doi.org/10.1210/jcem.86.8.7778>.
- [17] Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, Mullington JM. Effect of sleep loss on C-Reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol* 2004;43(4):678–83. <https://doi.org/10.1016/j.jacc.2003.07.050>.
- [18] Parthasarathy S, Vasquez MM, Halonen M, Bootzin R, Quan SF, Martinez FD, Guerra S. Persistent insomnia is associated with mortality risk. *Am J Med* 2015;128(3):268. <https://doi.org/10.1016/j.amjmed.2014.10.015>.
- [19] Shearer WT, Reuben JM, Mullington JM, Price NJ, Lee BN, O'brian Smith E, Szuba MP, Van Dongen HPA, Dinges DF. Soluble TNF- α receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol* 2001;107(1):165–70. <https://doi.org/10.1067/mai.2001.112270>.
- [20] Bain AR, Weil BR, Diehl KJ, Greiner JJ, Stauffer BL, DeSouza CA. Insufficient sleep is associated with impaired nitric oxide-mediated endothelium-dependent vasodilation. *Atherosclerosis* 2017;265:41–6. <https://doi.org/10.1016/j.atherosclerosis.2017.08.001>.
- [21] Alter-Wolf S, Blomberg BB, Riley RL. Deviation of the B cell pathway in senescent mice is associated with reduced surrogate light chain expression and altered immature B cell generation, phenotype, and light chain expression. *J Immunol* 2009;182(1):138–47. <https://doi.org/10.4049/jimmunol.182.1.138>.
- [22] Wu Y, Zhai L, Zhang D. Sleep duration and obesity among adults: a meta-analysis of prospective studies. *Sleep Med* 2014;15(12):1456–62. <https://doi.org/10.1016/j.sleep.2014.07.018>.
- [23] Khan MS, Aouad R. The effects of insomnia and sleep loss on cardiovascular disease. *Sleep Med Clin* 2017;12(2):167–77. <https://doi.org/10.1016/j.jsmc.2017.01.005>.
- [24] Javaheri S, Redline S. Insomnia and risk of cardiovascular disease. *Chest* 2017;152(2):435–44. <https://doi.org/10.1016/j.chest.2017.01.026>.
- [25] Spiegelhalder K, Fuchs L, Ladwig J, Kyle SD, Nissen C, Voderholzer U, Feige B, Riemann D. Heart rate and heart rate variability in subjectively reported insomnia. *J Sleep Res* 2011;20(1):137–45. <https://doi.org/10.1111/j.1365-2869.2010.00863.x>.
- [26] Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Breen EC, Witarama T, Yokomizo M, Lavretsky H, Carroll JE, Motivala SJ, Bootzin R, Nicassio P. Cognitive behavioral therapy vs. Tai Chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. *Sleep* 2014;37(9):1543–52. <https://doi.org/10.5665/sleep.4008>.
- [27] Cassidy S, Chau JY, Catt M, Bauman A, Trenell MI. Low physical activity, high television viewing and poor sleep duration cluster in overweight and obese adults: a cross-sectional study of 398,984 participants from the UK Biobank. *Int J Behav Nutr Phys Activ* 2017;14(1). <https://doi.org/10.1186/s12966-017-0514-y>.
- [28] St-Onge M-P, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. *Int J Obes* 2014;38(3):411–6. <https://doi.org/10.1038/ijo.2013.114>.
- [29] Koo DL, Nam H, Thomas RJ, Yun CH. Sleep disturbances as a risk factor for stroke. *J Stroke* 2018;20(1):12–32. <https://doi.org/10.5853/jos.2017.02887>.
- [30] Rahman A, Hasan AU, Nishiyama A, Kobori H. Altered circadian timing system-mediated non-dipping pattern of blood pressure and associated cardiovascular disorders in metabolic and kidney diseases. *Int J Mol Sci* 2018;19(2). <https://doi.org/10.3390/ijms19020400>.
- [31] Carrillo-Larco RM, Bernabe-Ortiz A, Sacksteder KA, Diez-Canseco F, Cárdenas MK, Gilman RH, Miranda JJ. Association between sleep difficulties as well as duration and hypertension: is BMI a mediator? *Glob Health Epidemiol Genom* 2017;2:e12. <https://doi.org/10.1017/gheg.2017.10>.
- [32] Brotman DJ, Davidson MB, Boumitri M, Vidt DG. Impaired diurnal blood pressure variation and all-cause mortality. *Am J Hypertens* 2008;21(1):92–7. <https://doi.org/10.1038/ajh.2007.7>.
- [33] Jackowska M, Steptoe A. Sleep and future cardiovascular risk: prospective analysis from the English Longitudinal Study of Ageing. *Sleep Med* 2015;16(6):768–74. <https://doi.org/10.1016/j.sleep.2015.02.530>.
- [34] Sauvet F, Leftheriotis G, Gomez-Merino D, Langrume C, Drogou C, Van Beers P, Bourrilhon C, Florence G, Chennaoui M. Effect of acute sleep deprivation on vascular function in healthy

- subjects. *J Appl Physiol* 2010;108(1):68–75. <https://doi.org/10.1152/japplphysiol.00851.2009>.
- [35] Sauvet F, Drogou C, Bougard C, Arnal PJ, Dispersyn G, Bourrilhon C, Rabat A, Van Beers P, Gomez-Merino D, Faraut B, Leger D, Chennaoui M. Vascular response to 1 week of sleep restriction in healthy subjects. A metabolic response? *Int J Cardiol* 2015;190(1):246–55. <https://doi.org/10.1016/j.ijcard.2015.04.119>.
- [36] Lusardi P, Zoppi A, Preti P, Pesce RM, Piazza E, Fogari R. Effects of insufficient sleep on blood pressure in hypertensive patients: a 24-h study. *Am J Hypertens* 1999;12(1 I):63–8. [https://doi.org/10.1016/S0895-7061\(98\)00200-3](https://doi.org/10.1016/S0895-7061(98)00200-3).
- [37] Knutson KL, Van Cauter E, Rathouz PJ, Yan LL, Hulley SB, Liu K, Lauderdale DS. Association between sleep and blood pressure in midlife: the CARDIA sleep study. *Arch Intern Med* 2009;169(11):1055–61. <https://doi.org/10.1001/archinternmed.2009.119>.
- [38] Yadav D, Hyun DS, Ahn SV, Koh SB, Kim JY. A prospective study of the association between total sleep duration and incident hypertension. *J Clin Hypertens* 2017;19(5):550–7. <https://doi.org/10.1111/jch.12960>.
- [39] Fernandez-Mendoza J, He F, LaGrotte C, Vgontzas AN, Liao D, Bixler EO. Impact of the metabolic syndrome on mortality is modified by objective short sleep duration. *J Am Heart Assoc* 2017;6(5). <https://doi.org/10.1161/JAHA.117.005479>.
- [40] Fernandez-Mendoza J, He F, Vgontzas AN, Liao D, Bixler EO. Objective short sleep duration modifies the relationship between hypertension and all-cause mortality. *J Hypertens* 2017;35(4):830–6. <https://doi.org/10.1097/HJH.0000000000001253>.
- [41] Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK, Malaspina D. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* 2006;47(5):833–9. <https://doi.org/10.1161/01.HYP.0000217362.34748.e0>.
- [42] Deng H-B, Tam T, Chung-Ying Zee B, Chung RY-N, Su X, Jin L, Chan T-C, Chang L-Y, Yeoh E-K, Xiang QL. Short sleep duration increases metabolic impact in healthy adults: a population-based cohort study. *Sleep* 2017;40(10). <https://doi.org/10.1093/sleep/zsx130>.
- [43] Wang Y, Mei H, Jiang YR, Sun WQ, Song YJ, Liu SJ, Jiang F. Relationship between duration of sleep and hypertension in adults: a meta-analysis. *J Clin Sleep Med* 2015;11(9):1047–56. <https://doi.org/10.5664/jcsm.5024>.
- [44] Lin M, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertens Res* 2013;36(11):985–95. <https://doi.org/10.1038/hr.2013.70>.
- [45] Javaheri S, Storfer-Isser A, Rosen CL, Redline S. Sleep quality and elevated blood pressure in adolescents. *Circulation* 2008;118(10):1034–40. <https://doi.org/10.1161/CIRCULATIONAHA.108.766410>.
- [46] Bal C, Öztürk A, Çiçek B, Özdemir A, Zararsız G, Ünalan D, Zararsız GE, Korkmaz S, Göksüyük D, Eldem V, İsmailogulları S, Erdem E, Mazıcıoğlu MM, Kurtoğlu S. The relationship between blood pressure and sleep duration in Turkish children: a cross-sectional study. *J Clin Res Pediatr Endocrinol* 2018;10(1):51–8. <https://doi.org/10.4274/jcrpe.4557>.
- [47] Fernandez-Mendoza J, Vgontzas AN, Liao D, Shaffer ML, Velasco Bueno A, Basta M, Bixler EO. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension* 2012;60(4):929–35. <https://doi.org/10.1161/HYPERTENSIONAHA.112.193268>.
- [48] Bathgate CJ, Edinger JD, Wyatt JK, Krystal AD. Objective but not subjective short sleep duration associated with increased risk for hypertension in individuals with insomnia. *Sleep* 2016;39(5):1037–45. <https://doi.org/10.5665/sleep.5748>.
- [49] Hinderliter AL, Routledge FS, Blumenthal JA, Koch G, Hussey MA, Wohlgemuth WK, Sherwood A. Reproducibility of blood pressure dipping: relation to day-to-day variability in sleep quality. *J Am Soc Hypert* 2013;7(6):432–9. <https://doi.org/10.1016/j.jash.2013.06.001>.
- [50] Loredo JS, Nelesen R, Ancoli-Israel S, Dimsdale JE. Sleep quality and blood pressure dipping in normal adults. *Sleep* 2004;27(6):1097–103. <https://doi.org/10.1093/sleep/27.6.1097>.
- [51] Silva AP, Moreira C, Bicho M, Paiva T, Clara JG. Nocturnal sleep quality and circadian blood pressure variation. *Revista portuguesa de cardiologia: órgão oficial da Sociedade Portuguesa de Cardiologia = Portuguese Journal of Cardiology: an Official Journal of the Portuguese Society of Cardiology* 2000;19(10):991–1005.
- [52] Sherwood A, Routledge FS, Wohlgemuth WK, Hinderliter AL, Kuhn CM, Blumenthal JA. Blood pressure dipping: ethnicity, sleep quality, and sympathetic nervous system activity. *Am J Hypertens* 2011;24(9):982–8. <https://doi.org/10.1038/ajh.2011.87>.
- [53] Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Hond ED, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension* 2005;46(1):156–61. <https://doi.org/10.1161/01.HYP.0000170138.56903.7a>.
- [54] Haack M, Serrador J, Cohen D, Simpson N, Meier-Ewert H, Mullington JM. Increasing sleep duration to lower beat-to-beat blood pressure: a pilot study. *J Sleep Res* 2013;22(3):295–304. <https://doi.org/10.1111/jsr.12011>.
- [55] Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006;29(3):657–61. <https://doi.org/10.2337/diacare.29.03.06/dc05-0879>.
- [56] Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, Chrousos GP. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab* 2004;89(5):2119–26. <https://doi.org/10.1210/jc.2003-031562>.
- [57] Kinuhata S, Hayashi T, Sato KK, Uehara S, Oue K, Endo G, Kambe H, Fukuda K. Sleep duration and the risk of future lipid profile abnormalities in middle-aged men: the Kansai Healthcare Study. *Sleep Med* 2014;15(11):1379–85. <https://doi.org/10.1016/j.sleep.2014.06.011>.
- [58] Lao XQ, Liu X, Deng HB, Chan TC, Ho KF, Wang F, Vermeulen R, Tam T, Wong MCS, Tse LA, Chang LY, Yeoh EK. Sleep quality, sleep duration, and the risk of coronary heart disease: a prospective cohort study with 60, 586 adults. *J Clin Sleep Med* 2018;14(1):109–17. <https://doi.org/10.5664/jcsm.6894>.
- [59] Ayas NT, White DP, Manson JAE, Stampfer MJ, Speizer FE, Malhotra A, Hu FB. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med* 2003;163(2):205–9. <https://doi.org/10.1001/archinte.163.2.205>.
- [60] Mallon L, Broman J-E, Hetta J. Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a

- middle-aged Swedish population. *J Intern Med* 2002;251(3):207–16. <https://doi.org/10.1046/j.1365-2796.2002.00941.x>.
- [61] Meisinger C, Heier M, Löwel H, Schneider A, Döring A. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study. *Sleep* 2007;30(9):1121–7. <https://doi.org/10.1093/sleep/30.9.1121>.
- [62] Chandola T, Ferrie JE, Perski A, Akbaraly T, Marmot MG. The effect of short sleep duration on coronary heart disease risk is greatest among those with sleep disturbance: a prospective study from the Whitehall II cohort. *Sleep* 2010;33(6):739–44. <https://doi.org/10.1093/sleep/33.6.739>.
- [63] Ishii S, Karlamangla AS, Bote M, Irwin MR, Jacobs DR, Cho HJ, Seeman TE. Gender, obesity and repeated elevation of C-reactive protein: data from the CARDIA cohort. *PLoS One* 2012;7(4). <https://doi.org/10.1371/journal.pone.0036062Japan>.
- [64] Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. *Circulation* 2011;124(19):2073–81. <https://doi.org/10.1161/CIRCULATIONAHA.111.025858>.
- [65] Hsu CY, Chen YT, Chen MH, Huang CC, Chiang CH, Huang PH, Chen JW, Chen TJ, Lin SJ, Leu HB, Chan WL. The association between insomnia and increased future cardiovascular events: a nationwide population-based study. *Psychosom Med* 2015;77(7):743–51. <https://doi.org/10.1097/PSY.00000000000000199>.
- [66] Broström A, Strömberg A, Dahlström U, Fridlund B, Difficulties S, Sleepiness D. Health-related quality of life in patients with chronic heart failure. *J Cardiovasc Nurs* 2004;19(4):234–42. <https://doi.org/10.1097/00005082-200407000-00003>.
- [67] Wannamethee SG, Papacosta O, Lennon L, Whincup PH. Self-reported sleep duration, napping, and incident heart failure: prospective associations in the British regional heart study. *J Am Geriatr Soc* 2016;64(9):1845–50. <https://doi.org/10.1111/jgs.14255>.
- [68] Kim Y, Wilkens LR, Schembre SM, Henderson BE, Kolonel LN, Goodman MT. Insufficient and excessive amounts of sleep increase the risk of premature death from cardiovascular and other diseases: the Multiethnic Cohort Study. *Prev Med* 2013;57(4):377–85. <https://doi.org/10.1016/j.ypmed.2013.06.017>.
- [69] Westerlund A, Bellocchio R, Sundström J, Adami HO, Åkerstedt T, Trolle Lagerros Y. Sleep characteristics and cardiovascular events in a large Swedish cohort. *Eur J Epidemiol* 2013;28(6):463–73. <https://doi.org/10.1007/s10654-013-9802-2>.
- [70] Laugsand LE, Strand LB, Platou C, Vatten LJ, Janszky I. Insomnia and the risk of incident heart failure: a population study. *Eur Heart J* 2014;35(21):1382–93. <https://doi.org/10.1093/eurheartj/eht019>.
- [71] Ingelsson E, Lind L, Ärnlöv J, Sundström J. Sleep disturbances independently predict heart failure in overweight middle-aged men. *Eur J Heart Fail* 2007;9(2):184–90. <https://doi.org/10.1016/j.ejheart.2006.05.012>.
- [72] von Ruesten A, Weikert C, Fietze I, Boeing H, Bayer A. Association of sleep duration with chronic diseases in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. *PLoS One* 2012;7(1):e30972. <https://doi.org/10.1371/journal.pone.0030972>.
- [73] Chen JC, Brunner RL, Ren H, Wassertheil-Smoller S, Larson JC, Levine DW, Allison M, Naughton MJ, Stefanick ML. Sleep duration and risk of ischemic stroke in postmenopausal women. *Stroke* 2008;39(12):3185–92. <https://doi.org/10.1161/STROKEAHA.108.521773>.
- [74] Katharina Helbig A, Stöckl D, Heier M, Ladwig K-H, Meisinger C, Ferri R. Symptoms of insomnia and sleep duration and their association with incident strokes: findings from the population-based MONICA/KORA Augsburg cohort study. *PLoS One* 2015;10(7):e0134480. <https://doi.org/10.1371/journal.pone.0134480>.
- [75] Ruiter Petrov ME, Letter AJ, Howard VJ, Kleindorfer D. Self-reported sleep duration in relation to incident stroke symptoms: nuances by body mass and race from the REGARDS study. *J Stroke Cerebrovasc Dis* 2014;23(2):e123. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.09.009>.
- [76] Leng Y, Cappuccio FP, Wainwright NWJ, Surtees PG, Luben R, Brayne C, Khaw KT. Sleep duration and risk of fatal and nonfatal stroke: a prospective study and meta-analysis. *Neurology* 2015;84(11):1072–9. <https://doi.org/10.1212/WNL.0000000000001371>.
- [77] Toshiaki K, Wada K, Nakamura K, Tsuji M, Tamura T, Konishi K, Nagata C. Sleep duration and the risk of mortality from stroke in Japan: the Takayama Cohort Study. *J Epidemiol* 2016;26(3):123–30. <https://doi.org/10.2188/jea.je20140272>.
- [78] He Q, Sun H, Wu X, Zhang P, Dai H, Ai C, Shi J. Sleep duration and risk of stroke: a dose-response meta-analysis of prospective cohort studies. *Sleep Med* 2017;32:66–74. <https://doi.org/10.1016/j.sleep.2016.12.012>.
- [79] Li W, Wang D, Cao S, Yin X, Gong Y, Gan Y, Zhou Y, Lu Z. Sleep duration and risk of stroke events and stroke mortality: a systematic review and meta-analysis of prospective cohort studies. *Int J Cardiol* 2016;223:870–6. <https://doi.org/10.1016/j.ijcard.2016.08.302>.
- [80] Pan A, De Silva DA, Yuan JM, Koh WP. Sleep duration and risk of stroke mortality among Chinese adults: Singapore Chinese health study. *Stroke* 2014;45(6):1620–5. <https://doi.org/10.1161/STROKEAHA.114.005181>.
- [81] Wu MP, Lin HJ, Weng SF, Ho CH, Wang JJ, Hsu YW. Insomnia subtypes and the subsequent risks of stroke: report from a nationally representative cohort. *Stroke* 2014;45(5):1349–54. <https://doi.org/10.1161/STROKEAHA.113.003675>.
- [82] Fernandez-Mendoza J, Calhoun S, Bixler EO, Pejovic S, Karataraki M, Liao D, Vela-Bueno A, Ramos-Platon MJ, Sauder KA, Vgontzas AN. Insomnia with objective short sleep duration is associated with deficits in neuropsychological performance: a general population study. *Sleep* 2010;33(4):459–65. <https://doi.org/10.1093/sleep/33.4.459>.

This page intentionally left blank

Chapter 20

Sleep health and diabetes: The role of sleep duration, quality, disorders, and circadian rhythm on diabetes

Mary Carrasco^{a, b}, Carolina Scaramutti-Gladfelter^{a, b}, Sandra Wittleder^c, Rhoda Moise^b, Sujata Thawani^d, Sophia Tong^e, Debbie Chung^b, Girardin Jean-Louis^b and Azizi A. Seixas^{a, b}

^aDepartment of Informatics and Health Data Science, University of Miami Miller School of Medicine, Miami, FL, United States; ^bDepartment of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States; ^cDepartment of Medicine, NYU Grossman School of Medicine, New York, NY, United States; ^dDepartment of Neurology, NYU Langone Health, New York, NY, United States;

^eMacaulay Honors College, Hunter College, CUNY, New York, NY, United States

Overview

The current chapter extensively examines the role of sleep health as both a risk and protective factor in relation to diabetes outcomes. It offers a comprehensive review of the existing literature, exploring how various aspects of sleep, including duration, quality, sleep architecture (such as spindles, rapid eye movement sleep, and slow wave sleep), sleep disorders (like insomnia and obstructive sleep apnea), and circadian rhythm, influence the likelihood of developing type 2 diabetes and its associated complications. The chapter captures how inadequate sleep duration, poor sleep quality, and disruptions in sleep architecture may contribute to the development of diabetes, leading to unhealthy glucose levels, poor glycemic control, insulin resistance, and elevated hemoglobin A1c levels. Conversely, we also highlight evidence suggesting that certain sleep parameters, when optimized, could potentially mitigate the risk of diabetes and related outcomes. To provide a thorough understanding of the mechanisms underlying the relationship between sleep and diabetes, we draw upon a wide range of research and evidence, including epidemiological, observational, clinical trials, and experimental studies [1]. By elucidating both the risk and protective effects of sleep health, this chapter aims to inform strategies for diabetes prevention and management in clinical practice and population health management.

Understanding physiological and mechanistic causes of diabetes

Type 2 diabetes (T2D) is characterized by a complex interplay of pathophysiological mechanisms that disrupt normal glucose metabolism and lead to hyperglycemia. Central to the development of T2D is insulin resistance, where tissues exhibit reduced responsiveness to insulin, impairing glucose uptake and regulation. This insulin resistance prompts the pancreas to produce more insulin to compensate, resulting in elevated insulin levels (hyperinsulinemia). However, over time, the pancreatic beta cells may struggle to meet the increased demand for insulin secretion, leading to inadequate insulin levels to control blood glucose effectively. Beta cell dysfunction can arise from chronic exposure to elevated glucose and insulin levels, leading to cellular stress and damage. In addition, genetic factors and inflammatory mediators may contribute to beta-cell dysfunction. As beta-cell function declines, insufficient insulin secretion further exacerbates hyperglycemia, contributing to the progression of T2D. This combination of insulin resistance and beta-cell dysfunction culminates in persistent hyperglycemia, a hallmark feature of T2D that underlies many of its complications [2]. The combination of insulin resistance and beta-cell dysfunction results in persistent hyperglycemia, characterized by elevated blood glucose levels. Hyperglycemia contributes

to the development of various complications associated with T2D, including cardiovascular disease, neuropathy, nephropathy, and retinopathy. Moreover, sustained hyperglycemia can further exacerbate insulin resistance and beta-cell dysfunction, creating a vicious cycle that perpetuates the progression of the disease (Fig. 20.1).

In addition to insulin resistance and beta-cell dysfunction, oxidative stress plays a significant role in the pathophysiology of T2D. Hyperglycemia and insulin resistance promote the production of reactive oxygen species (ROS) and oxidative stress. ROS can damage cellular structures, including lipids, proteins, and DNA, leading to impaired cellular function and increased inflammation [2]. Oxidative stress can disrupt signaling pathways involved in insulin action, further exacerbating insulin resistance and beta-cell dysfunction. The resulting cellular damage and inflammation contribute to the pathogenesis of T2D and its associated complications (Fig. 20.2).

Mitochondrial dysfunction further exacerbates metabolic abnormalities in T2D, disrupting cellular energy production and contributing to insulin resistance. Impaired mitochondrial function contributes to metabolic abnormalities and insulin resistance. Mitochondria play a crucial role in cellular energy production through oxidative phosphorylation. Dysfunction in mitochondrial metabolism can lead to decreased adenosine triphosphate (ATP) production, impairing cellular energy homeostasis and contributing to insulin resistance. Dysfunctional

mitochondria can produce excess ROS, exacerbating oxidative stress and further impairing insulin signaling pathways. Chronic exposure to elevated glucose and fatty acids can disrupt ER function, triggering ER stress. ER stress activates signaling pathways leading to inflammation, insulin resistance, beta-cell dysfunction, and apoptosis, further exacerbating the progression of T2D. These cellular stress responses, including oxidative stress, mitochondrial dysfunction, and ER stress, collectively contribute to the progression of T2D and its associated complications (Fig. 20.3).

Chronic low-grade inflammation is another key player in the pathophysiology of T2D, often observed in conjunction with obesity, insulin resistance, and metabolic dysfunction. Inflammation impairs insulin signaling pathways, contributing to insulin resistance and beta-cell dysfunction. Inflammatory processes not only impair insulin signaling but also contribute to the progression of T2D complications. In addition, inflammatory mediators can directly damage pancreatic beta cells, further exacerbating insulin deficiency. The resulting inflammation contributes to the pathophysiology of T2D and its associated complications. The confluence of obesity and downstream inflammatory processes leads to the secretion of pro-inflammatory cytokines and adipokines, creating a state of systemic inflammation (Fig. 20.4).

In conclusion, the complex interplay of pathophysiological mechanisms underscores the profound impact of

Poor sleep can impair beta cell function in type II diabetes leading to inadequate insulin levels

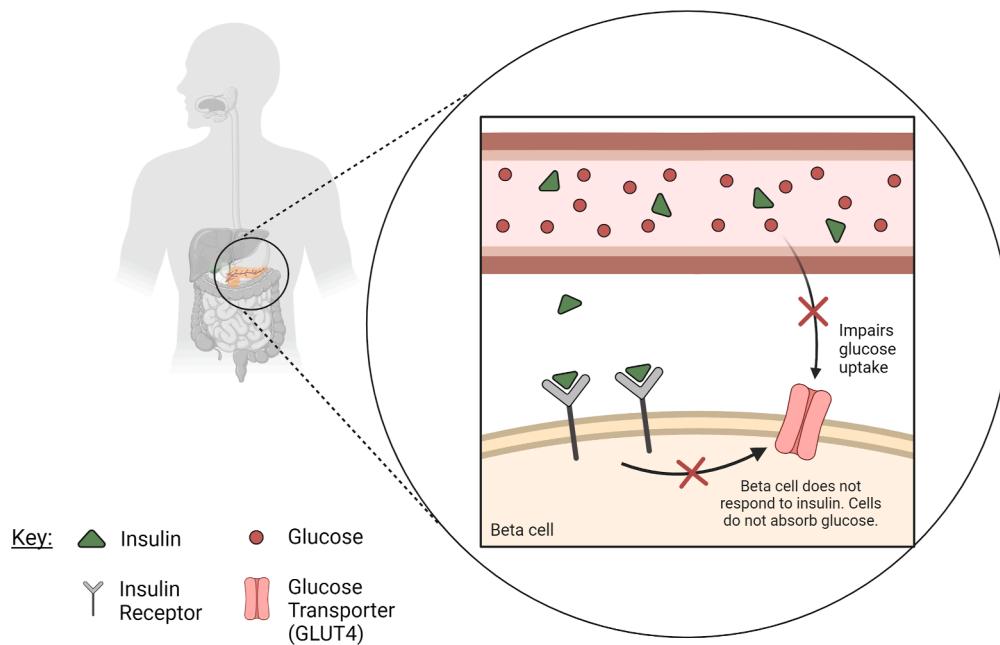


FIGURE 20.1 The role of poor sleep and impaired beta cell function in type 2 diabetes leading to insufficient insulin levels.

Poor sleep can exacerbate insulin resistance, resulting in hyperinsulinemia and hyperglycemia in type II diabetes

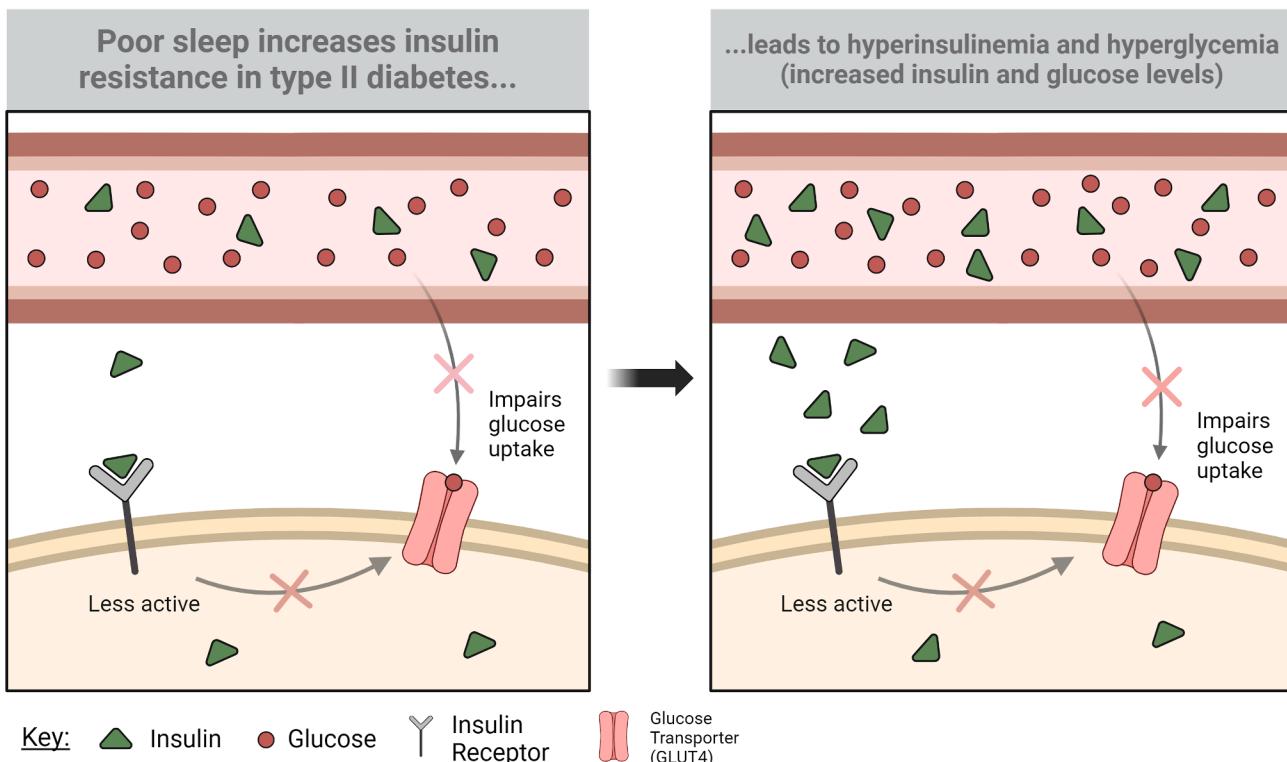


FIGURE 20.2 Hyperinsulinemia and hyperglycemia in type 2 diabetes as a result of increased insulin resistance due to poor sleep.

T2D on both clinical management and population health. With more than half a billion individuals affected globally, and projections indicating a doubling of this figure within the next 30 years, T2D stands as one of the top 10 leading causes of death and disability worldwide, with varying prevalence rates across regions [3]. Understanding the intricacies of T2D is vital for developing effective strategies to prevent, manage, and treat the condition. While diet/nutrition and exercise have received considerable attention in T2D management, the role of sleep remains relatively understudied. Bridging this knowledge gap is imperative to comprehensively address the modifiable factors influencing T2D pathophysiology. By exploring the modulatory effects of diet/nutrition, exercise, and sleep, we can unlock insights into novel therapeutic avenues and personalized interventions. By doing so, we aim to improve clinical outcomes for individuals with T2D and alleviate the broader burden of the disease on population health, ultimately paving the way for more effective management and prevention strategies in the future.

Objective and subjective sleep health parameters and diabetes risk

Sleep health in humans is multifactorial and heterogeneous, and captures their 24-h biological and behavioral sleep-wake profile. Framing sleep within a circadian biology perspective re-conceptualizes how we understand sleep-wake cycle and how behaviors and biological processes during the day and night influence each other. From this perspective, sleep consists of several: (1) subjective parameters: such as sleep quality/satisfaction, alertness, sleepiness, and (2) objective parameters: such as sleep duration, efficiency (sleep latency, wake after sleep onset), and timing. Abnormal levels of these parameters have been linked with adverse functional and health outcomes, such as accidents, cognitive impairment, impaired performance, cardiovascular-cardiometabolic health conditions (obesity, hypertension, and diabetes), poor brain health (dementia and accelerated aging), mental health, and mortality. The focus of the current chapter is to describe extant evidence

Poor sleep can impair mitochondria function in type II diabetes leading to metabolic abnormalities and insulin resistance.

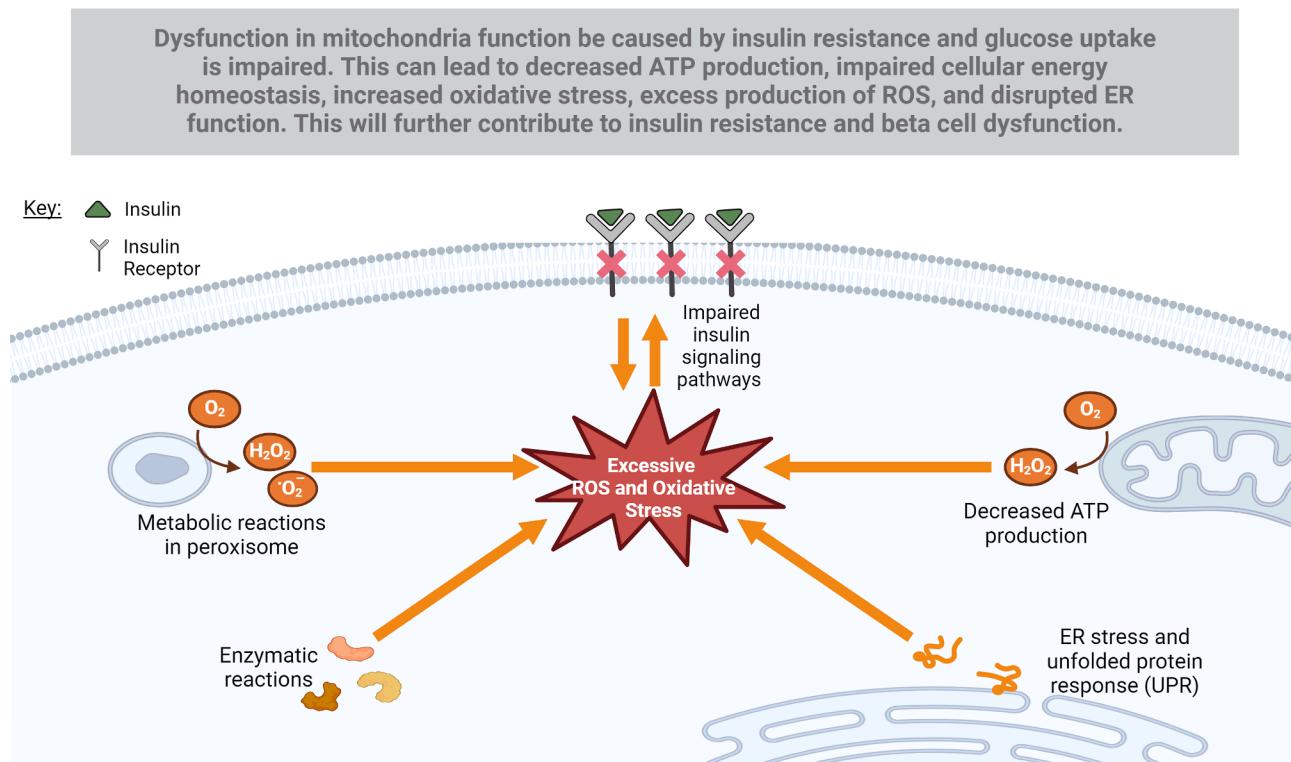


FIGURE 20.3 The role of poor sleep in mitochondrial function impairment in type 2 diabetes which leads to metabolic abnormalities and insulin resistance.

linking sleep parameters and diabetes risk/diabetes outcomes. Our epistemological stance throughout the chapter is that associations between sleep disturbance and diabetes are bidirectional, where poor sleep is considered an antecedent and a consequence of diabetes, which has been buttressed by seminal systematic reviews and meta-analyses. Relative to other behavioral risk factors, such as diet and exercise, sleep is as strong of a risk factor for cardiometabolic conditions, such as diabetes [4].

Sleep duration and diabetes

The link between sleep duration and diabetes risk, outcomes, and surrogate markers, such as glucose levels, insulin resistance, advanced glycated end products, and obesity, is supported by overwhelming epidemiological and experimental evidence. Epidemiological studies in the United States and globally have shown a high prevalence of short (≤ 6 h/24 h period) and long sleep (≥ 9 h/24 h period) durations and strong association with diabetes risk and diabetes outcomes [5]. Complementarily, experimental and biological studies have substantiated the link between sleep duration and diabetes by providing mechanistic

explanations and pathways as to how short or long sleep durations engender diabetes.

Direct relationship between insufficient sleep duration and diabetes

Insufficient sleep duration is recognized as an important unmet public health problem and has been included as a national health priority in Healthy People 2030. Insufficient sleep duration (≤ 6 h in a 24-h period) is associated with diabetes disease (Type II Diabetes), diabetes outcomes (such as insulin resistance and unhealthy glucose), and preclinical and surrogate markers such as obesity and prediabetes, in cross-sectional, experimental, and prospective studies. Some of the most convincing cross-sectional and epidemiological evidence indicate that chronic sleep deprivation is associated with diabetes and diabetes outcomes such as unhealthy glucose levels, insulin resistance, and insulin sensitivity in youth and adults. Gangwisch et al. [6], in a meta-analysis of seven prospective studies, reported that adults with insufficient sleep duration were 28% more likely to be at risk for type 2 diabetes. Dutil and Chaput [7] in a narrative review of 23

Poor sleep can increase chronic low-grade inflammation which causes increased insulin resistance and beta cell dysfunction in type II diabetes.

Increased chronic low-grade inflammation will impair insulin signaling pathways, contributing to insulin resistance and beta cell dysfunction and damage. This will exacerbate the progression of type II diabetes complications.

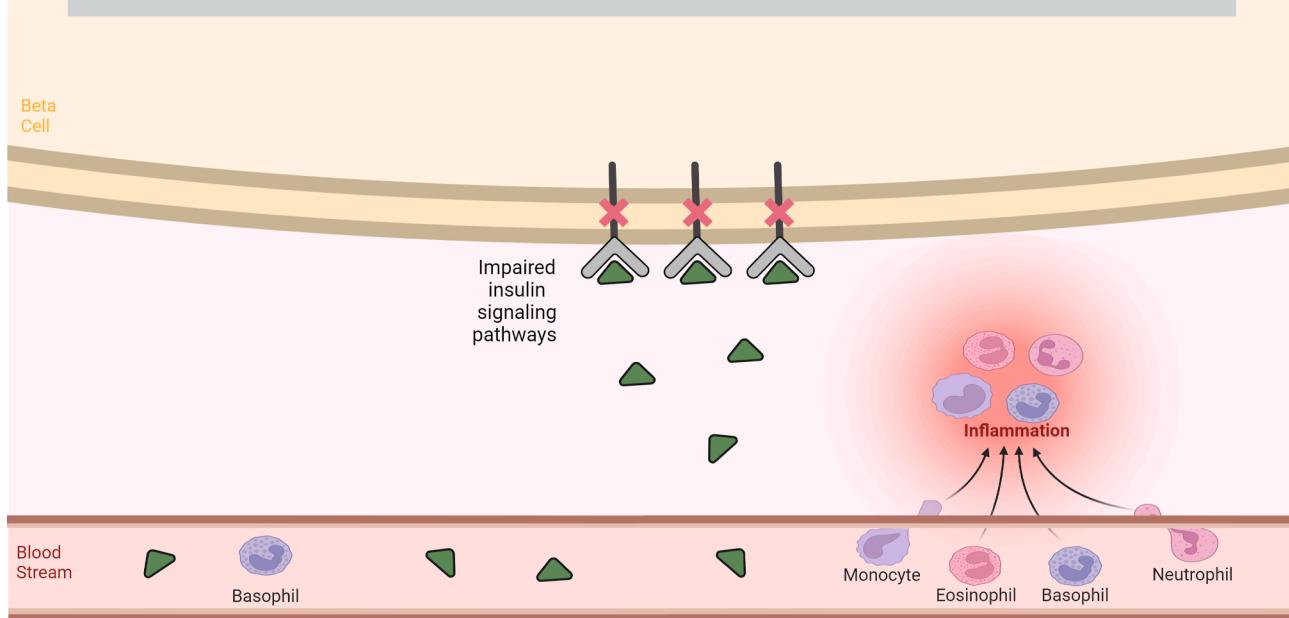


FIGURE 20.4 Increased chronic low-grade inflammation due to poor sleep leading to increased insulin resistance and beta cell dysfunction in type 2 diabetes.

studies and Landhuis et al. [8] in a cohort study found that children, adolescents, and young adults who are habitual short sleepers are at increased risk of developing prediabetes and diabetes. Engeda et al. [9] found that individuals who reported sleeping ≤ 5 h/night were two times more likely to report prediabetes (fasting glucose 5.6–6.9 mmol/L) than those who slept 7–9 h. In a nationally representative study with a sample of 11,815 individuals from the National Health and Nutrition Examination Survey 2005–10 dataset, Ford et al. [10] found that insufficient/short sleepers compared with average sleepers (7–9 h in a 24 h period) were more likely to have greater levels of adjusted mean levels of insulin, 2-h glucose and hemoglobin A1c. They also found that levels of insulin and 2-h glucose varied by sex and race/ethnicity. Specifically, adjusted mean levels of insulin varied by sex between insufficient/short sleepers and average sleepers (*insufficient/short sleepers*: male = 60.7 ± 1.5 pmol/L and female = 51.2 ± 1.4 pmol/L; *average sleepers*: male = 56.0 ± 1.1 and female = 52.3 ± 1.1 pmol/L). While, adjusted mean levels of 2-h glucose varied by race/ethnicity between insufficient/short sleepers and average

sleepers (*insufficient/short sleepers*: Whites = 6.6 ± 0.1 mmol/L, Blacks = 6.1 ± 0.1 pmol/L, Mexican American = 6.8 ± 0.2 mmol/L; *average sleepers*: Whites = 6.4 ± 0.1 , Blacks = 6.3 ± 0.1 mmol/L, and Mexican American = 6.5 ± 0.2 mmol/L).

Several mechanistic explanations have been proposed to enhance our understanding of the association between inadequate sleep duration and diabetes. In one prominent theory, long-term sleep deprivation leading to accumulated sleep debt is believed to trigger metabolic dysregulation, including increased adiposity and insulin resistance, thereby contributing to the development and progression of diabetes. Building upon the mechanistic understanding of the association between insufficient sleep duration and diabetes, Arora et al. [11] conducted a 12-month prospective investigation to evaluate the impact of an intensive lifestyle intervention, encompassing usual care, diet, and physical activity, on diabetes outcomes across five sites in the United Kingdom. Their findings revealed a compelling link between sleep debt, characterized by chronic sleep deprivation and insufficient sleep, and metabolic dysfunction. Specifically, individuals with sleep

debt were 72% more likely to be obese compared with those without, with the risk exacerbating over time. At 6 and 12 months, individuals with sleep debt demonstrated a two to threefold increased likelihood of obesity (body mass index [BMI]; $\geq 30 \text{ kg/m}^2$) or insulin resistance. Similarly, Kim et al. [12] conducted a cohort study involving 17,983 Korean adults, where they found that prediabetics reporting insufficient or short sleep duration were 44%–68% more likely to develop diabetes. Importantly, these associations were mediated by factors such as adiposity, fatty liver, and insulin resistance [12].

Sleep restriction may alter insulin signaling in adipocytes, thereby affecting insulin resistance, which in turn influences nonesterified fatty acid (NEFA) metabolism. In a randomized controlled trial, it was observed that sleep restriction adversely affected NEFA metabolism, and the findings suggested that a mere two nights of recovery sleep may not suffice to normalize NEFA metabolism and blood glucose levels, hinting at the potential for prolonged sleep restriction to exert further deleterious effects. Another potential mechanism is illuminated by a meta-analysis of 16 cross-sectional studies, revealing an indirect association between inadequate sleep and diabetes through nontraditional eating habits. These habits often deviate from the conventional three-meals-a-day regimen, leading to consumption of high-calorie foods at irregular intervals. Prolonged adherence to such poor eating and sleeping patterns can contribute to the development of chronic health conditions, including obesity, cardiovascular disease, and cardiometabolic problems.

Leng et al. [13] found in an 8-year prospective study that napping, a compensatory method often used to mitigate adverse effects of sleep deprivation and sleepiness, was not associated with reduced odds of diabetes. In fact, they found that individuals who: (1) napped had a 30%–58% greater likelihood of developing diabetes over time adjusting for age, sex, BMI, and waist circumference across different regression models; (2) were short sleepers were 46% more likely to develop diabetes compared with average sleepers; and (3) were habitual short sleepers and napped during the day had double the odds of diabetes, as compared to average sleepers who did not nap. These findings suggest that napping and insufficient/short sleep may have an adverse synergistic on diabetes.

One mechanism that might explain the relationship between insufficient sleep duration and diabetes outcomes posits that significant sleep deprivation may lead to lower glucose tolerance and insulin sensitivity. Spiegel et al. [14] and Buxton et al. [15] found that individuals who slept 4–5 h per night for a week had lower glucose tolerance and insulin sensitivity. Chronic sleep deprivation (4–5 h for more than 4 days) and the reduction in insulin sensitivity has significant physiological and health consequences as they may modify cellular integrity in subcutaneous

adipocytes [16]. However, the adverse effects of chronic sleep deprivation on abnormal insulin production and metabolism may only be ephemeral as data shows that the body compensates over a period of time. Robertson et al. [17] found that after restricting individuals' sleep by 1.5 h for 3 weeks, individuals' insulin sensitivity rebounded to normal levels or did not worsen after the first week of unstable insulin levels and insulin insensitivity.

Chronic sleep restriction and loss, as a result of insufficient/short sleep, is associated with greater disturbances in metabolic pathways that drive the development of insulin resistance leading to T2D. Sleep restriction (4 h in bed) induced a reduction in whole-body and tissue-specific insulin sensitivity [18]. Early morning nonesterified fatty acid levels were greater in young healthy men after sleep restriction compared with normal sleep which may partially contribute to insulin resistance [19]. At the cellular level, adipose tissue insulin sensitivity, determined by the insulin concentration for the half-maximal stimulation of the pAkt/tAkt ratio, decreases during sleep restriction [16]. Repeated bouts of restricted sleep may induce chronic hyperinsulinemia, stimulating downstream pathways like pancreatic beta cell failure and lipogenesis, driving the development of diabetes and obesity, respectively.

Indirect relationship between insufficient/short sleep and diabetes

A growing body of research indicates that the association between insufficient/short sleep and diabetes may be moderated or mediated by sleep disorders (obstructive sleep apnea and insomnia) as well as biological, demographic, and psychosocial factors such as obesity, sex, and glycemic control. Overwhelming evidence from observational and experimental studies indicates that the insufficient/short sleep and diabetes relationship is moderated or mediated by excess adiposity, either in the form of high body mass index or waist circumference. Although the proximal effects of sleep on diabetes are undeniable, evidence for the distal and indirect effects are as compelling, albeit less causal. Both epidemiological and experimental studies have linked sleep and diabetes via obesity/visceral adiposity.

Obesity moderates or mediates the relationship between sleep and diabetes. Sleep curtailment is also associated with a dysregulation of the neuroendocrine control of appetite, as well as a reduction in the satiety hormone leptin and an increase in the hunger-promoting hormone ghrelin. Thus, sleep loss may alter the ability of leptin and ghrelin to accurately signal caloric need, acting in concert to produce an internal misperception of insufficient energy availability [20]. Previous evidence indicates that the relationship between short sleep and obesity is mediated by

several factors which includes, but is not limited to, increased appetite/dietary intake, physical activity, and/or thermoregulation. A meta-analysis of 16 cross-sectional studies indicates that short sleepers are more likely to have nontraditional eating habits that deviate from the standard three-meals-a-day regimen, generally resulting in eating very high-caloric foods at rare periods of the day. Over time, these poor eating and sleeping patterns can lead to chronic health conditions, such as obesity, cardiovascular disease, and cardiometabolic conditions.

While the association between diabetes and obesity, particularly as indicated by body mass index (BMI), is well-established, recent trends reveal an increase in newly diagnosed diabetics who are not overweight. This shift has prompted a deeper investigation into the relationship between diabetes and visceral adiposity. Visceral adipose tissue, situated deep within the abdomen and surrounding internal organs, has emerged as a significant factor in the development of type 2 diabetes. Studies have consistently demonstrated a strong correlation between visceral adiposity and diabetes, highlighting its role in insulin sensitivity deterioration, akin to the effects observed in sleep apnea [21]. Therefore, understanding the impact of visceral adiposity, beyond traditional measures of obesity such as BMI, may provide valuable insights into the complex interplay between sleep duration, adiposity, and diabetes risk.

Changes in energy intake may also mediate the relationship among obesity, sleep duration, and diabetes. The energy balance equation states that under conditions in which energy intake equates to energy expenditure, no change in body weight will occur. Excess energy intake (i.e., positive energy balance) above energy expenditure results in weight gain leading to overweight and obesity. Pooled epidemiological evidence suggests a consistent association between short sleep duration and higher total energy intake and higher total fat intake. Healthy men increased caloric intake by 22% the day after one night of sleep restriction. Similar results on sleep restriction and increased energy intake were also found in healthy women resulting in net weight gain after four nights. The changes in energy intake that accompany sleep loss may be explained by changes in the hormonal environment, previously described by leptin and ghrelin. The hormonal imbalance of leptin and ghrelin stimulates the desire to consume energy-dense, nutrient-poor foods.

Along with energy intake, physical activity levels are affected by sleep duration. Individuals who reported shorter sleep (<6 h/night) spend more time in sedentary behaviors, have fewer daily activity counts, and spent less time in moderate to vigorous physical activity (MVPA) compared with individuals with >6 h/night. Adults at risk for type 2 diabetes restricted to sleep of 5.5 h/night compared to 8.5 h/night reduced moderate-and-vigorous

physical activity MVPA by 24% and increased sedentary behavior. Short sleep duration may confer conditions of increased energy intake and reductions in physical activity, thus perpetuating obesity status.

According to Gohil and Hannon [22], insufficient/short sleep is associated with an unhealthy diet and increased cardiovascular and cardiometabolic risk factors including insulin resistance and hyperglycemia, which in turn leads to elevated diabetes risk. In spite of compelling evidence that obesity and elevated waist circumference may mediate the relationship between short sleep and diabetes, there is contradictory evidence that there may be a genetic/hereditary component to the sleep-diabetes link. A study found that lean young adults with a history of diabetes and who are habitual short sleepers were susceptible to diabetes compared with those who slept more than 6 h each day [23].

Chronic insufficient sleep indirectly affects circadian rhythms, which in turn contributes to the association between sleep and diabetes. It is believed that such endogenous alterations and dysregulations adversely affect the quality of sleep and may lead to negative health outcomes, specifically maladaptive and nonhomeostatic glycemic control. There is further debate as to whether the biological and cardiometabolic processes disrupted by habitual insufficient/short sleep are reversible, as some believe that chronic sleep deprivation epigenetically induces an unhealthy metabolic memory whereby an individual is unable to process insulin regardless of the quantity and quality of food ingested [23,24]. Though the literature is unsettled, new findings indicating that extending sleep among short sleepers may have positive effects on cardiometabolic health may further buttress the argument that insufficient/short sleep is inextricably linked to diabetes.

Another indirect pathway in the sleep duration-diabetes relationship centers around circadian disruption. Chronic insufficient sleep indirectly affects circadian rhythms, which consequently influences the association between sleep and diabetes. Such alterations in endogenous rhythms may lead to negative health outcomes, including maladaptive glycemic control. Debate surrounds the reversibility of the biological and cardiometabolic disruptions caused by habitual insufficient sleep, with some suggesting that chronic sleep deprivation epigenetically induces an unhealthy metabolic memory [23,24]. Despite the equivocality of the literature, recent findings suggest that extending sleep among short sleepers may positively impact cardiometabolic health, further supporting the link between insufficient sleep and diabetes.

Social and demographic factors in sleep duration

The relationship between sleep duration and diabetes risk is not uniform across all demographic groups, with

emerging evidence suggesting that race and sex play significant roles in moderating this association. Studies have highlighted disparities in sleep patterns and diabetes prevalence among different racial and ethnic groups, as well as between men and women. For instance, research indicates that racial and ethnic minorities, such as African Americans and Hispanic/Latina individuals, are more likely to experience shorter sleep duration and poorer sleep quality compared with their white counterparts. In addition, sex differences in sleep duration and diabetes risk have been observed, with studies suggesting that women may be more vulnerable to the adverse metabolic effects of inadequate sleep compared with men. Understanding how race and sex influence the relationship between sleep and diabetes is crucial for developing targeted interventions and improving health outcomes across diverse populations.

In assessing the relationship between sleep duration and diabetes risk, several studies have shed light on the influence of race and ethnicity. For example, Zizi et al. [25] conducted a study analyzing data from the National Health Interview Survey (NHIS) and found that both black and white individuals with short sleep duration (≤ 5 h) had a higher likelihood of having diabetes compared with those sleeping 6–8 h. Similarly, those reporting long sleep duration (≥ 9 h) had an increased risk of diabetes, particularly among black individuals. These findings suggest that race and sleep duration may interact to influence diabetes risk independently of other sociodemographic and medical factors. In another study using data from the Sister Study, McWhorter et al. [26] found that racial and ethnic minorities, particularly black and Hispanic/Latina women, experienced a higher risk of type 2 diabetes associated with poor sleep compared with white women with recommended sleep duration. Specifically, frequent napping was associated with a higher risk of type 2 diabetes, highlighting the importance of considering multiple dimensions of sleep in assessing diabetes risk, particularly among racial and ethnic minority populations.

A meta-analysis incorporating data from five studies comprising 74,226 subjects (31,611 males, 42,615 females) sheds light on the relationship between sleep duration, sex, and the risk of developing type II diabetes. The findings reveal that women with long sleep duration (LSD) have a significantly higher risk of developing type II diabetes compared with men ($OR = 0.70$; 95% CI 0.59–0.84, $Z = 4.00$, $P < .001$). Conversely, men with short sleep duration (SSD) tend to exhibit a higher risk of developing type II diabetes compared with women, although this difference did not reach statistical significance ($OR = 1.09$, 95% CI 0.73–1.62, $Z = 0.42$, $P = .68$). Subgroup analysis by regional populations further suggests that men in Europe and America with SSD are at a heightened risk of type II diabetes ($OR = 1.52$, 95% CI 1.04–2.21, $Z = 2.18$, $P = .03$). These findings underscore

the importance of considering gender-specific differences in sleep duration when evaluating diabetes risk, with implications for targeted prevention and management strategies [27].

Long sleep duration's influence on type 2 diabetes, insulin resistance, and obesity

Based on the overwhelming evidence that short sleep is a significant risk factor in the development and maintenance of diabetes and diabetes outcomes, the perfunctory assumption is that increasing sleep duration will mitigate any adverse consequences of habitual insufficient/short sleep. In fact, studies show that extending sleep was associated with improvements in insulin sensitivity. However, the evidence appears to be more nuanced where longer sleep duration is generally associated with decreased diabetes risk; however, studies have indicated that long sleep duration (>8 h/24 h period) and increasing sleep duration drastically can be harmful [28,29].

Protective effects of longer sleep and diabetes

Byberg et al. [30] in a study of 771 participants in Denmark investigated the effect short or long sleep durations have on glucose homeostasis and tolerance. The researchers found that an additional hour of sleep was associated with 0.3 mmol/mol (0.3%) and 25% reduction in HbA(1c) and impaired glucose regulation, respectively. These findings support a conventional view that longer sleep may protect or stave off diabetes. However, recent findings are beginning to show contradictory evidence.

Negative associations between long sleep on diabetes

Although longer sleep duration may protect an individual from diabetes, there is growing evidence that too much sleep may have an adverse effect. Cespedes et al. [28] found that an extreme increase in sleep duration by two or more hours among women, who were habitual short sleepers, increased their risk for diabetes. Ferrie et al. [31] found similar findings as Cespedes and colleagues in the UK Whitehall Study when they investigated the association between change in sleep duration and incident diabetes, over a 20-year span. They found that compared with individuals who slept 7 h/24 h period, those who reported a ≥ 2 h sleep increase had a 65% greater likelihood of diabetes ($OR = 1.65$, 95% CI = 1.15–2.37) after adjusting for age, employment status ethnicity, and sex. Interestingly, BMI and weight change attenuated the association between long sleep and diabetes ($OR = 1.50$, 95% CI = 1.04–2.16) suggesting that the relationship between long sleep and diabetes may be indirect or mediated by obesity.

Indirect relationship between long sleep and diabetes

Similar to Gohil and Hannon [22] (in the short sleep duration section above) and Ferrie et al. [31] found that diabetes and long sleep were indirectly associated via obesity. In a sample of 2848 participants, Brady and colleagues found that both short sleep and long sleep durations were independently associated with elevated body mass index and waist circumference. They also found that fasting insulin was positively associated with sleep duration, while plasma adiponectin levels (a marker inversely associated with insulin resistance) were negatively associated with sleep duration.

A second factor that might explain the indirect relationship between long sleep duration and diabetes is frequent napping. Han et al. [32], in a prospective study with middle-aged Chinese adults, found that long sleep and habitual napping were associated with increased risk of diabetes. Specifically, individuals who slept ten or more hours were 42% more likely to develop diabetes, compared with those who slept 7–8 h. In addition, individuals who frequently napped for more than 90 min were 28% more likely to develop diabetes compared with those who did not nap. These associations were further strengthened when long sleep and napping were combined. Individuals who slept for ten hours and more and who napped for more than 60 min were 72% more likely to have diabetes compared with those who slept 7–8 h and did not nap.

Summary

The relationship between sleep duration and diabetes is complex, with evidence suggesting a U-shaped association between sleep duration (short and long sleep) and diabetes outcomes. Epidemiological studies, including both cross-sectional and longitudinal investigations, have consistently demonstrated an increased risk of diabetes among individuals with both insufficient and excessive sleep durations. Furthermore, experimental studies have provided mechanistic insights into how inadequate sleep duration may directly and indirectly contribute to the development and progression of diabetes. However, it is important to note that the relationship between sleep and diabetes is not solely determined by sleep duration alone. Other sleep-related factors, such as subjective parameters of sleep (sleep quality, social jetlag, and excessive daytime sleepiness), sleep disorders (e.g., insomnia and obstructive sleep apnea), and circadian misalignment, also play significant roles in influencing diabetes risk and outcomes. Understanding the multifaceted nature of sleep and its impact on diabetes is essential for developing targeted interventions to mitigate the risk of diabetes and improve health outcomes.

Qualitative sleep parameters (sleep quality, excessive daytime sleepiness, and social jet lag) and diabetes

Outside of sleep quantity (e.g., duration), qualitative parameters of sleep such as sleep quality, excessive daytime sleepiness, and social jet lag, are considered some of the strongest correlates and predictors of diabetes. Epidemiological and experimental studies provide overwhelming evidence that qualitative parameters gathered through subjective (via self-report), or objective (via devices) means are reliably and consistently associated with diabetes and diabetes outcomes.

Sleep quality

Sleep quality has been linked to the development of diabetes and the worsening of symptoms. In a meta-analysis that analyzed the relationship between sleep quality and diabetes, Cappuccio et al. [33] found quantity and quality of sleep predicted diabetes risk. Specifically, difficulty initiating sleep ($RR = 1.57, 95\% CI = 1.25-1.97$) and difficulty maintaining sleep ($RR = 1.84, CI: 1.39-2.43$) were both strongly associated with diabetes risk at follow-up. In addition to cross-sectional evidence, Martyn-Nemeth et al. [34] investigated whether sleep quality was associated with glycemic control and variability (GV), or fear of hypoglycemia (FOH) over a 3 year period with continuous glucose monitoring among 48 men and women with type I diabetes. Poor sleep quality was positively associated with higher levels of nocturnal GV and FOH. These findings highlight a potential bi-directional relationship between sleep quality and diabetes outcomes, with the implication that improving diabetes outcomes may improve sleep quality and vice versa.

Sleep quality may also be associated with diabetes management. In a meta-analysis comparing sleep disturbances (e.g., insufficient sleep duration, insomnia, obstructive sleep apnea, and abnormal sleep timing) with overweight, family history of diabetes, and physical inactivity, the risk ratios of sleep variables, such as poor sleep quality, were comparable to traditional risk factors in terms of diabetes risk [4]. In fact, poor sleep quality was associated with greater risk for diabetes ($RR: 1.40, 95\% CI = 1.21-1.63$). Taken together, sleep disturbances and poor sleep quality play a role in the development of diabetes in healthy populations and among diabetics affects the management of the diseases. Byberg et al. [30] in a study of 771 participants in Denmark found that a 1-point increase in sleep quality was associated with a 2% increase in insulin sensitivity and a 1% decrease in the homeostatic function of β -cell function, cells responsible for metabolizing glucose. These findings highlight the importance of healthy sleep in maintaining the homeostasis of glucose metabolism.

Excessive daytime sleepiness and social jetlag

Raj et al. [35] investigated the prevalence of excessive daytime sleepiness, among individuals with Type II diabetes, and whether excessive daytime sleepiness was associated with glycemic control, in a sample of 102 individuals living in India. Though the prevalence of excessive daytime sleepiness was only 17.5%, the researchers found in regression analyses that a one-unit increase in Epworth Sleepiness Scale (a subjective measure of daytime sleepiness) was significantly associated with a 0.143 .1 dL HbA1c increase. In addition to daytime sleepiness, social jetlag is another qualitative sleep parameter that is associated with diabetes. Koopman et al. [36], in a cross-sectional study from the New Hoorn Study cohort ($n = 1585$), investigated the association between social jetlag (defined as difference between midpoint of weekday sleep hours and midpoint of weekend sleep hours) and metabolic syndrome and diabetes. The researchers found that individuals less than 61 years of age who reported social jetlag (1–2 h) had approximately a two-fold greater risk of metabolic syndrome and prediabetes/diabetes compared with their counterparts who reported <1 h of social jetlag.

Physiological mechanisms

Despite overwhelming evidence that sleep quality and diabetes are related, less is known about the biological mechanisms that engender this relationship. Several mechanisms are argued to be at play and for this book chapter, we only discuss a few, those that have the most robust evidence. They are insulin resistance, leptin and ghrelin hormones, and inflammation.

Insulin resistance

Evidence suggests an association between diabetes risk and sleep deprivation, even among healthy subjects [37]. For instance, in a seminal study, healthy subjects restricted to 4 h in bed demonstrated increased markers of insulin resistance [14]. Thus, sleep deprivation and poor sleep quality are potential mechanisms through which insulin resistance manifests. Follow-up studies are investigating processes upstream of insulin signaling to better understand the mechanistic pattern through which sleep loss can induce insulin resistance. For instance, restriction of sleep may alter insulin signaling in adipocytes which may be driving insulin resistance [38].

Leptin and ghrelin hormones

Research has implicated metabolic hormones leptin and ghrelin in the relationship between sleep and diabetes risk. Leptin, a molecule released from adipose tissue, signals

feelings of satiety in the brain and increases energy expenditure. Leptin release from adipose tissue binds to leptin receptors in the hypothalamus to reduce appetite, and thus decrease energy intake. Research demonstrates sleep deprivation is associated with decreased leptin and associated perceptions of hunger [38–40]. On the contrary, ghrelin is a hormone secreted by the stomach that triggers hunger. Research shows sleep deprivation has also been associated with increased ghrelin or perceptions of hunger [20,41,42].

Inflammation

Evidence also points to inflammatory cytokines, tumor necrosis factor (a cell signaling protein indicative of inflammation), and interleukin six, as potential factors at play in the relationship between diabetes and sleep disturbances, specifically chronic sleep deprivation. Although there is some dispute, research has linked tumor necrosis factor with sleep restriction and inflammation [43,44]. Also, interleukin-6, a pro-inflammatory molecule secreted by T-cells and macrophages like tumor necrosis factor, is associated with chronic inflammation and also plays a role in stimulating energy utilization in adipose tissue [37]. Interleukin-6 presents operates within the human circadian rhythm, with its peak expression at night around sleep onset, but is suppressed by slow-wave sleep linked with homeostatic restorative biological processes such as processing glucose [45]. Therefore, the presence of inflammation will compromise homeostatic processes in metabolizing glucose and thus may lead to insulin insensitivity.

Sleep disorders and diabetes

Sleep and circadian disorders, such as obstructive sleep apnea, insomnia, and circadian misalignment disorders represent some of the most robust evidence linking sleep and diabetes. The evidence can be compartmentalized into two: (1) evidence showing that individuals with sleep disorders are at greater risk of developing diabetes compared with those without a sleep or circadian disorder history; and (2) evidence indicating that treatment of sleep and circadian disorders lowers an individual's risk of developing diabetes and improves their ability to better manage their diabetes.

Obstructive sleep apnea (OSA)

Obstructive sleep apnea (OSA), a prevalent sleep-disordered breathing condition, is characterized by partial or complete upper airway obstruction during sleep, leading to recurrent episodes of apneas and hypopneas, necessitating reflexive awakenings to restore adequate airflow and

oxygen levels. These interruptions in sleep continuity result in oxygen desaturation and physiological stress, disrupting essential homeostatic processes. Reutrakul and Mokhlesi [46] revealed a significant association between obstructive sleep apnea (OSA) and type 2 diabetes, with OSA prevalence ranging from 55% to 86% among individuals with diabetes. They observed more severe symptoms and a higher incidence of OSA in men, and the prevalence was particularly pronounced, reaching 86%, among obese populations with type 2 diabetes. This highlights the substantial overlap between OSA and diabetes risk, emphasizing the importance of clinicians prioritizing the identification and management of comorbid OSA in patients with diabetes.

In addition, the bidirectional relationship between OSA and diabetes underscores the complex interplay between sleep-disordered breathing and metabolic dysfunction. While OSA exacerbates the risk and severity of diabetes, diabetes, in turn, contributes to the development and progression of OSA. The coexistence of OSA and diabetes amplifies the likelihood of poor glycemic control, cardiovascular complications, and diminished quality of life among affected individuals. Furthermore, emerging evidence suggests that untreated OSA increases the risk of microvascular and macrovascular complications in patients with diabetes, including retinopathy, nephropathy, neuropathy, coronary artery disease, and heart failure. Addressing the comorbidity of OSA and diabetes requires a multifaceted approach, incorporating interventions aimed at improving sleep quality, optimizing glycemic control, and managing cardiometabolic risk factors. By recognizing and addressing the intertwined nature of OSA and diabetes, clinicians can effectively mitigate the adverse health outcomes associated with these prevalent and interconnected conditions. Untreated OSA induces metabolic disturbances, contributing to compromised cardiometabolic health. Intermittent hypoxia, reduced sleep duration, and sleep fragmentation associated with OSA exert detrimental effects on glucose metabolism, exacerbating the risk of type 2 diabetes. Given the substantial overlap between OSA and diabetes risk, clinicians must prioritize the identification and management of comorbid OSA among patients with diabetes.

Obesity stands out as one of the most significant risk factors for the onset of obstructive sleep apnea (OSA), with its prevalence escalating in tandem with increasing body mass index (BMI). In the general population, OSA's prevalence hovers around 0.15%–0.3%; however, within the obese demographic, it skyrockets to an estimated 19%–31%. The intersection of type 2 diabetes mellitus (T2DM) and OSA compounds health challenges, amplifying blood pressure, exacerbating sleep disturbances, diminishing health-related quality of life, and compromising adherence to diabetes self-management protocols. In addition,

individuals grappling with both conditions often confront heightened cardiovascular risks and metabolic dysregulation, further underscoring the critical need for integrated management strategies to address the dual burden of T2DM and OSA.

Insomnia

Insomnia, a prevalent sleep disorder, plagues individuals with type 2 diabetes at rates notably higher than those in the general population. Meta-analyzed data indicate that approximately 39% of individuals with type 2 diabetes experience symptoms of insomnia, marking a fourfold increase compared with those without diabetes [47]. This prevalence escalates with age and in the presence of comorbidities, painting a concerning picture of the intertwined nature of sleep disturbances and diabetes management. Research demonstrates associations between insomnia and compromised glycemic control, as evidenced by higher HbA1c levels and fasting glucose levels among those with insomnia symptoms. In addition, the presence of insomnia is correlated with an elevated risk of diabetic retinopathy and high cholesterol levels, emphasizing the multifaceted impact of this sleep disorder on metabolic health and diabetes-related complications [47].

Beyond its direct physiological effects, insomnia casts a wide net of consequences that extend into mental health and overall well-being. Studies have consistently highlighted the co-occurrence of insomnia and depressive symptoms among individuals with type 2 diabetes, underscoring the bidirectional relationship between sleep disturbances and mood disorders. Furthermore, insomnia poses a significant threat to longevity, with individuals with diabetes experiencing an increased mortality rate who consistently deal with sleeplessness. Importantly, insomnia negatively impacts quality of life, impairing various domains such as emotional well-being, physical health, and social functioning. These findings underscore the imperative for integrated approaches to managing diabetes that address not only glycemic control but also the complex interplay between sleep disorders like insomnia and diabetes-related health outcomes.

Insomnia and Painful Diabetic Neuropathy (PDN)

The role of sleep as a pain modulator has been thoroughly explored. However, the association between insomnia and Painful Diabetic Neuropathy (PDN) remains understudied. Individuals with PDN suffer from higher rates of obstructive sleep apnea (OSA) and other sleep disorders in contrast with individuals who have type-2 diabetes (T2DM) but no PDN [48]. Davoudi et al. found that the prevalence of disordered sleep among the PDN population

is approximately 85%. In accordance with the association between PDN and insomnia, a clinical study composed of 30 subjects with T2DM, 20 of whom were diagnosed with PDN and 10 without, underwent one-night polysomnogram (PSG) followed by sleep latency tests. The subjects with PDN showed an increased risk of developing sleep-disordered breathing, primarily obstructive sleep apnea (OSA), increased sleep efficiency, increased sleep fragmentation, and nocturnal hypoxia, leading to excessive daytime sleeping and poor glycemic control, in comparison with those with only T2DM. Other comorbid conditions associated with diabetes, such as cerebral small vessel disease, play a role in causing disordered sleep. Despite mounting evidence, more studies are needed to elucidate the pathophysiologic relationship between diabetic neuropathy and sleep quality.

Treatment for disordered sleep due to PDN requires a comprehensive approach that primarily focuses on sleep and secondarily targets pain, which will aid in the reduction in sleep disturbances caused by pain. In addition, the intricate and bidirectional relationship between disordered sleep and PDN becomes more complex due to the concurrence of PDN and mood disorders, which tend to have a negative effect on both sleep and perception of pain. Finding effective treatment options for anxiety, depression, and other neuropsychiatric conditions is crucial to help those suffering from PDN-induced insomnia.

Epidemiological and population-level studies

Epidemiological evidence on the relationship between sleep disorders and diabetes is quite compelling [49–52] citing direct and indirect associations. Bakker et al. [53] found, in a sample of 2151 participants in the Multi-Ethnic Study of Atherosclerosis, that individuals with an apnea-hypopnea index (AHI) $\geq 15/\text{h}$ (moderate to severe range) had a 2-fold greater likelihood of having abnormal fasting glucose levels, compared with individuals with a low AHI score—low sleep apnea risk (0–4.9/h) [53]. Interestingly, sleep duration was not associated with abnormal fasting glucose after adjusting for the effects of apnea-hypopnea index, a proxy for OSA. The putative relationship between sleep apnea and diabetes might vary by race/ethnicity and gender, as men compared with women and whites compared with blacks have a greater odds of having abnormal glucose levels and beta cell functioning if they have sleep apnea [54]. The relationship between sleep apnea and diabetes is further buttressed by evidence indicating that treatment of sleep apnea, via continuous positive airway pressure, is associated with diabetes risk reduction. Labarca et al. [48] found that continuous positive airway pressure treatment significantly lowered diabetes risk and reduced abnormal glucose levels.

Similarly, the epidemiological evidence linking insomnia and diabetes is robust. Hein et al. [55] conducted a study among insomnia patients to better understand the prevalence of and risk factors associated with type 2 diabetes. They found that 21.3% of 1311 individuals with insomnia had type 2 diabetes and alcohol consumption of ≥ 4 units/day, $\text{BMI} \geq 25 \text{ kg/m}^2$, age $50 \geq 50$, being male, C-reactive protein $\geq 4.5 \text{ mg/L}$, early morning awakenings, high blood pressure, total sleep hours $< 6.5 \text{ h}$, apnea-hypopnea index $\geq 15/\text{h}$, elevated triglyceride, and periodic limb movements index $\geq 26/\text{h}$ were risk factors in the insomnia-diabetes association [55]. In a sample of 5078 diabetic individuals from China, Tan et al. and Zhang et al. [29,56] found that the prevalence of insomnia was 20.2% and that individuals with insomnia compared with those without insomnia were 31% more likely to have type 2 diabetes, after controlling age, alcohol, body mass index, chronic health conditions, depression, and smoking. Men and individuals between the ages 40–59 years with insomnia were more at risk for diabetes compared with their counterparts. Further proof of the insomnia-diabetes association is provided in evidence indicating that successful management of insomnia may lead to improved glycemic control, glucose tolerance, and reduced risk of diabetes. Carroll et al. [57] found that treatment of insomnia symptoms improved sleep quality and reduced the risk of chronic disease, like diabetes, in older adults with sleep disturbances.

Mechanistic studies

The relationship between sleep disorders (i.e., sleep apnea and insomnia) and diabetes is multifactorial and thus difficult to simplify. Sleep loss, a common resultant of sleep disorders, has a negative impact on cardiometabolic health, inducing glucose intolerance and insulin resistance, which if not treated over time will lead to diabetes. However, increasing sleep duration can reverse this process, especially among those who have abnormal glucose levels and prediabetes. Sleep deprivation also has an effect on leptin and ghrelin, hormones responsible for physiological drives of appetite and satiety. Specifically, sleep loss decreases leptin levels and increases ghrelin levels [58]. These hormonal changes promote over-eating and increase risk of obesity and in turn diabetes [59]. Deng et al. [60] found that compared with average sleep duration, short sleep increased risk of obesity by 12% but these effects might be reversed or muted through adequate sleep (7–8 h) [61].

Circadian rhythm and diabetes

The circadian rhythm of living organisms relates to the 24-h wake-sleep clock that regulates all biological, chemical, and physiological processes in the central and peripheral

nervous systems. Human circadian rhythm is influenced by internal (endogenous) and exogenous (external) cues. Endogenous cues include genetic markers such as the MTNR1B genotype, chronotype, and intrinsic circadian rhythm. While exogenous cues include environmental factors such as light, dark, noise, and temperature that influence wake-sleep timing and behaviors, such as activity, food consumption, and sleep. Circadian rhythm regulates gluconeogenesis, such as insulin sensitivity, insulin secretion, and energy expenditure over a 24-h period [62–64]. Misalignment and de-synchrony: (1) of the wake-sleep cycle and clock; and (2) between central and peripheral nervous systems will disrupt innate biological timing of the suprachiasmatic nucleus (master clock) and peripheral clocks of cells, tissues, and organs which can disrupt normal homeostatic metabolic processes, such as glucose metabolism. These disruptions may lead to mis-timed or irregular eating schedules and thus compromising healthy metabolism of foods and therefore spikes in glucose and insulin resistance. Circadian misalignment may also lead to elevated plasma cortisol levels or activation of the sympathetic nervous system thus increasing Type 2 diabetes mellitus (T2DM) and obesity risk via insulin sensitivity in adipose tissue [65–67].

Independent and interactive associations between endogenous circadian and diabetes

Evidence for the association between circadian rhythm and diabetes can be categorized in two categories: independent and interactive effects. In a cross-sectional study of nearly 10,000 European individuals enrolled in five studies as part of the Candidate Gene Association Resource (CARe), Tare et al. [68] examined 16 fasting glucose variants and aggregate genetic risk scores. The researchers found that short sleep duration was associated with T2DM in CARe ($P = .08$) [68]. However, sleep duration did not mediate or modify the association of circadian rhythm genes and diabetes, thus suggesting that circadian rhythm is independently associated with diabetes risk.

However, other studies have found that an interactive effect between circadian rhythm and sleep duration. Nisa et al. [69] found significant changes in oral glucose tolerance tests in 1025 Chinese women carrying the circadian rhythm-related melatonin receptor 1B genotype MTNR1B. Study findings indicate that women with different MTNR1B genotypes and the short sleep duration-related G allele had significant long-term postpartum changes in their 2 h oral glucose tolerance tests regardless of inadequate, adequate, or excessive gestational weight gain, albeit women with greater gestational weight gain being more at risk for gestational diabetes. These findings highlight that both circadian rhythm and short sleep combined increases an individual's risk for diabetes.

Other circadian-related studies have found that people with evening chronotype, those who prefer to conduct activities of daily living later in the day, have higher metabolic syndrome and diabetes risk. Anothaisintawee et al. [4] found that evening chronotype in individuals living with diabetes reported poor glycemic control, independent of sleep health compared with individuals who are not evening chronotypes. In their cross-sectional study, Anothaisintawee et al. [4] explored the relationship between chronotype, social rhythms, and hemoglobin A1c levels in 1014 adults living with prediabetes. The researchers found that later mid-sleep time on a nonworkday adjusted for sleep debt was significantly associated with HbA1c levels ($P = .049$), after adjusting for confounding factors [4]. Similarly, Reutrakul and Van Cauter [50] found that evening chronotype and larger dinner size were associated with poor glycemic control in patients living with T2DM, independent of poor sleep health.

Insulin regulation may be affected by time of day. Endogenous misalignment between fatty acids that regulate glucose metabolism and the circadian clock could adversely affect the primary systems it regulates such as appetite, energy expenditure, dyslipidemia, and insulin resistance [70]. Circadian rhythm balance which maintained at the cellular level in adipose tissue may affect insulin levels. At the cellular level, there appears to be a circadian component to regulating glucose levels in adipose tissue. Carrasco-Benso et al. [71] investigated whether human adipose tissue expressed intrinsic circadian rhythms related to insulin sensitivity mechanisms in obese participants. The researchers found significant differences in subcutaneous adipose tissue and circadian rhythm insulin signaling ($P < .00001$). Insulin sensitivities reached their highest at noon, climbing 54% higher than at midnight. Thus, an underlying endogenous circadian rhythm may serve as a mechanism for insulin sensitivity.

Exogenous

Sleep timing, a component of circadian rhythm, and diet have been reported as significant factors that affect insulin sensitivity. Delayed sleep times may increase food intake during times of peak appetite. This may result in higher energy intake and contribute to positive energy balance [65]. Consuming the majority of calories earlier in the day rather than in the evening is one approach to overcoming these adverse effects as it regulates metabolism and prevents weight gain [72]. Similarly, Shapiro et al. [73] reported glucose levels reached their peak in the early morning, hovering nearly 30% above the lowest daytime glucose level. Insulin secretion rates and glucose levels were nearly in sync in half of participants. Overlapping morning glucose levels with circadian rhythm alignment affects insulin sensitivity.

Endogenous and exogenous

In some instances, both endogenous and exogenous circadian processes may be associated with diabetes risk. Sleep timing and/or duration combined with later chronotype have been associated with high insulin resistance in Hispanic adults. Egan et al. [74] examined cross-sectional data from over 13,000 individuals enrolled in a community-based study. Researchers evaluated sleep timing and chronotype against fasting glucose levels, insulin resistance, glucose levels 2 h postoral glucose ingestion, and hemoglobin A1c. Chronotype (+1.2%/h later, $P < .05$) and midpoint of sleep duration (+1.5%/h later, $P < 0.05$) were positively associated with insulin resistance.

Circadian misalignment and diabetes

Circadian misalignment can occur if: (1) sleep and wake are inappropriately timed, (2) the sleep–wake cycle is not aligned with the feeding rhythm, and (3) central and peripheral rhythms are misaligned. Potential adverse health outcomes include hormonal changes that affect appetite, unregulated eating patterns, poor glucose metabolism, and mood problems. Circadian misalignment is linked with cardiovascular disease, diabetes, obesity, cancer, and mental illness [75].

Circadian misalignment combined with short sleep duration has been associated with reduced glucose tolerance. Eckel et al. [76] investigated the influence of morning circadian misalignment due to short nighttime sleep on insulin sensitivity. High sustained melatonin levels after waking up resulted in poor insulin sensitivity. In addition, sleeping 5-h/night during the work week and irregularly timed food intake resulted in approximately 20% reduced insulin sensitivity. Reduced insulin sensitivity triggers a higher glucose response, which can lead to diabetes mellitus. Insulin sensitivity was when sleep duration was increased over time. Buxton et al. [77] examined the prolonged effect of sleep restriction combined with circadian disruption on metabolic health. They found that restricting the amount of sleep for 3 weeks (average total sleep time of 5.6 h) and inducing circadian disruption for 28-h “days” resulted in significantly decreased metabolic rate, and increased postprandial plasma, increasing obesity and diabetes risk. Circadian balance was restored within 9 days of sleep recovery.

In addition, Rao et al. [18] found that circadian misalignment and the central circadian pacemaker influence glucose tolerance differently. Decreased pancreatic β -cell function in the evening hours and decreased insulin sensitivity, resulting in reduced glucose tolerance in the evening compared with the morning was directly related to circadian misalignment. The above-mentioned evidence

provides compelling evidence for the association between synchrony of the peripheral circadian clock and glucose rhythm alignment.

Circadian misalignment due to short sleep not only affects glucose tolerance but increases carbohydrate cravings. Al Khatib et al. [78] assessed the effect of sleep extension on dietary intake among adult short sleepers (5 to <7 h). Individuals whose sleep was extended had reduced fat (percentage), carbohydrate (grams), and free sugar (grams) intake compared with those whose sleep was not extended. No significant differences were found in energy balance or markers of cardiometabolic health.

The exacerbating role of sleep on well-being, quality of life, health, and mortality among diabetics

People with diabetes have problems with sleep. These problems have the potential to create many more issues if sleep is not addressed. For example, diabetic retinopathy (DR) is a common microvascular complication of diabetes. DR affects 40%–50% of diabetic patients and can cause blindness if not treated [79]. Sleep apnea has been well defined as a direct risk of DR. Altaf et al. [79] found that in as short as 4 years, sleep apnea advances the development of retinopathy for people with diabetes. Sleep apnea has also been associated with endothelial dysfunction for diabetic patients. Endothelial cells release substances that control vascular relaxation and contraction as well as enzymes that control blood clotting, immune function, and platelet adhesion. Endothelial dysfunction is caused by diabetes, and sleep disturbances decrease endothelial production [80,81]. A third consequence of sleep and diabetes association is poor quality of life and well-being. Recognizing that sleep duration and sleep quality are related to diabetes, insulin resistance, and poor glycemic control, researchers have found that poor sleep in diabetes patients was inversely associated with quality of life [82,83].

Healthy sleep and reduced diabetes risk

The National Sleep Foundation, the American Academy of Sleep Medicine, and the Sleep Research Society all recommend that adults should receive 7–9 h of sleep daily to reduce health risk and optimize wellness [84]. Adults who sleep between the recommended hours are less likely to be at risk for diabetes compared with those who sleep fewer or longer hours [85–87]. In today’s society, inadequate sleep has become increasingly common. Most people self-report sleeping an average of <7 h each day [88]. In a study intervention for overweight young adults, Tasali et al. [88] found that extending sleep duration was

associated with reduced drive to consume sweet or salty foods and restores glucose tolerance.

Summary

The book chapter on sleep and diabetes provides a comprehensive exploration of the intricate relationship between sleep and diabetes, spanning various dimensions of sleep health and their impact on diabetes risk and outcomes. First, the chapter delves into the association between sleep duration and diabetes, highlighting evidence from epidemiological studies demonstrating a U-shaped relationship between sleep duration and diabetes risk. Short and long sleep durations are both linked to an increased risk of diabetes, with potential mechanisms including alterations in glucose metabolism, insulin sensitivity, and hormonal regulation. Second, the chapter examines the role of sleep quality in diabetes, emphasizing subjective parameters such as sleep satisfaction, alertness, and sleepiness, along with objective measures like sleep efficiency and latency. Poor sleep quality is associated with heightened diabetes risk and worse glycemic control, underscoring the importance of addressing sleep disturbances in diabetes management.

The chapter explores specific sleep disorders, notably obstructive sleep apnea (OSA) and insomnia, and their bidirectional relationship with diabetes. OSA, characterized by recurrent upper airway obstruction during sleep, is prevalent among individuals with diabetes and contributes to metabolic dysfunction and poor glycemic control. Similarly, insomnia, marked by difficulty initiating or maintaining sleep, is associated with increased diabetes risk and complications, including poorer glycemic control and higher prevalence of microvascular and macrovascular complications. In addition, the chapter examines the impact of circadian disruption on diabetes, elucidating how disturbances in the body's internal clock can disrupt metabolic homeostasis and contribute to insulin resistance and glucose dysregulation. Factors such as shift work, jet lag, and irregular sleep-wake patterns are implicated in circadian disruption and may exacerbate diabetes risk. Finally, the chapter explores the concept of healthy sleep and its role in diabetes prevention and management. Strategies for promoting healthy sleep hygiene, such as maintaining a consistent sleep schedule, creating a conducive sleep environment, and practicing relaxation techniques, are discussed in the context of diabetes care. Overall, this chapter underscores the importance of addressing sleep disturbances as integral components of diabetes prevention and management strategies, highlighting the need for interdisciplinary approaches that integrate sleep health into diabetes care paradigms.

References

- [1] Arora T, Taheri S. Sleep optimization and diabetes control: a review of the literature. *Diab Ther* 2015;6(4):425–68. <https://doi.org/10.1007/s13300-015-0141-z>.
- [2] Lima JEBF, Moreira NCS, Sakamoto-Hojo ET. Mechanisms underlying the pathophysiology of type 2 diabetes: from risk factors to oxidative stress, metabolic dysfunction, and hyperglycemia. *Mutat Res Genet Environ Mutagen* 2022;503437. <https://doi.org/10.1016/j.mrgentox.2021.503437>.
- [3] Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, Vos T. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2023;402. [https://doi.org/10.1016/S0140-6736\(23\)01301-6](https://doi.org/10.1016/S0140-6736(23)01301-6).
- [4] Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstant A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. *Sleep Med Rev* 2016;30. <https://doi.org/10.1016/j.smrv.2015.10.002>.
- [5] Pankowska MM, Lu H, Wheaton AG, Liu Y, Lee B, Greenlund KJ, Carlson SA. Prevalence and geographic patterns of self-reported short sleep duration among US adults, 2020. *Prev Chronic Dis* 2023;20. <https://doi.org/10.5888/PCD20.220400>.
- [6] Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. *Sleep* 2005;28(10):1289–96. <https://doi.org/10.1093/sleep/28.10.1289>.
- [7] Dutil C, Chaput J-P. Inadequate sleep as a contributor to type 2 diabetes in children and adolescents. *Nutr Diabetes* 2017;7(5). <https://doi.org/10.1038/nutd.2017.19>.
- [8] Landhuis CE, Perry DK, Hancox RJ. Association between childhood and adolescent television viewing and unemployment in adulthood. *Prev Med* 2012;54(2):168–73. <https://doi.org/10.1016/j.ypmed.2011.11.007>.
- [9] Engeda J, Mezuk B, Ratliff S, Ning Y. Association between duration and quality of sleep and the risk of pre-diabetes: evidence from NHANES. *Diabet Med* 2013;30(6):676–80. <https://doi.org/10.1111/dme.12165>.
- [10] Ford ES, Wheaton AG, Chapman DP, Li C, Perry GS, Croft JB. Associations between self-reported sleep duration and sleeping disorder with concentrations of fasting and 2-h glucose, insulin, and glycosylated hemoglobin among adults without diagnosed diabetes. *J Diabetes* 2014;6(4):338–50. <https://doi.org/10.1111/1753-0407.12101>.
- [11] Arora T, Chen MZ, Cooper AR, Andrews RC, Taheri S. The impact of sleep debt on excess adiposity and insulin sensitivity in patients with early type 2 diabetes mellitus. *J Clin Sleep Med* 2016;12(5):673–80. <https://doi.org/10.5664/jcsm.5792>.
- [12] Kim A, Yu HY, Lim J, Ryu C-M, Kim YH, Heo J, Choo M-S. Improved efficacy and in vivo cellular properties of human embryonic stem cell derivative in a preclinical model of bladder pain syndrome. *Sci Rep* 2017;7(1):8872. <https://doi.org/10.1038/s41598-017-09330-x>.
- [13] Leng Y, Cappuccio FP, Surtees PG, Luben R, Brayne C, Khaw KT. Daytime napping, sleep duration and increased 8-year risk of type 2 diabetes in a British population. *Nutr Metabol Cardiovasc Dis* 2016;26. <https://doi.org/10.1016/j.numecd.2016.06.006>.

- [14] Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354(9188):1435–9. [https://doi.org/10.1016/S0140-6736\(99\)01376-8](https://doi.org/10.1016/S0140-6736(99)01376-8).
- [15] Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes* 2010;59(9):2126–33. <https://doi.org/10.2337/db09-0699>.
- [16] Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction. *Ann Intern Med* 2012;157(8):549. <https://doi.org/10.7326/0003-4819-157-8-201210160-00005>.
- [17] Robertson MD, Russell-Jones D, Umpleby AM, Dijk DJ. Effects of three weeks of mild sleep restriction implemented in the home environment on multiple metabolic and endocrine markers in healthy young men. *Metab Clin Exp* 2013;62(2):204–11. <https://doi.org/10.1016/j.metabol.2012.07.016>.
- [18] Rao MN, Neylan TC, Grunfeld C, Mulligan K, Schambelan M, Schwarz J-M. Subchronic sleep restriction causes tissue-specific insulin resistance. *J Clin Endocrinol Metabol* 2015;100(4):1664–71. <https://doi.org/10.1210/jc.2014-3911>.
- [19] Broussard JL, Chapotot F, Abraham V, Day A, Delebecque F, Whitmore HR, Tasali E. Sleep restriction increases free fatty acids in healthy men. *Diabetologia* 2015;58(4):791–8. <https://doi.org/10.1007/s00125-015-3500-4>.
- [20] Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007;11. <https://doi.org/10.1016/j.smrv.2007.01.002>.
- [21] Bozorgmanesh M, Hadaegh F, Azizi F. Predictive performance of the visceral adiposity index for a visceral adiposity-related risk: type 2 diabetes. *Lipids Health Dis* 2011;10(1):88. <https://doi.org/10.1186/1476-511X-10-88>.
- [22] Gohil A, Hannon TS. Poor sleep and obesity: concurrent epidemics in adolescent youth. *Front Endocrinol* 2018;9. <https://doi.org/10.3389/fendo.2018.00364>.
- [23] Darukhanavala A, Booth JN, Bromley L, Whitmore H, Imperial J, Penev PD. Changes in insulin secretion and action in adults with familial risk for type 2 diabetes who curtail their sleep. *Diab Care* 2011;34(10):2259–64. <https://doi.org/10.2337/dc11-0777>.
- [24] Trento M, Broglia F, Riganti F, Basile M, Borgo E, Kucich C, Porta M. Sleep abnormalities in type 2 diabetes may be associated with glycemic control. *Acta Diabetol* 2008;45(4):225–9. <https://doi.org/10.1007/s00592-008-0047-6>.
- [25] Zizi F, Pandey A, Murray-Bachmann R, Vincent M, McFarlane S, Ogedegbe G, Jean-Louis G. Race/ethnicity, sleep duration, and diabetes mellitus: analysis of the National Health Interview Survey. *Am J Med* 2012;125. <https://doi.org/10.1016/j.amjmed.2011.08.020>.
- [26] McWhorter KL, Park YM, Gaston SA, Fang KB, Sandler DP, Jackson CL. Multiple sleep dimensions and type 2 diabetes risk among women in the Sister Study: differences by race/ethnicity. *BMJ Open Diab Res Care* 2019;7. <https://doi.org/10.1136/bmjdrc-2019-000652>.
- [27] Wang C, Liu Y, Chen X, Zhu J, Wu Q, Chen H, Chen R. Meta-analysis of correlation between sleep duration and gender difference in adults with type 2 diabetes. *Sleep Breath* 2023;27. <https://doi.org/10.1007/s11325-023-02841-0>.
- [28] Cespedes EM, Bhupathiraju SN, Li Y, Rosner B, Redline S, Hu FB. Long-term changes in sleep duration, energy balance and risk of type 2 diabetes. *Diabetologia* 2016;59(1):101–9. <https://doi.org/10.1007/s00125-015-3775-5>.
- [29] Tan X, Chapman CD, Cedernaes J, Benedict C. Association between long sleep duration and increased risk of obesity and type 2 diabetes: a review of possible mechanisms. *Sleep Med Rev* 2017;4:11. <https://doi.org/10.1016/j.smrv.2017.11.001>.
- [30] Byberg S, Hansen ALS, Christensen DL, Vistisen D, Aadahl M, Linneberg A, Witte DR. Sleep duration and sleep quality are associated differently with alterations of glucose homeostasis. *Diab Med* 2012;29(9). <https://doi.org/10.1111/j.1464-5491.2012.03711.x>.
- [31] Ferrie JE, Kivimäki M, Akbaraly TN, Tabak A, Abell J, Davey Smith G, Shipley MJ. Change in sleep duration and type 2 diabetes: the Whitehall II study. *Diab Care* 2015;38(8):1467–72. <https://doi.org/10.2337/dc15-0186>.
- [32] Han X, Liu B, Wang J, Pan A, Li Y, Hu H, He M. Long sleep duration and afternoon napping are associated with higher risk of incident diabetes in middle-aged and older Chinese: the Dongfeng-Tongji cohort study. *Ann Med* 2016;48. <https://doi.org/10.3109/07853890.2016.1155229>.
- [33] Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33(2):414–20. <https://doi.org/10.2337/dc09-1124>.
- [34] Martyn-Nemeth P, Schwarz Farabi S, Mihailescu D, Nemeth J, Quinn L. Fear of hypoglycemia in adults with type 1 diabetes: impact of therapeutic advances and strategies for prevention - a review. *J Diab Comp* 2016;30. <https://doi.org/10.1016/j.jdiacomp.2015.09.003>.
- [35] Raj JP, Hansdak SG, Naik D, Mahendri NV, Thomas N. SLEEp among diabetic patients and their GlycaEmic control (SLEDGE) - a pilot observational study. *J Diab* 2018;11. <https://doi.org/10.1111/1753-0407.12825>.
- [36] Koopman ADM, Rauh SP, Van 'T Riet E, Groeneveld L, Van Der Heijden AA, Elders PJ, Rutters F. The association between social jetlag, the metabolic syndrome, and type 2 diabetes mellitus in the general population: the new Hoorn study. *J Biol Rhythm* 2017;32(4):359–68. <https://doi.org/10.1177/0748730417713572>.
- [37] Grandner MA, Seixas A, Shetty S, Shenoy S. Sleep duration and diabetes risk: population trends and potential mechanisms. *Curr Diab Rep* 2016;16. <https://doi.org/10.1007/s11892-016-0805-8>.
- [38] St-Onge M-P. The role of sleep duration in the regulation of energy balance: effects on energy intakes and expenditure. *J Clin Sleep Med* 2013;9. <https://doi.org/10.5664/jcsm.2348>.
- [39] Omisade A, Buxton OM, Rusak B. Impact of acute sleep restriction on cortisol and leptin levels in young women. *Physiol Behav* 2010;99(5):651–6. <https://doi.org/10.1016/j.physbeh.2010.01.028>.
- [40] Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004;141(11):846–50.
- [41] Spiegel K, Leproult R, Cauter E Van. Rythmes et sommeil Impact d'une dette de sommeil sur les rythmes physiologiques. *Rev Neurol* 2003;159:6–11.
- [42] Van Cauter E. Sleep disturbances and insulin resistance. *Diabet Med* 2011;42. <https://doi.org/10.1111/j.1464-5491.2011.03459.x>.
- [43] Vgontzas AN, Zoumakis E, Bixler EO, Lin H-M, Follett H, Kales A, Chrousos GP. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin*

- Endocrinol Metabol 2004;89(5):2119–26. <https://doi.org/10.1210/jc.2003-031562>.
- [44] Pfeffer K. Biological functions of tumor necrosis factor cytokines and their receptors. *Cytok Growth Factor Rev* 2003;14(3–4):185–91. [https://doi.org/10.1016/S1359-6101\(03\)00022-4](https://doi.org/10.1016/S1359-6101(03)00022-4).
- [45] Kapsimalis F, Basta M, Varouchakis G, Gourgoulianis K, Vgontzas A, Kryger M. Cytokines and pathological sleep. *Sleep Med* 2008;9(6):603–14. <https://doi.org/10.1016/j.sleep.2007.08.019>.
- [46] Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state-of-the-art review. *Chest* 2017;152. <https://doi.org/10.1016/j.chest.2017.05.009>.
- [47] Schipper SBJ, Van Veen MM, Elders PJM, van Straten A, Van Der Werf YD, Knutson KL, Rutters F. Sleep disorders in people with type 2 diabetes and associated health outcomes: a review of the literature. *Diabetologia* 2021;64. <https://doi.org/10.1007/s00125-021-05541-0>.
- [48] Labarca G, Ortega F, Arenas A, Reyes T, Rada G, Jorquera J. Extrapulmonary effects of continuous airway pressure on patients with obstructive sleep apnoea: protocol for an overview of systematic reviews. *BMJ Open* 2017;7(6). <https://doi.org/10.1136/bmjopen-2016-015315>.
- [49] Buxton OM, Marcelli E. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. *Soc Sci Med* 2010;71(5):1027–36. <https://doi.org/10.1016/j.socscimed.2010.05.041>.
- [50] Reutrakul S, Van Cauter E. Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes. *Ann N Y Acad Sci* 2014;1311(1):151–73. <https://doi.org/10.1111/nyas.12355>.
- [51] Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diab Care* 2009;32(11):1980–5. <https://doi.org/10.2337/dc09-0284>.
- [52] Lin C-L, Chien W-C, Chung C-H, Wu F-L. Risk of type 2 diabetes in patients with insomnia: a population-based historical cohort study. *Diab Metabol Res Rev* 2017;e2930. <https://doi.org/10.1002/dmrr.2930>.
- [53] Bakker JP, Weng J, Wang R, Redline S, Punjabi NM, Patel SR. Associations between obstructive sleep apnea, sleep duration, and abnormal fasting glucose the multi-ethnic study of atherosclerosis. *Am J Respir Crit Care Med* 2015;192(6):745–53. <https://doi.org/10.1164/rccm.201502-0366OC>.
- [54] Temple KA, Leproult R, Morselli L, Ehrmann DA, Cauter V Van, Mokhlesi E. Sex differences in the impact of obstructive sleep apnea on glucose metabolism. *Obstructive sleep apnea on glucose metabolism*. *Front Endocrinol* 2018;9:376. <https://doi.org/10.3389/fendo.2018.00376>.
- [55] Hein M, Lanquart J-P, Loas G, Hubain P, Linkowski P. Prevalence and risk factors of type 2 diabetes in insomnia sufferers: a study on 1311 individuals referred for sleep examinations. *Sleep Med* 2018;46:37–45. <https://doi.org/10.1016/j.sleep.2018.02.006>.
- [56] Zhang Y, Lin Y, Zhang J, Li L, Liu X, Wang T, Gao Z. Association between insomnia and type 2 diabetes mellitus in Han Chinese individuals in Shandong Province, China. *Sleep Breath* 2018;1–6. <https://doi.org/10.1007/s11325-018-1687-6>.
- [57] Carroll JE, Seeman TE, Olmstead R, Melendez G, Sadakane R, Bootzin R, Irwin MR. Improved sleep quality in older adults with insomnia reduces biomarkers of disease risk: pilot results from a randomized controlled comparative efficacy trial. *Psychoneuroendocrinology* 2015;55:184–92. <https://doi.org/10.1016/j.psyneuen.2015.02.010>.
- [58] McHill AW, Hull JT, McMullan CJ, Klerman EB. Chronic insufficient sleep has a limited impact on circadian rhythmicity of subjective hunger and awakening fasted metabolic hormones. *Front Endocrinol* 2018;9(Jun). <https://doi.org/10.3389/fendo.2018.00319>.
- [59] Nedeltcheva AV, Scheer FAJL. Metabolic effects of sleep disruption, links to obesity and diabetes. *Curr Opin Endocrinol Diab Obes* 2014;21(4):293–8. <https://doi.org/10.1097/MED.0000000000000082>.
- [60] Deng H-B, Tam T, Zee BC-Y, Chung RY-N, Su X, Jin L, Lao XQ. Short sleep duration increases metabolic impact in healthy adults: a population-based cohort study. *Sleep* 2017;40. <https://doi.org/10.1093/sleep/zsx130>.
- [61] Kim CE, Shin S, Lee H-W, Lim J, Lee J, Shin A, Kang D. Association between sleep duration and metabolic syndrome: a cross-sectional study. *BMC Public Health* 2018;18(1):720. <https://doi.org/10.1186/s12889-018-5557-8>.
- [62] Gerhart-Hines Z, Lazar MA. Circadian metabolism in the light of evolution. *Endocr Rev* 2015;36. <https://doi.org/10.1210/er.2015-1007>.
- [63] Marcheva B, Ramsey KM, Peek CB, Affinati A, Maury E, Bass J. Circadian clocks and metabolism. *Handb Exp Pharmacol* 2013;217:127–55. <https://doi.org/10.1007/978-3-642-25950-0-6>.
- [64] Wang Y-H, Wu H-H, Ding H, Li Y, Wang Z-H, Li F, Zhang J-P. Changes of insulin resistance and β -cell function in women with gestational diabetes mellitus and normal pregnant women during mid- and late pregnant period: a case-control study. *J Obstet Gynaecol Res* 2013;39(3):647–52. <https://doi.org/10.1111/j.1447-0756.2012.02009.x>.
- [65] Potter GDM, Skene DJ, Arendt J, Cade JE, Grant PJ, Hardie LJ. Circadian rhythm and sleep disruption: causes, metabolic consequences, and countermeasures. *Endocr Rev* 2016;37. <https://doi.org/10.1210/er.2016-1083>.
- [66] Qian J, Scheer FAJL. Circadian system and glucose metabolism: implications for physiology and disease. *Trends Endocrinol Metabol* 2016;27(5):282–93. <https://doi.org/10.1016/j.tem.2016.03.005>.
- [67] Shimizu I, Yoshida Y, Minamino T. A role for circadian clock in metabolic disease. *Hypertens Res* 2016;39. <https://doi.org/10.1038/hr.2016.12>.
- [68] Tare A, Lane JM, Cade BE, Grant SF, Chen TH, Punjabi NM, Saxena R. Sleep duration does not mediate or modify association of common genetic variants with type 2 diabetes. *Diabetologia* 2014;57. <https://doi.org/10.1007/s00125-013-3110-y>.
- [69] Nisa H, Qi KHT, Leng J, Zhou T, Liu H, Li W, Qi L. The circadian rhythm-related MTNR1B genotype, gestational weight gain, and postpartum glycemic changes. *J Clin Endocrinol Metab* 2018;103(6):2284–90. <https://doi.org/10.1210/jc.2018-00071>.
- [70] Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. *Metabolism* 2017;84. <https://doi.org/10.1016/j.metabol.2017.11.017>.
- [71] Carrasco-Benso MP, Rivero-Gutierrez B, Lopez-Minguez J, Anzola A, Diez-Noguera A, Madrid JA, Garaulet M. Human adipose tissue expresses intrinsic circadian rhythm in insulin sensitivity. *Fed Am Soc Exp Biol J* 2016;30(9):3117–23. <https://doi.org/10.1096/fj.201600269RR>.
- [72] Jakubowicz D, Barnea M, Wainstein J, Froy O. High Caloric intake at breakfast vs. dinner differentially influences weight loss of

- overweight and obese women. *Obesity* 2013;21(12):2504–12. <https://doi.org/10.1002/oby.20460>.
- [73] Shapiro ET, Tillil H, Polonsky KS, Fang VS, Rubenstein AH, Van Cauter E. Oscillations in insulin secretion during constant glucose infusion in normal man: relationship to changes in plasma glucose. *J Clin Endocrinol Metab* 1988;67(2):307–14.
- [74] Egan KJ, Knutson KL, Pereira AC, von Schantz M. The role of race and ethnicity in sleep, circadian rhythms and cardiovascular health. *Sleep Med Rev* 2017;33:70–8. <https://doi.org/10.1016/j.smrv.2016.05.004>.
- [75] Baron KG, Reid KJ. Circadian misalignment and health. *Int Rev Psychiatr* 2014;26(2):139–54. <https://doi.org/10.3109/09540261.2014.911149>.
- [76] Eckel RH, Depner CM, Perreault L, Markwald RR, Smith MR, McHill AW, Wright KP. Morning circadian misalignment during short sleep duration impacts insulin sensitivity. *Curr Biol* 2015;25(22):3004–10. <https://doi.org/10.1016/j.cub.2015.10.011>.
- [77] Buxton OM, Cain SW, O'Connor SP, Porter JH, Duffy JF, Wang W, Shea SA. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. *Sci Transl Med* 2012;4(129):129ra43. <https://doi.org/10.1126/scitranslmed.3003200>.
- [78] Al Khatib HK, Hall WL, Creedon A, Ooi E, Masri T, McGowan L, Pot GK. Sleep extension is a feasible lifestyle intervention in free-living adults who are habitually short sleepers: a potential strategy for decreasing intake of free sugars? A randomized controlled pilot study. *Am J Clin Nutr* 2018;107(1):43–53. <https://doi.org/10.1093/ajcn/nqx030>.
- [79] Altaf QA, Dodson P, Ali A, Raymond NT, Wharton H, Fellows H, Tahrania AA. Obstructive sleep apnea and retinopathy in patients with type 2 diabetes: a longitudinal study. *Am J Respir Crit Care Med* 2017;196(7):892–900. <https://doi.org/10.1164/rccm.201701-0175OC>.
- [80] Bironneau V, Goupi F, Ducluzeau PH, Le Vaillant M, Abraham P, Henni S, Gagnadoux F. Association between obstructive sleep apnea severity and endothelial dysfunction in patients with type 2 diabetes. *Cardiovasc Diabetol* 2017;16(1):39. <https://doi.org/10.1186/s12933-017-0521-y>.
- [81] Rajendran P, Rengarajan T, Thangavel J, Nishigaki Y, Sakthisekaran D, Sethi G, Nishigaki I. The vascular endothelium and human diseases. *Int J Biol Sci* 2013;9(10):1057–69. <https://doi.org/10.7150/ijbs.7502>.
- [82] Lou P, Qin Y, Zhang P, Chen P, Zhang L, Chang G, Zhang N. Association of sleep quality and quality of life in type 2 diabetes mellitus: a cross-sectional study in China. *Diab Res Clin Pract* 2015;107(1):69–76. <https://doi.org/10.1016/J.DIABRES.2014.09.060>.
- [83] Gabric K, Matetic A, Vilovic M, Kurir TT, Rusic D, Galic T, Bozic J. Health-related quality of life in type 2 diabetes mellitus patients with different risk for obstructive sleep apnea. *Pat Prefer Adher* 2018;12:765–73. <https://doi.org/10.2147/PPA.S165203>.
- [84] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, Doncarlos L, Ware JC. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 2015;1(1):40–3. <https://doi.org/10.1016/j.slehd.2014.12.010>.
- [85] Chao C-Y, Wu J-S, Yang Y-C, Shih C-C, Wang R-H, Lu F-H, Chang C-J. Sleep duration is a potential risk factor for newly diagnosed type 2 diabetes mellitus. *Metabolism* 2011;60(6):799–804. <https://doi.org/10.1016/J.METABOL.2010.07.031>.
- [86] Chaput J-P, Després J-P, Bouchard C, Tremblay a. Association of sleep duration with type 2 diabetes and impaired glucose tolerance. *Diabetologia* 2007;50(11):2298–304. <https://doi.org/10.1007/s00125-007-0786-x>.
- [87] Maskarinec G, Jacobs S, Amshoff Y, Setiawan VW, Shvetsov YB, Franke AA, Le Marchand L. Sleep duration and incidence of type 2 diabetes: the multiethnic cohort. *Sleep Health* 2018;4(1):27–32. <https://doi.org/10.1016/J.SLEH.2017.08.008>.
- [88] Tasali E, Chapotot F, Wroblewski K, Schoeller D. The effects of extended bedtimes on sleep duration and food desire in overweight young adults: a home-based intervention. *Appetite* 2014;80:220–4. <https://doi.org/10.1016/J.APPET.2014.05.021>.

Chapter 21

Social jetlag, circadian disruption, and cardiometabolic disease risk

Susan Kohl Malone^a, Maria A. Mendoza^a and Freda Patterson^b

^aRory Meyers College of Nursing, New York University, New York, NY, United States; ^bDepartment of Behavioral Health and Nutrition, College of Health Sciences, University of Delaware, Newark, DE, United States

Introduction

The sun rises and sets over the earth in a predictable pattern. This pattern has existed for billions of years and has influenced the behavior of all living things. Behavioral rhythms have aligned with these light-dark rhythms and conferred an evolutionary advantage. Humans have adapted to the light–dark cycle so that activity occurs during the day and rest occurs during the night. Increased visibility afforded by daylight optimizes foraging and safety while being active. Reduced visibility during the night optimizes sleeping and fasting. Daily rhythms, such as light–dark, are known as circadian rhythms from the Latin words “circa,” for about, and “dias,” for a day. Physiological processes rely on predictable circadian rhythms. These processes include sleeping and waking, cardiac function, such as heart rate and blood pressure, and metabolic processes, such as glucose, lipid, and energy metabolism. Disrupting circadian rhythms can profoundly impact cardiometabolic health and well-being. Poor cardiometabolic health can also disrupt the circadian system. This chapter will briefly introduce the cardiometabolic syndrome, the circadian system, circadian disruption, and social jetlag as a form of circadian disruption.

Circadian regulation of cardiac and metabolic functioning will be reviewed and the influence of environmental, behavioral, and biological rhythms on cardiometabolic health will be discussed (Fig. 21.1).

Definitions and epidemiology

Cardiometabolic syndrome

The cardiometabolic syndrome also known as metabolic syndrome (MetS) or syndrome X is a cluster of metabolic dysfunctions that include insulin resistance, impaired

glucose tolerance, dyslipidemia, hypertension, and central adiposity. The presence of three or more of these cardiometabolic risk factors is predictive of diabetes and cardiovascular disease. Individuals with MetS are more likely to die from coronary heart disease and stroke than individuals without MetS.

The pathophysiologic mechanism in MetS originates from insulin resistance. The pancreatic beta cells produce insulin which binds with cells in the liver, fat, muscles, and blood vessels. Normally in the liver, insulin suppresses glucose production. In the setting of insulin resistance, there is impaired glucose production or hepatic gluconeogenesis. It is not clearly understood why insulin also plays a role in hepatic lipogenesis causing increased free fatty acids and triglycerides in the blood stream causing dyslipidemia. This leads to an atherogenic state characterized by increased triglycerides, low high-density lipoprotein cholesterol (HDL-c), and increased small, dense low-density lipoproteins.

Other key pathologic mechanisms in MetS include obesity, specifically abnormal ectopic fat distribution and inflammation. The obesity is described as increased visceral rather than subcutaneous fat. There is also accumulation of fat in the liver causing nonalcoholic fatty liver disease. This adipose tissue hypertrophy leads to insulin resistance. Moreover, the hypertrophic adipocytes result in a low inflammatory state from the release of proinflammatory factors such as adipocytokines, plasminogen activator inhibitor-1, tumor necrosis factor alpha, interleukin 6, C-reactive protein, and fibrinogen.

Data from the National Health and Nutrition Examination Survey (NHANES) indicate that in 2011–12, approximately one third of adults in the United States (34.7%) had MetS [1], representing a 35% prevalence increase as compared to 1998–94 [2]. The distribution of

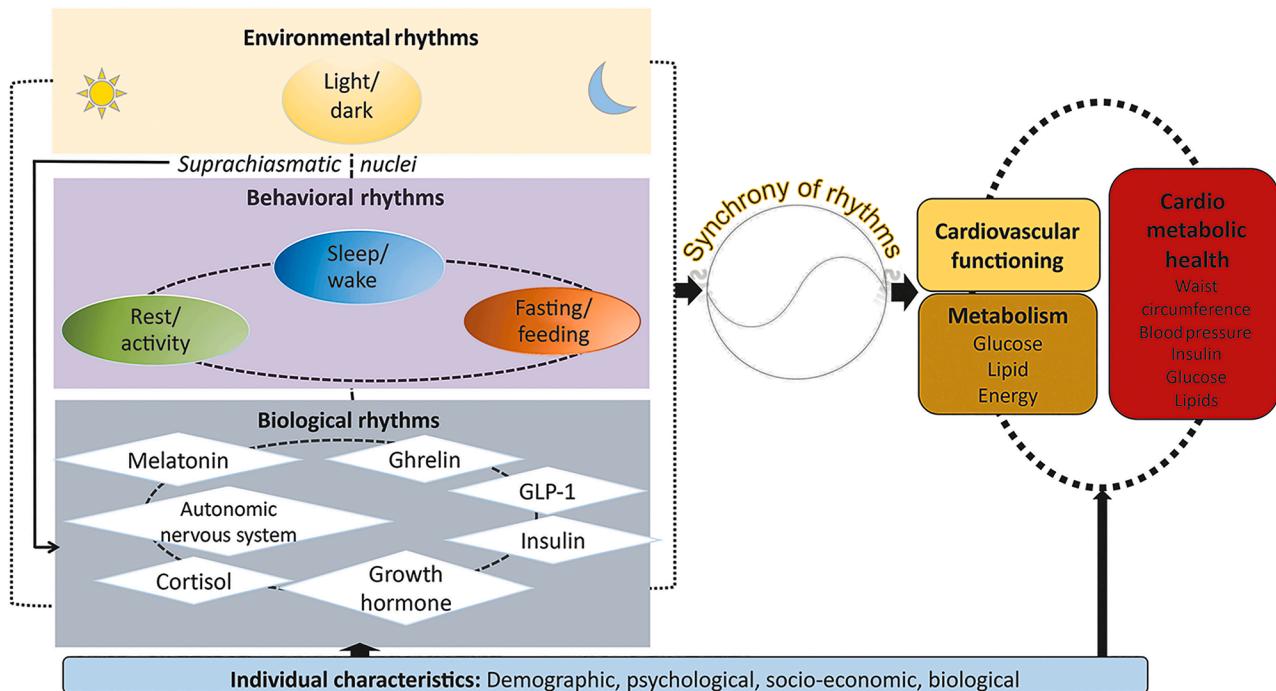


FIGURE 21.1 The influence of environmental, behavioral, and biological rhythms on cardiometabolic health.

MetS prevalence varies according to sex, race, age, and education levels. Specifically, a greater proportion of women meet the diagnostic criteria for MetS as compared to men (36.6% vs. 32.8%, respectively) [1]. In terms of racial differences, 38.6% of Hispanic, 37.4% of non-Hispanic white, and 35.5% of black adults reported having METs in 2012 [1]. Between 1988 and 1994 and 2007–12, the largest increase in the prevalence of MetS was reported in non-Hispanic black men (55%), then non-Hispanic white women (44%), and non-Hispanic black women (41%) [2]. Advanced age and lower educational attainment are associated with increased rates of MetS. Approximately one in five (18.3%) 20–39 year olds, as compared to one in two (46.7%) adults aged 60 years and older have MetS [1]. As compared to college graduates, those with a less than high school education had a 56% increased odds of having METs ($OR = 1.56$, 95% CI = 1.32–1.84) [2].

Circadian rhythms

Circadian rhythms have been increasingly linked to cardiometabolic health. Circadian rhythms provide a temporal structure for events. Knowing when predictable events will occur allows for preparation and optimal functioning. Being prepared is so important that living things have translated the light-dark rhythm of the solar clock into their very being by creating internal biological clocks. These biological clocks predict daily changes in the environment

and prepare the body for anticipated behaviors. As a result, the right hormones are in the right place at the right time. For example, cortisol, the alerting and arousal hormone, increases prior to and just after waking to prepare the body for the upcoming demands of the day [3,4]. Optimal performance follows and survival advantage is conferred.

Life would be chaos without the temporal structure of circadian rhythms. Biological clocks must be set to the same time as the solar clock to effectively anticipate predictable 24-h patterns. However, biological clocks tick slightly slower than the solar clock, a little over 24 h each day. It is essential to synchronize biological and solar clocks to prevent chaos and to optimize function. Light is the primary synchronizer. The light/dark cycle resets the biological clock to tick in sync with the solar clock every day.

The eye is key to this synchronization. Specialized cells in the eye's retina, the retinal ganglion cells, perceive light and dark. This light/dark message is carried along a neural pathway, the retino-hypothalamic tract, and delivered to the master clock, a specialized cluster of cells in the hypothalamus known as the suprachiasmatic nuclei (SCN). The SCN transmits stimulatory and inhibitory messages to about 35 brain regions, particularly hypothalamic regions controlling hormone release and autonomic nervous system control [5]. The SCN also transmits these messages to the autonomic nervous system which regulates tissue specific sensitivity to these hormones. These hormonal and neuronal messages convey a sense of time to the body.

But the SCN is not the only clock. Every cell of the body possesses a clock; liver cells, pancreatic cells, muscle tissue cells, etc. These specific body cell clocks synchronize behavioral and physiological processes to the light–dark cycle. The SCN plays an important role in this synchronization; however, the synchronization process is complex and still not completely understood. What is known is that disrupting the synchrony between the clocks impacts cognitive, behavioral, and psychological functioning.

Sleep–wake rhythms are one of the most pronounced 24-h behavioral rhythms in humans. Sleeping and waking partition essential cognitive and physiological tasks to certain times of day. Sleep opens the door for information processing and memory consolidation because sensory input is minimal compared to the wake period. Energy consumed during the day can be diverted to the brain rather than used to meet the energy needs of daytime activities. Sleep also opens the door for the body to “clean up” toxins that have built up along the metabolic pathways from daytime energy consumption. Despite a universal 24-h cycle for sleeping and waking in humans, sleep–wake times vary between individuals. Some people prefer early bedtimes and wake times; others prefer late bedtimes and wake times.

Sleep–wake times, or the clock times for sleeping and waking, are influenced by multiple factors. These factors include light–dark cycles within a time zone, developmental stage, social obligations, and genetic factors. For example, sunrise and sunset are 4 min later for every one-degree of longitude from east to west. Sleep–wake times replicate this by delaying 4-min for every one-degree longitude. Developmentally, sleep–wake times are early in childhood, delay throughout adolescents, reach a peak in lateness around 20 years of age, and gradually advance thereafter until approximately 60 years of age. Social obligations such as late-night gatherings and early morning work commitments also impact sleep–wake times. Individual differences in the intrinsic pace of the biological clock also affects sleep–wake times, such that faster paced clock (e.g., 24.2 h) contribute to earlier sleep periods than slower paced clocks (e.g., 24.4 h) [6]. Racial differences in clock pace have been reported with blacks of African descent exhibiting faster internal clocks than their white counterparts [7,8]. Genetic factors also contribute to sleep–wake times as several single nucleotide polymorphisms have been linked to genes with well-known circadian roles, such as PER2 [9,10].

Circadian disruption and social jetlag

Circadian disruption is defined as an altered tau, amplitude, and/or mean level of a rhythm [11]. These disrupted rhythms can be environmental, exemplified by reduced daytime and increased nighttime light exposure;

behavioral, exemplified by reduced nocturnal and increased daytime sleep; as well as biological. Suboptimal functioning follows when the synchrony between environmental, behavioral, and biological rhythms is disrupted. Staying awake during the night when your body is secreting sleep-promoting hormones, such as melatonin results in suboptimal wakefulness. Conversely, sleeping during the day when hormones promoting sleep are missing lead to curtailed sleep duration and altered sleep architecture. Specifically, REM and SWS sleep are reduced and REM sleep shifts from the later to the earlier part of the sleep period [12].

Irregular sleep–wake times contribute to a loss of synchrony between environmental, behavioral, and biological rhythms. Irregular sleep–wake times can be chronic, as in shift work, or transient, as in transmeridian travel. Chronic, irregular sleep–wake times also characterize social jetlag. Social jetlag is defined as the difference in sleep–wake times between work and free days [13]. Different work and free day sleep–wake times result from the different schedules people adopt. For example, people tend to go to bed late but rise early for work on work days, contributing to short work-day sleep. To compensate for sleep debt incurred during the work week, people often sleep longer on free days by waking later. The result is late-bed/early-rise times on work days and late-bed/late-rise times on free days. Social jetlag can also occur when early bedtimes and early rise times are adopted during the work week, but social obligations on free days lead to late bedtimes. Seventy percent of a European population sample has reported social jetlag of at least 1 h or more. The widespread and chronic nature of social jetlag has raised concern about potential adverse cardiometabolic health effects like those found in shift work [14].

Circadian disruption and cardiometabolic health

Data clearly show that the odds of MetS are significantly higher in shift workers as compared to nonshift workers [15]. Specifically, across 13 pooled observational studies, the association between “ever exposed to night shift work” and MetS risk was 1.57 (95% CI = 1.24–1.98, $P = .001$), while a higher risk was indicated in workers with longer exposure to night shifts ($RR = 1.77$, 95% CI = 1.32–2.36, $P = .936$) [16]. Consistent with these pooled data, prospective data over a median 6.6 year period showed that the risk of METs development increased with accumulated years of shift work, independent of possible confounders [17]. Not yet clear from this body of work is the cut-point of time spent doing shift-work that confers exponentially greater risk for MetS.

In addition to shift work being independently and prospectively associated with an increased risk for MetS,

there is evidence that the individual risk factors for MetS (abdominal obesity, hypertension, atherogenic dyslipidemia, and impaired glucose tolerance) [18] are associated with shift work. For example, shift workers were shown to have a 50% increased odds of hypertension [19], while an elevated waist circumference was shown to be more common in night and rotating shift workers: specifically, waist circumference increased by 1.089 cm per 1000 night duties and by 0.99 cm per 10,000 night shift hours in a sample of nurses [20]. Prospective data also show that among persistent shift workers, the presence of 1–2 MetS factors conferred a more than 12-fold risk of developing MetS 5 years later [21]. Thus, the trajectory toward a MetS diagnosis is shown to accelerate with each accumulated risk factor diagnosis in populations whose circadian function is disrupted, such as shift workers.

Data linking social jetlag and MetS are limited and findings are inconsistent. Social jetlag has been associated with a greater likelihood of having MetS, or individual MetS risk factors in some [22–24], but not all [25,26], studies. Adults with type 2 diabetes reporting > 30 min of social jetlag did not have poorer glucose regulation than adults with ≤30 min of social jetlag [25,26]. Adults younger than 61 years of age were more likely to have MetS if they reported 1–2 h of social jetlag (1.29, 95% CI = 0.9–1.9) or ≥ 2 h of social jetlag (2.13, 95% CI = 1.3–3.4) than adults with <1 h of social jetlag [27]. However, there was no association between social jetlag and MetS in adults ≥ 61 years of age [27]. Social jetlag has been associated with poorer metabolic but not cardiac outcomes as evidenced by higher triglyceride, fasting insulin, and insulin resistance levels as well as greater waist circumferences and lower HDL-c levels but not heart rate or blood pressure [23].

Reasons for these inconsistent findings are uncertain. Chronological age may be a contributing factor. Younger adults may be more likely to suffer the deleterious effects of social jetlag, but they are also more likely to have greater social jetlag than older adults. Differences may also stem from variability in vulnerability to the adverse cardiometabolic effects from social jetlag between individuals. Support for interindividual variability is garnered from evidence of significant differences in weight gain and neurobehavioral deficits following sleep loss among individuals but stability of weight gain and neurobehavioral deficits within individuals [28,29].

Circadian control of the cardiometabolic system

Links between MetS and circadian disruption are plausible because the cardiometabolic system is influenced by multiple biological, behavioral, and environmental factors that

have been shown to have endogenous circadian rhythms. Identifying endogenous biological rhythms requires separating these biological factors from the behavioral and environmental factors affecting them, such as sleeping and waking or light and dark. This is accomplished by keeping individuals constantly awake with low activity levels in very dim light and providing evenly spaced meals of equal caloric content, or in other words, keeping individuals in constant routine conditions [30]. Endogenous rhythms can also be separated from behavioral and environmental factors by scheduling sleeping and waking every 28 h rather than every 24 h, or forced de-synchrony conditions. Both constant routine and forced desynchrony conditions have been used in experimental studies to elucidate the circadian regulation of the cardiometabolic system. Simulated shift work protocols have also been used to elucidate the effects of circadian disruption on individual cardiometabolic outcomes in controlled laboratory environments.

Cardiovascular functioning

Cardiovascular demands change drastically in response to activity levels. Faster heart rates and higher blood pressures are needed to deliver sufficient nutrients throughout the body during activity as opposed to rest. The circadian system can anticipate and prepare for predictable changes in cardiovascular demands. Several constant routine and forced desynchrony studies have revealed that cardiovascular parameters, including heart rate and blood pressure, have an endogenous rhythm [31–34]. Heart rates peak between 11:00 and 12:00 and dip by about seven beats per minute between 2:00 and 3:00 [31,32]. Blood pressures peak between 18:00 and 21:00 with a 3–6 mmHg greater systolic and a 2–3 mmHg greater diastolic blood pressure than the trough blood pressure [35,36]. Chronotype, or an individual's preference for morning or evening activities [37], may advance or delay this endogenous rhythm. For example, peak heart rates are 6 h later for evening compared to morning types [33].

Metabolism

The metabolic system is tightly coupled to the circadian system [38–40]. The circadian system informs the metabolic system of anticipated periods for activity/feeding and rest/fasting, thereby optimizing energy utilization and storage across the 24-h day. The SCN conveys day/night messages to the body through neuronal and hormonal messages that orchestrate biological and behavioral rhythms for glucose and lipid metabolism, energy expenditure, and appetite. The SCN ensures that the right hormones and right behaviors are in the right place at the right time of day. These biological rhythms collectively favor efficient metabolism to coincide with daytime feeding and

activity in humans. But the SCN is also influenced by the metabolic system through nutrient messages that convey the energy status of the body. This bidirectional regulation between the circadian and the metabolic systems ensures that glucose homeostasis is maintained.

Glucose metabolism

A robust daily rhythm for glucose metabolism has been well-established. 24/7 glucose availability is critical to support the central nervous system, which uses 20% of glucose consumed but cannot store or synthesize glucose. Morning energy needs for activity and feeding are anticipated by the circadian system and several reports of higher morning-versus-evening fasting glucose levels that are offset by greater insulin secretion support this premise [41–44]. Morris et al. reported a 5% higher morning, compared to evening, fasting glucose level in healthy young adults [42]. Yet, not all studies report higher morning-versus-evening fasting glucose levels [45,46]. Age has been conjectured as an underlying reason for these disparate findings. Higher morning-versus-evening fasting glucose has been reported in younger, but not older adults (<35 and >65 years of age, respectively) [47]. However others have reported that healthy youth do not have a morning–evening differences in fasting glucose [46]. This mixed evidence raises speculation that age is an underlying factor in morning versus evening differences in fasting glucose.

On the other hand, glucose responses to meals consistently demonstrate an endogenous rhythm. Evening glucose responses to meals, oral glucose challenges, and intravenous glucose are higher and remain elevated longer than morning responses in healthy adults [42,48–54]. Postmeal glucose excursions to identical meals in the morning and the evening are 2.3 and 3.3 mmol/L, respectively, in healthy young adults [48]. Glucose tolerance is 17% lower in the evening versus the morning [42]. These morning-to-evening declines in glucose tolerance are partially driven by circadian modulation of target tissue sensitivity. Insulin-producing beta cells of the pancreas become less sensitive to glucose across the day; other peripheral tissues become less sensitive to insulin across the day. SCN excised rats lack daily glucose and insulin sensitivity rhythms exemplifying the critical role of the circadian system in glucose regulation [55].

Lipid metabolism

Endogenous rhythms may optimize lipid absorption, storage, and transport by synchronizing these metabolic activities with anticipated sleep–wake and feeding-fasting behaviors. Fifteen percent to twenty percent of lipid metabolites have demonstrated endogenous rhythms that are

characterized by morning peaks and afternoon/evening declines during constant routine conditions [56,57]. However, large interindividual differences in the specific lipid metabolites exhibiting rhythmicity exist and up to 12-h differences in the timing of the rhythms have been demonstrated [57]. This evidence suggests that several distinct circadian phenotypes for lipid metabolism exist [57].

Several studies using various study protocols have demonstrated that low density lipoprotein cholesterol (LDL-c) and total cholesterol levels are higher in the morning compared to the evening [58–60]. Miida reported that LDL-c was 0.09–0.13 mmol/L higher at waking than at midnight [60]. Declining LDL-c and total cholesterol levels from morning to evening may be explained by enhanced daytime lipid clearance from the circulation. This premise is supported by evidence that apolipoproteins which are used to transport lipids are lower following night versus day time meals [61]. Higher triglyceride [61,62] and very-low-density lipoproteins [61] levels have also been reported following night versus day time meals in rotating shift workers and healthy young adults.

Energy metabolism

It is uncertain whether there is an endogenous rhythm for energy metabolism. One method for estimating energy metabolism is through indirect calorimetry. Indirect calorimetry calculates metabolic rate by measuring the heat produced by oxidizing macronutrients, such as carbohydrates and fats. Some [63], but not [31] all, studies report an endogenous rhythm for postprandial energy metabolism based on diet-induced thermogenesis [63,64]. Disparate findings may stem from methodological differences, such as responses to meals versus snacks. Morris et al. found that diet-induced thermogenesis was 44% lower in the evening than in the morning in healthy young adults [63]. These same authors reported that postprandial energy expenditure was 4% lower in the evening than the morning [63]. This suggests that eating larger meals in the morning and smaller meals in the evening would be beneficial for weight homeostasis and/or weight loss. Yet, large breakfast and small dinner eating patterns are not the norm in Western cultures. Dinner is the largest meal of the day [65].

Some contend that changes in appetite across the day may explain why dinner is the largest meal [66]. Healthy adults rate their hunger as lowest after waking in the morning and highest in the evening at approximately 20:00 [67,68]. These rhythms are exacerbated during sleep restriction [68] and are unrelated to meal times [69]. However, time pressure and social cues significantly influence meal sizes [70,71].

Environmental rhythms and cardiometabolic health

The 24-h transitions from light to dark (LD) provide a strong zeitgeber for metabolic system regulation in both animals and humans [72]. In free-living conditions characterized by bright daylight and the absence of artificial nightlight, behavioral rhythms such as feeding and activity shift earlier [73]. However, in human-constructed environments where daylight can be reduced and exposure to artificial nightlight increased, circadian rhythms and the regulation of the metabolic system can be negatively impacted.

The widespread use of electric lighting in the early-to-mid twentieth century enabled the artificial extension of daytime to the point where today virtually all adults living in developed countries experience light pollution [74]. Sources of LAN include urban street lighting (5–15 lx) and electronic tablets (~40 lx depending on size of screen) [75]. Data suggest that approximately one-third of adults and youth leave an electronic device (e.g., television or tablet) on while sleeping [76]. Constant exposure to light desynchronizes circadian activity in rodents [77], while experimental studies show that such exposure is associated with poor metabolic indices including increased body mass and reduced glucose tolerance [78].

In terms of human studies into the association between LAN, circadian rhythms, and metabolic health, light exposure > 180 lx has been shown to phase shift circadian rhythms and suppress melatonin concentration [79]. Shift workers represent a population who are chronically exposed to LAN and experience disproportionately higher rates of poor metabolic health. A large body of work consistently reports the positive association between shift work with increased hypertension, cholesterol, and obesity [80,81]. Meanwhile, observational studies in the general population have also shown higher levels of LAN to be significantly associated with obesity even after adjustment for confounders such as sleep duration, tobacco use, and physical activity [82,83]. Larger waist circumferences, higher LDL-c and lower HDL-c levels have been associated with bedroom LAN ≥ 3 lx versus < 3 lx in older community dwelling adults [84]. Morning and evening blue light exposure increases insulin resistance in healthy adults [85].

One mechanism that may go toward explaining the association between LAN, circadian disruption, and poor metabolic health is the suppression of melatonin and glucagon like peptide-1 (GLP-1). Melatonin is an endogenously synthesized molecule that is produced by the pineal gland and serves to help regulate sleep and wakefulness. Melatonin production may be inhibited by exposure to nighttime light of sufficient intensity and duration [86]—even 1 h of exposure to 45 lx was shown to decrease melatonin levels by 60% [87]. Reduced melatonin

secretion has been associated with an increased risk for obesity [88] and type-2 diabetes [89]. Relatedly, suppressed melatonin production delays sleep onset and is associated with shorter sleep duration. Short sleep duration is a reliable determinant of metabolic syndrome, and as such represents a viable mechanism through which LAN is a risk factor for metabolic syndrome. GLP-1 limits post-meal glucose excursions by stimulating insulin secretion. Constant light exposure reduces the amplitude of GLP-1 rhythms in adults with obesity and type 2 diabetes [90].

LAN exposure also impacts heart rate and heart rhythm. Brighter lights increase heart rates and the effect of light on heart rates are strongest during the middle of the night and early morning [91]. Disrupting light-dark cycles has also been shown to disrupt heart rate rhythms and lengthen QT intervals in mice [92]. These lines of evidence suggest an association also exists between LAN, circadian rhythms, and cardiovascular health.

Behavioral rhythms and cardiometabolic health

Behavioral rhythms also influence cardiometabolic regulation. Synchronizing behaviors, such as sleep and fasting with darkness, as well as activity and feeding with daylight, lead to appropriately timed levels of glucose, insulin, glucocorticoids, and metabolically relevant hormones. Behavioral circadian disruption can occur when the SCN, entrained by light, sends sleep-promoting signals and lipid mobilization messages but food intake sends wake-promoting signals and fat storage messages. This mixed circadian signaling between the SCN and peripheral clocks in other tissues, such as the pancreas and adipose tissue has been shown to negatively impact the cardiometabolic regulation in several controlled laboratory studies [12,70,93,94].

Acutely disrupting sleep-wake patterns may impact cardiometabolic regulation through changes in metabolically relevant hormones and diet induced thermogenesis [70]. Cortisol, a hormone that raises glucose, peaks at sleep onset rather than at waking and has a blunted rhythm during forced desynchrony protocols [70,95]. The morning rise in cortisol is also significantly lower, and the evening nadir is significantly higher when adults are deprived of night time sleep [96]. Leptin, a satiety hormone, has been shown to decrease [70], and glucose has been shown to rise [95], even to prediabetic levels in some participants [70] under forced desynchrony protocols. Adverse metabolic effects have been demonstrated regardless of whether sleep is advanced or delayed [95]. Daytime sleep has also been associated with a decrease in total daily energy expenditure, diet-induced thermogenesis, and leptin levels compared to night time sleep [97].

Several studies suggest that humans' metabolic systems do not adapt to disrupted sleep–wake patterns. Rather, adverse metabolic effects persist even after exposure to longer disrupted sleep–wake patterns [93,94,98]. Fasting insulin levels increased 18%, postmeal glucose levels rose 14%, and resting metabolic rate decreased 8% during a 3-week protocol in healthy younger and older adults [93]. Chronic shift workers still demonstrated higher postmeal glucose levels despite a 10% increase in late phase insulin secretion during daytime versus nighttime sleep in a controlled laboratory environment [94]. Smaller and more prolonged disruptions in sleep–wake patterns have also been shown to significantly reduce leptin levels [98]. Blunted cortisol rhythms have been associated with irregular sleep patterns in community dwelling adults [99]. All told, chronic disruption in sleep–wake patterns as might occur during shift work or social jetlag may be a contributing factor for adverse cardiometabolic health outcomes.

Short sleep duration has also been associated with poor cardiometabolic health and is often linked with irregular sleep–wake patterns [12]. Several laboratory studies have demonstrated that the effects of disrupted sleep–wake patterns on the metabolic system are independent of and in addition to that of short sleep duration. Leproult et al. demonstrated that insulin resistance was doubled during circadian disruption plus sleep restriction versus sleep restriction alone in men but not women [100]. Leptin levels were significantly reduced following irregular sleep patterns despite sleeping longer than 6.5 h [98]. Eckel et al. reported that insulin resistance increased 20% during a simulated social jetlag study [101]. These studies provide evidence into the additive deleterious metabolic effects of circadian disruption.

Meal timing has been linked to cardiometabolic health, particularly weight regulation. Several weight loss studies support the benefits of earlier eating habits for optimal weight and glucose regulation. Shifting caloric intake earlier in the day optimizes weight loss efforts. A 10% decrease in BMI was achieved by eating 50% of total daily calories at breakfast in women with MetS undergoing weight loss treatment [102]. Only a 5% decrease in BMI was achieved by eating 50% of total daily calories at dinner [102]. Improvements in waist circumference were also greater in the early versus later eaters. Waist circumference decreased 8.5 versus 3.9 cm in the earlier versus later eaters, respectively ($P < .0001$) [102]. Similarly, overweight and obese adults who ate their main meal earlier in the day lost 25% more weight than overweight and obese individuals who ate their main meal later in the day despite similar caloric intake and physical activity [103].

Potential mechanisms linking meal timing with weight regulation include morning–evening differences in diet-induced thermogenesis and changes in the gut microbiome. Diet-induced thermogenesis is greater following

morning, versus evening meals [63]. Morning–evening difference in diet-induced thermogenesis has been shown to be driven by endogenous circadian rhythms rather than behavioral rhythms [63]. Therefore, eating early in the day is required to take advantage of the increased metabolic rates for eating. The gut microbiome is primed to support energy metabolism during the day and detoxification during the night [104]. Irregular sleeping and eating patterns are associated with changes in the gut microbiome that are characterized by increased firmicutes, a condition associated with obesity [104].

Other metabolic benefits are reaped by eating earlier versus later meals. Early eaters with MetS had greater reductions in total cholesterol, fasting insulin, insulin resistance, and fasting glucose, as well as a greater increase in HDL-cholesterol compared to later eaters [102]. In a randomized cross over study, earlier meal times were associated with greater nighttime peaks in leptin and higher melatonin levels overall in healthy young adults during the earlier versus later sleep time (22:30 bedtimes–6:30 wake times versus 1:30 bedtimes–8:30 wake times, respectively) [105]. Later meals are associated with greater and longer lasting triglyceride elevations compared to earlier meals [106]. Regular eating habits have also been linked to improved fasting lipid and postprandial insulin profiles and thermogenesis [107].

All told, the relationship between behavioral rhythms and cardiometabolic health suggest that increasing regularity and promoting earlier timing for sleeping and eating habits may improve cardiometabolic health for many people.

Biological rhythms and cardiometabolic health

Autonomic nervous system

An important determinant of endogenous cardiac rhythms is the circadian nature of the autonomic nervous system [108]. The SCN projects directly to the paraventricular nucleus, the hypothalamic area regulating autonomic nervous system control [109]. Through this pathway, the SCN conveys day/night messages to the autonomic nervous system and facilitates cardiovascular changes needed to support anticipated day and night time behaviors. During the day, the sympathetic system dominates and contributes to faster heart rates [110]. During the night, the parasympathetic system dominates and contributes to slower heart rates, which open the door for greater nocturnal heart rate variability [111]. Hence, heart rate variability is used to noninvasively estimate cardiac autonomic regulation [112,113]. Greater night time, compared to daytime, heart rate variability exemplifies nocturnal parasympathetic dominance [114]. The critical role of the circadian system

in cardiac autonomic regulation is illustrated by the loss of heart rate variability and nocturnal blood pressure dips in SCN-excised rats [109,115].

The placement of sleep (or the timing of sleep and activity) within the 24-h day matters, in part because the endogenous circadian system modulates the parasympathetic-sympathetic activity that occurs during sleep. When sleep occurs during the day, parasympathetic activity is diminished compared to the same amount of sleep during the night [116]. Enhanced parasympathetic activity of night time sleep provides optimal cardiovascular protection underscoring the importance of syncing sleep-wake patterns with day-night patterns. Circadian disruption may diminish the cardiovascular protection afforded by night time sleep.

Parasympathetic-sympathetic activity also varies across sleep stages [117,118]. Heart rates are slower and blood pressures are lower due to greater parasympathetic activity during nonrapid eye movement sleep (N-REM) compared to rapid eye movement sleep (REM) [119]. Parasympathetic activity increases from stages one to three of N-REM. Heart rates and blood pressures approach waking levels during REM sleep due to sympathetic activity [116,119]. This suggests that interrupted sleep or daytime sleep, as needed in shift work, result in overall greater sympathetic activity.

The circadian nature of the autonomic nervous system is also a determinant of endogenous metabolic rhythms. Through SCN projections to the paraventricular nucleus [109], the SCN conveys day/night messages to the autonomic nervous system. The autonomic nervous system then signals peripheral organs through its extensive network of parasympathetic and sympathetic nerve fibers. Key metabolic organs including the liver, pancreas, and visceral adipose tissue share a common neuronal connection with the paraventricular nucleus, dorsal medial nucleus, and SCN [120]. Paraventricular neuronal stimulation activates sympathetic input to the liver and adipose tissue stimulating gluconeogenesis and lipolysis respectively. Paraventricular autonomic fibers also project through other pathways to the pineal gland and regulate the release of melatonin. These neuronal messages contribute to the metabolic changes needed to support anticipated day and night time behaviors. Glucose metabolism rhythms are lost when connections between the liver and autonomic nervous system are disrupted. Impaired glucose tolerance and the loss of glucose stimulated insulin secretion rhythms and adipose tissue insulin sensitivity are caused by removing the pineal gland in animals.

Metabolically relevant hormones

Important determinants of endogenous metabolic rhythms, such as glucose and lipid metabolism, energy expenditure,

and appetite, are the circadian nature of the several metabolically relevant hormones and target tissue sensitivity to these hormones. These hormones include insulin and glucagon-like peptide 1 (GLP-1), as well as counter-regulatory hormones, such as cortisol, growth hormone, melatonin, and appetite regulatory hormones, such as ghrelin and leptin.

Insulin

Insulin is central to glucose homeostasis. Insulin promotes glucose entry into metabolically active cells such as muscles for energy use. Insulin also promotes energy storage by suppressing fat breakdown in adipose tissue and by stimulating the liver to store glucose as glycogen. Evidence for an endogenous rhythm for insulin is mixed [70,93,121,122]. One study reported 21% lower fasting insulin levels in the morning versus evening in healthy adults [42]. Moreover, insulin secretion rates are lowest between midnight and 6:00 a.m. and highest between noon and 6:00 p.m. [122] corresponding with daytime feeding and nocturnal fasting rhythms.

Optimal glucose regulation in the early day is conferred by greater beta cell and peripheral tissue sensitivity to glucose and insulin, respectively. Early phase insulin release is 27% lower in the evening versus the morning exemplifying pancreatic beta cell sensitivity decline [42,54]. Postmeal insulin secretion increases 25%–50% in the evening versus the morning exemplifying peripheral tissue sensitivity decline [96,123]. Greater declines in insulin sensitivity are estimated for subcutaneous adipose tissue [124]. Carrasco-Benso et al. reported a 54% decline in subcutaneous adipose tissue insulin sensitivity from noon to evening in obese adults [124]. These findings may have important implications for the insulin resistant state in many obese individuals. Moreover, subcutaneous adipose tissue insulin resistance is greater in people reporting shorter sleep and later bedtimes suggesting a complex interplay between biological and behavioral rhythms for adipose tissue insulin sensitivity [124].

Glucagon-like peptide 1 (GLP-1)

GLP-1 is a nutrient-sensing hormone secreted by the L-cells of the intestine. GLP-1 influences the magnitude of the insulin response from the beta cells. Basal GLP-1 secretion and L-cell sensitivity have demonstrated endogenous rhythms. GLP-1 secretion peaks at 6:00 a.m. coinciding with increased beta cell sensitivity to GLP-1 [90,125]. Early-phase GLP-1 responses to meals is also greatest following morning meals suggesting enhanced L-cell sensitivity to glucose in the morning [90,125]. Collectively, greater basal and early phase postmeal secretion contributes to enhanced insulin secretion and optimal glucose regulation upon waking. Evidence is

conflicted for variations in afternoon and evening postmeal L-cell sensitivity. GLP-1 secretion was greater following morning/afternoon versus evening meals in one study (08:00 vs. 17:00) [126] but not another (11:00 vs. 23:00) [90]. In the latter study, GLP-1 secretion was 23% higher at 23:00 versus 11:00 [90]. Short sleep as well as delaying sleep reduces GLP-1 secretion [95,127], although these results may differ by sex [127]. The amplitude of GLP-1 rhythms is flattened in adults with obesity and T2D [90].

Cortisol

Cortisol secretions are strongly regulated by the circadian system and, to a lesser extent, behavioral rhythms [70]. Cortisol begins rising 1–2 h after sleep onset, peaks within 1 h of morning waking, and declines thereafter across the 24-h day [70]. Cortisol rhythms parallel those of insulin sensitivity, such that high cortisol levels coincide with increased insulin sensitivity and vice versa [53]. Similarly, postmeal cortisol secretions decline by 33% from morning to evening [48]. These parallel declines in cortisol secretion and insulin sensitivity counter what is known about cortisol's insulin antagonizing effects [128]. Plat et al. reconciled this seeming incongruence by demonstrating that cortisol profoundly decreases insulin sensitivity; however, insulin's response lags [129]. Insulin sensitivity begins declining 4–6 h after cortisol's peak and continues declining for >16 h [129]. This lag between cortisol and insulin sensitivity partially explains morning-to-evening increases in insulin resistance and declines in glucose tolerance. Cortisol rhythms persist with aging, albeit cortisol peaks earlier in the morning and the amplitude of cortisol rhythms are diminished [130]. Cortisol rhythm amplitudes are diminished by irregular and daytime, as opposed to night time sleep [95]. These diminished cortisol amplitudes may be associated with poorer health outcomes [131].

Melatonin

Melatonin secretion is strongly regulated by the circadian system [132]. Norepinephrine stimulates melatonin release from the pineal gland with the onset of darkness or approximately 14 h after wake times [132,133]. Melatonin secretion varies with the length of the dark period, is suppressed by light, and directly opposes insulin secretion [122].

Melatonin directly inhibits nocturnal insulin secretion at melatonin levels well within the physiological range [134,135]. Exogenous melatonin administration also reduces insulin secretion and worsens glucose levels in some studies [136–138]. Early morning waking in sleep-restricted, young healthy adults has been linked to increased insulin resistance [101]. Melatonin was implicated in these findings because insulin resistance increased

the longer melatonin levels remained high after waking [101].

Melatonin receptors exist throughout the body [139]. When melatonin binds to melatonin receptor 1B (MTNR1B) on the insulin-producing beta cells of the pancreas [140,141], insulin secretion is suppressed [135,142], nocturnal hypoglycemia is prevented, and beta-cell oxidative stress is reduced [143,144]. Common genetic variants in MTNR1B [142,145–147] overexpress MTNR1B receptors and lead to reduced insulin secretion [148]. Although melatonin suppresses insulin secretion in all persons, it may do so more in certain genotypes [149].

Contrasting melatonin's initial insulin suppressing effects, prolonged melatonin exposure has been shown to sensitize the beta cells to the action of the intestinal incretin hormone, GLP-1, on stimulating insulin secretion [134]. This evidence suggests that following nocturnal sleep, melatonin plays a role in preparing the body for morning feeding [134]. Melatonin may also influence other metabolically relevant hormones, such as cortisol and leptin. For example, cortisol and leptin rhythmicity is lost when the pineal gland is removed in rats or hamsters [141].

Reduced melatonin levels and a lower amplitude of melatonin rhythms have been reported in adults with type 2 diabetes and MetS [150,151], older versus younger adults, and late versus early chronotypes. Autonomic neuropathy and/or diabetic retinopathy may underlie reduced melatonin levels and flattened melatonin amplitudes in adults with type 2 diabetes because of impaired transmission of light-dark information to the pineal gland [152]. Age-associated changes in sleep-wake patterns relative to melatonin rhythms [153] suggest that some older adults may be waking during the biological night when melatonin is still being secreted. It is unknown whether these age-associated changes in sleep-wake patterns relative to melatonin secretion.

Growth hormone

Growth hormone lacks a diurnal rhythm but is linked to sleep-wake behaviors [96,154]. Growth hormone is secreted almost immediately following the onset of non-REM sleep [155] and typically occurs between 22:00 and 02:00 in nocturnal sleepers [96]. Glucose rises and insulin resistance increases by 50% following the growth hormone surge [156] marking the prominent shift in energy substrates from glucose to lipids during the night. Growth hormone secretion decreases with aging [157].

Ghrelin and leptin

Ghrelin and leptin are appetite regulatory hormones associated with hunger and satiety, respectively. Ghrelin is produced by the parietal cell of the stomach. Leptin is produced by adipocytes and the stomach. Leptin and

between-meal ghrelin exhibit diurnal rhythms. Leptin rises across the day and peaks at approximately 3:00 in healthy young adults [105]. Loss of this diurnal rhythm in SCN excised rats exemplifies that leptin is regulated by the circadian system and is not solely regulated by feeding behaviors [158,159]. Ghrelin levels are strongly regulated by meals with levels rising before eating and falling sharply after eating. However, between-meal ghrelin levels have been shown to also follow a diurnal rhythm that rises progressively across the day, peaks at 01:00 and falls to its lowest level in the morning 06:00 [160].

Bidirectional regulation

Information from the body is also relayed back to the brain. Many SCN neural fibers terminate near the arcuate nucleus (ARC) of the hypothalamus providing a plausible anatomical way that circulating metabolic hormones and nutrients may interact with the central circadian pacemaker [161]. It is here at the ARC–SCN connection where hunger and satiety messages (ghrelin and leptin) intersect with glucose homeostasis messages (insulin) and convey the status of the body to the brain [161]. Nutrient signals may modulate the circadian system itself. Switching from high-carbohydrate/low-fat diet to a low-carbohydrate/high-fat diet alters peripheral and central circadian clocks [162]. The tau, or period, of the central clock becomes longer and may be uncoupled from the clocks of peripheral organs that are important for metabolic regulation [162].

Other behavioral patterns can also impact the circadian clock and alter the endogenous rhythms of metabolically relevant hormones. For example, melatonin onset is delayed by 1.1 h following periods of no exercise in healthy young adults [163,164]. Heart rate variability increases following morning exercise indicating greater parasympathetic stimulation [163]. Heart rates increase following evening exercise indicating greater sympathetic activity [163]. Irregular sleep–wake patterns, irregular or late eating patterns, daytime inactivity, and prolonged nighttime activity (short sleep) may lead to the hypothalamus getting confused biological signals across the 24 h day that then contribute to flattened rhythms for metabolically relevant hormones and metabolic processes [161].

Metabolic disorders, such as obesity and type 2 diabetes, may also disrupt the circadian system. Obese adults lack diurnal rhythms in glucose tolerance [123]. Beta-cell sensitivity to glucose and peripheral tissue sensitivity to insulin fails to decline from morning to evening [123] leading to disruptions between cortisol and insulin sensitivity rhythms [165]. Evening-versus-morning glucose responses to meals, oral glucose challenges, and intravenous glucose are consistently higher and remain elevated longer in healthy [42,48–54], but not obese [123], adults. Reduced amplitudes for heart rate, blood pressure, and body

temperature rhythms have been reported in adults with overweight/obesity, prediabetes, and type 2 diabetes [166]. It is uncertain whether disrupted circadian rhythms contribute to the onset of these metabolic disorders. It may be that the onset of these metabolic disorders underlies the development of circadian disruption and ongoing circadian disruption may further negatively impact metabolic health.

Conclusion and future directions

The circadian system regulates cardiac and metabolic functioning. Altering the synchrony between environmental, behavioral, and biological rhythms disrupts the circadian system and adversely impacts cardiometabolic health. Understanding these rhythms will be important for advancing, accelerating, and personalizing future cardiometabolic health promotion and treatment interventions. Behavioral rhythms such as sleep–wake and feeding–fasting are potentially modifiable. Meal timing, or chrononutrition, is a promising area of research for optimizing weight loss intervention strategies. Medication timing to maximize effectiveness and mitigate side effects is an important area of research for treating cardiometabolic disease [167]. The wide-spread prevalence of social jetlag and potential implications of social jetlag for cardiometabolic health warrant further investigation in community dwelling persons. Open questions persist. How much circadian disruption is too much? Who is most vulnerable? Who is resistant? Answering these questions may open a new horizon for personalizing cardiometabolic health promotion and treatment interventions.

References

- [1] Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA* 2015;313(19):1973–4. <https://doi.org/10.1001/jama.2015.4260>.
- [2] Moore JX, Chaudhary N, Akinyemiju T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, National Health and Nutrition Examination Survey. *Prev Chronic Dis* 1988;14:1988.
- [3] Fries E, Dettenborn L, Kirschbaum C. The cortisol awakening response (CAR): facts and future directions. *Int J Psychophysiol* 2009;72(1):67–73. <https://doi.org/10.1016/j.ijpsycho.2008.03.014>.
- [4] Clow A, Hucklebridge F, Thorn L. The cortisol awakening response in context, vol 93. Elsevier BV; 2010. p. 153–75. [https://doi.org/10.1016/s0074-7742\(10\)93007-9](https://doi.org/10.1016/s0074-7742(10)93007-9).
- [5] Buijs RM, Escobar C, Swaab DF. The circadian system and the balance of the autonomic nervous system. *Handb Clin Neurol* 2013;117:173–91. <https://doi.org/10.1016/B978-0-444-53491-0.00015-8>.
- [6] Duffy JF, Rimmer DW, Czeisler CA. Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. *Behav Neurosci* 2001;115(4):895–9. <https://doi.org/10.1037/0735-7044.115.4.895>.

- [7] Eastman CI, Molina TA, Dziepak ME, Smith MR. Blacks (African Americans) have shorter free-running circadian periods than whites (Caucasian Americans). *Chronobiol Int* 2012;29(8):1072–7. <https://doi.org/10.3109/07420528.2012.700670>.
- [8] Eastman CI, Tomaka VA, Crowley SJ. Sex and ancestry determine the free-running circadian period. *J Sleep Res* 2017;26(5):547–50. <https://doi.org/10.1111/jsr.12521>.
- [9] Lane JM, Vlasac I, Anderson SG, Kyle SD, Dixon WG, Bechtold DA, Gill S, Little MA, Luik A, Loudon A, Emsley R, Scheer FAJL, Lawlor DA, Redline S, Ray DW, Rutter MK, Saxena R. Genome-wide association analysis identifies novel loci for chronotype in 100,420 individuals from the UK Biobank. *Nat Commun* 2016;7:20411723. <https://doi.org/10.1038/ncomms10889>.
- [10] Hu Y, Shmygelska A, Tran D, Eriksson N, Tung JY, Hinds DA. GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person. *Nat Commun* 2016;7. <https://doi.org/10.1038/ncomms10448>.
- [11] Smolensky MH, Hermida RC, Reinberg A, Sackett-Lundeen L, Portaluppi F. Circadian disruption: new clinical perspective of disease pathology and basis for chronotherapeutic intervention. *Chronobiol Int* 2016;33(8):1101–19. <https://doi.org/10.1080/07420528.2016.1184678>.
- [12] Gonnissen HKJ, Mazuy C, Rutters F, Martens EAP, Adam TC, Westerterp-Plantenga MS. Sleep architecture when sleeping at an unusual circadian time and associations with insulin sensitivity. *PLoS ONE* 2013;8(8). <https://doi.org/10.1371/journal.pone.0072877>.
- [13] Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. *Chronobiol Int* 2006;23:497–509. <https://doi.org/10.1080/07420520500545979>.
- [14] Torquati L, Mielke GI, Brown WJ, Kolbe-Alexander T. Shift work and the risk of cardiovascular disease. A systematic review and meta-analysis including dose–response relationship. *Scand J Work Environ Health* 2017;44(3). <https://doi.org/10.5271/sjweh.3700>.
- [15] Lu YC, Wang CP, Yu TH, Tsai IT, Hung WC, Lu IC, Hsu CC, Tang WH, Hoang JY, Chung FM, Yen Jean MC. Shift work is associated with metabolic syndrome in male steel workers—the role of resistin and WBC count-related metabolic derangements. *Dia-betol Metab Syndr* 2017;9(1). <https://doi.org/10.1186/s13098-017-0283-4>.
- [16] Wang F, Zhang L, Zhang Y, Zhang B, He Y, Xie S, Li M, Miao X, Chan EYY, Tang JL, Wong MCS, Li Z, Yu ITS, Tse LA. Meta-analysis on night shift work and risk of metabolic syndrome. *Obes Rev* 2014;15(9):709–20. <https://doi.org/10.1111/obr.12194>.
- [17] De Bacquer D, Van Risseghem M, Clays E, Kittel F, De Backer G, Braeckman L. Rotating shift work and the metabolic syndrome: a prospective study. *Int J Epidemiol* 2009;38(3):848–54. <https://doi.org/10.1093/ije/dyn360>.
- [18] Sookoian S, Gemma C, Fernández Gianotti T, Burgueño A, Alvarez A, González CD, Pirola CJ. Effects of rotating shift work on biomarkers of metabolic syndrome and inflammation. *J Intern Med* 2007;261(3):285–92. <https://doi.org/10.1111/j.1365-2796.2007.01766.x>.
- [19] Yeom JH, Sim CS, Lee J, Yun SH, Park SJ, Yoo CI, Sung JH. Effect of shift work on hypertension: cross sectional study. *Ann Occup Environ Med* 2017;29(1):20524374. <https://doi.org/10.1186/s40557-017-0166-z>.
- [20] Peplonska B, Bukowska A, Sobala W, Sirtori CR. Association of rotating night shift work with BMI and abdominal obesity among nurses and midwives. *PLoS ONE* 2015;10(7):e0133761. <https://doi.org/10.1371/journal.pone.0133761>.
- [21] Lin YC, Hsiao TJ, Chen PC. Persistent rotating shift-work exposure accelerates development of metabolic syndrome among middle-aged female employees: a five-year follow-up. *Chronobiol Int* 2009;26(4):740–55. <https://doi.org/10.1080/074205209029029>.
- [22] Parsons MJ, Moffitt TE, Gregory AM, Goldman-Mellor S, Nolan PM, Poulton R, Caspi A. Social jetlag, obesity and metabolic disorder: investigation in a cohort study. *Int J Obes* 2015;39(5):842–8. <https://doi.org/10.1038/ijo.2014.201>.
- [23] Wong PM, Hasler BP, Kamarck TW, Muldoon MF, Manuck SB. Social jetlag, chronotype, and cardiometabolic risk. *J Clin Endocrinol Metab* 2015;100(12):4612–20. <https://doi.org/10.1210/jc.2015-2923>.
- [24] Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jetlag and obesity. *Curr Biol* 2012;22(10):939–43. <https://doi.org/10.1016/j.cub.2012.03.038>.
- [25] Reutrakul S, Siwasaranond N, Nimitphong H, Saetung S, Chirakalwasan N, Ongphiphadhanakul B, Thakkinstian A, Hood MM, Crowley SJ. Relationships among sleep timing, sleep duration and glycemic control in type 2 diabetes in Thailand. *Chronobiol Int* 2015;32(10):1469–76. <https://doi.org/10.3109/07420528.2015.1105812>.
- [26] Reutrakul S, Hood MM, Crowley SJ, Morgan MK, Teodori M, Knutson KL, Van Cauter E. Chronotype is independently associated with glycemic control in type 2 diabetes. *Diab Care* 2013;36(9):2523–9. <https://doi.org/10.2337/dc12-2697>.
- [27] Koopman ADM, Rauh SP, van 't Riet E, Groeneveld L, van der Heijden AA, Elders PJ, Dekker JM, Nijpels G, Beulens JW, Rutters F. The association between social jetlag, the metabolic syndrome, and type 2 diabetes mellitus in the general population: The New Hoorn Study. *J Biol Rhythm* 2017;32(4):359–68. <https://doi.org/10.1177/0748730417713572>.
- [28] Van Dongen HPA, Baynard MD, Maislin G, Dinges DF. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep* 2004;27(3):423–33.
- [29] Spaeth AM, Dinges DF, Goel N. Phenotypic vulnerability of energy balance responses to sleep loss in healthy adults. *Sci Rep* 2015;5. <https://doi.org/10.1038/srep14920>.
- [30] Duffy JF, Dijk DJ. Getting through to circadian oscillators: why use constant routines? *J Biol Rhythm* 2002;17(1):4–13. <https://doi.org/10.1177/074873002129002294>.
- [31] Krauchi K, Wirz-Justice A. Circadian rhythm of heat production, heart rate, and skin and core temperature under unmasking conditions in men. *Am J Physiol Regul Integr Comp Physiol* 1994;267(3):R819. <https://doi.org/10.1152/ajpregu.1994.267.3.r819>.
- [32] Van Dongen HP, Maislin G, Kerkhof GA. Repeated assessment of the endogenous 24-hour profile of blood pressure under constant routine. *Chronobiol Int* 2009;18(1):85–98. <https://doi.org/10.1081/CBI-100001178>.
- [33] Kerkhof GA, Van Dongen HPA, Bobbitt AC. Absence of endogenous circadian rhythmicity in blood pressure? *Am J Hypertens* 1998;11(3 Pt):373–7. [https://doi.org/10.1016/S0895-7061\(97\)00461-5](https://doi.org/10.1016/S0895-7061(97)00461-5).

- [34] Hu K, Ivanov PC, Hilton MF, Chen Z, Timothy Ayers R, Eugene Stanley H, Shea SA. Endogenous circadian rhythm in an index of cardiac vulnerability independent of changes in behavior. *Proc Natl Acad Sci USA* 2004;101(52):18223–7. <https://doi.org/10.1073/pnas.0408243101>.
- [35] Scheer FAJL, Hu K, Evoniuk H, Kelly EE, Malhotra A, Hilton MF, Shea SA. Impact of the human circadian system, exercise, and their interaction on cardiovascular function. *Proc Natl Acad Sci USA* 2010;107(47):20541–6. <https://doi.org/10.1073/pnas.1006749107>.
- [36] Shea SA, Hilton MF, Hu K, Scheer FAJL. Existence of an endogenous circadian blood pressure rhythm in humans that peaks in the evening. *Circ Res* 2011;108(8):980–4. <https://doi.org/10.1161/CIRCRESAHA.110.233668>.
- [37] Adan A, Archer SN, Hidalgo MP, Di Milia L, Natale V, Randler C. Circadian typology: a comprehensive review. *Chronobiol Int* 2012;29(9):1153–75. <https://doi.org/10.3109/07420528.2012.719971>.
- [38] Bechtold DA. Energy-responsive timekeeping. *J Genet* 2008;87(5):447–58. <https://doi.org/10.1007/s12041-008-0067-6>.
- [39] Perelis M, Ramsey KM, Bass J. The molecular clock as a metabolic rheostat. *Diab Obes Metabol* 2015;17(1):99–105. <https://doi.org/10.1111/dom.12521>.
- [40] Green CB, Takahashi JS, Bass J. The meter of metabolism. *Cell* 2008;134(5):728–42. <https://doi.org/10.1016/j.cell.2008.08.022>.
- [41] Troisi RJ, Cowie CC, Harris MI. Diurnal variation in fasting plasma glucose: implications for diagnosis of diabetes in patients examined in the afternoon. *JAMA* 2000;284(24):3157–9. <https://doi.org/10.1001/jama.284.24.3157>.
- [42] Morris CJ, Yang JN, Garcia JI, Myers S, Bozzi I, Wang W, Buxton OM, Shea SA, Scheer FAJL. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. *Proc Natl Acad Sci USA* 2015;112(17):E2225. <https://doi.org/10.1073/pnas.1418955112>.
- [43] Hulmán A, Færch K, Vistisen D, Karsai J, Nyári TA, Tabák AG, Brunner EJ, Kivimäki M, Witte DR. Effect of time of day and fasting duration on measures of glycaemia: analysis from the Whitehall II Study. *Diabetologia* 2013;56(2):294–7. <https://doi.org/10.1007/s00125-012-2770-3>.
- [44] Ahmed S, Dalla Man C, Nandy DK, Levine JA, Bharucha AE, Rizza RA, Basu R, Carter RE, Cobelli C, Kudva YC, Basu A. Diurnal pattern to insulin secretion and insulin action in healthy individuals. *Diabetes* 2012;61(11):2691–700. <https://doi.org/10.2337/db11-1478>.
- [45] Meneilly GS, Elahi D, Minaker KL, Rowe JW. The dawn phenomenon does not occur in normal elderly subjects. *J Clin Endocrinol Metab* 1986;63(2):292–6. <https://doi.org/10.1210/jcem-63-2-292>.
- [46] Marin G, Rose SR, Kibarian M, Barnes K, Cassorla F. Absence of dawn phenomenon in normal children and adolescents. *Diab Care* 1988;11(5):393–6. <https://doi.org/10.2337/diacare.11.5.393>.
- [47] Rosenthal MJ, Argoud GM. Absence of the dawn glucose rise in nondiabetic men compared by age. *J Gerontol* 1989;44(2):M57. <https://doi.org/10.1093/geronj/44.2.M57>.
- [48] Van Cauter E, Shapiro ET, Tillil H, Polonsky KS. Circadian modulation of glucose and insulin responses to meals: relationship to cortisol rhythm. *Am J Physiol Endocrinol Metab* 1992;262(4):E467. <https://doi.org/10.1152/ajpendo.1992.262.4.e467>.
- [49] Aparicio NJ, Puchulu FE, Gagliardino JJ, Ruiz M, Llorens JM, Ruiz J, Lamas A, De Miguel R. Circadian variation of the blood glucose, plasma insulin and human growth hormone levels in response to an oral glucose load in normal subjects. *Diabetes* 1974;23(2):132–7. <https://doi.org/10.2337/diab.23.2.132>.
- [50] Zimmet PZ, Wall JR, Rome R, Stimmmer L, Jarrett RJ. Diurnal variation in glucose tolerance: associated changes in plasma insulin, growth hormone, and non-esterified fatty acids. *Br Med J* 1974;1(5906):485–8. <https://doi.org/10.1136/bmj.1.5906.485>.
- [51] Pinkhasov BB, Selyatinskaya VG, Astrakhantseva EL, Anufrienko EV. Circadian rhythms of carbohydrate metabolism in women with different types of obesity. *Bull Exp Biol Med* 2016;161(3):323–6. <https://doi.org/10.1007/s10517-016-3406-2>.
- [52] Jarrett RJ, Baker IA, Keen H, Oakley NW. Diurnal variation in oral glucose tolerance: blood sugar and plasma insulin levels morning, afternoon, and evening. *BMJ* 1972;1(5794):199–201. <https://doi.org/10.1136/bmj.1.5794.199>.
- [53] Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocr Rev* 1997;18(5):716–38. <https://doi.org/10.1210/edrv.18.5.0317>.
- [54] Carroll KF, Nestel PJ. Diurnal variation in glucose tolerance and in insulin secretion in man. *Diabetes* 1973;22(5):333–48. <https://doi.org/10.2337/diab.22.5.333>.
- [55] Yamamoto H, Nagai K, Nakagawa H. Role of SCN in daily rhythms of plasma glucose, FFA, insulin and glucagon. *Chronobiol Int* 1987;4(4):483–91. <https://doi.org/10.3109/07420528709078539>.
- [56] Dallmann R, Viola AU, Tarokh L, Cajochen C, Brown SA. The human circadian metabolome. *Proc Natl Acad Sci USA* 2012;109(7):2625–9. <https://doi.org/10.1073/pnas.1114410109>.
- [57] Chern-Pin Chua E, Shui G, Lee IT-G, Lau P, Tan L-C, Yeo S-C, Lam BD, Bulchand S, Summers SA, Puvanendran K, Rozen SG, Wenk MR, Gooley JJ. Extensive diversity in circadian regulation of plasma lipids and evidence for different circadian metabolic phenotypes in humans. *Proc Natl Acad Sci USA* 2013;110(35):14468–73. <https://doi.org/10.1073/pnas.1222647110>.
- [58] Sennels HP, Jørgensen HL, Fahrenkrug J. Diurnal changes of biochemical metabolic markers in healthy young males - The Bispebjerg study of diurnal variations. *Scand J Clin Lab Investig* 2015;75(8):686–92. <https://doi.org/10.3109/00365513.2015.1080385>.
- [59] Kerkhof LW, Dycke EHJ. Diurnal variation of hormonal and lipid biomarkers in a molecular epidemiology-like setting. *PLoS ONE* 2015;10(8):2015.
- [60] Miida T, Nakamura Y, Mezaki T, Hanyu O, Maruyama S, Horikawa Y, Izawa S, Yamada Y, Matsui H, Okada M. LDL-cholesterol and HDL-cholesterol concentrations decrease during the day. *Ann Clin Biochem* 2002;39(3):241–9. <https://doi.org/10.1258/0004563021901946>.
- [61] Romon M, Le Fur C, Lebel P, Edmé JL, Fruchart JC, Dallongeville J. Circadian variation of postprandial lipemia. *Am J Clin Nutr* 1997;65(4):934–40. <https://doi.org/10.1093/ajcn/65.4.934>.
- [62] Lund J, Arendt J, Hampton SM, English J, Morgan LM. Postprandial hormone and metabolic responses amongst shift workers in Antarctica. *J Endocrinol* 2001;171(3):557–64. <https://doi.org/10.1677/joe.0.1710557>.

- [63] Morris CJ, Garcia JI, Myers S, Yang JN, Trienekens N, Scheer FAJL. The human circadian system has a dominating role in causing the morning/evening difference in diet-induced thermogenesis. *Obesity* 2015;23(10):2053–8. <https://doi.org/10.1002/oby.21189>.
- [64] Romon M, Edme JL, Boulenguez C, Lescroart JL, Frimat P. Circadian variation of diet-induced thermogenesis. *Am J Clin Nutr* 1993;57(4):476–80. <https://doi.org/10.1093/ajcn/57.4.476>.
- [65] Centers for Disease Control and Prevention. Statistics NCFH. What we eat in America. 2009.
- [66] Waterhouse J, Jones K, Edwards B, Harrison Y, Nevill A, Reilly T. Lack of evidence for a marked endogenous component determining food intake in humans during forced desynchrony. *Chronobiol Int* 2009;21(3):445–68. <https://doi.org/10.1081/CBI-120038628>.
- [67] Scheer FAJL, Morris CJ, Shea SA. The internal circadian clock increases hunger and appetite in the evening independent of food intake and other behaviors. *Obesity* 2013;21(3):421–3. <https://doi.org/10.1002/oby.20351>.
- [68] Sargent C, Zhou X, Matthews RW, Darwent D, Roach GD. Daily rhythms of hunger and satiety in healthy men during one week of sleep restriction and circadian misalignment. *Int J Environ Res Public Health* 2016;13(2):16604601. <https://doi.org/10.3390/ijerph13020170>.
- [69] Wehrens SMT, Christou S, Isherwood C. Meal timing regulates the human circadian system. *Curr Biol* 2017;27(12):1768–75.
- [70] Scheer FAJL, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci USA* 2009;106(11):4453–8. <https://doi.org/10.1073/pnas.0808180106>.
- [71] Schoeller DA, Celli LK, Sinha MK, Caro JF. Entrainment of the diurnal rhythm of plasma leptin to meal timing. *J Clin Investig* 1997;100(7):1882–7. <https://doi.org/10.1172/JCI119717>.
- [72] Plano SA, Casiraghi LP, Moro PG, Paladino N, Golombek DA, Chiesa JJ. Circadian and metabolic effects of light: implications in weight homeostasis and health. *Front Neurol* 2017;8. <https://doi.org/10.3389/fneur.2017.00558>.
- [73] Wright KP, McHill AW, Birks BR, Griffin BR, Rusterholz T, Chinoy ED. Entrainment of the human circadian clock to the natural light-dark cycle. *Curr Biol* 2013;23(16):1554–8. <https://doi.org/10.1016/j.cub.2013.06.039>.
- [74] Falchi F, Cinzano P, Duriscoe D, Kyba CCM, Elvidge CD, Baugh K, Portnov BA, Rybnikova NA, Furgoni R. The new world atlas of artificial night sky brightness. *Sci Adv* 2016;2(6). <https://doi.org/10.1126/sciadv.1600377>.
- [75] Gaston KJ, Bennie J, Davies TW, Hopkins J. The ecological impacts of nighttime light pollution: a mechanistic appraisal. *Biol Rev* 2013;88(4):912–27. <https://doi.org/10.1111/brv.12036>.
- [76] Sleep in America poll, sleep in the modern family. 2014.
- [77] Coomans CP, Van Den Berg SAA, Houben T, Van Klinken JB, Van Den Berg R, Pronk ACM, Havekes LM, Romijn JA, Van Dijk KW, Biermasz NR, Meijer JH. Detrimental effects of constant light exposure and high-fat diet on circadian energy metabolism and insulin sensitivity. *Fed Am Soc Exp Biol J* 2013;27(4):1721–32. <https://doi.org/10.1096/fj.12-210898>.
- [78] Fonken LK, Nelson RJ. The effects of light at night on circadian clocks and metabolism. *Endocr Rev* 2014;35(4):648–70. <https://doi.org/10.1210/er.2013-1051>.
- [79] Boivin DB, Duffy JF, Kronauer RE, Czeisler CA. Dose-response relationships for resetting of human circadian clock by light. *Nature* 1996;379(6565):540–2. <https://doi.org/10.1038/379540a0>.
- [80] Wang XS, Armstrong MEG, Cairns BJ, Key TJ, Travis RC. Shift work and chronic disease: the epidemiological evidence. *Occup Med* 2011;61(2):78–89. <https://doi.org/10.1093/occmed/kqr001>.
- [81] Pietroiusti A, Neri A, Somma G, Coppeta L, Iavicoli I, Bergamaschi A, Magrini A. Incidence of metabolic syndrome among night-shift healthcare workers. *Occup Environ Med* 2010;67(1):54–7. <https://doi.org/10.1136/oem.2009.046797>.
- [82] McFadden E, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. The relationship between obesity and exposure to light at night: cross-sectional analyses of over 100,000 women in the breakthrough generations study. *Am J Epidemiol* 2014;180(3):245–50.
- [83] Koo YS, Song JY, Joo EY, Lee HJ, Lee E, Lee SK, Jung KY. Outdoor artificial light at night, obesity, and sleep health: cross-sectional analysis in the KoGES study. *Chronobiol Int* 2016;33(3):301–14. <https://doi.org/10.3109/07420528.2016.1143480>.
- [84] Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S, Ikada Y, Kurumata N. Exposure to light at night, nocturnal urinary melatonin excretion, and obesity/dyslipidemia in the elderly: a cross-sectional analysis of the HEIJO-KYO study. *J Clin Endocrinol Metab* 2013;98(1):337–44. <https://doi.org/10.1210/jc.2012-2874>.
- [85] Cheung IN, Zee PC, Shalman D, Malkani RG, Kang J, Reid KJ. Morning and evening blue-enriched light exposure alters metabolic function in normal weight adults. *PLoS ONE* 2016;11(5):19326203. <https://doi.org/10.1371/journal.pone.0155601>.
- [86] Brainard GC, Rollag MD, Hanifin JP. Photic regulation of melatonin in humans: ocular and neural signal transduction. *J Biol Rhythms* 1997;12(6):537–46. <https://doi.org/10.1177/074873049701200608>.
- [87] Brainard GC, Lewy AJ, Menaker M, Fredrickson RH, Stephen Miller L, Weleber RG, Vincent C, Hudson D. Dose-response relationship between light irradiance and the suppression of plasma melatonin in human volunteers. *Brain Res* 1988;454(1–2):212–8. [https://doi.org/10.1016/0006-8993\(88\)90820-7](https://doi.org/10.1016/0006-8993(88)90820-7).
- [88] Tan DX, Manchester LC, Fuentes-Broto L, Paredes SD, Reiter RJ. Significance and application of melatonin in the regulation of brown adipose tissue metabolism: relation to human obesity. *Obes Rev* 2011;12(3):167–88. <https://doi.org/10.1111/j.1467-789X.2010.00756.x>.
- [89] McMullan CJ, Schernhammer ES, Rimm EB, Hu FB, Forman JP. Melatonin secretion and the incidence of type 2 diabetes. *JAMA* 2013;309(13):1388–96. <https://doi.org/10.1001/jama.2013.2710>.
- [90] Gil-Lozano M, Hunter PM, Behan L-A, Gladanac B, Casper RF, Brubaker PL. Short-term sleep deprivation with nocturnal light exposure alters time-dependent glucagon-like peptide-1 and insulin secretion in male volunteers. *Am J Physiol Endocrinol Metab* 2016;310(1):E41. <https://doi.org/10.1152/ajpendo.00298.2015>.
- [91] Scheer FAJL, Van Doornen LJP, Buijs RM. Light and diurnal cycle affect human heart rate: possible role for the circadian pacemaker. *J Biol Rhythms* 1999;14(3):202–12. <https://doi.org/10.1177/074873099129000614>.
- [92] West AC, Smith L, Ray DW, Loudon ASI, Brown TM, Bechtold DA. Misalignment with the external light environment drives metabolic and cardiac dysfunction. *Nat Commun* 2017;8(1):20411723.

- [93] Buxton OM, Cain SW, O'Connor SP, Porter JH, Duffy JF, Wang W, Czeisler CA, Shea SA. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. *Sci Transl Med* 2012;4(129):19466242. <https://doi.org/10.1126/scitranslmed.3003200>.
- [94] Morris CJ, Purvis TE, Mistretta J, Scheer FAJL. Effects of the internal circadian system and circadian misalignment on glucose tolerance in chronic shift workers. *J Clin Endocrinol Metab* 2016;101(3):1066–74. <https://doi.org/10.1210/jc.2015-3924>.
- [95] Gonnissen HKJ, Rutters F, Mazuy C, Martens EAP, Adam TC, Westerterp-Plantenga MS. Effect of a phase advance and phase delay of the 24-h cycle on energy metabolism, appetite, and related hormones. *Am J Clin Nutr* 2012;96(4):689–97. <https://doi.org/10.3945/ajcn.112.037192>.
- [96] Van Cauter E, Blackman JD, Roland D, Spire JP, Refetoff S, Polonsky KS. Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. *J Clin Invest* 1991;88(3):934–42. <https://doi.org/10.1172/JCI115396>.
- [97] McHill AW, Melanson EL, Higgins J, Connick E, Moehlman TM, Stothard ER, Wright KP. Impact of circadian misalignment on energy metabolism during simulated nightshift work. *Proc Natl Acad Sci USA* 2014;111(48):17302–7. <https://doi.org/10.1073/pnas.1412021111>.
- [98] Nguyen J, Wright KP. Influence of weeks of circadian misalignment on leptin levels. *Nat Sci Sleep* 2010;2:9–18.
- [99] Bei B, Seeman TE, Carroll JE, Wiley JF. Sleep and physiological dysregulation: a closer look at sleep intraindividual variability. *Sleep* 2017;40(9):15509109. <https://doi.org/10.1093/sleep/zsx109>.
- [100] Leproult R, Holmbäck U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes* 2014;63(6):1860–9. <https://doi.org/10.2337/db13-1546>.
- [101] Eckel RH, Depner CM, Perreault L, Markwald RR, Smith MR, McHill AW, Higgins J, Melanson EL, Wright KP. Morning circadian misalignment during short sleep duration impacts insulin sensitivity. *Curr Biol* 2015;25(22):3004–10. <https://doi.org/10.1016/j.cub.2015.10.011>.
- [102] Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity* 2013;21(12):2504–12. <https://doi.org/10.1002/oby.20460>.
- [103] Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee YC, Ordovás JM, Scheer FAJL. Timing of food intake predicts weight loss effectiveness. *Int J Obes* 2013;37(4):604–11. <https://doi.org/10.1038/ijo.2012.229>.
- [104] Thaiss CA, Zeevi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler AC, Abramson L, Katz MN, Korem T, Zmora N, Kuperman Y, Biton I, Gilad S, Harmelin A, Shapiro H, Halpern Z, Segal E, Elinav E. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* 2014;159(3):514–29. <https://doi.org/10.1016/j.cell.2014.09.048>.
- [105] Qin LQ, Li J, Wang Y, Wang J, Xu JY, Kaneko T. The effects of nocturnal life on endocrine circadian patterns in healthy adults. *Life Sci* 2003;73(19):2467–75. [https://doi.org/10.1016/S0024-3205\(03\)00628-3](https://doi.org/10.1016/S0024-3205(03)00628-3).
- [106] Morgan L, Arendt J, Owens D, Folkard S, Hampton S, Deacon S, English J, Ribeiro D, Taylor K. Effects of the endogenous clock and sleep time on melatonin, insulin, glucose and lipid metabolism. *J Endocrinol* 1998;157(3):443–51. <https://doi.org/10.1677/joe.0.1570443>.
- [107] Farshchi HR, Taylor MA, Macdonald IA. Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity, and fasting lipid profiles in healthy obese women. *Am J Clin Nutr* 2005;81(1):16–24. <https://doi.org/10.1093/ajcn/81.1.16>.
- [108] Guo YF, Stein PK. Circadian rhythm in the cardiovascular system: chronocardiology. *Am Heart J* 2003;145(5):779–86. [https://doi.org/10.1016/S0002-8703\(02\)94797-6](https://doi.org/10.1016/S0002-8703(02)94797-6).
- [109] Scheer FAJL, Ter Horst GJ, van der Vliet J, Buijs RM. Physiological and anatomic evidence for regulation of the heart by suprachiasmatic nucleus in rats. *Am J Physiol Heart Circ Physiol* 2001;280(3):H1391. <https://doi.org/10.1152/ajpheart.2001.280.3.h1391>.
- [110] White WB. Ambulatory blood pressure monitoring: dippers compared with non-dippers. *Blood Press Monit* 2000;5(1):S17. <https://doi.org/10.1097/00126097-200005001-00004>.
- [111] Vandewalle G, Middleton B, Rajaratnam SMW, Stone BM, Thorleifsdottir B, Arendt J, Derk-Jan DIJK. Robust circadian rhythm in heart rate and its variability: influence of exogenous melatonin and photoperiod. *J Sleep Res* 2007;16(2):148–55. <https://doi.org/10.1111/j.1365-2869.2007.00581.x>.
- [112] Akselrod S, Gordon D, Ubels F, Shannon D, Berger A, Cohen R. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;213(4504):220–2. <https://doi.org/10.1126/science.6166045>.
- [113] Saul JP, Rea RF, Eckberg DL, Berger RD, Cohen RJ. Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity. *Am J Physiol Heart Circ Physiol* 1990;258(3):H713. <https://doi.org/10.1152/ajpheart.1990.258.3.h713>.
- [114] Hilton MF, Umali MU, Czeisler CA, Wyatt JK, Shea SA. Endogenous circadian control of the human autonomic nervous system. *Comp Cardiol* 2000:197–200.
- [115] Witte K, Schnecko A, Buijs RM, van der Vliet J, Scalbert E, Delagrange P, Guardiola-Lemaitre B, Lemmer B. Effects of scn lesions on orcadian blood pressure rhythm in normotensive and transgenic hypertensive rats. *Chronobiol Int* 2009;15(2):135–45. <https://doi.org/10.3109/07420529808998678>.
- [116] Boudreau P, Yeh WH, Dumont GA, Boivin DB. Circadian variation of heart rate variability across sleep stages. *Sleep* 2013;36(12):1919–28. <https://doi.org/10.5665/sleep.3230>.
- [117] Ahnve S, Theorell T, Åkerstedt T, Fröberg JE, Halberg F. Circadian variations in cardiovascular parameters during sleep deprivation - a noninvasive study of young healthy men. *Eur J Appl Physiol Occup Physiol* 1981;46(1):9–19. <https://doi.org/10.1007/BF00422170>.
- [118] Bernardi L, Valle F, Coco M, Calciati A, Sleight P. Physical activity influences heart rate variability and very-low-frequency components in Holter electrocardiograms. *Cardiovasc Res* 1996;32(2):234–7. [https://doi.org/10.1016/0008-6363\(96\)00081-8](https://doi.org/10.1016/0008-6363(96)00081-8).
- [119] Mancia G. Autonomic modulation of the cardiovascular system during sleep. *N Engl J Med* 1993;328(5):347–9. <https://doi.org/10.1056/NEJM199302043280511>.
- [120] Bartness TJ, Song CK, demas GE. SCN efferents to peripheral tissues: implications for biological rhythms. *J Biol Rhythms* 2001;16(3):196–204. <https://doi.org/10.1177/074873001129001908>.
- [121] Van Cauter E, Desir D, Decoster C, Franchise F, Edmond OB. Nocturnal decrease in glucose tolerance during constant glucose

- infusion. *J Clin Endocrinol Metab* 1989;69(3):604–11. <https://doi.org/10.1210/jcem-69-3-604>.
- [122] Boden G, Ruiz J, Urbain JL, Chen X. Evidence for a circadian rhythm of insulin secretion. *Am J Physiol Endocrinol Metab* 1996;271(2):E246. <https://doi.org/10.1152/ajpendo.1996.271.2.e246>.
- [123] Lee A, Ader M, Bray GA, Bergman RN. Diurnal variation in glucose tolerance: cyclic suppression of insulin action and insulin secretion in normal-weight, but not obese, subjects. *Diabetes* 1992;41(6):750–9. <https://doi.org/10.2337/diab.41.6.750>.
- [124] Carrasco-Benso MP, Rivero-Gutierrez B, Lopez-Minguez J, Anzola A, Diez-Noguera A, Madrid JA, Lujan JA, Augustin OM, Scheer FAJL, Garaulet M. Human adipose tissue expresses intrinsic circadian rhythm in insulin sensitivity. *FASEB J* 2016;30(9):3117–23. <https://doi.org/10.1096/fj.201600269rr>.
- [125] Lindgren O, Mari A, Deacon CF, Carr RD, Winzell MS, Vikman J, Ahrén B. Differential islet and incretin hormone responses in morning versus afternoon after standardized meal in healthy men. *J Clin Endocrinol Metab* 2009;94(8):2887–92. <https://doi.org/10.1210/jc.2009-0366>.
- [126] Lindgren CM, Heid IM, Randall JC, Lamina C, Steinhorsdottir V, Qi L, Speliotis EK, Thorleifsson G, Willer CJ, Herrera BM, Jackson AU, Lim N, Scheet P, Soranzo N, Amin N, Aulchenko YS, Chambers JC, Drong A, Luan JNA, Lyon HN, Rivadeneira F, Sanna S, Timpson NJ, Zillikens MC, Jing HZ, Almgren P, Bandinelli S, Bennett AJ, Bergman RN, Bonnycastle LL, Bumpstead SJ, Chanock SJ, Cherkas L, Chines P, Coin L, Cooper C, Crawford G, Doering A, Dominicak A, Doney ASF, Ebrahim S, Elliott P, Erdos MR, Estrada K, Ferrucci L, Fischer G, Forouhi NG, Gieger C, Grallert H, Groves CJ, Grundy S, Guiducci C, Hadley D, Hamsten A, Havulinna AS, Hofman A, Holle R, Holloway JW, Illig T, Isomaa B, Jacobs LC, Jameson K, Jousilahti P, Karpe F, Kuusisto J, Laitinen J, Lathrop GM, Lawlor DA, Mangino M, McArdle WL, Meitinger T, Morken MA, Morris AP, Munroe P, Narisu N, Nordström A, Nordström P, Oostra BA, Palmer CNA, Payne F, Peden JF, Prokopenko I, Renström F, Ruokonen A, Salomaa V, Sandhu MS, Scott LJ, Scuteri A, Silander K, Song K, Yuan X, Stringham HM, Swift AJ, Tuomi T, Uda M, Vollenweider P, Waeber G, Wallace C, Walters GB, Weedon MN, Witterman JCM, Zhang C, Zhang W, Caulfield MJ, Collins FS, Smith GD, Day INM, Franks PW, Hattersley AT, Hu FB, Jarvelin MR, Kong A, Kooper JS, Laakso M, Lakatta E, Mooser V, Morris AD, Peltonen L, Samani NJ, Spector TD, Strachan DP, Tanaka T, Tuomilehto J, Uitterlinden AG, Van Duijn CM, Wareham NJ, Watkins H, Waterworth DM, Boehnke M, Deloukas P, Groop L, Hunter DJ, Thorsteinsdottir U, Schlessinger D, Wichmann HE, Frayling TM, Abecasis GR, Hirschhorn JN, Loos RJF, Stefansson K, Mohlke KL, Barroso I, McCarthy MI. Genome-wide association scan meta-analysis identifies three loci influencing adiposity and fat distribution. *PLoS Genet* 2009;5(6). <https://doi.org/10.1371/journal.pgen.1000508>.
- [127] St-Onge MP, O'Keeffe M, Roberts AL, RoyChoudhury A, Laferrière B. Short sleep duration, glucose dysregulation and hormonal regulation of appetite in men and women. *Sleep* 2012;35(11):1503–10. <https://doi.org/10.5665/sleep.2198>.
- [128] Dinneen S, Alzaid A, Miles J, Rizza R. Metabolic effects of the nocturnal rise in cortisol on carbohydrate metabolism in normal humans. *J Clin Investig* 1993;92(5):2283–90. <https://doi.org/10.1172/JCI116832>.
- [129] Plat L, Byrne MM, Sturis J, Polonsky KS, Mockel J, Fery F, Van Cauter E. Effects of morning cortisol elevation on insulin secretion and glucose regulation in humans. *Am J Physiol Endocrinol Metab* 1996;270(1):E36. <https://doi.org/10.1152/ajpendo.1996.270.1.e36>.
- [130] Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *J Clin Endocrinol Metab* 1996;81(7):2468–73. <https://doi.org/10.1210/jcem.81.7.8675562>.
- [131] Sephton EL, Dedert EA. Diurnal cortisol rhythm as a predictor of lung cancer survival. *J. Melat Hum Rhythms* 2006;30:21–37.
- [132] Peschke E, Mühlbauer E. New evidence for a role of melatonin in glucose regulation. *Best Pract Res Clin Endocrinol Metabol* 2010;24(5):829–41. <https://doi.org/10.1016/j.beem.2010.09.001>.
- [133] Burgess HJ, Savic N, Sletten T, Roach G, Gilbert SS, Dawson D. The relationship between the dim light melatonin onset and sleep on a regular schedule in young healthy adults. *Behav Sleep Med* 2003;1(2):102–14. https://doi.org/10.1207/S15402010BSM0102_3.
- [134] Kemp DM, Ubeda M, Habener JF. Identification and functional characterization of melatonin Mel 1a receptors in pancreatic β cells: potential role in incretin-mediated cell function by sensitization of cAMP signaling. *Mol Cell Endocrinol* 2002;191(2):157–66. [https://doi.org/10.1016/s0303-7207\(02\)00064-3](https://doi.org/10.1016/s0303-7207(02)00064-3).
- [135] Mühlbauer E, Albrecht E, Hofmann K, Bazwinsky-Wutschke I, Peschke E. Melatonin inhibits insulin secretion in rat insulinoma β -cells (INS-1) heterologously expressing the human melatonin receptor isoform MT2. *J Pineal Res* 2011;51(3):361–72. <https://doi.org/10.1111/j.1600-079x.2011.00898.x>.
- [136] Cagnacci A, Arangino S, Renzi A, Paoletti AM, Melis GB, Cagnacci P, Volpe A. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. *Clin Endocrinol* 2001;154(3):339–46. <https://doi.org/10.1046/j.1365-2265.2001.01232.x>.
- [137] Rubio-Sastre P, Scheer FAJL, Gómez-Abellán P, Madrid JA, Garaulet M. Acute melatonin administration in humans impairs glucose tolerance in both the morning and evening. *Sleep* 2014;37(10):1715–9. <https://doi.org/10.5665/sleep.4088>.
- [138] Garaulet M, Gómez-Abellán P, Rubio-Sastre P, Madrid JA, Saxena R, Scheer FAJL. Common type 2 diabetes risk variant in MTNR1B worsens the deleterious effect of melatonin on glucose tolerance in humans. *Metabolism* 2015;64(12):1650–7. <https://doi.org/10.1016/j.metabol.2015.08.003>.
- [139] Lardone PJ, Álvarez-Sánchez N, Guerrero JM, Carrillo-Vico A. Melatonin and glucose metabolism: clinical relevance. *Curr Pharm Design* 2014;20(30):4841–53. <https://doi.org/10.2174/138161281966131119101032>.
- [140] Vanecek J. Cellular mechanisms of melatonin action. *Physiol Rev* 1998;78(3):687–721. <https://doi.org/10.1152/physrev.1998.78.3.687>.

- [141] Peschke E, Peschke D. Evidence for a circadian rhythm of insulin release from perfused rat pancreatic islets. *Diabetologia* 1998;41(9):1085–92. <https://doi.org/10.1007/s001250051034>.
- [142] Lyssenko V, Nagorny CLF, Erdos MR, Wierup N, Jonsson A, Spéglé P, Bugiani M, Saxena R, Fex M, Pulizzi N, Isomaa B, Tuomi T, Nilsson P, Kuusisto J, Tuomilehto J, Boehnke M, Altshuler D, Sundler F, Eriksson JG, Jackson AU, Laakso M, Marchetti P, Watanabe RM, Mulder H, Groop L. Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. *Nat Genet* 2009;41(1):82–8. <https://doi.org/10.1038/ng.288>.
- [143] Costes S, Boss M, Thomas AP, Matveyenko AV. Activation of melatonin signaling promotes β -cell survival and function. *Mol Endocrinol* 2015;29(5):682–92. <https://doi.org/10.1210/me.2014-1293>.
- [144] Park J-H, Shim H-M, Na A-Y, Bae K-C, Bae J-H, Im S-S, Cho H-C, Song D-K. Melatonin prevents pancreatic β -cell loss due to glucotoxicity: the relationship between oxidative stress and endoplasmic reticulum stress. *J Pineal Res* 2014;56(2):143–53. <https://doi.org/10.1111/jpi.12106>.
- [145] Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, Loos RJF, Manning AK, Jackson AU, Aulchenko Y, Potter SC, Erdos MR, Sanna S, Hottenga JJ, Wheeler E, Kaakinen M, Lyssenko V, Chen WM, Ahmadi K, Beckmann JS, Bergman RN, Bochud M, Bonnycastle LL, Buchanan TA, Cao A, Cervino A, Coin L, Collins FS, Crisponi L, De Geus EJC, Dehghan A, Deloukas P, Doney ASF, Elliott P, Freimer N, Gateva V, Herder C, Hofman A, Hughes TE, Hunt S, Illig T, Inouye M, Isomaa B, Johnson T, Kong A, Krestyaninova M, Kuusisto J, Laakso M, Lim N, Lindblad U, Lindgren CM, McCann OT, Mohlke KL, Morris AD, Naitza S, Orrù M, Palmer CNA, Pouta A, Randall J, Rathmann W, Saramies J, Scheet P, Scott LJ, Scuteri A, Sharp S, Sijbrands E, Smit JH, Song K, Steinthorsdottir V, Stringham HM, Tuomi T, Tuomilehto J, Uitterlinden AG, Voight BF, Waterworth D, Wichmann HE, Willemse G, Witteman JCM, Yuan X, Zhao JH, Zegger E, Schlessinger D, Sandhu M, Boomsma DI, Uda M, Spector TD, Penninx BWJH, Altshuler D, Vollenweider P, Jarvelin MR, Lakatta E, Waeber G, Fox CS, Peltonen L, Groop LC, Mooser V, Cupples LA, Thorsteinsdottir U, Boehnke M, Barroso I, Van Duijn C, Dupuis J, Watanabe RM, Stefansson K, McCarthy MI, Wareham NJ, Meigs JB, Abecasis GR. Variants in MTNR1B influence fasting glucose levels. *Nat Genet* 2009;41(1):77–81. <https://doi.org/10.1038/ng.290>.
- [146] Bouatia-Naji N, Bonnefond A, Cavalcanti-Proençá C, Sparsø T, Holmkvist J, Marchand M, Delplanque J, Lobbens S, Rocheleau G, Durand E, De Graeve F, Chèvre J-C, Borch-Johnsen K, Hartikainen A-L, Ruokonen A, Tichet J, Marre M, Weill J, Heude B, Tauber M, Lemaire K, Schuit F, Elliott P, Jørgensen T, Charpentier G, Hadjadj S, Cauchi S, Vaxillaire M, Sladek R, Visvikis-Siest S, Balkau B, Lévy-Marchal C, Pattou F, Meyre D, Blakemore AIF, Jarvelin M-R, Walley AJ, Hansen T, Dina C, Pedersen O, Froguel P. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. *Nat Genet* 2009;41(1):89–94. <https://doi.org/10.1038/ng.277>.
- [147] Zheng C, Dalla Man C, Cobelli C, Groop L, Zhao H, Bale AE, Shaw M, Duran E, Pierpoint B, Caprio S, Santoro N. A common variant in the MTNR1b gene is associated with increased risk of impaired fasting glucose (IFG) in youth with obesity. *Obesity* 2015;23(5):1022–9. <https://doi.org/10.1002/oby.21030>.
- [148] Jonsson A, Ladenwall C, Singh Ahluwalia T, Kravic J, Krus U, Taneera J, Isomaa B, Tuomi T, Renström E, Groop L, Lyssenko V. Effects of common genetic variants associated with type 2 diabetes and glycemic traits on α - and β -cell function and insulin action in humans. *Diabetes* 2013;62(8):2978–83. <https://doi.org/10.2337/db12-1627>.
- [149] Tuomi T, Nagorny CLF, Singh P, Bennet H, Yu Q, Alenkqvist I, Isomaa B, Östman B, Söderström J, Pesonen A-K, Martikainen S, Räikkönen K, Forsén T, Hakaste L, Almgren P, Storm P, Asplund O, Shcherbina L, Fex M, Fadista J, Tengholm A, Wierup N, Groop L, Mulder H. Increased melatonin signaling is a risk factor for type 2 diabetes. *Cell Metab* 2016;23(6):1067–77. <https://doi.org/10.1016/j.cmet.2016.04.009>.
- [150] Corbalán-Tutau D, Madrid JA, Nicolás F, Garaulet M. Daily profile in two circadian markers “melatonin and cortisol” and associations with metabolic syndrome components. *Physiol Behav* 2014;123:231–5. <https://doi.org/10.1016/j.physbeh.2012.06.005>.
- [151] Robeva R, Kirilov G, Tomova A, Kumanov P. Melatonin-insulin interactions in patients with metabolic syndrome. *J Pineal Res* 2008;44(1):52–6. <https://doi.org/10.1111/j.1600-079X.2007.00527.x>.
- [152] Hikichi T, Tateda N, Miura T. Alteration of melatonin secretion in patients with type 2 diabetes and proliferative diabetic retinopathy. *Clin Ophthalmol* 2011;5(1):655–60. <https://doi.org/10.2147/OPTH.S19559>.
- [153] Scholtens RM, van Munster BC, van Kempen MF, de Rooij SEJA. Physiological melatonin levels in healthy older people: a systematic review. *J Psychosomat Res* 2016;86:20–7. <https://doi.org/10.1016/j.jpsychores.2016.05.005>.
- [154] Pietrowsky R, Meyer R, Kern W, Born J, Fehm HL. Effects of diurnal sleep on secretion of cortisol, luteinizing hormone, and growth hormone in man. *J Clin Endocrinol Metab* 1994;78(3):683–7. <https://doi.org/10.1210/jcem.78.3.8126142>.
- [155] Holl RW, Hartman ML, Veldhuis JD, Taylor WM, Thorner MO. Thirty-second sampling of plasma growth hormone in man: correlation with sleep stages. *J Clin Endocrinol Metab* 1991;72(4):854–61. <https://doi.org/10.1210/jcem-72-4-854>.
- [156] Scheen AJ, van Cauter E. The roles of time of day and sleep quality in modulating glucose regulation: clinical implications. *Horm Res Paediatr* 1998;49(3–4):191–201. <https://doi.org/10.1159/000023170>.
- [157] Ali I, Lizarralde G, Veldhuis JD. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. *J Clin Endocrinol Metab* 1991;73(5):1081–8. <https://doi.org/10.1210/jcem-73-5-1081>.
- [158] Kalsbeek A, Fliers E, Romijn JA, la Fleur SE, Wortel J, Bakker O, Endert E, Buijjs RM. The suprachiasmatic nucleus generates the diurnal changes in plasma leptin levels. *Endocrinology* 2001;142(6):2677–85. <https://doi.org/10.1210/endo.142.6.8197>.
- [159] Otway DT, Frost G, Johnston JD. Circadian rhythmicity in murine pre-adipocyte and adipocyte cells. *Chronobiol Int* 2009;26(7):1340–54. <https://doi.org/10.3109/07420520903412368>.
- [160] Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a

- role in meal initiation in humans. *Diabetes* 2001;50(8):1714–9. <https://doi.org/10.2337/diabetes.50.8.1714>.
- [161] Buijs RM, Scheer FA, Kreier F, Yi C, Bos N, Goncharuk VD, Kalsbeek A. Organization of circadian functions: interaction with the body. *Prog Brain Res* 2006;153:341–60. [https://doi.org/10.1016/s0079-6123\(06\)53020-1](https://doi.org/10.1016/s0079-6123(06)53020-1).
- [162] Pivovarova O, Jürchott K, Rudovich N, Hornemann S, Ye L, Möckel S, Murahovschi V, Kessler K, Seltmann A-C, Maser-Gluth C, Mazuch J, Kruse M, Busjahn A, Kramer A, Pfeiffer AFH. Changes of dietary fat and carbohydrate content alter central and peripheral clock in humans. *J Clin Endocrinol Metab* 2015;100(6):2291–302. <https://doi.org/10.1210/jc.2014-3868>.
- [163] Yamanaka Y, Hashimoto S, Takasu NN, Tanahashi Y, Nishide SY, Honma S, Honma KI. Morning and evening physical exercise differentially regulate the autonomic nervous system during nocturnal sleep in humans. *Am J Physiol Regul Integr Comp Physiol* 2015;309(9):R1112. <https://doi.org/10.1152/ajpregu.00127.2015>.
- [164] Buxton OM, Frank S, L’Hermite-Baleriaux M, Leproult R, Turek FW, Van Cauter E. Roles of intensity and duration of nocturnal exercise in causing phase delays of human circadian rhythms. *Am J Physiol* 1997;273(3):536–42.
- [165] Van Cauter EV, Polonsky KS, Blackman JD, Roland D, Sturis J, Byrne MM, Scheen AJ. Abnormal temporal patterns of glucose tolerance in obesity: relationship to sleep-related growth hormone secretion and circadian cortisol rhythmicity. *J Clin Endocrinol Metab* 1994;79(6):1797–805. <https://doi.org/10.1210/jcem.79.6.7989487>.
- [166] Gubin DG, Nelaeva AA, Uzhakova AE, Hasanova YV, Cornelissen G, Weinert D. Disrupted circadian rhythms of body temperature, heart rate and fasting blood glucose in prediabetes and type 2 diabetes mellitus. *Chronobiol Int* 2017;34(8):1136–48. <https://doi.org/10.1080/07420528.2017.1347670>.
- [167] Roush GC, Fapohunda J, Kostis JB. Evening dosing of antihypertensive therapy to reduce cardiovascular events: a third type of evidence based on a systematic review and meta-analysis of randomized trials. *J Clin Hypertens* 2014;16(8):561–8. <https://doi.org/10.1111/jch.12354>.

This page intentionally left blank

Part V

Sleep and behavioral health

This page intentionally left blank

Chapter 22

Sleep and food intake

Isaac Smith^a, Katherine Saed^a and Marie-Pierre St-Onge^{a, b, c}

^aInstitute of Human Nutrition, Columbia University Irving Medical Center, New York, NY, United States; ^bDivision of Endocrinology, Department of Medicine, Columbia University Irving Medical Center, New York, NY, United States; ^cSleep Center of Excellence, Department of Medicine, Columbia University Irving Medical Center, New York, NY, United States

Abbreviations

2-AG	2-Arachidonoylglycerol
GABA	Gamma aminobutyric acid
GLP-1	Glucagon-like peptide 1
HPA	Hypothalamic pituitary axis
LNAAs	Large neutral amino acids
NHANES	National Health and Nutrition Examination Survey
REM	Rapid-eye movement
TIB	Time in bed
TSD	Total sleep deprivation

Introduction

As explored in previous chapters, it is clear that getting a good night's sleep is critical to one's overall health and well-being. But average sleep duration in adults deviates from the joint recommendation of 7–9 h/night by the American Academy of Sleep Medicine and the Sleep Research Society [1]. In fact, in 2007–10, 37.3% of U.S. adults older than 20 years of age reported sleeping 6 h/night or less [2]. Yet, insufficient sleep has not always been such a pervasive issue in the United States: between 1985 and 2004, the percentage of short sleepers rose by up to 31%, while average sleep duration declined slightly [3].

Interestingly, the trend toward shorter sleep duration in the United States developed alongside the dramatic rise in obesity. Between 1980 and 2000, the prevalence of obesity increased substantially among adult men and women [4]. Partly because it presents with numerous health consequences including heart disease, diabetes, and certain forms of cancer, the obesity epidemic continues to be targeted as one of the most important public health concerns of the 21st century [5]. The cooccurrence of the obesity epidemic and the increasing prevalence of short sleep duration, however, may be more deeply rooted. As detailed in Chapter 17, there is substantial epidemiological

evidence to support the association between short sleep duration and obesity [6–8]. There is also accumulating evidence of a causal impact of short sleep on obesity risk. But, as described previously by Capers et al. [9] and St-Onge [10], the majority of clinical interventional studies have not been long enough to truly determine if causality exists between habitual short sleep duration and obesity. Obesity is the result of prolonged positive energy balance, whereby intake exceeds expenditures. If short sleep duration is a causal factor in this pathway, it must influence either one of the two main drivers of energy balance [11]—a process that may require a threshold "sleep debt" to be attained in order for significant body weight change to occur [10]. While the influence of sleep restriction on total daily energy expenditure remains tentative, the causal influence of short sleep on food intake has been well-established and will be discussed in detail in Part 1 of this chapter.

In Part 2 of this chapter, a number of factors that may play a role in the relation between sleep and food intake will be discussed. For instance, some have proposed that decreased time in bed (TIB) leads to greater wake time available to consume and thus increased food intake [8]. However, more than merely a simple time availability issue, some have illustrated a physiological mechanism implicating hormonal variation, largely ghrelin and leptin, as driving increased hunger and appetite, supporting the effect of short sleep in increasing food intake [12]. In addition, since appetite is regulated by both physiological and psychological processes, nonhormonal mechanisms have also been described implicating reward pathways of the brain [13] and impaired inhibitory executive functioning/impulse control as influencers of food intake due to short sleep [14]. A number of novel hypotheses have been proposed as well, including stress [15] and alterations in the endocannabinoid system [16] but those have not been

sufficiently studied to warrant in-depth description in this chapter.

While there has been a wealth of research that strongly links short sleep duration to increased food intake, there has also been a suggestion of bidirectionality in this relationship, implicating dietary factors in modulating sleep duration and/or quality. Part 3 will focus on how food intake can influence sleep duration and quality.

Part 1: Sleep loss and food intake

Between 1969 and 2001, per capita caloric consumption in developed nations rose by 400 kcal/day and, given a continuation of this trend, is expected to increase past 3500 kcal/day by the year 2050 [17]. Interestingly, this trend toward increased food intake parallels both trends toward greater obesity rates [4] and shorter sleep duration [3]. Indeed, numerous observational studies of habitual sleep and dietary intake have found an inverse association between sleep duration and energy intake [18–20] or diet quality [21–25]. Data from the National Health and Nutrition Examination Survey (NHANES), for instance, revealed that short sleepers (5–6 h) had greater total energy intake than average sleepers [26]. Sleep duration is not only associated with total energy intake but may be particularly related to intakes of specific macronutrients. In a large epidemiological study of Korean adults, sleep duration was positively correlated with protein intake and negatively correlated with carbohydrate intake [27]. In a separate analysis of the same population, women with short sleep duration consumed more carbohydrates, men with short sleep duration consumed more fat, and both men and women with short sleep duration consumed less protein [28]. In the United States, sleep duration was negatively correlated with fat intake [25]. However, despite the large number of cross-sectional population studies that demonstrate this association, causality cannot be assumed from epidemiological studies alone. Prospective studies and randomized controlled trials are necessary to ascertain the causal link between sleep and food intake.

Many short-term, highly restrictive, experimentally controlled sleep studies have been conducted to determine whether sleep restriction increases food intake in adults. In the longest of these studies to date, Nedeltcheva et al. demonstrated that restricting TIB to 5.5 h/night as compared to 8.5 h/night for 14 nights increased food intake by 297 kcal among 11 healthy overweight volunteers [29]. Although the difference in total energy intake or intake from meals was not significant between sleep duration periods, energy intake from snacks, in particular, was increased in the short sleep condition. The lack of statistical significance on total energy intake may have been due to inadequate sample size since St-Onge et al. noted a similar increase in total energy intakes of 296 kcal/day

when 26 men and women were restricted to 4 h TIB for four nights relative to a control period of 9 h TIB [30]. The authors further noted that women tended to have greater increase in energy intakes relative to men (unpublished data), but others have reported the converse [31]. Many other short-term studies have presented similar findings on the link between sleep restriction and food intake [32–34]. In fact, a recent meta-analysis concluded that sleep restriction, in normal sleepers, leads to an increase in energy intakes of ~385 kcal/day [35], an amount that, if sustained over time, could lead to substantial weight gain. These conclusions have been corroborated in multiple opinion and systematic reviews [2,9,10,14].

Experimentally induced sleep restriction studies have also provided evidence of macronutrient-specific increases in intakes as a result of short sleep. Two previously mentioned intervention studies found that acute sleep restriction increased carbohydrate intakes in healthy adults [29,33]. In a separate study, fat and saturated fat intakes were specifically increased after 5 days of restricted sleep, compared to adequate sleep, in 15 healthy men and women [36]. Other intervention studies have found similar effects of acute sleep restriction on fat intake in healthy adults [34,37]. Yet whether the combined effects of short sleep duration on increased energy, carbohydrate, and fat intakes contribute to positive energy balance and weight gain long term is relatively understudied, given that most studies have been of relatively short duration (mostly 4–5 days and <14 days).

Ultimately, body weight is the outcome of the balance between energy intake and energy expenditure. Although the effect of short sleep duration on energy balance regulation is outside the scope of this chapter, it is interesting to note that reviews and meta-analyses have found no significant effect of sleep restriction on energy expenditure [9,10]. This is mostly due to high between-study heterogeneity and the diverse components of energy expenditure that are difficult to measure under controlled conditions of acute sleep restriction studies. Nonetheless, the evidence suggests that a positive energy balance as a result of increased food intake, given no net compensation in energy expenditure, may be achieved as a result of sleep restriction. In fact, Markwald et al. found that, compared to five nights of 9 h TIB, five nights of sleep restriction to 5 h TIB increased food intake and promoted positive energy balance and weight gain [33]. Few others have attempted to replicate the same finding. Unfortunately, given the paucity of evidence that supports this association, it would be premature to claim that short sleep duration causing increased food intake, in short-term studies, leads to positive energy balance and long-term weight gain. However, one thing seems clear: how we sleep affects how much we eat and the types of food that we choose.

Part 2: Proposed mechanisms explaining the sleep–food intake relation

A number of mechanisms have been proposed to explain the relation between short sleep duration and increased food intake. These are categorized as homeostatic (i.e., hormonal) and nonhomeostatic (i.e., hedonic). The differences between these concepts were highlighted in one study that compared chosen portion sizes after sleep deprivation in either a fasted or sated state [38]. Participants were asked to rate desired portion sizes, using computer-generated pictures of foods of different energy content. Interestingly, after one night of total sleep deprivation (TSD), average portion sizes chosen were higher both before and after consumption of a 600-kcal breakfast, as compared to those chosen after a night of adequate sleep (8 h TIB). Greater portion sizes chosen in the fasted state represent an increased homeostatic drive to eat after TSD relative to adequate sleep, whereas greater portions sizes chosen after breakfast consumption, in a sated state, represent an increased hedonic drive to eat. The most studied of these homeostatic and nonhomeostatic mechanisms are graphically displayed in Fig. 22.1. It is important to keep in mind that each pathway may contribute to food intake independently and with varying magnitude. Additionally, many of these pathways lack adequate evidence to fully support causality. For this reason, more research into each of these fields should be completed in order to fully understand the relationship between short sleep duration and increased food intake.

Homeostatic mechanisms

Changes in hormonal modulation of food intake by sleep duration was first demonstrated by Spiegel et al., whereby ghrelin levels increased by 28% and leptin levels decreased by 18% after three nights of 4 h TIB compared to 10 h TIB in young healthy men [39]. These findings are consistent with the notion that restricting sleep leads to positive energy balance since leptin is an adipose-derived cytokine that sends satiety signals to the brain [40], and ghrelin is an orexigenic hormone that sends appetitive signals from the stomach to the brain [41]. But limitations of this study included unnatural feeding conditions and low external generalizability. Since that landmark study, a plethora of studies assessing changes in leptin and ghrelin in response to sleep manipulations have produced mixed results [13,42–46]. Such heterogeneity was highlighted in a meta-analysis that noted no net effect of sleep restriction on leptin and ghrelin levels [9]. It is clear that additional studies are needed to draw definitive conclusions about the impact of sleep restriction on leptin and ghrelin

concentrations and how changes in these hormones as a result of sleep disturbances further impact food intake regulation.

While the majority of research on hormonal variation has focused on leptin and ghrelin, other hormones, such as glucagon-like peptide 1 (GLP-1) and peptide YY, satiety factors released by the small and large intestines in response to food [47,48], have also been implicated in the relationship between short-sleep duration and increased food intake. St-Onge et al., for instance, demonstrated that GLP-1 was downregulated following meals consumed after sleep restriction (4 h TIB) compared to habitual sleep (9 h TIB) in young healthy adult women [30]. This finding was not observed in men. In fact, in eight healthy young men, postprandial GLP-1 was actually upregulated after one night of TSD [49]. In contrast, the postprandial GLP-1 response was delayed, but not diminished, following TSD in 12 healthy young men [50]. Thus, considering these dramatic sex differences and the scarcity and inconsistency of evidence linking GLP-1 variations to sleep restriction, more research considering the role of GLP-1 in modulating food intake after sleep restriction is imperative. Interestingly, the same can be said for peptide YY, of which there is even less experimental research related to its relationship with sleep. Although systemic reviews have considered the role of short sleep duration on peptide YY concentration [10], no experimental studies have established any substantial relationship between the two.

Nonhomeostatic mechanisms

Although food intake is under hormonal regulation, food consumption occurs despite physiological hunger (hedonic control). In fact, Chaput and St-Onge have argued that sleep may have a stronger influence on nonhormonal controls of food intake, rather than hormonal controls [13]. To that effect, Sivak noted that hormonal variance accounted for a very small proportion of the average body mass gained by participants enrolled in a sleep restriction study: 3% for leptin and 1% for ghrelin [51]. Some have posited that in a society with consistent and abundant access to food, the less one sleeps, the longer one is awake, the more opportunity is available to fall prey to the allure of palatable food, leading to overconsumption [8,10,51]. Indeed, the explanation may be more complex than a simple time-availability condition. It has been hypothesized that eating and food choice are likely at the center of a balancing act between reward-driven motivations to eat and inhibitory executive functioning and impulse control [52]. It seems likely that if either of these processes are impaired, overeating—or poor food choice—may prevail. This relationship is graphically displayed in Fig. 22.1.

One of these pathways that has been quite well-established and is continuing to accumulate evidence is

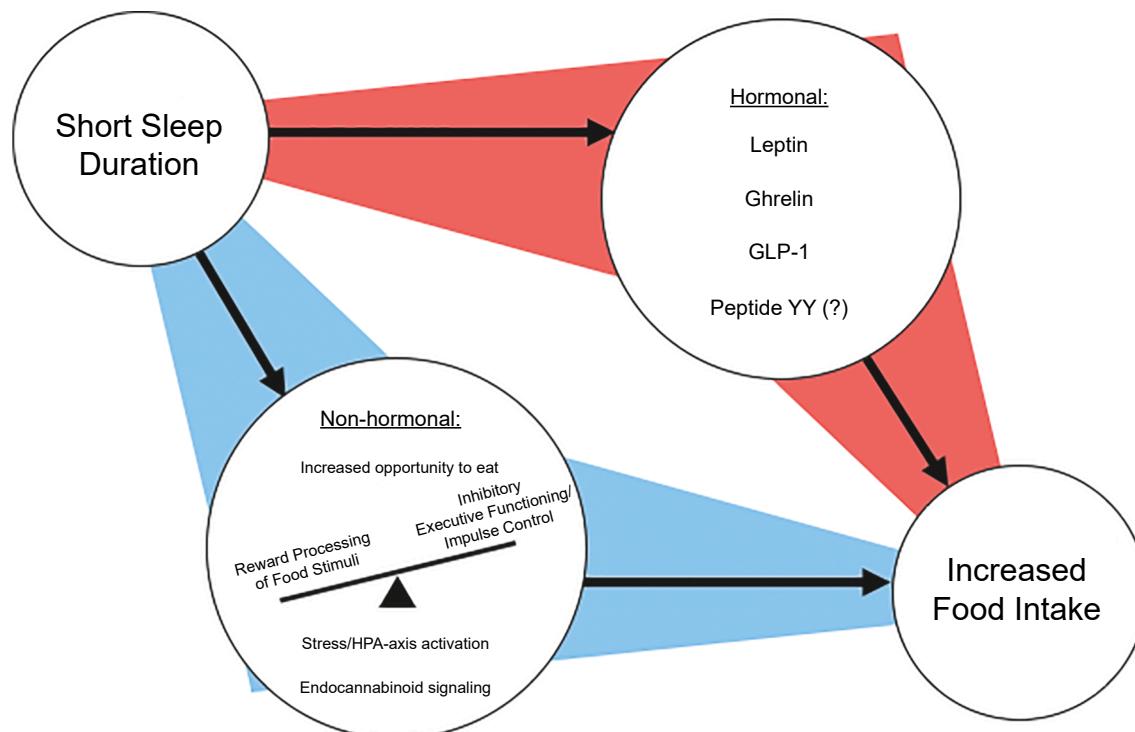


FIGURE 22.1 Proposed mechanisms to explain the relation between sleep and food intake. Short sleep duration in humans has been shown to (A) decrease leptin levels, (B) increase ghrelin levels, and (C) decrease GLP-1 levels. The effect of short sleep duration on (D) peptide YY is not as well-known. Short sleep duration (E) increases opportunity to eat when conditions favor abundance, (F, G) shift the balance of reward and impulse control toward enhanced reward and impaired inhibitory executive functioning and impulse control, (H) increase stress and activate the HPA-axis, and (I) delay and enhance the endocannabinoid signaling pathway. Each of these pathways has been shown to increase food intake in human participants.

the action of hedonic stimulus processing in the brain in response to food stimuli. Functional magnetic resonance imaging of normal-weight men after one night of TSD showed an increase in activity in response to food stimuli in the right anterior cingulate cortex, a brain region often associated with reward processing, when compared to one night of sleep [53]. This result was found after participants were given a caloric load, further suggesting the influence of nonhomeostatic mechanisms. These findings have been corroborated in another functional magnetic resonance imaging study that showed increased activity in response to food stimuli in other brain regions associated with pleasure and reward processing after sleep was restricted to 4 h/night compared to 9 h/night for five nights [54]. Greater activation in reward pathways or greater sensitivity to reward has been correlated with obesity and a greater risk for overeating [55,56].

On the other end of this balancing act is impaired executive functioning and impulse control. The first experimental study analyzing the effect of sleep deprivation on cognitive performance took place in 1896 [57]. Since then, hundreds of studies have been published on this relationship [58]. Nilsson et al., for instance, found that executive functioning was impaired after one night of TSD in 22 healthy adults [59]. Various aspects of cognitive

performance, executive function, and decision-making have been linked with both sleep restriction and deprivation [60–62]. Relatedly, studies have shown that TSD leads to greater impulsivity compared to adequate sleep [63,64]. And, after sleep restriction, brain regions associated with cognitive processing, decision-making, and self-control were activated to a lesser extent in response to food stimuli as compared to habitual sleep [54]. Moreover, impaired executive functioning is associated with uncontrolled eating [65] and impulsivity and impaired executive functioning have been shown to increase food intake in ad libitum eating tasks [52]. Therefore, short sleep duration seems to deactivate brain regions associated with executive functioning and impulse control and activate those associated with reward processing in response to food stimuli. Both of these effects are associated with a greater risk for overeating. Thus, taken together, evidence suggests that the imbalance between hedonic stimulus processing and inhibitory executive functioning and impulse control may partly mediate the effect of short sleep duration on food intake.

Due to the insufficiency of evidence linking any one particular mechanism to the relationship as graphically displayed in Fig. 22.1, however, more novel mechanisms have been proposed. Of these, the modulating effect of

stress on the relationship between sleep and food intake is relatively well-established. In a recent review analyzing the effect of sleep on stress, Wolkow et al. concluded that sleep may act as a potent stressor to elicit both physiological and psychological responses [66]. Additionally, stress has a causal relationship with hyperactivity in the hypothalamic-pituitary-adrenal (HPA) axis, although this relationship is complex and bidirectional [67]. Nonetheless, hyperactivity in the HPA-axis has been observed in response to both TSD and sleep restriction [68–70]. Activation of the HPA-axis, self-reported levels of stress, and objective stressful conditions have all been correlated with increased food intake [68]. Acute exposure to stressful conditions increased food intake, when compared to a stress-free condition, in normal weight women [71]. Others have replicated these results using various stimuli to promote a stressful environment, many in the absence of physiological hunger [72–75]. Although not specifically conducted in the context of sleep restriction, these illustrate the potential role of sleep restriction, as a stressor, in eliciting increased food intake and suggest that the effect of short sleep duration on food intake may be partly mediated by the stress-inducing/HPA-axis activating effects of inadequate sleep.

A more novel mechanism that has been implicated in the relationship between short sleep duration and increased food intake is the effect of circulating levels of 2-arachidonoylglycerol (2-AG), the most abundant endocannabinoid [76]. The endocannabinoid system mediates hedonic food intake, reaches a nadir during mid-sleep, and exhibits a large diurnal peak during lunch hours [16]. Sleep restriction results in an increase and delay of the diurnal peak in 2-AG along with reports of increased hunger and appetite and inability to inhibit intake of palatable snacks [77]. A review of novel mechanisms in the development of obesity suggests that, due to its ability to control appetite, the endocannabinoid system may play an important role in increased food intake due to short sleep duration [16].

Many other mechanisms have been proposed. Such mechanisms, including circadian disruptions in the gut microbiota [16] and emotional dysregulation [14], have been studied to a much lesser extent, have a paucity of evidence to explain any association, and will not be discussed herein. Nonetheless, these mechanisms are included in this discussion as they require additional study.

Part 3: Influence of food intake on sleep duration and quality

Although the previous sections covered the evidence surrounding the impact of sleep duration on food intake and food intake regulation, there is evidence that food choice may also influence sleep duration and quality. As described

below, intakes of specific macronutrients and foods may have an impact on the quality of overnight sleep. In addition, specific foods and various dietary supplements have been studied for their potential beneficial impact on sleep. A holistic dietary approach that incorporates several of these components may be the ideal solution for long-term healthy sleep. As discussed earlier in this chapter, studies have shown that short sleepers have higher energy intake, most commonly from fat [22] and snacks [25], than normal sleepers. On the other hand, numerous epidemiological studies have opined the reverse: a negative association between carbohydrate intakes and sleep quality [78–80]. In Japanese women, high intake of noodles and confectionery was shown to be associated with poor sleep quality, while high intake of fish and vegetables was associated with good sleep quality [81]. There was also a trend toward declining sleep quality with increased carbohydrate intake. As was highlighted earlier, the directionality between these variables cannot be established from cross-sectional studies. Just as poor sleep could result in unhealthy dietary intakes, it may very well be that unhealthful diets lead to poor sleep. If such is the case, then improving dietary intakes could be a target for improving sleep quality.

Caloric consumption

Energy restriction has been shown to reduce melatonin secretion [82], which would be expected to lead to difficulties initiating sleep. Indeed, short-term, voluntary fasting by total rejection of food or intake of < 300 kcal per day for 2–7 days significantly reduced circulating melatonin concentrations. Glucose supplementation during these short-term fasts returned melatonin concentrations to normal [82]. However, the study did not report on sleep duration. Nonetheless, patients with anorexia have been shown to have poorer sleep quality and greater sleep disturbances than healthy control participants [83], pointing to a negative influence of energy restriction on sleep.

Protein

Neurotransmitters regulating sleep are influenced by what we eat, including serotonin [84], gamma-amino butyric acid (GABA), orexin, melanin-concentrating hormone, galanin, noradrenaline, and histamine [85]. The synthesis of serotonin is dependent on the precursor tryptophan, an amino acid found in high concentration in poultry and soy. Serotonin is the precursor to melatonin, which is released by the pineal gland and a known regulator of sleep. Tryptophan consumption could therefore contribute to increased serotonin production, melatonin production, and sleep onset [84]. In fact, studies have shown that tryptophan doses as low as 1 g improve sleep latency and

subjective sleep quality [84]. However, tryptophan uptake in the brain is mediated through a competitive mechanism, and consumption of other macronutrients and competing amino acids can influence serotonin production from tryptophan. High plasma concentration of tryptophan relative to other amino acids promotes entry of tryptophan through the blood–brain barrier promoting production of serotonin and triggering release of melatonin from the pineal gland (Fig. 22.2).

Increasing tryptophan access to the brain can be accomplished through multiple mechanisms: pure tryptophan supplementation, increased carbohydrate intake [86], or consumption of tryptophan-rich α -lactalbumin protein [87]. Tryptophan loading has been shown to dose-dependently increase circulating melatonin in humans throughout the day, but this effect was more pronounced at night [87]. The nocturnal administration of tryptophan has been shown to increase physiological concentrations of serotonin and melatonin [88], therefore facilitating sleep [89].

Evidence for a role of tryptophan on sleep quality can be extrapolated from studies in aging adults. There is a reduction in the ability of tryptophan to cross the

blood–brain barrier with increasing age, leading to a reduction in biosynthesis of serotonin and melatonin, which may explain the reduction in sleep quality and duration that occurs with aging [90]. It can be hypothesized that low intakes of tryptophan may lead to increased occurrence of sleep problems and supplementation with this amino acid may improve sleep. In one study, normal weight elderly volunteers suffering from sleep difficulties were provided with 30 g of tryptophan-enriched ready-to-eat cereal, containing 60 mg tryptophan, at breakfast and dinner. Most sleep parameters improved following this treatment compared to the control period consisting of a diet with standard ready-to-eat cereal containing 22.5 mg of tryptophan per dose and compared to participants' habitual diet. Of particular note, there was also an increase in total sleep time indicating that tryptophan consumption may be a potential treatment for those suffering from sleep disorders and disturbances [90].

Carbohydrates

Increasing carbohydrate intake promotes tryptophan entry in the brain. This is accomplished by triggering a high

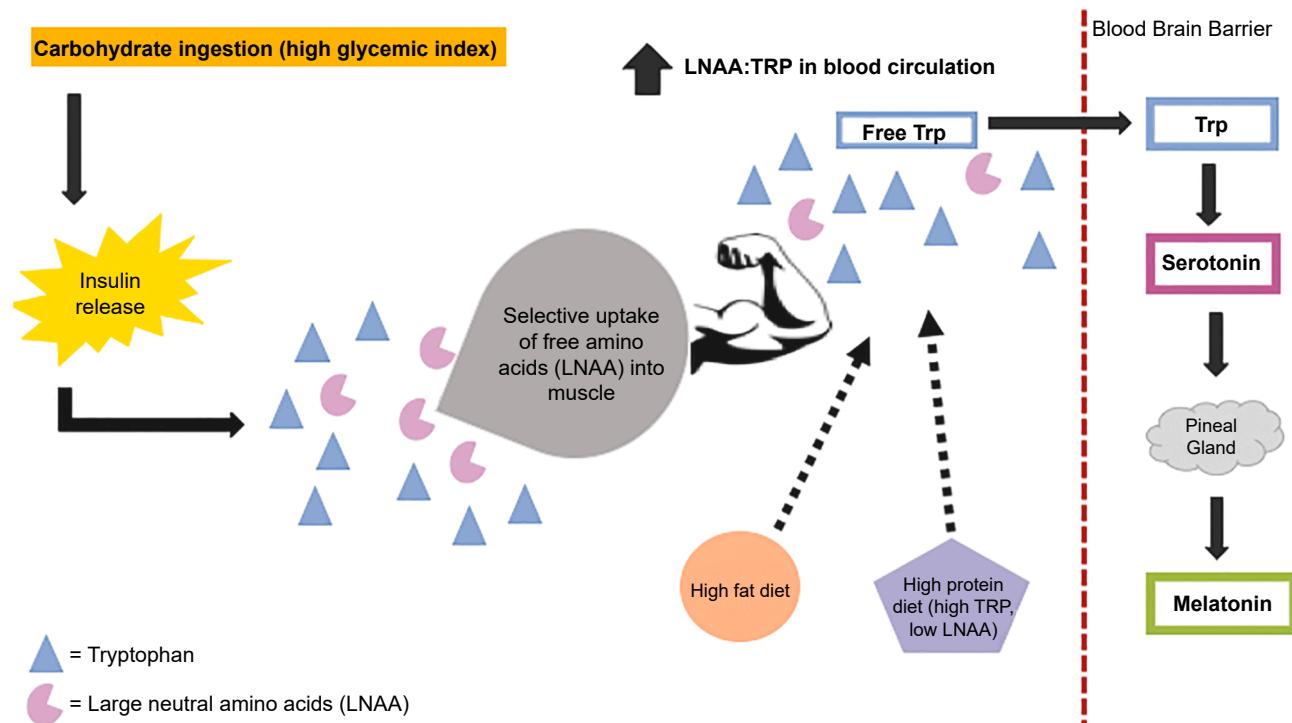


FIGURE 22.2 Dietary tryptophan triggers biosynthesis of melatonin. The synthesis of serotonin is dependent on the availability of tryptophan. Serotonin is necessary for increased melatonin release from the pineal gland. Macronutrient intake influences this process and plays a role in sleep induction. Carbohydrate ingestion, particularly high glycemic index food choices, increases circulating glucose concentration, which triggers insulin release resulting in selective uptake of large neutral amino acids into the muscle. Tryptophan is taken up with lower efficiency further increasing the ratio of tryptophan to large neutral amino acids (LNAA) in the blood, sending large amounts of tryptophan across the blood–brain barrier leading to sleep induction. High-fat diets and diets high in plant proteins rich in tryptophan and low in LNAA may also favorably influence the Trp:LNAA ratio in blood, leading to increased serotonin and melatonin production in the brain.

insulinemic response, which results in the uptake of amino acids into the muscle. High-glycemic index, carbohydrate-rich meals are particularly efficient in increasing circulating glucose concentrations and triggering this response (Fig. 22.2). This then leads to reduced tryptophan uptake up by muscle, therefore increasing its ratio relative to other amino acids in the blood, the net effect being greater amounts of tryptophan reaching the brain to trigger serotonin synthesis and ultimately promoting sleep induction [91,92]. This mechanism provides a possible explanation as to how high carbohydrate meals increase drowsiness and promote sleep. Indeed, a study by Porter and Horne found that a high-carbohydrate meal resulted in increased rapid-eye movement (REM) sleep, decreased light sleep, and decreased wakefulness throughout the night [93]. Similarly, clinical trials have reported that participants tended to feel sleepier and less awake after being given a high-glycemic index meal compared to a low-glycemic index meal [94], and sleep latency was shorter when participants were provided a high carbohydrate diet (56% carbohydrate, 22% protein, and 22% fat) compared to control diets (50% carbohydrate, 35% fat, and 15% protein) [95]. However, in contrast to the prevailing theoretical mechanism as presented in Fig. 22.2, research into the effects of carbohydrate intake on sleep quality show mixed results. The reader is referred to a detailed review of carbohydrate intakes and sleep [143].

In an intervention study, providing six healthy women with a low-carbohydrate diet (50 g/day) for 7 days increased REM latency compared to baseline [96]. In a secondary analysis, St-Onge et al. noted that higher intakes of sugar and nonsugar carbohydrates were also associated with more nocturnal arousals during sleep [97]. Notably, lower intake of fiber and greater intake of saturated fat were associated with a lighter, less deep sleep profile. That both a positive and negative association has been demonstrated between intake of carbohydrates and sleep indicates that the study design, namely observational versus interventional and the quality of the carbohydrate may be important factors when evaluating the impact of carbohydrate intake on sleep.

Evidence is also accumulating to suggest a relationship between timing of carbohydrate intake and sleep quality [98,99]. For instance, high-glycemic index meals ingested 4 h before bedtime reduced sleep-onset latency to a greater extent than the same meal ingested 1 h before bedtime [94]. Thus, a small adjustment in the composition of the evening meal may be a potential therapeutic strategy to improve sleep initiation. Yet the evidence is insufficient to support this recommendation.

Three mechanisms have been proposed to explain the apparent relationship between timing of carbohydrate ingestion and sleep quality. First, a longer time lapse

between meal and bedtimes may be necessary to allow for the digestive and absorptive processes to occur and impact serotonin synthesis. Second, late eating may contribute to a phase delay, which exacerbates circadian disruption, leading to further reduced sleep duration [100]. Third, late eating may influence food choice due to the availability of foods at that time.

Fat

Consumption of a fatty meal has been shown to increase self-reported sleepiness in an intervention study [101]. This confirms data from a longitudinal study of Chinese adults showing that those with high dinner fat intake at baseline had persistent short sleep over 5 years in a prospective cohort study [99]. This study showed that the association between macronutrient intake and sleep differs by meal timing, because similar associations were not observed when the authors considered total daily fat intake or fat intakes earlier in the day. High-fat dinner intake was positively associated with short sleep duration in Chinese adults, while high-fat breakfast intake was inversely associated with falling asleep during the day [99]. The authors postulated that fat intake from dinner could alter circadian regulation in humans leading to shorter sleep and thus recommended limiting fat intake particularly at dinner to maintain adequate sleep. However, this study was not an intervention and causality cannot be implied from these results.

One potential mechanism to explain the link between increased fat intake and improved sleep quality is via circulating tryptophan levels. Greater free fatty acid levels increase free tryptophan in circulation, resulting in increased uptake of tryptophan into the central nervous system and biosynthesis of serotonin and melatonin [84]. Another potential hypothesis that explains the relationship between increased fat intake and poor sleep quality is based on the function of sleep in macromolecular biosynthesis of proteins, lipids, cholesterol, and heme [102]. It is hypothesized that an increased consumption of high-fat foods results in a decreased need for biosynthesis of these macromolecules, thus decreasing the signal for sleep [25]. An alternative explanation is based on the function of sleep in energy conservation. Relative to protein, fat ingestion has a lower thermogenic effect [102]. Thus, the need for energy conservation is not as great following consumption of high-fat foods. The overall effect of decreased energy expenditure after increased fat intake is a reduction in the need for energy conservation and, thus, reduced sleep duration and/or quality [25]. As with carbohydrate intake, because both positive and negative associations have been found between fat intake and sleep, it is likely that the quantity, quality, and timing of fat intake may play a role in this relationship.

To that effect, omega-3 fatty acid deficiencies have been associated with poor sleep [103], while supplementation of omega-3 or consumption of high omega-3 foods are potentially beneficial in promoting sleep [104]. In a randomized controlled trial, daily dietary supplementation with 600 mg/day of docosahexaenoic acid increased sleep duration by 58 min in children relative to placebo [104]. This was accompanied with fewer night-waking episodes, although no subjective improvements were evident.

Vitamins and supplements

Melatonin

Melatonin has been found in many foods; eggs and fish are the best animal sources, and nuts, cereals, legumes, seeds, and mushrooms are rich plant-based food sources. Melatonin is also a natural compound found in cow's milk. This might explain why milk has traditionally been used for its sleep inducing effects [105]. However, a double-blinded study in elderly participants did not find any effect of ingesting 500 g/day of normal commercial milk on sleep at night or alertness the following morning [106]. On the other hand, consumption of a melatonin-rich milk led to better sleep at night in 80 elderly participants [105]. This discrepancy is likely explained by differences in quantity of melatonin contained in the milk.

Sleep disorders and difficulty sleeping have been shown to increase circulating reactive oxygen species [107,108]. Melatonin can directly scavenge free radicals and stimulate antioxidant enzymes [109]. Thus, in addition to its role in the regulation of circadian rhythms [110,111], intake of melatonin-rich foods may provide benefits in improving sleep and weight management due to its antioxidant, antiinflammatory, and antidiobesity effects [112]. There is some evidence that melatonin may help treat delayed sleep phase syndrome with short-term use and help those struggling to fall asleep by initiating sleep onset [113]. That said, the short-term use of melatonin for the treatment of primary sleep disorders is not recommended [114].

B vitamins

The secretion of endogenous melatonin is also influenced by external factors such as artificial light exposure and vitamin B12 intake [105]. Yet supplementation with B12 to treat circadian rhythms disorders is not recommended [113]. Other B vitamins, such as niacin, have been shown to improve sleep quality [115]. Administration of niacin to six participants with normal sleep increased REM sleep and improved sleep efficiency in individuals with insomnia. Given that niacin is biosynthesized from dietary tryptophan, researchers postulated that the administration

of niacin may lead to decreased biosynthesis and thus, increased tryptophan available for the production of serotonin and melatonin [105].

Isoflavones

Isoflavones are soy-based phytoestrogens known to offer potential therapeutic effects for many hormone-dependent conditions including certain forms of cancer, menopausal symptoms, and cardiovascular disease [116]. Additionally, phytoestrogens may influence serotonin levels and the sleep-wake cycle. Isoflavones are purported to have similar effects on sleep quality as estrogen replacement therapy, which has been shown to alleviate symptoms of insomnia and increase sleep efficiency in postmenopausal women [117]. In a cross-sectional study conducted in Japanese men and women, it was reported that daily isoflavone intake was associated with an optimal sleep duration of 7–8 h/night and better sleep quality [118]. However, clinical studies are warranted to confirm the effects of isoflavone intakes on insomnia symptoms and overall sleep quality.

Magnesium

Magnesium is an essential macro-mineral in the body and is involved in over 300 biochemical reactions [119]. Magnesium requirements remain relatively unchanged through adulthood yet aging increases the risk of magnesium deficiency [120]. Coincidentally, sleep quality has also been shown to decrease with age. For this reason, some have proposed that the increased risk for magnesium deficiency in the elderly mediates the decline in sleep quality [120]. Indeed, in the elderly, magnesium supplementation has been shown to increase sleep duration and efficiency, decrease sleep onset latency, and improve insomnia severity index scores. Daily dietary or supplemental magnesium has been shown to improve subjective and objective measures of insomnia and may become useful in managing these symptoms [120]. Almonds, a good source of both magnesium and melatonin, may be a natural method to improve sleep [121]. Studies are needed to evaluate the influence of food sources of magnesium on sleep quality and whether magnesium supplementation, in the absence of inadequate intakes, can improve sleep quality.

Fruits

Tart cherries contain phenolic compounds that have anti-inflammatory and antioxidant properties [122]. As a result of these properties, tart cherries have been shown to improve sleep quality and reduce insomnia symptoms. Additionally, this may be explained, in part, by the rise in circulating melatonin concentrations that occurs after daily

ingestion of tart cherry juice. In healthy adults with no reported sleep disturbances, consumption of tart cherry juice decreased napping throughout the day and resulted in improved sleep quality throughout the night.

Similarly, consumption of kiwifruit has been shown to improve sleep quality [107]. Currently, three mechanisms have been proposed to explain this effect. First, kiwifruit has the highest proportion of vitamin C, an antioxidant vitamin, relative to other fruits. Given the relation between reactive oxidant species and sleep, a high concentration of vitamin C might partly explain the improvement in sleep quality. Second, kiwifruit contain relatively high amounts of serotonin, which is involved in sleep–wake regulation. Third, kiwifruit is a rich source of folate. Folate deficiency has been linked with poor sleep and insomnia [26].

Walnuts have also been associated with improved sleep [123]. Walnuts are known to be rich in many nutrients including phosphorus, copper, and magnesium [124]. Likewise, they are a good source of melatonin and healthy fats, such as omega-3 fatty acids [123]. In addition, walnut consumption increases blood melatonin concentration, which has been shown to correlate with increased anti-oxidant capacity and may lead to improved sleep.

Alternative medicine

Valerian

Valerian is a flowering plant that has been shown to improve symptoms associated with insomnia and anxiety [125]. Valerian is thought to induce a calming effect by binding to GABA type A receptors [126]. Yet, the evidence for a role of valerian on sleep remains inconclusive due to contradictory findings. Some studies have found no effect on sleep of a single dose of valerian [127–129], while others have reported improved sleep without the negative side effects normally associated with insomnia medication or sleep aids [125,130,131]. Results of a recent meta-analysis showed significant improvement in subjective sleep quality, while objective parameters remained unchanged [132]. Unfortunately, significant drowsiness and dizziness may follow supplementation with valerian [133]. As a result, valerian supplementation has not been advised for management of insomnia symptoms [134].

Kava

Kava, a plant extracted from *Piper methysticum* Forst, has been used for its sedative effect for millennia [135]. Research has shown positive effects on sleep, but supplementation may have lingering effects that hinder normal day-to-day activities. In the past, kava has been used to treat symptoms of anxiety and depression [136]. The suspected receptors of kava lactones, the primary psychoactive constituents of kava, include GABA, serotonin, and

dopamine receptors [137]. No randomized controlled trials have been conducted to explore the efficacy of kava in the treatment of sleep disorders and therefore, its effect on sleep remains unknown.

Total dietary approaches

The Mediterranean diet has a healthy profile of fat, protein, and fiber obtained mainly from the consumption of fish, olive oil, fruits and vegetables, and nuts [138]. It has been postulated that the anti-inflammatory and antioxidant pathways link the Mediterranean diet to improved sleep largely because it consists of foods high in antioxidants, healthy fats, resveratrol, and polyphenols, including phytoestrogens [139,140]. One study concluded that a lower risk of having poor sleep quality was associated with a higher adherence to a Mediterranean diet pattern [141]. Additionally, plant-based proteins tend to be relatively high in the amino acid tryptophan [97], which, as mentioned previously, is a precursor to melatonin and serotonin, the two neurotransmitters involved in sleep regulation. In addition, diets higher in complex carbohydrates and lower in saturated fats, such as plant-based diets and the Mediterranean diet, may have benefits on sleep quality [97].

While information on the relation of total dietary approaches, such as the Mediterranean diet, and sleep quality is emerging, knowledge on the effects of their individual components on sleep quality support a potential causal role. For instance, polyunsaturated fats, omega-3 fatty acids, B vitamins, melatonin, magnesium, and high-quality plant proteins are all highly concentrated in the Mediterranean diet. As described previously, each of these individual components has been associated with improvements in sleep quality and/or duration. For that reason, it may be worthwhile to mention that following a total dietary approach might be a more effective and feasible method to improve sleep quality than addressing individual dietary components.

Conclusion

As detailed in Part 1 of this chapter, acute short sleep duration has a marked effect on food intake. Further, a resulting positive energy balance and weight gain are likely implicated with increased food intake, given no net compensation in energy expenditure. That said, the long-term effects of chronic short sleep duration as a causal factor for obesity and chronic diseases are relatively unknown and understudied. Likewise, it is important to keep in mind that the majority of the mechanisms that explain the relationship between sleep and food intake presented in Part 2 have mixed results or are not yet fully developed. Nonetheless, the presented hypotheses represent areas of active

research that will propel our understanding of the relationship between sleep and food intake and lead to developments of potential targets for intervention.

Obesity is one of the leading causes of preventable death in the United States [142]. Any effort to reduce the impact and proliferation of this epidemic is a worthwhile pursuit. As more evidence to support the relation between sleep and obesity accumulates, it becomes clear that short sleep duration has wide-spread public health implications. This brings about important questions as to the potential for sleep extension as a potential strategy for decreasing food intake. Studies to assess sleep extension strategies as adjunct therapy to standard weight management protocols should also be undertaken. The answer to these questions necessitates more research into the chronic effects of sleep on food intake, the mechanisms underlying the sleep–food intake relation, the effects of short sleep duration on energy balance and weight gain, and the feasibility and efficacy of sleep extension.

While the evidence strongly links short sleep duration to increased food intake, there has also been a suggestion of bidirectionality in this relationship. As explored in Part 3 of this chapter, food choice appears to have an impact on sleep. Most documented studies have been epidemiological and have not provided objective measures of sleep and diet. As a result, the link between food choice and sleep quality may not be as well established as the link between short sleep duration and increased food intake, as discussed in Part 1 and Part 2 of this chapter. That said, emerging research into these fields promises insight into the role that food choice may play in the management of sleep disorders, particularly short sleep, insomnia, and sleep apnea. Impacting both mental and physical quality of life, these sleep disorders have become important public health concerns that warrant further study into preventive strategies. Moreover, sleep disorders may increase the risk of morbidity. Because current medications come with numerous side effects and limited efficacy, lifestyle strategies to improve sleep quality, and duration may be preferable. Based on the best evidence, a balanced and varied diet rich in fresh fruits, vegetables, whole grains, and high-quality protein sources, which contain plenty of tryptophan as well as adequate micronutrients, including several vitamins and minerals, may be a step in the right direction. Yet, in order to recommend these changes with confidence, further interventional research is needed to bring us closer to a defined conclusion.

References

- [1] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M, Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep* 2015;38(6):843–4. <https://doi.org/10.5665/sleep.4716>.
- [2] Dashti HS, Scheer FAJL, Jacques PF, Lamon-Fava S, Ordovás JM. Short sleep duration and dietary intake: epidemiologic evidence, mechanisms, and health implications. *Adv Nutr* 2015;6(6):648–59. <https://doi.org/10.3945/an.115.008623>.
- [3] Ford ES, Cunningham TJ, Croft JB. Trends in self-reported sleep duration among US adults from 1985 to 2012. *Sleep* 2015;38(5):829–32. <https://doi.org/10.5665/sleep.4684>.
- [4] Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA J Am Med Assoc* 2016;315(21):2284–91. <https://doi.org/10.1001/jama.2016.6458>.
- [5] Bray GA. Medical consequences of obesity. *J Clin Endocrinol Metab* 2004;89(6):2583–9. <https://doi.org/10.1210/jc.2004-0535>.
- [6] Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, Miller MA. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep* 2008;31(5):619–26. <https://doi.org/10.1093/sleep/31.5.619>.
- [7] Chen X, Beydoun MA, Wang Y. Is sleep duration associated with childhood obesity? A systematic review and meta-analysis. *Obesity* 2008;16(2):265–74. <https://doi.org/10.1038/oby.2007.63>.
- [8] Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. *Obesity* 2008;16(3):643–53. <https://doi.org/10.1038/oby.2007.118>.
- [9] Capers PL, Fobian AD, Kaiser KA, Borah R, Allison DB. A systematic review and meta-analysis of randomized controlled trials of the impact of sleep duration on adiposity and components of energy balance. *Obes Rev* 2015;16(9):771–82. <https://doi.org/10.1111/obr.12296>.
- [10] St-Onge M-P. Sleep-obesity relation: underlying mechanisms and consequences for treatment. *Obes Rev* 2017;18:34–9. <https://doi.org/10.1111/obr.12499>.
- [11] Romieu I, Dossus L, Barquera S, Blotière HM, Franks PW, Gunter M, Hwalla N, Hursting SD, Leitzmann M, Margetts B, Nishida C, Potischman N, Seidell J, Stepien M, Wang Y, Westerterp K, Winichagoon P, Wiseman M, Willett WC. Energy balance and obesity: what are the main drivers? *Cancer Causes Control* 2017;28(3):247–58. <https://doi.org/10.1007/s10552-017-0869-z>.
- [12] Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007;11(3):163–78. <https://doi.org/10.1016/j.smrv.2007.01.002>.
- [13] Chaput JP, St-Onge MP. Increased food intake by insufficient sleep in humans: are we jumping the gun on the hormonal explanation? *Front Endocrinol* 2014;5. <https://doi.org/10.3389/fendo.2014.00116>.
- [14] Lundahl A, Nelson TD. Sleep and food intake: a multisystem review of mechanisms in children and adults. *J Health Psychol* 2015;20(6):794–805. <https://doi.org/10.1177/1359105315573427>.
- [15] Geiker NRW, Astrup A, Hjorth MF, Sjödin A, Pijls L, Markus CR. Does stress influence sleep patterns, food intake, weight gain, abdominal obesity and weight loss interventions and vice versa? *Obes Rev* 2018;19(1):81–97. <https://doi.org/10.1111/obr.12603>.
- [16] Broussard JL, Cauter EV. Disturbances of sleep and circadian rhythms: novel risk factors for obesity. *Curr Opin Endocrinol*

- Diabetes Obes 2016;23(5):353–9. <https://doi.org/10.1097/MED.0000000000000276>.
- [17] Kearney J. Food consumption trends and drivers. *Phil Trans Biol Sci* 2010;365(1554):2793–807. <https://doi.org/10.1098/rstb.2010.0149>.
- [18] Haghishatdoost F, Karimi G, Esmailzadeh A, Azadbakht L. Sleep deprivation is associated with lower diet quality indices and higher rate of general and central obesity among young female students in Iran. *Nutrition* 2012;28(11–12):1146–50. <https://doi.org/10.1016/j.nut.2012.04.015>.
- [19] Patterson RE, Emond JA, Natarajan L, Wesseling-Perry K, Kolonel LN, Jardack P, Ancoli-Israel S, Arab L. Short sleep duration is associated with higher energy intake and expenditure among African-American and non-hispanic white adults. *J Nutr* 2014;144(4):461–6. <https://doi.org/10.3945/jn.113.186890>.
- [20] Stern JH, Grant AS, Thomson CA, Tinker L, Hale L, Brennan KM, Woods NF, Chen Z. Short sleep duration is associated with decreased serum leptin, increased energy intake and decreased diet quality in postmenopausal women. *Obesity* 2014;22(5):E55. <https://doi.org/10.1002/oby.20683>.
- [21] Al-Disi D, Al-Daghri N, Khanam L, Al-Othman A, Al-Saif M, Sabico S, Chrousos G. Subjective sleep duration and quality influence diet composition and circulating adipocytokines and ghrelin levels in teen-age girls. *Endocr J* 2010;57(10):915–23. <https://doi.org/10.1507/endocrj.k10e-145>.
- [22] Weiss A, Xu F, Storfer-Isser A, Thomas A, Ievers-Landis CE, Redline S. The association of sleep duration with adolescents' fat and carbohydrate consumption. *Sleep* 2010;33(9):1201–9. <https://doi.org/10.1093/sleep/33.9.1201>.
- [23] Westerlund L, Ray C, Roos E. Associations between sleeping habits and food consumption patterns among 10–11-year-old children in Finland. *Br J Nutr* 2009;102(10):1531–7. <https://doi.org/10.1017/s0007114509990730>.
- [24] Moreira P, Santos S, Padrão P, Cordeiro T, Bessa M, Valente H, Barros R, Teixeira V, Mitchell V, Lopes C, Moreira A. Food patterns according to sociodemographics, physical activity, sleeping and obesity in Portuguese children. *Int J Environ Res Publ Health* 2010;7(3):1121–38. <https://doi.org/10.3390/ijerph7031121>.
- [25] Grandner MA, Kripke DF, Naidoo N, Langer RD. Relationships among dietary nutrients and subjective sleep, objective sleep, and napping in women. *Sleep Med* 2010;11(2):180–4. <https://doi.org/10.1016/j.sleep.2009.07.014>.
- [26] Grandner MA, Jackson N, Gerstner JR, Knutson KL. Dietary nutrients associated with short and long sleep duration. Data from a nationally representative sample. *Appetite* 2013;64:71–80. <https://doi.org/10.1016/j.appet.2013.01.004>.
- [27] Doo H, Chun H, Doo M. Associations of daily sleep duration and dietary macronutrient consumption with obesity and dyslipidemia in Koreans A cross-sectional study. *Medicine* 2016;95(45). <https://doi.org/10.1097/MD.0000000000005360>.
- [28] Doo M, Kim Y. Association between sleep duration and obesity is modified by dietary macronutrients intake in Korean. *Obes Res Clin Pract* 2016;10(4):424–31. <https://doi.org/10.1016/j.orcp.2015.08.010>.
- [29] Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. *Am J Clin Nutr* 2009;89(1):126–33. <https://doi.org/10.3945/ajcn.2008.26574>.
- [30] St-Onge MP, O'Keeffe M, Roberts AL, RoyChoudhury A, Laferrère B. Short sleep duration, glucose dysregulation and hormonal regulation of appetite in men and women. *Sleep* 2012;35(11):1503–10. <https://doi.org/10.5665/sleep.2198>.
- [31] Spaeth AM, Dinges DF, Goel N. Sex and race differences in caloric intake during sleep restriction in healthy adults. *Am J Clin Nutr* 2014;100(2):559–66. <https://doi.org/10.3945/ajcn.114.086579>.
- [32] Calvin AD, Carter RE, Adachi T, MacEdo PG, Albuquerque FN, Van Der Walt C, Bukartyk J, Davison DE, Levine JA, Somers VK. Effects of experimental sleep restriction on caloric intake and activity energy expenditure. *Chest* 2013;144(1):79–86. <https://doi.org/10.1378/chest.12-2829>.
- [33] Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, Wright KP. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Nat Acad Sci U S A* 2013;110(14):5695–700. <https://doi.org/10.1073/pnas.1216951110>.
- [34] Brondel L, Romer MA, Nouges PM, Touyarou P, Davenne D. Acute partial sleep deprivation increases food intake in healthy men. *Am J Clin Nutr* 2010;91(6):1550–9. <https://doi.org/10.3945/ajcn.2009.28523>.
- [35] Al Khatib HK, Harding SV, Darzi J, Pot GK. The effects of partial sleep deprivation on energy balance: a systematic review and meta-analysis. *Eur J Clin Nutr* 2017;71(5):614–24. <https://doi.org/10.1038/ejcn.2016.201>.
- [36] St-Onge MP, Roberts AL, Chen J, Kelleman M, O'Keeffe M, RoyChoudhury A, Jones PJH. Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. *Am J Clin Nutr* 2011;94(2):410–6. <https://doi.org/10.3945/ajcn.111.013904>.
- [37] Schmid SM, Hallschmid M, Jauch-Chara K, Wilms B, Benedict C, Lehnert H, Born J, Schultes B. Short-term sleep loss decreases physical activity under free-living conditions but does not increase food intake under time-deprived laboratory conditions in healthy men. *Am J Clin Nutr* 2009;90(6):1476–82. <https://doi.org/10.3945/ajcn.2009.27984Germany>.
- [38] Hogenkamp PS, Nilsson E, Nilsson VC, Chapman CD, Vogel H, Lundberg LS, Zarei S, Cedernaes J, Rångtell FH, Broman JE, Dickson SL, Brunstrom JM, Benedict C, Schiöth HB. Acute sleep deprivation increases portion size and affects food choice in young men. *Psychoneuroendocrinology* 2013;38(9):1668–74. <https://doi.org/10.1016/j.psyneuen.2013.01.012>.
- [39] Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004;141(11):846–50. <https://doi.org/10.7326/0003-4819-141-11-200412070-00008>.
- [40] Ahima RS, Saper CB, Flier JS, Elmquist JK. Leptin regulation of neuroendocrine systems. *Front Neuroendocrinol* 2000;21(3):263–307. <https://doi.org/10.1006/fnre.2000.0197>.
- [41] Van Der Lely AJ, Tschöp M, Heiman ML, Ghigo E. Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. *Endocr Rev* 2004;25(3):426–57. <https://doi.org/10.1210/er.2002-0029>.
- [42] Bosy-Westphal A, Hinrichs S, Jauch-Chara K, Hitze B, Later W, Wilms B, Settler U, Peters A, Kiosz D, Müller MJ. Influence of partial sleep deprivation on energy balance and insulin sensitivity

- in healthy women. *Obes Facts* 2008;1(5):266–73. <https://doi.org/10.1159/000158874>.
- [43] Omisade A, Buxton OM, Rusak B. Impact of acute sleep restriction on cortisol and leptin levels in young women. *Physiol Behav* 2010;99(5):651–6. <https://doi.org/10.1016/j.physbeh.2010.01.028>.
- [44] Pejovic S, Vgontzas AN, Basta M, Tsiaoussoglou M, Zoumakis E, Vgontzas A, Bixler EO, Chrousos GP. Leptin and hunger levels in young healthy adults after one night of sleep loss. *J Sleep Res* 2010;19(4):552–8. <https://doi.org/10.1111/j.1365-2869.2010.00844.x>.
- [45] Simpson NS, Banks S, Dinges DF. Sleep restriction is associated with increased morning plasma leptin concentrations, especially in women. *Biol Res Nurs* 2010;12(1):47–53. <https://doi.org/10.1177/1099800410366301>.
- [46] St-Onge MP. The role of sleep duration in the regulation of energy balance: effects on energy intakes and expenditure. *J Clin Sleep Med* 2013;9(1):73–80. <https://doi.org/10.5664/jcsm.2348>.
- [47] Shah M, Vella A. Effects of GLP-1 on appetite and weight. *Rev Endocr Metab Disord* 2014;15(3):181–7. <https://doi.org/10.1007/s11154-014-9289-5>.
- [48] Vincent RP, Le Roux CW. The satiety hormone peptide YY as a regulator of appetite. *J Clin Pathol* 2008;61(5):548–52. <https://doi.org/10.1136/jcp.2007.048488>.
- [49] Gil-Lozano M, Hunter PM, Behan L-A, Gladanac B, Casper RF, Brubaker PL. Short-term sleep deprivation with nocturnal light exposure alters time-dependent glucagon-like peptide-1 and insulin secretion in male volunteers. *Am J Physiol Endocrinol Metabol* 2016;310(1):E41. <https://doi.org/10.1152/ajpendo.00298.2015>.
- [50] Benedict C, Barclay JL, Ott V, Oster H, Hallschmid M. Acute sleep deprivation delays the glucagon-like peptide 1 peak response to breakfast in healthy men. *Nutr Diabetes* 2013;3(JUNE). <https://doi.org/10.1038/nutd.2013.20>.
- [51] Sivik M. Sleeping more as a way to lose weight. *Obes Rev* 2006;7 (3):295–6. <https://doi.org/10.1111/j.1467-789X.2006.00262.x>.
- [52] Rollins BY, Dearing KK, Epstein LH. Delay discounting moderates the effect of food reinforcement on energy intake among non-obese women. *Appetite* 2010;55(3):420–5. <https://doi.org/10.1016/j.appet.2010.07.014>.
- [53] Benedict C. Acute sleep deprivation enhances the brain's response to hedonic food stimuli: an fMRI study. *J Clin Endocrinol Metab* 2012;97(3):443–7.
- [54] St-Onge M-P, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. *Int J Obes* 2014;38(3):411–6. <https://doi.org/10.1038/ijo.2013.114>.
- [55] Davis C, Strachan S, Berkson M. Sensitivity to reward: implications for overeating and overweight. *Appetite* 2004;42(2):131–8. <https://doi.org/10.1016/j.appet.2003.07.004>.
- [56] Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. *J Abnorm Psychol* 2008;117(4):924–35. <https://doi.org/10.1037/a0013600>.
- [57] Patrick GTW, Allen Gilbert J. Studies from the psychological laboratory of the University of Iowa: on the effects of loss of sleep. *Psychol Rev* 1896;3(5):469–83. <https://doi.org/10.1037/h0075739>.
- [58] Goel N, Rao H, Durmer J, Dinges D. Neurocognitive consequences of sleep deprivation. *Semin Neurol* 2009;29 (04):320–39. <https://doi.org/10.1055/s-0029-1237117>.
- [59] Nilsson JP, Söderström M, Karlsson AU, Lekander M, Åkerstedt T, Lindroth NE, Axelsson J. Less effective executive functioning after one night's sleep deprivation. *J Sleep Res* 2005;14(1):1–6. <https://doi.org/10.1111/j.1365-2869.2005.00442.x>.
- [60] Beebe DW, Fallone G, Godiwala N, Flanigan M, Martin D, Schaffner L, Amin R. Feasibility and behavioral effects of an at-home multi-night sleep restriction protocol for adolescents. *J Child Psychol Psychiatry Allied Discip* 2008;49(9):915–23. <https://doi.org/10.1111/j.1469-7610.2008.01885.x>.
- [61] Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res* 2003;12 (1):1–12. <https://doi.org/10.1046/j.1365-2869.2003.00337.x>.
- [62] Harrison Y, Horne JA. The impact of sleep deprivation on decision making: a review. *J Exp Psychol Appl* 2000;6(3):236–49. <https://doi.org/10.1037/1076-898X.6.3.236>.
- [63] Anderson C, Platten CR. Sleep deprivation lowers inhibition and enhances impulsivity to negative stimuli. *Behav Brain Res* 2011;217(2):463–6. <https://doi.org/10.1016/j.bbr.2010.09.020>.
- [64] Drummond SPA, Paulus MP, Tapert SF. Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. *J Sleep Res* 2006;15(3):261–5. <https://doi.org/10.1111/j.1365-2869.2006.00535.x>.
- [65] Calvo D, Galioto R, Gunstad J, Spitznagel MB. Uncontrolled eating is associated with reduced executive functioning. *Clin Obes* 2014;4(3):172–9. <https://doi.org/10.1111/cob.12058>.
- [66] Wolkow A, Ferguson S, Aisbett B, Main L. Effects of work-related sleep restriction on acute physiological and psychological stress responses and their interactions: a review among emergency service personnel. *Int J Occup Med Environ Health* 2016;28 (2):183–208. <https://doi.org/10.13075/ijomeh.1896.00227>.
- [67] Zhu L-J, Liu M-Y, Li H, Liu X, Chen C, Han Z, Wu H-Y, Jing X, Zhou H-H, Suh H, Zhu D-Y, Zhou Q-G, Homberg J. The different roles of glucocorticoids in the hippocampus and hypothalamus in chronic stress-induced HPA axis hyperactivity. *PLoS One* 2014;9 (5):e97689. <https://doi.org/10.1371/journal.pone.0097689>.
- [68] Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: from physiological to pathological conditions. *Sleep Sci* 2015;8(3):143–52. <https://doi.org/10.1016/j.slsci.2015.09.002>.
- [69] Meerlo P, Koehl M, Van Der Borght K, Turek FW. Sleep restriction alters the hypothalamic-pituitary-adrenal response to stress. *J Neuroendocrinol* 2002;14(5):397–402. <https://doi.org/10.1046/j.0007-1331.2002.00790.x>.
- [70] Meerlo P, Sgoifo A, Suczeki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Med Rev* 2008;12(3):197–210. <https://doi.org/10.1016/j.smrv.2007.07.007>.
- [71] Born JM, Lemmens SGT, Rutters F, Nieuwenhuizen AG, Formisano E, Goebel R, Westerterp-Plantenga MS. Acute stress and food-related reward activation in the brain during food choice during eating in the absence of hunger. *Int J Obes* 2010;34 (1):172–81. <https://doi.org/10.1038/ijo.2009.221>.
- [72] Lemmens SG, Rutters F, Born JM, Westerterp-Plantenga MS. Stress augments food 'wanting' and energy intake in visceral overweight subjects in the absence of hunger. *Physiol Behav*

- 2011;103(2):157–63. <https://doi.org/10.1016/j.physbeh.2011.01.009>.
- [73] Chaput JP, Drapeau V, Poirier P, Teasdale N, Tremblay A. Glycemic instability and spontaneous energy intake: association with knowledge-based work. *Psychosom Med* 2008;70(7):797–804. <https://doi.org/10.1097/PSY.0b013e31818426fa>.
- [74] Rutters F, Nieuwenhuizen AG, Lemmens SGT, Born JM, Westerterp-Plantenga MS. Acute stress-related changes in eating in the absence of hunger. *Obesity* 2009;17(1):72–7. <https://doi.org/10.1038/oby.2008.493>.
- [75] Epel E, Lapidus R, McEwen B, Brownell K. Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. *Psychoneuroendocrinology* 2001;26(1):37–49. [https://doi.org/10.1016/s0306-4530\(00\)00035-4](https://doi.org/10.1016/s0306-4530(00)00035-4).
- [76] Hanlon EC, Tasali E, Leproult R, Stuhr KL, Doncheck E, De Wit H, Hillard CJ, Van Cauter E. Circadian rhythm of circulating levels of the endocannabinoid 2 arachidonoylglycerol. *J Clin Endocrinol Metab* 2015;100(1):220–6. <https://doi.org/10.1210/jc.2014-3455>.
- [77] Hanlon EC, Tasali E, Leproult R, Stuhr KL, Doncheck E, De Wit H, Hillard CJ, Van Cauter E. Sleep restriction enhances the daily rhythm of circulating levels of endocannabinoid 2-arachidonoylglycerol. *Sleep* 2016;39(3):653–64. <https://doi.org/10.5665/sleep.5546>.
- [78] Tanaka E, Yatsuya H, Uemura M, Murata C, Otsuka R, Toyoshima H, Tamakoshi K, Sasaki S, Kawaguchi L, Aoyama A. Associations of protein, fat, and carbohydrate intakes with insomnia symptoms among middle-aged Japanese workers. *J Epidemiol* 2013;23(2):132–8. <https://doi.org/10.2188/jeaj.e20120101>.
- [79] Tan X, Alén M, Cheng SM, Mikkola TM, Tenhunen J, Lytykäinen A, Wiklund P, Cong F, Saarinen A, Tarkka I, Partinen M, Cheng S. Associations of disordered sleep with body fat distribution, physical activity and diet among overweight middle-aged men. *J Sleep Res* 2015;24(4):414–24. <https://doi.org/10.1111/jsr.12283>.
- [80] Jaussent I, Dauvilliers Y, Ancelin M-L, Dartigues J-F, Tavernier B, Touchon J, Ritchie K, Berset A. Insomnia symptoms in older adults: associated factors and gender differences. *Am J Geriatr Psychiatr* 2011;19(1):88–97. <https://doi.org/10.1097/jgp.0b013e3181e049b6>.
- [81] Katagiri R, Asakura K, Kobayashi S, Suga H, Sasaki S. Low intake of vegetables, high intake of confectionary, and unhealthy eating habits are associated with poor sleep quality among middle-aged female Japanese workers. *J Occup Health* 2014;56(5):359–68. <https://doi.org/10.1539/joh.14-0051-oa>.
- [82] Peuhkuri K, Sihvola N, Korpela R. Dietary factors and fluctuating levels of melatonin. *Food Nutr Res* 2012;56:2012.
- [83] Sauchelli S, Jiménez-Murcia S, Sánchez I, Riesco N, Custal N, Fernández-García JC, Garrido-Sánchez L, Tinahones FJ, Steiger H, Israel M, Baños RM, Botella C, de la Torre R, Fernández-Real JM, Ortega FJ, Frühbeck G, Granero R, Tárrega S, Crujeiras AB, Rodríguez A, Estivill X, Beckmann JS, Casanueva FF, Menchón JM, Fernández-Aranda F. Orexin and sleep quality in anorexia nervosa: clinical relevance and influence on treatment outcome. *Psychoneuroendocrinology* 2016;65:102–8. <https://doi.org/10.1016/j.psyneuen.2015.12.014>.
- [84] Halson SL. Sleep in elite athletes and nutritional interventions to enhance sleep. *Sports Med* 2014;44(1):S13. <https://doi.org/10.1007/s40279-014-0147-0>.
- [85] Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005;437(7063):1257–63. <https://doi.org/10.1038/nature04284>.
- [86] Markus CR, Firk C, Gerhardt C, Kloek J, Smolders GJF. Effect of different tryptophan sources on amino acids availability to the brain and mood in healthy volunteers. *Psychopharmacology* 2008;201(1):107–14. <https://doi.org/10.1007/s00213-008-1254-0>.
- [87] Silber BY, Schmitt JA. Effects of tryptophan loading on human cognition, mood, and sleep. *Neurosci Biobehav Rev* 2010;34(3):387–407. <https://doi.org/10.1016/j.neubiorev.2009.08.005>.
- [88] Esteban S, Nicolaus C, Garmundi A, Rial RV, Rodríguez AB, Ortega E, Ibars CB. Effect of orally administered L-tryptophan on serotonin, melatonin, and the innate immune response in the rat. *Mol Cell Biochem* 2004;267(1–2):39–46. <https://doi.org/10.1023/B:MCBI.0000049363.97713.74>.
- [89] Andreas S, Hajak G, Natt P, Auge D, Ruther E, Kreuzer H. ST Strecken Veränderungen und Rhythmusstörungen bei obstruktiver Schlafapnoe. *Pneumologie* 1991;45(9):720–4.
- [90] Bravo R, Matito S, Cubero J, Paredes SD, Franco L, Rivero M, Rodríguez AB, Barriga C. Tryptophan-enriched cereal intake improves nocturnal sleep, melatonin, serotonin, and total antioxidant capacity levels and mood in elderly humans. *Age* 2013;35(4):1277–85. <https://doi.org/10.1007/s11357-012-9419-5>.
- [91] Behall KM, Howe JC. Effect of long-term consumption of amylose vs amylopectin starch on metabolic variables in human subjects. *Am J Clin Nutr* 1995;61(2):334–40. <https://doi.org/10.1093/ajcn/61.2.334>.
- [92] Lyons PM, Truswell AS. Serotonin precursor influenced by type of carbohydrate meal in healthy adults. *Am J Clin Nutr* 1988;47(3):433–9. <https://doi.org/10.1093/ajcn/47.3.433>.
- [93] Porter JM, Horne JA. Bed-time food supplements and sleep: effects of different carbohydrate levels. *Electroencephalogr Clin Neurophysiol* 1981;51(4):426–33. [https://doi.org/10.1016/0013-4694\(81\)90106-1](https://doi.org/10.1016/0013-4694(81)90106-1).
- [94] Afaghi A, O'Connor H, Chow CM. High-glycemic-index carbohydrate meals shorten sleep onset. *Am J Clin Nutr* 2007;85(2):426–30. <https://doi.org/10.1093/ajcn/85.2.426>.
- [95] Lindseth G, Lindseth P, Thompson M. Nutritional effects on sleep. *West J Nurs Res* 2013;35(4):497–513. <https://doi.org/10.1177/0193945911416379>.
- [96] Kwan RMF, Thomas S, Mir MA. Effects of a low carbohydrate isoenergetic diet on sleep behavior and pulmonary functions in healthy female adult humans. *J Nutr* 1986;116(12):2393–402. <https://doi.org/10.1093/jn/116.12.2393>.
- [97] St-Onge MP, Crawford A, Aggarwal B. Plant-based diets: reducing cardiovascular risk by improving sleep quality? *Curr Sleep Med Rep* 2018;4(1):74–8. <https://doi.org/10.1007/s40675-018-0103-x>.
- [98] Roky R, Chapotot F, Hakkou F, Taoudi Bencherkoun M, Buguet A. Sleep during Ramadan intermittent fasting. *J Sleep Res* 2001;10(4):319–27. <https://doi.org/10.1046/j.1365-2869.2001.00269.x>.
- [99] Cao Y, Taylor AW, Pan X, Adams R, Appleton S, Shi Z. Dinner fat intake and sleep duration and self-reported sleep parameters over five years: findings from the Jiangsu Nutrition Study of

- Chinese adults. *Nutrition* 2016;32(9):970–4. <https://doi.org/10.1016/j.nut.2016.02.012>.
- [100] Baron KG, Reid KJ, Horn LV, Zee PC. Contribution of evening macronutrient intake to total caloric intake and body mass index. *Appetite* 2013;60(1):246–51. <https://doi.org/10.1016/j.appet.2012.09.026>.
- [101] Wells AS, Read NW, Idzikowski C, Jones J. Effects of meals on objective and subjective measures of daytime sleepiness. *J Appl Physiol* 1998;84(2):507–15. <https://doi.org/10.1152/jappl.1998.84.2.507>.
- [102] Mackiewicz M, Shockley KR, Romer MA, Galante RJ, Zimmerman JE, Naidoo N, Baldwin DA, Jensen ST, Churchill GA, Pack AI. Macromolecule biosynthesis: a key function of sleep. *Physiol Genom* 2007;31(3):441–57. <https://doi.org/10.1152/physiolgenomics.00275.2006>.
- [103] Kidd PM. Omega-3 DHA and EPA for cognition, behavior, and mood: clinical findings and structural-functional synergies with cell membrane phospholipids. *Alternative Med Rev* 2007;12(3):207–27.
- [104] Montgomery P, Burton JR, Sewell RP, Spreckelsen TF, Richardson AJ. Fatty acids and sleep in UK children: subjective and pilot objective sleep results from the DOLAB study – a randomized controlled trial. *J Sleep Res* 2014;23(4):364–88. <https://doi.org/10.1111/jsr.12135>.
- [105] Peuhkuri K, Sihvola N, Korpela R. Diet promotes sleep duration and quality. *Nutr Res* 2012;32(5):309–19. <https://doi.org/10.1016/j.nutres.2012.03.009>.
- [106] Valtonen M, Niskanen L, Kangas AP, Koskinen T. Effects of melatonin-rich night-time milk on sleep and activity in elderly institutionalized subjects. *Nord J Psychiatr* 2005;59(3):217–21. <https://doi.org/10.1080/08039480510023034>.
- [107] Lin HH, Tsai PS, Fang SC, Liu JF. Effect of kiwifruit consumption on sleep quality in adults with sleep problems. *Asia Pac J Clin Nutr* 2011;20(2):169–74.
- [108] Tsaluchidou S, Cocchi M, Tonello L, Puri BK. Fatty acids and oxidative stress in psychiatric disorders. *BMC Psychiatry* 2008;8(S1). <https://doi.org/10.1186/1471-244X-8-s1-s5>.
- [109] Reiter RJ, Paredes SD, Manchester LC, Tan D-X. Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. *Crit Rev Biochem Mol Biol* 2009;44(4):175–200. <https://doi.org/10.1080/10409230903044914>.
- [110] Srinivasan V, Pandi-Perumal SR, Trahkt I, Warren Spence D, Poeggeler B, Hardeland R, Cardinali DP. Melatonin and melatonergic drugs on sleep: possible mechanisms of action. *Int J Neurosci* 2009;119(6):821–46. <https://doi.org/10.1080/00207450802328607>.
- [111] Wehr TA, Duncan WC, Sher L, Aeschbach D, Schwartz PJ, Turner EH, Postolache TT, Rosenthal NE. A circadian signal of change of season in patients with seasonal affective disorder. *Arch Gen Psychiatry* 2001;58(12):1108–14. <https://doi.org/10.1001/archpsyc.58.12.1108>.
- [112] Meng X, Li Y, Li S, Zhou Y, Gan R-Y, Xu D-P, Li H-B. Dietary sources and bioactivities of melatonin. *Nutrients* 2017;9(4):367. <https://doi.org/10.3390/nu9040367>.
- [113] Robert Auger R, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). An update for 2015. *J Clin Sleep Med* 2015;11(10):1199–236. <https://doi.org/10.5664/jcsm.5100>.
- [114] Schutte-Rodin SL, Broch L, Buysee D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008;4(5):487–504. <https://doi.org/10.5664/jcsm.27286>.
- [115] Robinson CR, Pegram GV, Hyde PR, Beaton JM, Smythies JR. The effects of nicotinamide upon sleep in humans. *Biol Psychiatry* 1977;12(1):139–43.
- [116] Setchell KDR, Cassidy A. Dietary isoflavones: biological effects and relevance to human health. *J Nutr* 1999;129(3):758S. <https://doi.org/10.1093/jn/129.3.758s>.
- [117] Hachul H, Brandão LC, D’Almeida V, Bittencourt LRA, Baracat EC, Tufik S. Isoflavones decrease insomnia in post-menopause. *Menopause* 2011;18(2):178–84. <https://doi.org/10.1097/gme.0b013e3181ecf9b9>.
- [118] Cui Y, Niu K, Huang C, Momma H, Guan L, Kobayashi Y, Guo H, Chujo M, Otomo A, Nagatomi R. Relationship between daily isoflavone intake and sleep in Japanese adults: a cross-sectional study. *Nutr J* 2015;14(1). <https://doi.org/10.1186/s12937-015-0117-x>.
- [119] Altura BM. Basic biochemistry and physiology of magnesium: a brief review. *Magnes Trace Elem* 1991;10(2–4):167–71.
- [120] Abbasi B, Kimiagar M, Sadeghniiat K, Shirazi MM, Hedayati M, Rashidkhani B. The effect of magnesium supplementation on primary insomnia in elderly: a double-blind placebo-controlled clinical trial. *J Res Med Sci* 2012;17(12):1161–9.
- [121] Zeng Y, Yang J, Du J, Pu X, Yang X, Yang S, Yang T. Strategies of functional foods promote sleep in human being. *Curr Signal Transduct Ther* 2014;9(3):148–55. <https://doi.org/10.2174/1574362410666150205165504>.
- [122] Howatson G, Bell PG, Tallent J, Middleton B, McHugh MP, Ellis J. Effect of tart cherry juice (*Prunus cerasus*) on melatonin levels and enhanced sleep quality. *Eur J Nutr* 2012;51(8):909–16. <https://doi.org/10.1007/s00394-011-0263-7>.
- [123] Reiter RJ, Manchester LC, Tan DX. Melatonin in walnuts: influence on levels of melatonin and total antioxidant capacity of blood. *Nutrition* 2005;21(9):920–4. <https://doi.org/10.1016/j.nut.2005.02.005>.
- [124] Brennan AM, Sweeney LL, Liu X, Mantzoros CS. Walnut consumption increases satiation but has no effect on insulin resistance or the metabolic profile over a 4-day period. *Obesity* 2010;18(6):1176–82. <https://doi.org/10.1038/oby.2009.409>.
- [125] Bent S, Padula A, Moore D, Patterson M, Mehling W. Valerian for sleep: a systematic review and meta-analysis. *Am J Med* 2006;119(12):1005–12. <https://doi.org/10.1016/j.amjmed.2006.02.026>.
- [126] Wheatley D. Medicinal plants for insomnia: a review of their pharmacology, efficacy and tolerability. *J Psychopharmacol* 2005;19(4):414–21. <https://doi.org/10.1177/0269881105053309>.
- [127] Donath F, Quispe S, Diefenbach K, Maurer A, Fietze I, Roots I. Critical evaluation of the effect of valeren extract on sleep structure and sleep quality. *Pharmacopsychiatry* 2000;33(2):47–53. <https://doi.org/10.1055/s-2000-7972>.
- [128] Diaper A, Hindmarch I. A double-blind, placebo-controlled investigation of the effects of two doses of a valeren preparation on the sleep, cognitive and psychomotor function of sleep-

- disturbed older adults. *Phytother Res* 2004;18(10):831–6. <https://doi.org/10.1002/ptr.1574>.
- [129] Hallam KT, Olver JS, McGrath C, Norman TR. Comparative cognitive and psychomotor effects of single doses of Valeriana officianalis and triazolam in healthy volunteers. *Hum Psychopharmacol* 2003;18(8):619–25. <https://doi.org/10.1002/hup.542>.
- [130] Leathwood PD, Chauffard F, Heck E, Munoz-Box R. Aqueous extract of valerian root (Valeriana officinalis L.) improves sleep quality in man. *Pharmacol Biochem Behav* 1982;17(1):65–71. [https://doi.org/10.1016/0091-3057\(82\)90264-7](https://doi.org/10.1016/0091-3057(82)90264-7).
- [131] Jacobs BP, Bent S, Tice JA, Blackwell T, Cummings SR. An internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. *Medicine* 2005;84(4):197–207. <https://doi.org/10.1097/01.md.0000172299.72364.95>.
- [132] Isabel Fernández-San-Martín M, Masa-Font R, Palacios-Soler L, Sancho-Gómez P, Calbó-Caldentey C, Flores-Mateo G. Effectiveness of Valerian on insomnia: a meta-analysis of randomized placebo-controlled trials. *Sleep Med* 2010;11(6):505–11. <https://doi.org/10.1016/j.sleep.2009.12.009>.
- [133] Morin CM, Benca R. Chronic insomnia. *Lancet* 2012;379 (9821):1129–41. [https://doi.org/10.1016/S0140-6736\(11\)60750-2](https://doi.org/10.1016/S0140-6736(11)60750-2).
- [134] Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American academy of sleep medicine clinical practice guideline. *J Clin Sleep Med* 2017;13 (2):307–49. <https://doi.org/10.5664/jcsm.6470>.
- [135] Wheatley D. Kava and Valerian in the treatment of stress-induced insomnia. *Phytother Res* 2001;15(6):549–51. <https://doi.org/10.1002/ptr.840>.
- [136] Yurcheshen M, Seehuus M, Pigeon W. Updates on nutraceutical sleep therapeutics and investigational research. *Evid-Based Complement Altern Med* 2015;2015:1–9. <https://doi.org/10.1155/2015/105256>.
- [137] Rowe A, Narlawar R, Groundwater PW, Ramzan I. Kavalactone pharmacophores for major cellular drug targets. *Mini Rev Med Chem* 2011;11(1):79–83. <https://doi.org/10.2174/138955711793564088>.
- [138] Castro-Quezada I, Román-Viñas B, Serra-Majem L. The mediterranean diet and nutritional adequacy: a review. *Nutrients* 2014;6 (1):231–48. <https://doi.org/10.3390/nu6010231>.
- [139] Jara Pérez-Jiménez M, Díaz-Rubio E, Saura-Calixto F. Contribution of macromolecular antioxidants to dietary antioxidant capacity: a study in the Spanish Mediterranean diet. *Plant Foods Hum Nutr* 2015;70(4):365–70. <https://doi.org/10.1007/s11130-015-0513-6>.
- [140] Estruch R. Anti-inflammatory effects of the Mediterranean diet: the experience of the PREDIMED study. *Proc Nutr Soc* 2010;69 (3):333–40. <https://doi.org/10.1017/s0029665110001539>.
- [141] Campanini MZ, Guallar-Castillón P, Rodríguez-Artalejo F, Lopez-García E. Mediterranean diet and changes in sleep duration and indicators of sleep quality in older adults. *Sleep* 2017;40(3). <https://doi.org/10.1093/sleep/zsw083>.
- [142] Hurt RT, Kulisek C, Buchanan LA, McClave SA. The obesity epidemic: challenges, health initiatives, and implications for gastroenterologists. *Gastroenterol Hepatol* 2010;6(12):780–92.
- [143] St-Onge MP, Cherta-Murillo A, Darimont C, Mantantzis K, Martin FP, Owen L. The interrelationship between sleep, diet, and glucose metabolism. *Sleep Med Rev* 2023;69:1017888. PMC10229376.

This page intentionally left blank

Chapter 23

Sleep and exercise

Christopher E. Kline

Physical Activity Research Center, Department of Health and Human Development, University of Pittsburgh, Pittsburgh, PA, United States

Exercise and sleep are interrelated behaviors that are each vital to optimal health and functioning. There has long been a consensus that exercise improves sleep, and accumulating evidence highlights the potential for exercise as a nonpharmacologic treatment option for disturbed sleep. Recent research has also emphasized that disturbed or insufficient sleep may impact physical activity levels. Together, these studies suggest a robust bidirectional relationship between exercise and sleep.

This chapter will provide an overview regarding the available research on the relationship between sleep and exercise. The majority of the chapter will review the impact of exercise on sleep, focusing on experimental research in adults with and without sleep disorders and discussing potential mechanisms of effect. The chapter will also discuss recent research on the bidirectional relationship between exercise and sleep and will conclude with a brief discussion regarding the potential synergistic impact of improving sleep and exercise on health.

Impact of exercise on sleep

Exercise has long been associated with better sleep [1] and is one of the most common sleep hygiene recommendations [2]. There are a number of reasons why exercise is an attractive nonpharmacologic alternative for treating disturbed sleep. Exercise is a relatively inexpensive, simple, and easily accessible treatment modality. Exercise does not possess the side effects (e.g., hypnotic medications), low acceptability (e.g., positive airway pressure), and/or barriers to access (e.g., cognitive-behavioral therapy for insomnia) that plague many of the standard sleep medicine treatments. Finally, exercise confers a number of mental and physical health benefits [3] that are independent of its effects on sleep, which is notable given the daytime impairment and comorbid health conditions that commonly plague those with disturbed sleep.

Observational research

Observational research involving cross-sectional samples and prospective epidemiologic cohorts has frequently reported a robust association between exercise and better sleep [1]. In general, higher levels of physical activity have been consistently associated with a lower likelihood of reporting insufficient sleep, general sleep disturbance, or insomnia symptoms [4,5]. These studies have traditionally relied upon self-reported (and often unvalidated) measures of leisure-time physical activity and sleep [1]. However, recent research involving objective assessment of exercise, fitness, and/or sleep has supported these earlier findings. For example, Dishman and colleagues found that the preservation of objectively measured cardiorespiratory fitness, a physiological measure that is strongly influenced by physical activity, was protective against the onset of self-reported sleep complaints in a sample of middle-aged adults [6]. Kline and colleagues reported that greater amounts of self-reported leisure-time physical activity were associated with better self-reported and polysomnographic (PSG) measures of sleep quality, continuity, and depth in a sample of middle-aged women [7]. More recently, studies have linked greater amounts of accelerometer-measured physical activity with higher accelerometer-measured sleep efficiency [8] and a moderate level of self-reported activity with lower incidence of PSG-measured short sleep duration and low sleep efficiency [9]. Overall, the finding that higher levels of physical activity are associated with better sleep has been consistent regardless of age, sex, and race, and across a wide range of sample sizes [1].

Observational research offers a number of advantages when examining the association between exercise and sleep, including the ability to explore relationships in potentially large samples with wide variability in sleep and activity habits. In addition, with observational research, it is possible to examine whether and how potential confounding factors (e.g., age and health status) influence the

association between exercise and sleep. However, because of the common expectation that exercise improves sleep, observational research that is limited to self-report measures may simply reflect this assumption [10]. Moreover, since exercise is often discontinued during times of elevated psychosocial stress [11], better sleep on days in which exercise occurs may be more indicative of reduced stress rather than exercise per se. Finally, the link between exercise and sleep could be explained by a variety of factors that are often poorly accounted for in epidemiologic analyses, including other daytime health behaviors [12], light exposure [13], and mental health [14].

Experimental research

Despite the intuitive appeal of exercise and supportive observational evidence of an association between greater amounts of physical activity and better sleep, the majority of experimental research has evaluated the efficacy of exercise for improving sleep in samples without consideration of baseline sleep disturbance. Nevertheless, the available research suggests that both acute exercise and chronic exercise training have mild to modest benefits on sleep among adults with no to mild sleep impairment and more robust effects on those with significant sleep disturbance.

Acute exercise

A large number of studies have examined the effect of an acute bout of exercise on the subsequent night's sleep, often in comparison with an inactive control day. However, the majority of studies have focused on adults without sleep complaints, thereby limiting any room for sleep improvement with exercise [15]. Nevertheless, an acute bout of exercise appears to result in small-to-moderate improvements in sleep, at least among relatively normal sleepers, though the effects may differ according to individual and/or exercise characteristics.

A 2015 meta-analysis of 41 studies found that an acute bout of exercise significantly increases total sleep time (TST; effect size $d = 0.22$), sleep efficiency (SE; $d = 0.25$), and slow-wave sleep (SWS; $d = 0.19$) and decreases sleep onset latency (SOL; $d = -0.17$), wake after sleep onset (WASO; $d = -0.38$), stage 1 nonrapid eye movement (NREM) sleep ($d = -0.35$), and rapid eye movement (REM) sleep ($d = -0.27$) in comparison with a day without exercise [16]. Interestingly, the meta-analysis also found several significant moderators of the effect of acute exercise on specific sleep parameters. Sample characteristics seemed to matter, as acute exercise increased SWS to a greater extent among those with a high baseline activity level compared with those with a low baseline level of activity, and greater reductions in stage 1 NREM

sleep and WASO were observed for men compared with women. Moreover, characteristics of the exercise bout significantly impacted the association between acute exercise and sleep; studies involving cycling resulted in a greater increase in SWS compared with studies involving running, and longer exercise duration was linked to greater increases in TST and SWS and greater reductions in SOL, REM sleep, and REM sleep latency. Participant age and exercise intensity did not moderate any associations, though. Caution is urged regarding the robustness of these potential moderators, since very few studies directly compared these factors for their impact on sleep. Nevertheless, the findings of this meta-analysis suggest that the effects of acute exercise on sleep may vary according to the characteristics of the individual and exercise bout [16].

In contrast to the potential moderators noted above, time of day has often been examined as a moderator of the effect of acute exercise on sleep. In the 2015 meta-analysis by Kredlow and colleagues, exercising <3 h prior to bedtime was associated with greater reductions of WASO and stage 1 NREM sleep, whereas exercising 3–8 h prior to bedtime did not lead to reductions in these sleep parameters [16]. This finding contradicts the common warning provided in sleep hygiene recommendations that exercise should be avoided close to bedtime due to the possibility of sleep impairment [17]. However, epidemiologic and experimental studies have found, with few exceptions [18], that late-night exercise does not impair sleep and, in some cases, improves sleep. For instance, a survey of 1000 adults found that evening exercisers (<4 h before bed) did not differ in any self-reported sleep parameters compared with nonexercisers, with over 90% of individuals who performed vigorous exercise in the evening actually reporting that their sleep was of equal or better quality and duration on days they exercised compared with days without exercise [19]. Likewise, moderate-to-vigorous-intensity exercise ending as close as 30 min before bedtime has not impaired objective or subjective sleep despite causing increases in heart rate and core body temperature that persisted into the early hours of sleep [20]. Other studies have shown better subjective and/or objective sleep following late-night exercise compared with a nonexercise day [21,22]. However, the focus on trained adults without sleep complaints in these experimental studies is a prominent limitation of this literature, as adults who are physically inactive and/or with significant sleep complaints may be more reactive to and/or recover less quickly from late-night exercise than those with high aerobic fitness and healthy sleep. Thus, consistent with the preliminary nature of other potential moderators, the optimal time of day of exercise to improve sleep remains unclear, though active adults without sleep complaints should not avoid late-night exercise for fear of sleep disruption.

Overall, while the small- to moderate-sized effects of acute exercise on sleep may prompt skepticism regarding their practical significance, it is important to reiterate that the vast majority of experimental studies examining acute exercise have focused on adults without sleep complaints. Thus, it is assumed that acute exercise would be even more efficacious among adults with disturbed sleep. Although this does appear to be the case for adults with insomnia (discussed later), future research should focus on the effect of acute exercise in adults with subclinical sleep complaints and/or sleep disorders and probe whether participant characteristics (e.g., age, sex, and activity level) and exercise bout characteristics (e.g., duration, mode, and timing) moderate these effects.

Chronic exercise training

Multiple studies have evaluated whether maintaining an exercise training regimen for a sustained duration of time (e.g., 12 weeks) improves sleep. Unfortunately, similar to studies focused on acute exercise and sleep, until recently most exercise training studies had focused on individuals with relatively normal sleep patterns at baseline; as one might expect, these studies demonstrated only mild, if any, sleep improvements following exercise training [23]. Recent work, noted below, has provided more robust evidence that exercise training improves sleep among those with significant sleep disturbance.

Meta-analyses of exercise training studies have reported significant effects of exercise training on multiple sleep parameters. In addition to reviewing the literature on the effect of acute exercise on sleep, Kredlow and colleagues also evaluated 25 exercise training studies in their 2015 meta-analysis. Exercise training significantly increased objective measures of TST ($d = 0.25$) and SE ($d = 0.30$) and self-reported sleep quality ($d = 0.74$) while also decreasing objective SOL ($d = -0.35$) [16]. In moderator analyses, the only participant characteristic found to moderate the effect of exercise training on sleep was age; exercise training was less effective at reducing SOL among older adults. Among exercise characteristics, longer durations of individual exercise bouts resulted in a greater SOL reduction and greater adherence to the exercise training regimen was associated with greater improvement in sleep quality, whereas a longer duration of the exercise regimen was associated with a smaller TST improvement [16]. Other meta-analyses, focused on middle-aged women [24] or older adults with sleep problems [25], have also noted significant improvements in self-reported sleep quality following exercise training.

Although Kredlow and colleagues suggested several potential moderators of the effect of exercise training on sleep [16], minimal research has directly examined which participant and/or exercise characteristics result in the

greatest improvement in sleep following exercise training. Recent research has focused on midlife women and older adults, two specific populations in which physical inactivity and sleep disturbance are both prevalent. As noted above, Kredlow found exercise to be less effective at reducing SOL among older adults; however, the overall body of evidence suggests that exercise is efficacious at improving sleep in these populations [24–26]. It is also unknown whether the type of exercise is important for sleep benefits. Although studies have shown that aerobic exercise and resistance exercise each can improve sleep [16,27], they have not been directly compared [28]. Moreover, significant improvements in sleep have been observed with meditative mind-body exercise (e.g., yoga, tai chi, and qigong) [29]; however, these studies have often been limited to self-reported sleep and have not been directly compared against aerobic or resistance exercise. Although tangentially addressed by Kredlow and colleagues, additional questions remain regarding whether a dose-response relationship exists between exercise and sleep and whether exercise intensity differentially impacts sleep; minimal research has directly compared different doses or intensities of exercise on sleep [30,31]. Finally, it remains unclear whether the effects of exercise training on sleep are dependent upon the extent to which fitness is improved [30,32]. Future research needs to elucidate the effects of different modes, intensities, and doses of exercise in various samples of adults with sleep disturbances and evaluate sleep using both subjective and objective measures to better understand the impact of exercise training on sleep.

Sedentary behavior

In addition to the health benefits of exercise, the public health impact of the entire physical activity continuum is increasingly recognized, with particular focus on the potentially deleterious effects of excessive sedentary behavior. As a behavior that is distinct from a lack of exercise, sedentary behavior occurs at the lowest end of the physical activity continuum and is formally defined as any waking behavior characterized by an energy expenditure ≤ 1.5 metabolic equivalents that is performed in a sitting, reclining, or lying posture [33].

Research on the potential relationship between sedentary behavior and sleep is in its infancy. A recent meta-analysis found that greater sedentary behavior was associated with 18% greater odds for insomnia and 38% greater odds for sleep disturbance [34]. Multiple cross-sectional studies have recently reported that greater sedentary behavior is associated with lower sleep efficiency [8], higher daytime sleepiness [35], and greater odds of having short sleep duration [36], poor sleep quality [36,37], and sleep problems [36]. In addition, cross-

sectional studies have found higher amounts of sedentary behavior to be associated with greater OSA severity, including higher objectively measured AHI [38,39] and greater odds of OSA [38] or OSA “high risk” classification [8,37]. However, the vast majority of the current evidence is limited to cross-sectional and observational study designs, with many relying on self-reported sedentary behavior [36–39] and/or self-reported sleep [35–37]. While sparse, experimental data have been consistent with observational findings. In a crossover trial of six adults whose sleep was experimentally restricted to 5 h/night for three nights, breaking up prolonged sedentary behavior with periodic walking breaks led to a 26% reduction in WASO and a 9% increase in SWS compared with days with uninterrupted sedentary behavior [40]. Finally, in a crossover trial of 25 adults with elevated BP, Kline, and colleagues recently found that alternating sitting with standing every 30 min during a simulated workday led to lower WASO on that night compared with uninterrupted sedentary behavior [41]. Together, these data provide preliminary support that excessive sedentary behavior is associated with worse sleep and that reducing sedentary behavior may improve sleep; however, much remains unknown about how best to reduce sedentary behavior for sleep benefits and which sleep parameters are most impacted.

Potential mechanisms of exercise

The mechanisms underlying how exercise improves sleep remain poorly understood. However, a number of potential mechanisms have been advanced.

Anxiolytic and antidepressant effects

Anxiety and depression are key consequences of disturbed sleep but also significant risk factors in the development and perpetuation of sleep disturbance [14]. Acute exercise reduces both subjective and physiologic markers of anxiety [42], and exercise training significantly reduces anxiety symptoms [43]. Similarly, acute exercise and exercise training have antidepressant effects that are similar in efficacy to pharmacotherapy [44]. Underlying the anxiolytic and antidepressant effects of exercise on sleep may be improvements in autonomic function, increases in circulating endocannabinoids, reductions in inflammation, and/or normalization of hypothalamic-pituitary-adrenal axis dysfunction [45,46].

Circadian phase-shifting effects

Exercise may improve sleep via its effects on the circadian system. Sleep/wake patterns are heavily influenced by the circadian system, and disturbances in circadian timing and blunted amplitude of the circadian system are primary

causes of circadian rhythm sleep disorders such as advanced sleep phase disorder, delayed sleep phase disorder, and irregular sleep/wake disorder [47]. In a laboratory setting, single and multiple bouts of aerobic exercise result in time-dependent alterations in the phase of the central circadian system [48], while muscular activity may serve as a synchronizing cue for the peripheral circadian system and provide input to the central clock [49]. Because the current phase-response curve for exercise is preliminary [48], the optimal timing of exercise for phase-shifting effects is unknown. Regardless of alterations in phase, though, there is evidence that greater amounts of physical activity are associated with greater amplitude of circadian clock gene expression [50] and circadian output markers [51].

Body temperature effects

Impaired heat loss mechanisms and blunted temperature downregulation at the time of sleep initiation have been observed among adults with insomnia [52]. Acute exercise performed in the late afternoon or evening may improve sleep by activating heat loss mechanisms to dissipate the exercise-induced increase in core temperature [53], as distal vasodilation has previously been shown to hasten sleep onset [54]. In addition, exercise training produces thermoregulatory adaptations (e.g., improved distal vaso-dilatory capacity, and increased distal blood flow) [55] that may facilitate a more rapid nocturnal dissipation of core body temperature.

Adenosine

Adenosine has been strongly linked to the homeostatic regulation of sleep [56]. Because acute exercise significantly increases extracellular adenosine levels, this may be a mechanism by which exercise promotes sleep. In rats, high-intensity exercise increased levels of adenosine in the brain [57]. Following acute exercise in humans, homeostatic sleep need (as measured by SWS) was significantly higher under a placebo condition compared with high caffeine intake, which blocks adenosine receptors [58].

Impact of exercise on sleep disorders

Perhaps the most compelling evidence regarding the effect of exercise on sleep has been observed among those with insomnia, sleep-disordered breathing, or restless legs syndrome. Although limited by a small evidence base, these data suggest that there is a role for exercise in the prevention and/or management of each of these sleep disorders.

Insomnia

Insomnia is characterized by difficulty initiating and/or maintaining sleep, awakening for the final time earlier than

desired, or unrefreshing or nonrestorative sleep. Diagnostic criteria for insomnia disorder, however, require that these sleep complaints occur with a minimum frequency and chronicity (e.g., ≥ 3 nights/week for ≥ 3 months) despite an adequate opportunity to sleep and are accompanied by dissatisfaction with sleep and significant daytime impairment [59]. Although hypnotic medication is the most common treatment, most medications are intended for short-term use and numerous studies have demonstrated an unfavorable risk/benefit ratio for hypnotics [60]. In contrast, cognitive behavioral therapy for insomnia is the recommended first-line treatment option for insomnia, but it is not readily available [61,62].

There is limited, yet reliable, evidence that exercise reduces the likelihood and severity of insomnia across both observational and experimental research [63]. In epidemiologic cohorts, greater amounts of physical activity have been consistently associated with a lower prevalence and incidence of insomnia [7,64,65]. Likewise, the few experimental studies have found that both acute exercise and chronic exercise training improve the sleep of adults with insomnia. In one of only two trials to evaluate acute exercise, moderate-intensity aerobic exercise performed in the late afternoon, but not moderate-intensity resistance exercise or vigorous aerobic exercise performed at the same time of day, improved subjective reports of SOL and TST and PSG-based measures of SOL, TST, and SE, compared with a nonexercise control night [66]. In contrast, another trial reported that an acute bout of aerobic exercise performed in the morning, but not in the afternoon, improved sleep in a sample of older adults with insomnia [67]. Meanwhile, randomized trials involving 4–6 months of exercise training produced significant improvements in sleep and indices of daytime function among samples of middle-aged and older adults with chronic insomnia [68,69]. More recently, a pilot study found that integrating light-intensity exercise into one's lifestyle for 8 weeks reduced insomnia severity but not self-reported or actigraphy-assessed sleep [70]. However, with sample sizes of <50 adults in each of these experimental trials, larger trials are needed to substantiate these results and identify the timing, mode, and dose of exercise for optimal improvement in sleep. Moreover, whether exercise reduces insomnia via separate mechanisms than those already discussed remains unclear.

Sleep-disordered breathing

Sleep-disordered breathing (SDB) serves as an umbrella term for a variety of sleep-related breathing disorders. As the most common form of SDB, obstructive sleep apnea (OSA) is characterized by repetitive episodes of airflow reduction or cessation due to upper airway collapse despite continued attempts at respiration, and is strongly linked

with excess weight. As another form of SDB that is much less common than OSA, central sleep apnea (CSA) is characterized by recurring bouts of airflow reduction or cessation that are due to a reduced central drive for respiration; CSA is most commonly observed in those with neurological conditions or congestive heart failure. Although positive airway pressure (PAP) is highly efficacious for adults with SDB, its effectiveness is greatly limited by low patient acceptance and adherence [71]. While oral appliances are a treatment option for adults with OSA who cannot tolerate PAP, they have only modest efficacy at reducing OSA severity and there is risk for dental side effects with long-term use [72].

In epidemiologic research, habitual exercise has consistently been associated with lower OSA risk [73,74], with some studies observing a dose-response relationship between weekly exercise duration and OSA risk [75,76]. Even among those with OSA, greater levels of exercise are associated with a more favorable cardiometabolic profile [77]. Although no study has focused on the effect of acute exercise on OSA, multiple studies have examined exercise training. Meta-analyses have found that 4–24 weeks of exercise training results in an approximately 30% reduction in OSA severity despite nonsignificant reductions in body weight [78,79]. In addition to reduced OSA severity, exercise training also improves multiple dimensions of daytime functioning (e.g., reduced sleepiness and improved quality of life) in samples of adults with OSA [79,80]. Moreover, preliminary evidence suggests that combining exercise with PAP may provide greater improvements in daytime functioning than can be achieved with PAP alone [81,82]. A variety of mechanisms have speculated how exercise reduces OSA severity. In addition to its modest impact on weight loss [83], exercise may strengthen and/or increase the fatigue resistance of upper airway dilator muscles [84] and/or minimize the respiratory instability that accompanies lighter sleep stages and initial sleep onset by inducing more SWS and greater sleep continuity [85]. The most widely explored mechanism, though, involves whether exercise reduces OSA by attenuating overnight fluid redistribution from the lower extremities to the upper body [86]. Multiple studies have observed concurrent reductions in the magnitude of the overnight rostral fluid shift with OSA reduction following 1–4 weeks of exercise training [87,88].

The effects of exercise training on CSA have been sparsely evaluated, with two experimental trials conducted involving patients with chronic heart failure. Exercise training reduced the overall apnea-hypopnea index (AHI) by 36%–65% in these studies; however, divergent effects were observed on the efficacy of specific SDB events. In one trial, exercise reduced central but not obstructive events [89], while exercise reduced the AHI of those with predominantly OSA but not those with CSA in another trial

[90]. Exercise training is hypothesized to reduce CSA severity by augmenting cardiac function and/or normalizing chemoreflex sensitivity, resulting in decreased circulation time and stable respiration.

Restless legs syndrome/periodic limb movements during sleep

Restless legs syndrome (RLS), also known as Willis–Ekbom disease, is characterized by an irresistible urge to move one's limbs, most often the legs. The overwhelming sensation to move, commonly described as a burning, prickly feeling, is usually most severe in the evening. Most adults with RLS also have periodic limb movements during sleep (PLMS), which involves recurring involuntary movements of the limbs during sleep. Unfortunately, the most common pharmacologic treatments for RLS and PLMS (e.g., dopaminergic agents, opioids, benzodiazepines, and anticonvulsants) are accompanied by significant side effects [91].

Exercise is a common recommendation for RLS management, since symptoms are often exacerbated by prolonged inactivity yet relieved with physical movement [92]. Though sparse, epidemiological research indicates that low levels of physical activity are associated with greater risk for RLS [93]. Likewise, there is limited experimental evidence regarding the effect of acute exercise or chronic exercise training on RLS or PLMS. Both acute exercise and exercise training have been shown to significantly reduce RLS symptoms [94,95]. In the only randomized trial on the topic, 12 weeks of exercise training (i.e., lower body resistance exercise and treadmill walking) significantly reduced RLS symptoms [96]. Finally, both acute vigorous exercise and 6 months of moderate-intensity exercise training have been shown to improve sleep and reduce PLMS severity [97]. Exercise is hypothesized to reduce RLS and PLMS symptoms via activation of the dopaminergic and opiate systems [97].

A bidirectional relationship: Impact of sleep on exercise

Although research on the relationship between exercise and sleep has generally focused on the impact of exercise on sleep, disturbed sleep may also precipitate reduced exercise [98]. Observational studies have found that disturbed sleep predicts lower levels of physical activity 2–7 years later [99,100]. Moreover, a number of recently published studies have concurrently assessed physical activity and sleep on a daily basis and explored whether sleep on a given night predicts the next day's physical activity and whether physical activity on a given day predicts that night's sleep. Findings from these studies have been

inconsistent, as they have observed that physical activity improves [101,102] or has no impact [103–105] on the subsequent night's sleep and that sleep predicts [103,106,107] or does not influence [101,104,105,108] the next day's activity levels. Thus, while these studies provide some evidence of a bidirectional relationship between sleep and exercise, it appears that small daily fluctuations in these behaviors may have negligible effects on each other and/or that the association may differ according to how these behaviors are measured and across different samples.

Cross-sectional studies comparing adults with poor sleep to those without sleep complaints provide additional evidence that poor sleep may impede physical activity. For instance, adults with short sleep duration or later sleep timing have less physical activity and greater sedentary behavior [109,110]. Moreover, adults with OSA have low levels of daytime activity [78] and are less active than adults without OSA [111,112]. In crossover experimental trials, restricting sleep to 4–5.5 h/night for 1–7 nights led to reduced daytime activity and/or increased sedentary behavior [113,114], potentially due to decreased vigor and alertness following sleep restriction [113].

By demonstrating reductions in physical activity with disturbed or restricted sleep, these studies raise the possibility that improving sleep may lead to greater daytime activity. Unfortunately, the limited experimental evidence that is currently available provides only weak support for this possibility. To date, research has been limited to adults whose OSA was treated with PAP; in only one of these studies has treatment increased physical activity levels relative to baseline [115]; in contrast, most studies have failed to observe any change in physical activity with treatment [78,116,117]. Overall, these studies suggest that improving sleep may be insufficient to change physical activity and that low activity levels may be linked to other factors (e.g., poor lifestyle habits) in addition to disturbed sleep [78].

Combined impact of exercise and sleep on health

Given that exercise and sleep are each independently linked with health outcomes yet are interrelated behaviors (Fig. 23.1), research has recently begun to explore the health impact when one behavior is promoted at the expense of another [118,119]. By recognizing that physical activity, sedentary, and sleep behaviors occur within the time constraint of a 24-h day, these analyses have examined how reallocating a specific duration of these movement behaviors is associated with various health outcomes [120]. While some studies have found that reallocating a portion of time spent in sedentary behavior to sleep was

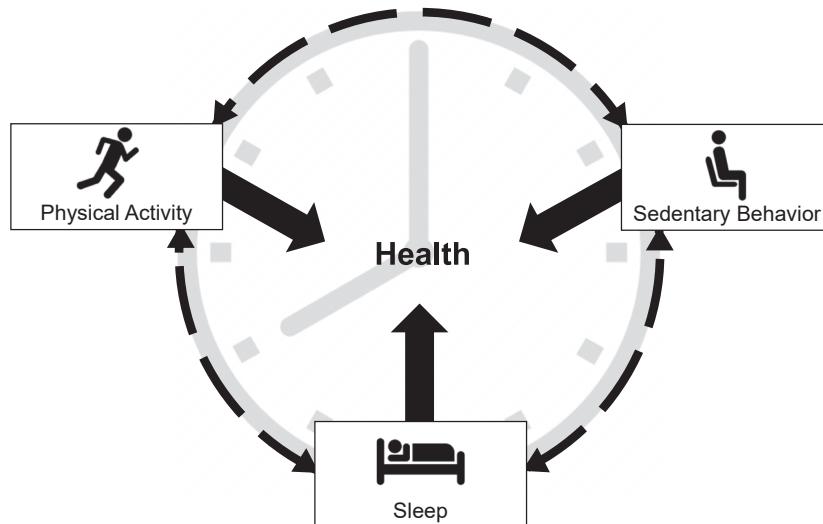


FIGURE 23.1 Interrelationships between movement behaviors and their isolated and combined impact on health. Various movement behaviors comprise each 24-h cycle. Each of these behaviors—sedentary behavior, various intensities of physical activity (light, moderate, and vigorous), and sleep—significantly impact health. However, each of these behaviors is related to each other in a bidirectional manner. Understanding the impact of different allocations of these behaviors is a current research emphasis. Adapted with permission from: Smith K, Rosenberger ME. Keeping seniors active—a 24 h approach. Stanford, CA: Stanford Center on Longevity; 2017. Available from: <http://longevity.stanford.edu/2017/08/11/keeping-seniors-active-a-24-hour-approach/>.

associated with lower mortality risk [121] and greater insulin sensitivity [122], most studies have observed the greatest health benefits when moderate-vigorous physical activity was increased at the expense of other movement behaviors [123,124]. Of note, though, many studies have neglected to even include sleep in these analyses [120]. Moreover, isotemporal substitution and compositional data analysis studies are limited in their examination of sleep since sleep duration is the only sleep-related predictor or outcome that can be utilized in the models. While duration is an important characteristic of sleep, sleep health encompasses a variety of other dimensions (e.g., timing, quality, and depth) [125] that cannot be easily probed with these statistical approaches.

There is also preliminary research exploring whether health improvements resulting from modification of sleep or exercise are dependent upon the other behavior. For example, there is increasing recognition that the effect of exercise on cognition may be at least partially mediated by the effect of exercise on sleep [126] and that the association between sleep and cardiometabolic health is impacted by physical activity [127,128]. Conversely, recent studies have documented that the potential health benefits of exercise or healthy sleep may be limited by the impact of disturbed sleep or physical inactivity, respectively. Among adults with OSA, reduced arterial stiffness following a physical activity and dietary intervention was dependent upon the extent of OSA severity improvement [129]. As an additional example, the typical improvement in

postprandial glucose metabolism resulting from breaking up prolonged sedentary time was not observed when the participants had their sleep restricted in a recent study [40].

Finally, research is now beginning to examine whether simultaneously intervening on sleep and exercise provides additive or even synergistic benefits on health compared with isolated intervention on these behaviors. Observational studies suggest that clusters of poor sleep and physical inactivity are linked to worse cardiovascular health [130,131] and greater mortality [132] than either behavior in isolation. However, experimental evidence is currently limited to one trial of adults with insomnia. In this study, adults who received physical activity counseling and sleep restriction therapy had greater improvements in sleep than those who received only sleep restriction therapy [133]. While the current evidence is scarce, multiple studies are currently underway [134,135] that will add insight into the health benefits related to simultaneous intervention on sleep and exercise.

Conclusion

Exercise is commonly assumed to lead to improved sleep. This assumption is consistently supported by observational research, and experimental research involving acute exercise and exercise training in samples with disturbed sleep have largely corroborated this claim. Nevertheless, much remains unknown regarding the efficacy of exercise for alleviating sleep disturbances and the underlying

mechanisms through which exercise improves sleep. With increasing recognition that the relationship between exercise and sleep is bidirectional, research is now seeking to identify whether combining sleep and exercise interventions are efficacious and whether the health benefits of exercise or sleep are dependent upon its impact on the other behavior. As we continue to refine our understanding of the relationship between exercise and sleep, it is clear that there is great potential for both exercise and sleep to be optimized for the purpose of improving health.

References

- [1] Youngstedt SD, Kline CE. Epidemiology of exercise and sleep. *Sleep Biol Rhyth* 2006;3:215–21. <https://doi.org/10.1111/j.1479-8425.2006.00235.x>.
- [2] Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: a review of empirical evidence. *Sleep Med Rev* 2015;22:23–36. <https://doi.org/10.1016/j.smrv.2014.10.001>.
- [3] Blair SN, Morris JN. Healthy hearts-and the universal benefits of being physically active: physical activity and health. *Ann Epidemiol* 2009;19(4):253–6. <https://doi.org/10.1016/j.anepepid.2009.01.019>.
- [4] Sherrill DL, Kotchou K, Quan SF. Association of physical activity and human sleep disorders. *Arch Int Med* 1998;158(17):1894–8. <https://doi.org/10.1001/archinte.158.17.1894>.
- [5] Zheng B, Yu C, Lin L, Du H, Lv J, Guo Y, Bian Z, Chen Y, Yu M, Li J, Chen J, Chen Z, Li L. Associations of domain-specific physical activities with insomnia symptoms among 0.5 million Chinese adults. *J Sleep Res* 2017;26(3):330–7. <https://doi.org/10.1111/jsr.12507>.
- [6] Dishman RK, Sui X, Church TS, Kline CE, Youngstedt SD, Blair SN. Decline in cardiorespiratory fitness and odds of incident sleep complaints. *Med Sci Sports Exerc* 2015;47(5):960–6. <https://doi.org/10.1249/MSS.0000000000000506>.
- [7] Kline CE, Irish LA, Krafty RT, Sternfeld B, Kravitz HM, Buysse DJ, Bromberger JT, Dugan SA, Hall MH. Consistently high sports/exercise activity is associated with better sleep quality, continuity and depth in midlife women: the SWAN Sleep study. *Sleep* 2013;36(9):1279–88.
- [8] Gubelmann C, Heinzer R, Haba-Rubio J, Vollenweider P, Marques-Vidal P. Physical activity is associated with higher sleep efficiency in the general population: the CoLaus study. *Sleep* 2018;41(7). <https://doi.org/10.1093/sleep/zsy070>.
- [9] Mesas AE, Hagen EW, Peppard PE. The bidirectional association between physical activity and sleep in middle-aged and older adults: a prospective study based on polysomnography. *Sleep* 2018;41(9). <https://doi.org/10.1093/sleep/zsy114>.
- [10] Gerber M, Brand S, Holsboer-Trachsler E, Pühse U. Fitness and exercise as correlates of sleep complaints: is it all in our minds? *Med Sci Sports Exerc* 2010;42(5):893–901. <https://doi.org/10.1249/MSS.0b013e3181c0ea8c>.
- [11] Burg MM, Schwartz JE, Kronish IM, Diaz KM, Alcantara C, Duer-Hefele J, Davidson KW. Does stress result in you exercising less? Or does exercising result in you being less stressed? Or is it both? Testing the Bi-directional stress-exercise association at the group and person (N of 1) level. *Ann Behav Med* 2017;51(6):799–809. <https://doi.org/10.1007/s12160-017-9902-4>.
- [12] Strine TW, Chapman DP. Associations of frequent sleep insufficiency with health-related quality of life and health behaviors. *Sleep Med* 2005;6(1):23–7. <https://doi.org/10.1016/j.sleep.2004.06.003>.
- [13] Chesson AL, Littner M, Davila D, Anderson WMD, Grigg-Damberger M, Hartse K, Johnson S, Wise M. Practice parameters for the use of light therapy in the treatment of sleep disorders. *Sleep* 1999;22(5):641–60. <https://doi.org/10.1093/sleep/22.5.641>.
- [14] Alvaro PK, Roberts RM, Harris JK. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep* 2013;36(7):1059–68. <https://doi.org/10.5665/sleep.2810>.
- [15] Youngstedt SD. Ceiling and floor effects in sleep research. *Sleep Med Rev* 2003;7(4):351–65. <https://doi.org/10.1053/smrv.2001.0239>.
- [16] Kredlow MA, Capozzoli MC, Hearon BA, Calkins AW, Otto MW. The effects of physical activity on sleep: a meta-analytic review. *J Behav Med* 2015;38(3):427–49. <https://doi.org/10.1007/s10865-015-9617-6>.
- [17] National Sleep Foundation. What is sleep. 2018. p. 2018.
- [18] Oda S, Shirakawa K. Sleep onset is disrupted following pre-sleep exercise that causes large physiological excitement at bedtime. *Eur J Appl Physiol* 2014;114(9):1789–99. <https://doi.org/10.1007/s00421-014-2873-2>.
- [19] Buman MP, Phillips BA, Youngstedt SD, Kline CE, Hirshkowitz M. Does nighttime exercise really disturb sleep? Results from the 2013 national sleep foundation sleep in America poll. *Sleep Med* 2014;15(7):755–61. <https://doi.org/10.1016/j.sleep.2014.01.008>.
- [20] Myllymäki T, Kyröläinen H, Savolainen K, Hokka L, Jakonen R, Juuti T, Martinmäki K, Kaartinen J, Kinnunen ML, Rusko H. Effects of vigorous late-night exercise on sleep quality and cardiac autonomic activity. *J Sleep Res* 2011;20(1):146–53. <https://doi.org/10.1111/j.1365-2869.2010.00874.x>.
- [21] Flausino NH, Da Silva Prado JM, de Queiroz SS, Tufik S, de Mello MT. Physical exercise performed before bedtime improves the sleep pattern of healthy young good sleepers. *Psychophysiology* 2012;49(2):186–92. <https://doi.org/10.1111/j.1469-8986.2011.01300.x>.
- [22] Brand S, Kalak N, Gerber M, Kirov R, Pühse U, Holsboer-Trachsler E. High self-perceived exercise exertion before bedtime is associated with greater objectively assessed sleep efficiency. *Sleep Med* 2014;15(9):1031–6. <https://doi.org/10.1016/j.sleep.2014.05.016>.
- [23] Youngstedt SD. Effects of exercise on sleep. *Clin Sports Med* 2005;24(2):355–65. <https://doi.org/10.1016/j.csm.2004.12.003>.
- [24] Rubio-Arias J, Marín-Cascales E, Ramos-Campo DJ, Hernández AV, Pérez-López FR. Effect of exercise on sleep quality and insomnia in middle-aged women: a systematic review and meta-analysis of randomized controlled trials. *Maturitas* 2017;100:49–56. <https://doi.org/10.1016/j.maturitas.2017.04.003>.
- [25] Yang PY, Ho KH, Chen HC, Chien MY. Exercise training improves sleep quality in middle-aged and older adults with sleep problems: a systematic review. *J Physiother* 2012;58(3):157–63. [https://doi.org/10.1016/S1836-9553\(12\)70106-6](https://doi.org/10.1016/S1836-9553(12)70106-6).

- [26] Varrasse M, Li J, Gooneratne N. Exercise and sleep in community-dwelling older adults. *Curr Sleep Med Rep* 2015;1(4):232–40. <https://doi.org/10.1007/s40675-015-0028-6>.
- [27] Kovacevic A, Mavros Y, Heisz JJ, Fiatarone Singh MA. The effect of resistance exercise on sleep: a systematic review of randomized controlled trials. *Sleep Med Rev* 2018;39:52–68. <https://doi.org/10.1016/j.smrv.2017.07.002>.
- [28] Bertani RF, Campos GO, Perseguin DM, Bonardi JT, Ferriolli E, Moriguti JC, Lima NKC. Resistance exercise training is more effective than interval aerobic training in reducing blood pressure during sleep in hypertensive elderly patients. *J Strength Cond Res* 2018;32(7):2085–90. <https://doi.org/10.1519/JSC.00000000000002354>.
- [29] Wang F, Eun-Kyoung Lee O, Feng F, Vitiello MV, Wang W, Benson H, Fricchione GL, Denninger JW. The effect of meditative movement on sleep quality: a systematic review. *Sleep Med Rev* 2016;30:43–52. <https://doi.org/10.1016/j.smrv.2015.12.001>.
- [30] Kline CE, Sui X, Hall MH, Youngstedt SD, Blair SN, Earnest CP, Church TS. Dose-response effects of exercise training on the subjective sleep quality of postmenopausal women: exploratory analyses of a randomised controlled trial. *BMJ Open* 2012;2(4). <https://doi.org/10.1136/bmjjopen-2012-001044>.
- [31] Singh NA, Stavrinou TM, Scarbek Y, Galambos G, Liber C, Fiatarone Singh MA. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *J Gerontol Ser A* 2005;60(6):768–76. <https://doi.org/10.1093/gerona/60.6.768>.
- [32] Tworoger SS, Yasui Y, Vitiello MV, Schwartz RS, Ulrich CM, Aiello EJ, Irwin ML, Bowen D, Potter JD, McTiernan A. Effects of a yearlong moderate-intensity exercise and a stretching intervention on sleep quality in postmenopausal women. *Am Acad Sleep Med* 2003;26(7):830–6. <https://doi.org/10.1093/sleep/26.7.830>.
- [33] Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, Chastin SFM, Altenburg TM, Chinapaw MJM, Aminian S, Arundell L, Hinkley T, Hnatiuk J, Atkin AJ, Belanger K, Chaput JP, Gunnell K, Larouche R, Manyanga T, Gibbs BB, Bassett-Gunter R, Biddle S, Biswas A, Chau J, Colley R, Coppinger T, Craven C, Cristi-Montero C, de Assis Teles Santos D, del Pozo Cruz B, del Pozo-Cruz J, Dempsey P, do Carmo Santos Gonçalves RF, Ekelund U, Ellingsen L, Ezeugwu V, Fitzsimons C, Florez-Pregonero A, Friel CP, Fröberg A, Giangregorio L, Godin L, Halloway S, Husu P, Kadir M, Karagounis LG, Koster A, Lakerveld J, Lamb M, LeBlanc AG, Lee EY, Lee P, Lopes L, Manns T, Ginis KM, McVeigh J, Meneguci J, Moreira C, Murtagh E, Patterson F, da Silva DRP, Pesola AJ, Peterson N, Pettitt C, Pilutti L, Pereira SP, Poitras V, Prince S, Rathod A, Rivière F, Rosenkranz S, Routhier F, Santos R, Smith B, Theou O, Tomasone J, Tucker P, Meyer RU, van der Ploeg H, Villalobos T, Viren T, Wallmann-Sperlich B, Wijndaele K, Wondergem R. Sedentary behavior research network (SBRN) - terminology consensus project process and outcome. *Int J Behav Nutr Phys Act* 2017;14(1).
- [34] Yang Y, Shin JC, Li D, An R. Sedentary behavior and sleep problems: a systematic review and meta-analysis. *Int J Behav Med* 2017;24(4):481–92. <https://doi.org/10.1007/s12529-016-9609-0>.
- [35] Loprinzi P, Nalley C, Selk A. Objectively-measured sedentary behavior with sleep duration and daytime sleepiness among U.S. adults. *J Behav Health* 2014;3(2):141. <https://doi.org/10.5455/jbh.20140310053242>.
- [36] Vancampfort D, Stubbs B, Firth J, Hagemann N, Myint-Germeyns I, Rintala A, Probst M, Veronese N, Koyanagi A. Sedentary behaviour and sleep problems among 42,489 community-dwelling adults in six low- and middle-income countries. *J Sleep Res* 2018;27(6):e12714. <https://doi.org/10.1111/jsr.12714>.
- [37] Buman MP, Kline CE, Youngstedt SD, Phillips B, Tulio De Mello M, Hirshkowitz M. Sitting and television viewing: novel risk factors for sleep disturbance and apnea risk? Results from the 2013 National Sleep Foundation Sleep in America poll. *Chest* 2015;147(3):728–34. <https://doi.org/10.1378/chest.14-1187>.
- [38] Kline CE, Krafty RT, Mulukutla S, Hall MH. Associations of sedentary time and moderate-vigorous physical activity with sleep-disordered breathing and polysomnographic sleep in community-dwelling adults. *Sleep Breath* 2017;21(2):427–34. <https://doi.org/10.1007/s11325-016-1434-9>.
- [39] Redolfi S, Yumino D, Ruttanaumpawan P, Yau B, Su M-C, Jennifer Lam T, Bradley D. Relationship between overnight rostral fluid shift and obstructive sleep apnea in nonobese men. *Am J Respir Crit Care Med* 2009;179(3):241–6. <https://doi.org/10.1164/rccm.200807-1076oc>.
- [40] Vincent GE, Jay SM, Sargent C, Kovac K, Lastella M, Vandelanotte C, Ridgers ND, Ferguson SA. Does breaking up prolonged sitting when sleep restricted affect postprandial glucose responses and subsequent sleep architecture?—a pilot study. *Chronobiol Int* 2018;35(6):821–6. <https://doi.org/10.1080/07420528.2018.1466789>.
- [41] Kline CE, Kowalsky RJ, Perdomo SJ, Barone Gibbs B. Use of a sit-stand desk reduces wake time during the subsequent night's sleep. *Med Sci Sports Exerc* 2017;49(5S):854–5. <https://doi.org/10.1249/01.mss.0000519306.71120.df>.
- [42] Ensari I, Greenlee TA, Motl RW, Petruzzello SJ. Meta-analysis of acute exercise effects on state anxiety: an update of randomized controlled trials over the past 25 years. *Depress Anxiety* 2015;32(8):624–34. <https://doi.org/10.1002/da.22370>.
- [43] Stubbs B, Vancampfort D, Rosenbaum S, Firth J, Cosco T, Veronese N, Salum GA, Schuch FB. An examination of the anxiolytic effects of exercise for people with anxiety and stress-related disorders: a meta-analysis. *Psychiatry Res* 2017;249:102–8. <https://doi.org/10.1016/j.psychres.2016.12.020>.
- [44] Blumenthal JA, Babyak MA, Doraiswamy PM, Watkins L, Hoffman BM, Barbour KA, Herman S, Craighead WE, Brosse AL, Waugh R, Hinderliter A, Sherwood A. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosomat Med* 2007;69(7):587–96. <https://doi.org/10.1097/PSY.0b013e318148c19a>.
- [45] Kandola A, Vancampfort D, Herring M, Rebar A, Hallgren M, Firth J, Stubbs B. Moving to beat anxiety: epidemiology and therapeutic issues with physical activity for anxiety. *Curr Psychiatry Rep* 2018;20(8). <https://doi.org/10.1007/s11920-018-0923-x>.
- [46] Hallgren M, Herring MP, Owen N, Dunstan D, Ekblom Ö, Helgadottir B, Nakitanda OA, Forsell Y. Exercise, physical activity, and sedentary behavior in the treatment of depression: broadening the scientific perspectives and clinical opportunities. *Front Psychiatry* 2016;7. <https://doi.org/10.3389/fpsyg.2016.00036>.
- [47] Morgenthaler TI, Lee-Chiong T, Alessi C, Friedman L, Aurora RN, Boehlecke B, Brown T, Chesson AL, Kapur V, Maganti R, Owens J,

- Pancer J, Swick TJ, Zak R. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders: an American Academy of Sleep Medicine Report. *Sleep* 2007;30(11):1445–59. <https://doi.org/10.1093/sleep/30.11.1445>.
- [48] Atkinson G, Edwards B, Reilly T, Waterhouse J. Exercise as a synchroniser of human circadian rhythms: an update and discussion of the methodological problems. *Eur J Appl Physiol* 2007;99(4):331–41. <https://doi.org/10.1007/s00421-006-0361-z>.
- [49] Schroder EA, Esser KA. Circadian rhythms, skeletal muscle molecular clocks, and exercise. *Exerc Sport Sci Rev* 2013;41(4):224–9. <https://doi.org/10.1097/JES.0b013e3182a58a70>.
- [50] Takahashi M, Haraguchi A, Tahara Y, Aoki N, Fukazawa M, Tanisawa K, Ito T, Nakaoaka T, Higuchi M, Shibata S. Positive association between physical activity and PER3 expression in older adults. *Sci Rep* 2017;7(1). <https://doi.org/10.1038/srep39771>.
- [51] Tranel HR, Schroder EA, England J, Black WS, Bush H, Hughes ME, Esser KA, Clasey JL. Physical activity, and not fat mass is a primary predictor of circadian parameters in young men. *Chronobiol Int* 2015;32(6):832–41. <https://doi.org/10.3109/07420528.2015.1043011>.
- [52] Raymann RJEM, Swaab DF, Van Someren EJW. Skin temperature and sleep-onset latency: changes with age and insomnia. *Physiol Behav* 2007;90(2–3):257–66. <https://doi.org/10.1016/j.physbeh.2006.09.008>.
- [53] Horne JA, Staff LHE. Exercise and sleep: body-heating effects. *Sleep* 1983;6(1):36–46. <https://doi.org/10.1093/sleep/6.1.36>.
- [54] Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Functional link between distal vasodilation and sleep-onset latency? *Am J Physiol Regul Integr Comp Physiol* 2000;278(3):R741. <https://doi.org/10.1152/ajpregu.2000.278.3.r741>.
- [55] Simmons GH, Wong BJ, Holowatz LA, Kenney WL. Changes in the control of skin blood flow with exercise training: where do cutaneous vascular adaptations fit in? *Exp Physiol* 2011;96(9):822–8. <https://doi.org/10.1111/expphysiol.2010.056176>.
- [56] Landolt HP. Sleep homeostasis: a role for adenosine in humans? *Biochem Pharmacol* 2008;75(11):2070–9. <https://doi.org/10.1016/j.bcp.2008.02.024>.
- [57] Dworak M, Diel P, Voss S, Hollmann W, Strüder HK. Intense exercise increases adenosine concentrations in rat brain: implications for a homeostatic sleep drive. *Neuroscience* 2007;150(4):789–95. <https://doi.org/10.1016/j.neuroscience.2007.09.062>.
- [58] Youngstedt SD, O'Connor PJ, Crabbe JB, Dishman RK. The influence of acute exercise on sleep following high caffeine intake. *Physiol Behav* 2000;68(4):563–70. [https://doi.org/10.1016/S0031-9384\(99\)00213-9](https://doi.org/10.1016/S0031-9384(99)00213-9).
- [59] Chung KF, Yeung WF, Ho FYY, Yung KP, Yu YM, Kwok CW. Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and Statistical Manual (DSM), International Classification of Diseases (ICD) and International Classification of Sleep Disorders (ICSD). *Sleep Med* 2015;16(4):477–82. <https://doi.org/10.1016/j.sleep.2014.10.018>.
- [60] Wilt TJ, MacDonald R, Brasure M, Olson CM, Carlyle M, Fuchs E, Khawaja IS, Diem S, Koffel E, Ouellette J, Butler M, Kane RL. Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Int Med* 2016;165(2):103–12. <https://doi.org/10.7326/M15-1781>.
- [61] Thomas A, Grandner M, Nowakowski S, Nesom G, Corbett C, Perlis ML. Where are the behavioral sleep medicine providers and where are they needed? A geographic assessment. *Behav Sleep Med* 2016;14(6):687–98. <https://doi.org/10.1080/15402002.2016.1173551>.
- [62] Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Barry MJ, Boyd C, Chow RD, Fitterman N, Harris RP, Humphrey LL, Manaker S, McLean R, Mir TP, Schünemann HJ, Vijan S, Wilt T. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Int Med* 2016;165(2):125–33. <https://doi.org/10.7326/M15-2175>.
- [63] Passos GS, Poyares DLR, Santana MG, Tufik S, de Mello MT. Is exercise an alternative treatment for chronic insomnia? *Clinics* 2012;67(6):653–9. [https://doi.org/10.6061/clinics/2012\(06\)17](https://doi.org/10.6061/clinics/2012(06)17).
- [64] Spörndly-Nees S, Åsenlöf P, Lindberg E. High or increasing levels of physical activity protect women from future insomnia. *Sleep Med* 2017;32:22–7. <https://doi.org/10.1016/j.sleep.2016.03.017>.
- [65] Inoue S, Yorifuji T, Sugiyama M, Ohta T, Ishikawa-Takata K, Doi H. Does habitual physical activity prevent insomnia? A cross-sectional and longitudinal study of elderly Japanese. *J Aging Phys Activ* 2013;21(2):119–39. <https://doi.org/10.1123/japa.21.2.119>.
- [66] Passos GS, Poyares D, Santana MG, Garbuio SA, Tufik S, De Mello MT. Effect of acute physical exercise on patients with chronic primary insomnia. *J Clin Sleep Med* 2010;6(3):270–5. <https://doi.org/10.5664/jcsm.27825>.
- [67] Morita Y, Sasai-Sakuma T, Inoue Y. Effects of acute morning and evening exercise on subjective and objective sleep quality in older individuals with insomnia. *Sleep Med* 2017;34:200–8. <https://doi.org/10.1016/j.sleep.2017.03.014>.
- [68] Reid KJ, Baron KG, Lu B, Naylor E, Wolfe L, Zee PC. Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. *Sleep Med* 2010;11(9):934–40. <https://doi.org/10.1016/j.sleep.2010.04.014>.
- [69] Hartescu I, Morgan K, Stevinson CD. Increased physical activity improves sleep and mood outcomes in inactive people with insomnia: a randomized controlled trial. *J Sleep Res* 2015;24(5):526–34. <https://doi.org/10.1111/jsr.12297>.
- [70] Yeung WF, Lai AYK, Ho FYY, Suen LKP, Chung KF, Ho JYS, Ho LM, Yu BYM, Chan LY, Lam TH. Effects of zero-time exercise on inactive adults with insomnia disorder: a pilot randomized controlled trial. *Sleep Med* 2018;52:118–27. <https://doi.org/10.1016/j.sleep.2018.07.025>.
- [71] Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011;15(6):343–56. <https://doi.org/10.1016/j.smrv.2011.01.003>.
- [72] Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *J Clin Sleep Med* 2015;11(7):773–828. <https://doi.org/10.5664/jcsm.4858>.
- [73] Da Silva RP, Martinez D, Pedroso MM, Righi CG, Martins EF, Silva LMT, Lenz MDGS, Fiori CZ. Exercise, occupational activity, and risk of sleep apnea: a cross-sectional study. *J Clin Sleep Med* 2017;13(2):197–204. <https://doi.org/10.5664/jcsm.6446>.

- [74] Murillo R, Reid KJ, Arredondo EM, Cai J, Gellman MD, Gotman NM, Marquez DX, Penedo FJ, Ramos AR, Zee PC, Daviglus ML. Association of self-reported physical activity with obstructive sleep apnea: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Prev Med* 2016;93:183–8. <https://doi.org/10.1016/j.ypmed.2016.10.009>.
- [75] Simpson L, McArdle N, Eastwood PR, Ward KL, Cooper MN, Wilson AC, Hillman DR, Palmer LJ, Mukherjee S. Physical inactivity is associated with moderate-severe obstructive sleep apnea. *J Clin Sleep Med* 2015;11(10):1091–9. <https://doi.org/10.5664/jcsm.5078>.
- [76] Peppard PE, Young T. Exercise and sleep-disordered breathing: an association independent of body habitus. *Sleep* 2004;27(3):480–4. <https://doi.org/10.1093/sleep/27.3.480>.
- [77] Monico-Neto M, Moreira Antunes HK, Dos Santos RVT, D’Almeida V, Lino de Souza A, Bittencourt A, Tufik LR. Physical activity as a moderator for obstructive sleep apnoea and cardiometabolic risk in the EPISONO study. *Eur Respir J* 2018;52(4):2018.
- [78] Mendelson M, Bailly S, Marillier M, Flore P, Borel JC, Vivodtzev I, Doutreleau S, Verges S, Tamisier R, Pépin JL. Obstructive sleep apnea syndrome, objectively measured physical activity and exercise training interventions: a systematic review and meta-analysis. *Front Neurol* 2018;9:16642295. <https://doi.org/10.3389/fneur.2018.00073>.
- [79] Iftikhar IH, Kline CE, Youngstedt SD. Effects of exercise training on sleep apnea: a meta-analysis. *Lung* 2014;192(1):175–84. <https://doi.org/10.1007/s00408-013-9511-3>.
- [80] Kline CE, Ewing GB, Burch JB, Blair SN, Durstine JL, Davis JM, Youngstedt SD. Exercise training improves selected aspects of daytime functioning in adults with obstructive sleep apnea. *J Clin Sleep Med* 2012;8(4):357–65. <https://doi.org/10.5664/jcsm.2022>.
- [81] Servantes DM, Javaheri S, Kravchychyn ACP, Storti LJ, Almeida DR, de Mello MT, Cintra FD, Tufik S, Bittencourt L. Effects of exercise training and cpap in patients with heart failure and OSA: a preliminary study. *Chest* 2018;154(4):808–17.
- [82] Ackel-D’Elia C, Silva ACda, Santos Silva R, Truksinas E, Sousa BS, Tufik S, Túlio de Mello M, Bittencourt LRA. Effects of exercise training associated with continuous positive airway pressure treatment in patients with obstructive sleep apnea syndrome. *Sleep Breath* 2012;16(3):723–35. <https://doi.org/10.1007/s11325-011-0567-0>.
- [83] Jakicic JM, Otto AD. Treatment and prevention of obesity: what is the role of exercise? *Nutr Rev* 2006;1. <https://doi.org/10.1111/j.1753-4887.2006.tb00235.x>.
- [84] Vincent HK, Shanelly RA, Stewart DJ, Demirel HA, Hamilton KL, Ray AD, Michlin C, Farkas GA, Powers SK. Adaptation of upper airway muscles to chronic endurance exercise. *Am J Respir Crit Care Med* 2002;166(3):287–93. <https://doi.org/10.1164/rccm.2104120>.
- [85] Séries F, Roy N, Marc I. Effects of sleep deprivation and sleep fragmentation on upper airway collapsibility in normal subjects. *Am J Respir Crit Care Med* 1994;150(2):481–5. <https://doi.org/10.1164/ajrccm.150.2.8049833>.
- [86] Kline CE. Exercise: shifting fluid and sleep apnoea away. *Eur Respir J* 2016;48(1):23–5. <https://doi.org/10.1183/13993003.00797-2016>.
- [87] Redolfi S, Bettinzoli M, Venturoli N, Ravanelli M, Pedroni L, Taranto-Montemurro L, Arnulf I, Similowski T, Tantucci C. Attenuation of obstructive sleep apnea and overnight rostral fluid shift by physical activity. *Am J Respir Crit Care Med* 2015;191(7):856–8. <https://doi.org/10.1164/rccm.201412-2192le>.
- [88] Mendelson M, Lyons OD, Yadollahi A, Inami T, Oh P, Bradley TD. Effects of exercise training on sleep apnoea in patients with coronary artery disease: a randomised trial. *Eur Respir J* 2016;48(1):142–50. <https://doi.org/10.1183/13993003.01897-2015>.
- [89] Yamamoto U, Mohri M, Shimada K, Origuchi H, Miyata K, Ito K, Abe K, Yamamoto H. Six-month aerobic exercise training ameliorates central sleep apnea in patients with chronic heart failure. *J Card Fail* 2007;13(10):825–9. <https://doi.org/10.1016/j.cardfail.2007.08.001>.
- [90] Ueno LM, Drager LF, Rodrigues ACT, Rondon MUPB, Braga AMFW, Mathias W, Krieger EM, Barreto ACP, Middlekauff HR, Lorenzi-Filho G, Negrão CE. Effects of exercise training in patients with chronic heart failure and sleep apnea. *Sleep* 2009;32(5):637–47. <https://doi.org/10.1093/sleep/32.5.637>.
- [91] Stiasny K, Hermann Oertel W, Trenkwalder C. Clinical symptomatology and treatment of restless legs syndrome and periodic limb movement disorder. *Sleep Med Rev* 2002;6(4):253–65. <https://doi.org/10.1053/smrv.2001.0193>.
- [92] Pigeon WR, Yurcheshen M. Behavioral sleep medicine interventions for restless legs syndrome and periodic limb movement disorder. *Sleep Med Clin* 2009;4(4):487–94. <https://doi.org/10.1016/j.jsmc.2009.07.008>.
- [93] Batool-Anwar S, Li Y, De Vito K, Malhotra A, Winkelmann J, Xiang G. Lifestyle factors and risk of restless legs syndrome: prospective cohort study. *J Clin Sleep Med* 2016;12(02):187–94. <https://doi.org/10.5664/jcsm.5482>.
- [94] Cederberg KL, Motl RW, Burnham TR. Magnitude and duration of acute-exercise intensity effects on symptoms of restless legs syndrome: a pilot study. *Sleep Biol Rhyth* 2018;16(3):337–44. <https://doi.org/10.1007/s41105-018-0158-6>.
- [95] Esteves AM, de Mello MT, Benedito-Silva AA, Tufik S. Impacto do exercício físico na Síndrome das Pernas Inquietas. *Sleep Sci* 2011;4(2):45–8.
- [96] Aukerman MM, Aukerman D, Bayard M, Tudiver F, Thorp L, Bailey B. Exercise and restless legs syndrome: a randomized controlled trial. *J Am Board Fam Med* 2006;19(5):487–93. <https://doi.org/10.3122/jabfm.19.5.487>.
- [97] Esteves AM, De Mello MT, Pradella-Hallinan M, Tufik S. Effect of acute and chronic physical exercise on patients with periodic leg movements. *Med Sci Sports Exerc* 2009;41(1):237–42. <https://doi.org/10.1249/MSS.0b013e318183bb22>.
- [98] Kline CE. The bidirectional relationship between exercise and sleep: implications for exercise adherence and sleep improvement. *Am J Lifestyle Med* 2014;8(6):375–9. <https://doi.org/10.1177/1559827614544437>.
- [99] Haario P, Rahkonen O, Laaksonen M, Lahelma E, Lallukka T. Bidirectional associations between insomnia symptoms and unhealthy behaviours. *J Sleep Res* 2013;22(1):89–95. <https://doi.org/10.1111/j.1365-2869.2012.01043.x>.
- [100] Hofeld B, Ruthig JC. A longitudinal examination of sleep quality and physical activity in older adults. *J Appl Gerontol* 2014;33(7):791–807. <https://doi.org/10.1177/0733464812455097>.

- [101] Best JR, Falck RS, Landry GJ, Liu-Ambrose T. Analysis of dynamic, bidirectional associations in older adult physical activity and sleep quality. *J Sleep Res* 2019;28(4):e12769. <https://doi.org/10.1111/jsr.12769>.
- [102] Dzierzewski JM, Buman MP, Giacobbi PR, Roberts BL, Aiken-Morgan AT, Marsiske M, McCrae CS. Exercise and sleep in community-dwelling older adults: evidence for a reciprocal relationship. *J Sleep Res* 2014;23(1):61–8. <https://doi.org/10.1111/jsr.12078>.
- [103] Baron KG, Reid KJ, Zee PC. Exercise to improve sleep in insomnia: exploration of the bidirectional effects. *J Clin Sleep Med* 2013;9(8):819–24.
- [104] Mitchell JA, Godbole S, Moran K, Murray K, James P, Laden F, Hipp JA, Kerr J, Glanz K. No evidence of reciprocal associations between daily sleep and physical activity. *Med Sci Sports Exerc* 2016;48(10):1950–6. <https://doi.org/10.1249/MSS.0000000000001000>.
- [105] Irish LA, Kline CE, Rothenberger SD, Krafty RT, Buysse DJ, Kravitz HM, Bromberger JT, Zheng H, Hall MH. A 24-hour approach to the study of health behaviors: temporal relationships between waking health behaviors and sleep. *Ann Behav Med* 2014;47(2):189–97. <https://doi.org/10.1007/s12160-013-9533-3>.
- [106] Lambiase MJ, Gabriel KP, Kuller LH, Matthews KA. Temporal relationships between physical activity and sleep in older women. *Med Sci Sports Exerc* 2013;45(12):2362–8. <https://doi.org/10.1249/MSS.0b013e31829e4cea>.
- [107] Tang NKY, Sanborn AN, Manchikanti L. Better quality sleep promotes daytime physical activity in patients with chronic pain? A multilevel analysis of the within-person relationship. *PLoS ONE* 2014;9(3):e92158. <https://doi.org/10.1371/journal.pone.0092158>.
- [108] Fortier MS, Guerin E, Williams T, Strachan S. Should I exercise or sleep to feel better? A daily analysis with physically active working mothers. *Mental Health Phys Act* 2015;8:56–61. <https://doi.org/10.1016/j.mhpaa.2015.03.001>.
- [109] Booth JN, Bromley LE, Darukhanavala AP, Whitmore HR, Imperial JG, Penev PD. Reduced physical activity in adults at risk for type 2 diabetes who curtail their sleep. *Obesity* 2012;20(2):278–84. <https://doi.org/10.1038/oby.2011.306>.
- [110] Shechter A, St-Onge MP. Delayed sleep timing is associated with low levels of free-living physical activity in normal sleeping adults. *Sleep Med* 2014;15(12):1586–9. <https://doi.org/10.1016/j.sleep.2014.07.010>.
- [111] Hargens TA, Martin RA, Strosnider CL, Giersch GEW, Womack CJ. Obstructive sleep apnea negatively impacts objectively measured physical activity. *Sleep Breath* 2019;23(2):447–54. <https://doi.org/10.1007/s11325-018-1700-0>.
- [112] Kline CE, Irish LA, Buysse DJ, Kravitz HM, Okun ML, Owens JE, Hall MH. Sleep hygiene behaviors among midlife women with insomnia or sleep-disordered breathing: the SWAN sleep study. *J Womens Health* 2014;23(11):894–903. <https://doi.org/10.1089/jwh.2014.4730>.
- [113] Bromley LE, Booth JN, Kilkus JM, Imperial JG, Penev PD. Sleep restriction decreases the physical activity of adults at risk for type 2 diabetes. *Sleep* 2012;35(7):977–84. <https://doi.org/10.5665/sleep.1964>.
- [114] Tajiri E, Yoshimura E, Hatamoto Y, Tanaka H, Shimoda S. Effect of sleep curtailment on dietary behavior and physical activity: a randomized crossover trial. *Physiol Behav* 2018;184:60–7. <https://doi.org/10.1016/j.physbeh.2017.11.008>.
- [115] Jean RE, Duttuluri M, Gibson CD, Mir S, Fuhrmann K, Eden E, Supariwala A. Improvement in physical activity in persons with obstructive sleep apnea treated with continuous positive airway pressure. *J Phys Act Health* 2017;14(3):176–82. <https://doi.org/10.1123/jpah.2016-0289>.
- [116] West SD, Kohler M, Nicoll DJ, Stradling JR. The effect of continuous positive airway pressure treatment on physical activity in patients with obstructive sleep apnoea: a randomised controlled trial. *Sleep Med* 2009;10(9):1056–8. <https://doi.org/10.1016/j.sleep.2008.11.007>.
- [117] Batool-Anwar S, Goodwin JL, Drescher AA, Baldwin CM, Simon RD, Smith TW, Quan SF. Impact of CPAP on activity patterns and diet in patients with obstructive sleep apnea (OSA). *J Clin Sleep Med* 2014;10(5):465–72. <https://doi.org/10.5664/jcsm.3686>.
- [118] Rosenberger ME, Fulton JE, Buman MP, Troiano RP, Grandner MA, Buchner DM, Haskell WL. The 24-hour activity cycle: a new paradigm for physical activity. *Med Sci Sports Exerc* 2019;51(3):454–64. <https://doi.org/10.1249/MSS.0000000000001811>.
- [119] Smith K, Rosenberger ME. Keeping seniors active—a 24 hour approach. 2017. p. 2017.
- [120] Grgic J, Dumuid D, Bengoechea EG, Shrestha N, Bauman A, Olds T, Pedisic Z. Health outcomes associated with reallocations of time between sleep, sedentary behaviour, and physical activity: a systematic scoping review of isotemporal substitution studies. *Int J Behav Nutr Phys Act* 2018;15(1):14795868. <https://doi.org/10.1186/s12966-018-0691-3>.
- [121] Stamatakis E, Rogers K, Ding D, Berrigan D, Chau J, Hamer M, Bauman A. All-cause mortality effects of replacing sedentary time with physical activity and sleeping using an isotemporal substitution model: a prospective study of 201,129 mid-aged and older adults. *Int J Behav Nutr Phys Act* 2015;12(1). <https://doi.org/10.1186/s12966-015-0280-7>.
- [122] Buman MP, Winkler EAH, Kurka JM, Hekler EB, Baldwin CM, Owen N, Ainsworth BE, Healy GN, Gardiner PA. Reallocating time to sleep, sedentary behaviors, or active behaviors: associations with cardiovascular disease risk biomarkers, NHANES 2005–2006. *Am J Epidemiol* 2014;179(3):323–34. <https://doi.org/10.1093/aje/kwt292>.
- [123] Biddle GJH, Edwardson CL, Henson J, Davies MJ, Khunti K, Rowlands AV, Yates T. Associations of physical behaviours and behavioural reallocations with markers of metabolic health: a compositional data analysis. *Int J Environ Res Public Health* 2018;15(10):16604601. <https://doi.org/10.3390/ijerph15102280>.
- [124] Dumuid D, Lewis LK, Olds TS, Maher C, Bondarenko C, Norton L. Relationships between older adults' use of time and cardio-respiratory fitness, obesity and cardio-metabolic risk: a compositional isotemporal substitution analysis. *Maturitas* 2018;110:104–10. <https://doi.org/10.1016/j.maturitas.2018.02.003>.
- [125] Buysse DJ. Sleep health: can we define it? Does it matter? *Sleep* 2014;37(1):9–17. <https://doi.org/10.5665/sleep.3298>.
- [126] Wilckens KA, Ferrarelli F, Walker MP, Buysse DJ. Slow-wave activity enhancement to improve cognition. *Trends Neurosci* 2018;41(7):470–82. <https://doi.org/10.1016/j.tins.2018.03.003>.
- [127] Kanagasabai T, Riddell MC, Ardern CI. Physical activity contributes to several sleep-cardiometabolic health relationships.

- Metab Syndr Relat Disord 2017;15(1):44–51. <https://doi.org/10.1089/met.2016.0103>.
- [128] Seixas AA, Vallon J, Barnes-Grant A, Butler M, Langford AT, Grandner MA, Schneeberger AR, Huthchinson J, Zizi F, Jean-Louis G. Mediating effects of body mass index, physical activity, and emotional distress on the relationship between short sleep and cardiovascular disease. Medicine 2018;97(37):e11939. <https://doi.org/10.1097/md.00000000000011939>.
- [129] Dobrosielski DA, Patil S, Schwartz AR, Bandeen-Roche K, Stewart KJ. Effects of exercise and weight loss in older adults with obstructive sleep apnea. Med Sci Sports Exerc 2015;47(1):20–6. <https://doi.org/10.1249/MSS.0000000000000387>.
- [130] Seixas AA, Henklewood DA, Williams SK, Jagannathan R, Ramos A, Zizi F, Jean-Louis G. Sleep duration and physical activity profiles associated with self-reported stroke in the United States: application of Bayesian belief network modeling techniques. Front Neurol 2018;9. <https://doi.org/10.3389/fneur.2018.00534>.
- [131] Wennman H, Kronholm E, Partonen T, Tolvanen A, Peltonen M, Vasankari T, Borodulin K. Interrelationships of physical activity and sleep with cardiovascular risk factors: a person-oriented approach. Int J Behav Med 2015;22(6):735–47. <https://doi.org/10.1007/s12529-015-9470-6>.
- [132] Wennman H, Kronholm E, Heinonen OJ, Kujala UM, Kaprio J, Partonen T, Bäckmand H, Sarna S, Borodulin K. Leisure time physical activity and sleep predict mortality in men irrespective of background in competitive sports. Progr Prev Med 2017;2(6): e0009. <https://doi.org/10.1097/pp9.0000000000000009>.
- [133] Wang J, Yin G, Li G, Liang W, Wei Q. Efficacy of physical activity counseling plus sleep restriction therapy on the patients with chronic insomnia. Neuropsychiatr Dis Treat 2015;11:2771–8. <https://doi.org/10.2147/NDT.S94724>.
- [134] Buman MP, Epstein DR, Gutierrez M, Herb C, Hollingshead K, Huberty JL, Hekler EB, Vega-López S, Ohri-Vachaspati P, Hekler AC, Baldwin CM. BeWell24: development and process evaluation of a smartphone “app” to improve sleep, sedentary, and active behaviors in US veterans with increased metabolic risk. Transl Behav Med 2016;6(3):438–48. <https://doi.org/10.1007/s13142-015-0359-3>.
- [135] Rayward AT, Murawski B, Plotnikoff RC, Vandelanotte C, Brown WJ, Holliday EG, Duncan MJ. A randomised controlled trial to test the efficacy of an m-health delivered physical activity and sleep intervention to improve sleep quality in middle-aged adults: the Refresh Study Protocol. Contemp Clin Trials 2018;73:36–50. <https://doi.org/10.1016/j.cct.2018.08.007>.

This page intentionally left blank

Chapter 24

Sleep and alcohol use

Subhajit Chakravorty^a, Audrey Mills^b, Kimberly Hayes^c and Ryan Krouse^d

^aPerelman School of Medicine, Philadelphia, PA, United States; ^bDrexel University College of Medicine, Philadelphia, PA, United States; ^cCpl.

Michael J. Crescenz VA Medical Center, Philadelphia, PA, United States; ^dCoatesville VA Medical Center, Coatesville, PA, United States

Introduction

Alcohol is a commonly used psychoactive substance in the community, with 56% of individuals 18 years or older reporting alcohol use in the past month. Its use has been linked to a wide range of sleep-related disorders and associated daytime consequences that may affect the individual's ability to function satisfactorily. Our understanding of alcohol's effect on sleep has improved dramatically over the last few decades because of advances in translational and clinical research at this interface. Alcohol may help an individual to fall asleep relatively quickly, but its deleterious effects involve disrupting underlying sleep mechanisms, interfering with the normal circadian mechanism, aggravating snoring and breathing-related sleep abnormalities, and triggering movements of the limbs during sleep. In this chapter, we examine the link between alcohol consumption (normal and pathological) and a range of sleep-related disorders.

Neurobiology of alcohol use

A vast majority of the metabolism of alcohol occurs in the liver via the alcohol dehydrogenase pathway [1]. A fraction of the alcohol consumed is metabolized in the brain through alternate mechanisms such as catalase (in cellular peroxisomes) and cytochrome P450 pathways. In the liver, alcohol (ethanol) is metabolized to acetaldehyde by an enzyme, alcohol dehydrogenase. Acetaldehyde is then converted to acetate by the enzyme, aldehyde dehydrogenase. Acetate is finally converted to acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle for its final metabolism. This metabolism of alcohol decreases the blood alcohol level in a time-dependent fashion and is directly related to the number of drinks consumed and the time elapsed since the last drink was ingested (Fig. 24.1). Acetaldehyde, the direct metabolite of alcohol, is also the most toxic byproduct of this pathway. In animal studies,

acetaldehyde has been shown to reduce REM sleep and CNS serotonin levels and may contribute to the sleep disturbance observed in alcohol use [2].

Insomnia and alcohol use

Introduction

Insomnia is probably the most investigated sleep disorder, although some studies have evaluated insomnia symptoms only, instead of it as a disorder. Insomnia disorder, as defined by the ICSD-3, necessitates the presence of one or more of the following complaints: difficulty initiating sleep, difficulty maintaining sleep, or waking up earlier than desired. These symptoms are associated with at least one of the following impairments: fatigue or malaise, attention or memory problems, impairment of psychosocial functioning, mood disturbance, daytime sleepiness, behavioral problems, reduced motivation or energy, proneness for errors, and concern or dissatisfaction with sleep. These complaints must occur despite an adequate opportunity and circumstance for sleep and are present for most nights of the week for 3 months or more [3].

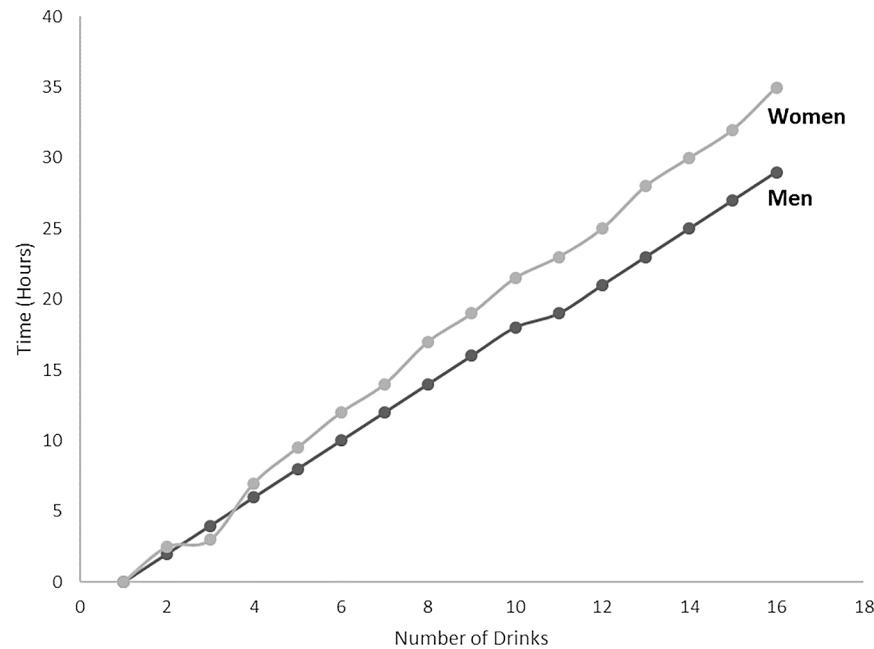
Epidemiology of alcohol use or misuse and sleep-related problems

While studies have predominantly shown that insomnia leads to alcohol consumption, some studies have also shown that drinking leads to insomnia. We will systematically approach this concept in the following sections.

Childhood sleep problems and future alcohol use

A few studies have shown that subjective sleep problems in children may lead to future alcohol consumption. A study of young boys from Western Pennsylvania (N = 145)

FIGURE 24.1 The time until blood alcohol level returns to zero versus number of drinks. Based on a body weight of 160 lbs. Adapted from data reported at <http://www.selfcounseling.com/help/alcohol/hourstozerobac.html>.



showed that poor sleep quality was associated with subsequent alcohol use as a young adult [4]. In adolescents, complaints of trouble sleeping as well as overtiredness have been associated with the onset of alcohol use in cross-sectional and longitudinal epidemiologic investigations [5,6]. However, one study failed to demonstrate such a relationship [7].

Adult sleep problems and alcohol use

Data on the relationship between insomnia and sleep is relatively robust in adults, with studies conducted across many countries. Among male Japanese industrial workers ($N = 271$), insomnia symptoms were associated with alcohol consumption more than half the days of the week ($OR = 2.6$, 95% CI: 1.1–5.7) [8]. Data from the Epidemiologic Catchment Area study (ECA, $N = 7954$) have shown that adults complaining of insomnia symptoms (10.2%) were at an increased risk for subsequently developing alcohol use disorder when evaluated a year later ($OR = 2.4$, 95% CI: 1.0–6.1) [9]. In a subsequent analysis of this dataset, uncomplicated insomnia symptoms (and without a lifetime history of psychiatric disorder) were associated with an increased risk of developing alcohol abuse a year later, as compared to those without baseline insomnia or any psychiatric disorder ($OR = 2.3$, 95% CI: 1.2–4.3) [10]. Similarly, in a longitudinal survey in Michigan, a lifetime history of insomnia symptoms was associated with an increased risk for incident diagnosis of alcohol use disorder 3.5 years later ($OR = 1.72$, 95% CI:

0.85–3.52) [11]. In a clinical sample of subjects with co-occurring alcohol use disorder and insomnia ($N = 63$), about half of the subjects (52%) reported having insomnia before their onset of alcohol use disorder [12]. Thus, the above data demonstrate that sleep problems at baseline may be linked to subsequent alcohol use or alcohol use disorder.

Do subjects with sleep problems gravitate toward alcohol consumption?

Some studies have demonstrated that individuals with insomnia prefer alcoholic drinks over nonalcoholic drinks. In a laboratory-based study, subjects with insomnia ($N = 11$) when compared with healthy sleepers ($N = 9$) chose more doses of alcohol and on more nights [13]. Furthermore, those complaining of insomnia may prefer alcohol to hypnotic medications. An epidemiologic investigation evaluated the use of alcohol ($N = 9226$) and hypnotic medications ($N = 9021$) as a sleep aid [14]. The results showed that the use of alcohol as a sleep aid was increased stepwise up to the age groups of 55–59 years and 40–44 years in men and women, respectively. Beyond these age categories, alcohol use decreased in a stepwise manner. Similar associations between insomnia and the use of alcohol as a hypnotic have been reported in other epidemiologic studies [15]. A survey of primary care patients demonstrated that the use of alcohol for sleep was positively associated with hazardous alcohol consumption ($OR = 4.53$, 95% CI: 2.9–6.9) [16]. Thus, individuals with

insomnia may prefer alcohol use to self-medicate their sleep problems.

Overnight polysomnographic sleep studies

The main polysomnographic sleep disturbances in active drinkers appear to be an increased sleep onset latency and increased duration of time spent awake after initially falling asleep. These changes may decrease the total time spent asleep [17].

Genetic studies

There is an emerging interest in evaluating associations between alcohol consumption, circadian clock genes, and other genes. Neuropeptide Y-deficient mice had increased use of alcohol, were less sensitive to the sedative or hypnotic effects of ethanol, and showed rapid recovery from ethanol-induced sleep [18]. The AA genotype of the single nucleotide polymorphism 10870 on the PER 2 gene has been associated with increased alcohol consumption in the presence of sleep problems only in adolescent males [19]. In a case-control study of subjects with alcohol abuse or alcohol use disorder ($N = 512$) and controls ($N = 511$), polymorphism of specific genes, including some clock genes such as RNTL, ARNTL2, VIP, and ADCYAP1, were associated with alcohol consumption and alcohol abuse. No association of PER2 with alcohol consumption or alcohol abuse/use disorder was seen in either gender [20]. In a sample of nonobese Japanese adult males ($N = 29$), the following associations between the clock genes and alcohol-related characteristics were seen: BMAL1 with alcohol consumption; PER2 and Gamma Glutamyl Transferase (GGT); and, CLOCK and GGT [21]. Thus, genetic polymorphisms of genes linked with alcohol use may also be associated with sleep.

Clinical findings

Insomnia and alcohol use among different populations

Heavy drinking is defined as the consumption in women of ≥ 4 standard drinks per day and in men ≥ 5 drinks per day. This behavior has been associated with insomnia symptoms in multiple populations, including adolescents, young adults, college students, older adults, Veterans, and firefighters.

(A) *Adolescents.* The KiGGS cross-sectional survey in Germany involving youth between the ages of 11–17 showed that the consumption of more than 5 drinks a week was associated with a 2-fold increased risk of insomnia complaints in both males and

females. Moreover, the risk of insomnia complaints was exacerbated with high alcohol use in females only (OR: 5.14, 95% CI: 2.89–9.13). In women, even low alcohol use (0–1 drinks/week) increased the risk for insomnia complaints (OR: 1.95, 95% CI: 1.42–2.66). Once the analysis was adjusted for caffeine use as a covariate, the predictive validity of alcohol on insomnia complaints was attenuated, suggesting an overestimation of alcohol's effect size on insomnia [22]. Adolescents between the ages of 14–20-year-old who presented to the ED, sleep problems were associated with unhealthy alcohol use and consuming alcohol to fall asleep [23]. Finally, among adolescents aged 12–21.9, alcohol use was associated with worse sleep quality [24]. Thus, alcohol consumption in this population is associated with sleep disturbance.

- (B) *College students.* Among heavy-drinking college students in New England, a reduction in weekly alcohol drinking was associated with improved sleep quality, implicating the role of sleep disturbance with alcohol consumption in this population [25].
- (C) *Adults.* A positive relationship between binge drinking and insomnia symptoms was seen in an epidemiologic investigation involving young adults. In this study, the effect of alcohol on sleep increased in magnitude with increased frequency of binge drinking [26]. In a nationally representative sample of Australian women between the ages of 25–30, binge drinking was associated with difficulty sleeping in a model adjusted for covariates [27]. In the Virginia Adult Twin Studies of Psychiatric and Substance Use Disorders ($N = 7500$), there was an 18% genetic overlap between insomnia and alcohol use disorder [28]. This genetic overlap further suggests that insomnia and alcohol misuse are genetically related and share similar etiological contributors, supporting the bi-directional nature of insomnia and alcohol use.

Although heavy drinking has been associated with insomnia symptoms in multiple populations, the causality is unclear from many of these cross-sectional studies. Haario and colleagues recently evaluated the relationship between insomnia and alcohol prospectively over 6 years, using longitudinal data from the Helsinki Health Study, a cohort of 40–60-year-old employees of the City of Helsinki ($N = 8960$) [29]. Their results showed that in the adjusted models, frequent insomnia symptoms at baseline were associated with subsequent heavy drinking (OR = 1.34, 95% C.I. = 1.07–1.68). Conversely, heavy drinking at baseline was associated with future insomnia symptoms (OR = 1.48, 95% C.I. = 1.22–1.80). This study added

evidence of the bi-directional relationship between alcohol use and insomnia.

- (D) *Older Adults.* Canham and colleagues evaluated the relationship between insomnia and binge drinking (4 or more drinks per session) in adults 50 or older. Their results demonstrated that older adults who binged on 2 or more days per week had 64% greater odds of insomnia than nonbinge drinkers. The odds of insomnia decreased to 35% in those with 2 or more binge drinking days per week when compared to non-binge drinkers. However, once smoking was added to the model, both these relationships fell just below the significance level [30]. A Canadian study of middle-aged and older adults showed a higher prevalence ratio (PR) of insomnia among binge drinkers (PR = 1.21, 95% C.I. = 1.02–1.43) [31]. In a Norwegian study involving middle to older adults, hazardous alcohol use interacted with insomnia and mental distress. Those with minimal levels of mental distress had higher odds of reporting insomnia (OR = 1.49, 95% C.I. = 1.20–1.85), whereas no such association was seen in those with high levels of mental distress [32]. In another study involving elderly Chinese respondents (N = 3176), frequent drinking (2 or more times per week) was associated with increased insomnia in men ($P = .04$). Conversely, occasional drinking in men was associated with lower odds of insomnia (OR = 0.59, 95% CI = 0.40–0.86) [33]. Thus, risky drinking in this population is associated with a higher risk of insomnia.
- (E) *Veterans and Firefighters.* Veterans are at a higher risk for insomnia. Among active US Army personnel before military deployment (N = 4101), alcohol use disorder was linked to a 1–1.5-fold increased risk of insomnia [34]. Cucciare and colleagues also demonstrated that binge drinking was linked to sleep-related complaints involving nightmares and sleep continuity disturbances [35]. Among firefighters (N = 112), Carey and colleagues demonstrated that the prevalence of sleep disturbance was 59%, whereas that of binge drinking was 58% among the respondents [36]. It is unclear how many of these firefighters had post-traumatic stress disorder, a risk factor associated with a higher prevalence of insomnia in those responding to traumatic events in the community. Thus, Haario cross-sectional data show that alcohol consumption and sleep disturbance are positively related to each other in veterans and firefighters.
- (F) *Pregnancy.* In a study involving Japanese women, those drinking during pregnancy had higher odds of complaining about difficulty initiating and maintaining sleep, and early morning awakening [37].

(G) *Perimenopausal state.* Although women in the perimenopausal phase of life have a higher prevalence of insomnia and psychiatric disorders, very little is known about the association of insomnia with alcohol consumption in this population. In a recent study, Blumel and colleagues evaluated sleep in middle-aged women across 11 Latin American countries. They found that 41.7% of peri-menopausal women reported insomnia on the Athens Insomnia Scale. The most prevalent insomnia symptom was an “awakening during the night” and problematic drinking was associated with sleep disturbance [38].

(H) *Individuals with Alcohol Use Disorder.* Alcohol Use Disorder (AUD) is a chronic brain disease that involves pathological alcohol consumption, biopsychosocial complications from the drinking, and a tendency for relapse when they stop drinking. A growing body of literature has demonstrated a higher prevalence of insomnia or sleep disturbance in individuals with AUD when compared to individuals in the community [17].

Insomnia in AUD

The prevalence of insomnia in AUD is estimated to be between 36% and 91% [17]. Consequences of insomnia in the population with AUD include continued relapse to drinking, lower quality of life, and decreased sleep duration, which, if sleep is less than 6 h, is known to have various physical and psychosocial health effects. We elaborate below on the findings related to insomnia from all stages of AUD, that include, active drinking, withdrawal, early recovery, and sustained recovery.

1. *Active Drinking in AUD.* This population is estimated to have insomnia, with a prevalence of approximately 74% using the Insomnia Severity Index and 76% using the Pittsburgh Sleep Quality Index (PSQI). In those actively drinking, the primary sleep continuity disturbances include increased sleep onset latency (SOL), shorter rapid eye movement (REM) sleep duration, increased wake after sleep onset time (WASO), and decreased total sleep time (TST) [17].
2. *During Acute Alcohol Withdrawal.* About 92% of patients in acute withdrawal from AUD have sleep disturbance. As alcohol withdrawal ends, insomnia may improve in some while it persists in others [17]. The cause of this heterogeneous presentation is currently unclear.
3. *During Early Recovery.* About 65% of patients with AUD report insomnia in early recovery, four to 8 weeks after cessation of alcohol use. The insomnia symptoms consist of increased SOL, greater WASO, and decreased TST [17].

- 4. During Sustained Recovery.** We define sustained recovery as abstinence from alcohol lasting longer than 3 months. The sleep-related abnormalities include greater SOL, decreased TST, and REM sleep irregularities. SOL is the first to normalize by around 9 months in recovery, whereas sleep fragmentation may persist up until 21 months. Napping during the day may perpetuate insomnia, as it increases WASO and decreases TST and SE [17].

Treatments

Does treatment of risky drinking improve insomnia?

Treatment of drinking does appear to improve sleep in several studies. Berman and colleagues evaluated a modified version of screening and online personalized feedback in 633 individuals with problematic drinking. Their results showed that 36% of the participants decreased their alcohol use during the 12 months with the intervention. Furthermore, those who reduced their alcohol use reported improved sleep quality, when compared to those who did not decrease their drinking (the associated Hedge's $g = 0.39$ showed a medium effect size of improvement) [39].

Pharmacologic treatments for insomnia in alcohol use disorder

The results of medication trials have demonstrated conflicting results for the treatment of insomnia. The medications evaluated include acamprosate, agomelatine, ramelteon, and triazolam. When compared to placebo, Trazodone improved sleep quality but decreased abstinence from alcohol [40]. Quetiapine demonstrated a short-term improvement in insomnia compared with placebo [41] but another study has shown that it may improve sleep continuity in those with insomnia at baseline [42].

Behavioral treatments for insomnia and alcohol use disorder

Progressive muscle relaxation (PMR) and Cognitive behavioral therapy for insomnia (CBT-I) are the primary behavioral interventions evaluated for treating insomnia in AUD. PMR improved sleep in patients, although its effect on alcohol consumption is unknown. CBT-I, a treatment modality primarily involving sleep restriction and stimulus control, has demonstrated preliminary efficacy in treating insomnia in this population. However, the available data shows that an improvement in insomnia may have little effect on improving abstinence from alcohol use [17].

In summary, the above body of knowledge shows us that insomnia likely has a bidirectional association with

heavy drinking, such that the presence of one disorder may subsequently lead to precipitation of the other. Insomnia is also highly prevalent across all the stages of AUD, and emerging data have shown that behavioral treatment is efficacious for treating insomnia in AUD.

Circadian rhythm abnormalities and alcohol use

Recent studies have demonstrated a relationship between alcohol consumption and disrupted circadian sleep-wake rhythms. Circadian rhythms result from the activity of the primary endogenous pacemaker, the suprachiasmatic nucleus (SCN) in the hypothalamus, and melatonin serves as a link between the circadian clock and the sleep-wake rhythms. The onset of melatonin secretion under dim light conditions [Dim Light Melatonin Onset (DLMO)] is a commonly used marker for evaluating the activity of the circadian pacemaker and for assessing the changes in the circadian phase, that is, advanced, or delayed [43]. Melatonin can be measured in blood or saliva samples. The peak of the salivary melatonin curve occurs around 2 AM in middle-aged males [44]. Another marker of sleep-wake rhythms is body temperature. Core body temperature varies across the circadian period (T_b) with a nadir of T_b around 5:00 a.m. Circadian sleep-wake rhythms may be “advanced” or “delayed” based on these shifts from normal variation, adjusting for an individual’s age.

Chronotype

The term chronotype denotes a person’s propensity to sleep during the time of the day, and constitutes the “evening,” “morning,” and the “indeterminate” types. The “evening” type (Eveningness) person or a person with a delayed sleep phase, prefers to go to bed later, wakes up later, has a greater need for sleep, and is commonly seen during adolescence and in those with psychiatric disorders. The “morning” type (Morningness) is also called the advanced sleep phase and is diametrically opposite to the delayed sleep phase on the chronotype spectrum. An individual with the “morning” type prefers to go to bed earlier and wake up earlier during the 24-h circadian day. Those in the “indeterminate” type do not meet the criteria for either the “morning” or the “evening” type. The “morning” and the “evening” types include about 25% of the population each whereas the “indeterminate” type constitutes about 50% of the population [45,46].

Clinical findings related to eveningness and alcohol use

The preference for a later sleep schedule in adolescents and the societal requirements for an earlier one may lead to

sleep-related complaints and increase the risk of substance abuse. A growing body of literature has demonstrated that eveningness is associated with higher alcohol consumption in adolescents, young adults, college students, and adults although two other studies failed to demonstrate such an association [47–51].

This relationship between eveningness and drinking may be complex and involve multiple underlying mechanisms. A study of 1127 twin pairs demonstrated that a genetic predisposition may exist in the relationship between eveningness and drinking. Among these twins, the “evening” type twins were more likely to consume higher amounts of alcohol and binge drink when compared to the “morning” type twins [52]. A later onset of melatonin secretion at night (DLMO) has been associated with greater severity of substance use problems in adolescents, college students, and young adults [53]. A recent study in adolescents demonstrated that greater circadian shifts in sleep between weekends and weekdays were associated with the decreased reactivity of the medial prefrontal cortex and striatum to reward [54]. The reduced responsiveness of these areas may play a role in the development of substance abuse problems in adolescents. Recent studies in adults have also shown that heavy drinking is also associated with eveningness, later weekend sleep timing, waking up later, and a misalignment in the sleep-wake schedule between weekdays and weekends [55]. Furthermore, a recent study showed the existence of a circadian variation in alcohol craving, with maximal severity in the evening and minimal in the morning. The frequency of drinking modulated this variation in craving but not the sleep timing or total duration [56]. Thus, eveningness is associated with alcohol consumption and may involve multiple underlying mechanisms.

Shiftwork and alcohol use

Alcohol's effect on shift work disorder is unclear due to the variability of findings across studies. Evening shift workers may have a higher risk of phase delay with alcohol use. In a study involving 22 healthy adult volunteers, consumption of 0.5 g/kg of alcohol for 7 days delayed the circadian phase in those working on the night shift, whereas workers on the daytime shift failed to demonstrate such a phase delay [57]. In a second study evaluating shift workers in four industries (printing, postal, nursing, and oil), long, rotating shifts increased the risk of binge drinking behavior but without an overall increase in alcohol consumption [58]. In the third study, night shift workers were more likely to complain of insomnia and endorse risky drinking behavior [59]. These emerging trends suggest that shift workers may indulge in unhealthy drinking patterns, and alcohol consumption may harm their sleep-wake cycle.

Chronopharmacokinetic studies

Research suggests that the bioavailability and metabolism of alcohol may be higher in the morning compared to later in the day [60]. Alcohol consumption may dampen circadian rhythms by blunting the body temperature variation or impairing melatonin secretion. In one study, alcohol consumption led to an overall blunting of the diurnal core body temperature rhythm [61] and in another study, moderate alcohol consumption decreased salivary melatonin levels, a measure of circadian activity [62]. These findings indicate that alcohol may blunt circadian biological rhythms.

Individuals with AUD

Prior research studies have also shown a disruption in circadian rhythm in individuals with AUD. In one study, individuals recovering from AUD showed a delayed evening rise of melatonin, lower melatonin levels during the earlier part of the night, and an associated increased sleep latency [63]. In another study, relative to controls, individuals with AUD demonstrated a slower rate of rise in melatonin level and a lower maximal amplitude of endogenous melatonin secretion [64]. Furthermore, a recent study showed that risky drinking was associated with eveningness, later midsleep timing, and shorter sleep duration [65]. The alcohol-related blunting of the circadian rhythm may also be a reason why patients with pathological alcohol use may complain of insomnia and insufficient sleep duration.

In conclusion, a growing body of literature demonstrates a bi-directional link between alcohol use and circadian rhythms. This blunted circadian rhythm in individuals with AUD may manifest as insomnia symptoms.

Sleep duration abnormalities and alcohol use

Sleep duration is the amount of sleep obtained during sleep at night or across 24 hours. The recommended sleep duration range to support optimal health in adults is 7–9 h [66]. Prior research studies have categorized abnormalities of sleep duration into short sleep duration (<6 h a night) and long sleep duration (≥ 9 h a night).

Short and long sleep duration

The estimated prevalence of short sleep duration in the general community varies from 9.3% to 40%. In adults, it has been linked to an increased risk of mortality, physical injuries, cardio-metabolic and psychiatric problems, and suicide [67]. In contrast to short sleep duration, very little is known about long sleep duration, although some studies

have linked it to cardiovascular diseases, anxiety, and depressive disorder [68,69].

Short sleep duration and alcohol consumption

Some prior epidemiologic studies have demonstrated an association between drinking and short sleep duration. In a survey of respondents in the Oxfordshire area in the UK, an inverse relationship was shown between alcohol consumption and sleep duration, especially in male respondents [70]. In another survey involving 21–25-year-old males (N = 955), those who complained of short sleep duration (<6 h a day) had the highest number of alcohol-related problems (missed school/work and blackouts), in contrast to those with long sleep duration [67]. Moreover, they also had a higher proportion of parents who sought psychiatric help, relative to those with normal sleep duration. A recent study evaluated drinking patterns and sleep duration among healthy adults in the Quebec Family Study in the Quebec metropolitan area of Canada [71]. The results showed that short sleepers (<6 h a night) consumed more alcohol than those with normal and long sleep duration. In models adjusted for covariates, those who reported short sleep duration had more risky drinking during the week. Respondents of either sex who endorsed short sleep duration were more likely to consume alcohol daily.

Long sleep duration and alcohol

In the study of young adults mentioned above [67], long sleepers (more than 9 h per day) reported a later mean age of onset of drinking and fewer drinking days per month, when compared to those with short sleep duration and normal sleep duration (7–8 h a night). They were concerned about the effects of alcohol and were considering abstention. Another large epidemiologic study evaluated the relationship between sleep duration and alcohol consumption in 110,441 Americans [72]. Their results demonstrated that increased weekly alcohol consumption was associated with an increased risk of reporting abnormal sleep duration which included both short (≤ 6 h a night) and long sleep duration (≥ 9 h), while the lowest risk was for individuals who consumed 6–12 drinks a week.

Clinical findings in adolescents and young adults

Prior studies have reported abnormalities in sleep duration in actively drinking adolescents and college students. In one study involving preadolescent boys, insufficient sleep duration was linked to a higher risk of subsequent alcohol use as adults [4]. In another study of adolescent students, respondents who reported longer sleep duration had a lower risk of heavy drinking [73]. A study of college

students showed a similar trend where inadequate sleep was correlated with more alcohol-related consequences [74]. In contrast to the above findings, some other studies failed to demonstrate an association between alcohol use and sleep duration [7].

In summary, pathological alcohol consumption, such as heavy drinking and AUD, may increase the risk of sleep duration abnormalities, especially short sleep duration. Future studies should evaluate the relationship between alcohol consumption and long sleep duration, and how insomnia interacts with short sleep duration in the context of heavier alcohol use.

Breathing-related sleep disorders and alcohol use

Breathing-related sleep events

Breathing-related sleep events consist of snoring, apneas, and hypopneas. Snoring results from a mismatch between an increased airflow and a reduced upper airway tone. Apnea is defined as a complete cessation of airflow for 10 or more seconds. Hypopnea is a partial airflow obstruction that is 30% or greater (for 10 or more seconds) and is associated with either a decrease in arterial oxygen desaturation that is at least 4% in magnitude or an episode of arousal (for 10 or more seconds) [75].

Breathing-related sleep disorders

Breathing-related sleep disorders are broadly classified into obstructive sleep apnea syndrome and central sleep apnea syndromes, with the main difference between them being the presence of respiratory effort in the former and absence in the latter. These conditions are diagnosed with either in-laboratory polysomnography (PSG) or home sleep testing (HST) using a portable monitor.

The ICSD-3 recommends a diagnosis of obstructive sleep apnea syndrome (OSA) based solely on overnight sleep study measures or a combination of symptoms and findings from a sleep study. Subjective information suggestive of OSA includes a history of habitual snoring, waking up with breath holding or gasping/choking, complaints of sleepiness, fatigue, or insomnia, and a prior diagnosis of cardiovascular disease, diabetes, mood disorder, or cognitive dysfunction. One or more of these criteria mentioned above is required to diagnose OSA, along with PSG/HST testing demonstrating at least five respiratory events/hour of sleep that are predominantly obstructive. Alternatively, OSA is diagnosed by having ≥ 15 obstructive respiratory events per hour of sleep on PSG/HST testing [3]. A similar criterion is used for central sleep apnea syndrome where the respiratory events are predominantly central sleep events and consist of episodes of

complete cessation of airflow and breathing effort for 10 or more seconds.

Effect of alcohol use on breathing during sleep

Alcohol can impair normal breathing during sleep by one of two possible mechanisms: first, it can impair the normal arousal response to airway occlusion [76]; second, it can relax a muscle at the base of the tongue (the genioglossus muscle). This relaxation leads to an increased resistance in the upper airway, airway collapse, and triggers snoring in some healthy adults and aggravation of snoring in habitual snorers [77,78]. In addition to snoring, moderate alcohol consumption can aggravate respiratory events with or without a drop in arterial oxygen saturation levels, especially within the first 2–3 h of sleep [77,78]. However, one study did not demonstrate this association between alcohol use and increased sleep-related breathing events in the laboratory [79]. A recent meta-analysis of 14 studies examined the effect of alcohol on breathing parameters in sleep and replicated some of these findings. The authors demonstrated that when compared to placebo, alcohol increased the apnea-hypopnea index (breathing-related sleep events) and reduced the oxyhemoglobin saturation in the blood. Furthermore, these differences were more pronounced in those with a history of habitual snoring and those already diagnosed with obstructive sleep apnea [80].

Obstructive sleep apnea has also been associated with AUD in prior studies. These individuals have more breathing-related sleep events than healthy controls, during early withdrawal from alcohol in in-laboratory studies and as seen in a population-based study from Taiwan [81,82]. Treatment-seeking patients with AUD may have a higher prevalence of obstructive sleep apnea than control subjects [83].

Thus, alcohol consumption is associated with breathing-related sleep disorders. It may aggravate snoring and increase respiratory events during sleep, especially those with pre-existing snoring and obstructive sleep apnea. These relationships may be significant in middle-aged individuals with AUD, a population with a higher prevalence of breathing-related sleep events. Finally, to the best of our knowledge, there are no studies that have evaluated the effects of alcohol on central sleep apnea or mixed apnea (in those with or without AUD) or have evaluated the longitudinal trends in breathing-related sleep indices when subjects transition from heavy drinking to sustained recovery. In the absence of data on treatment for obstructive sleep apnea in AUD, current treatments include recommendations to avoid or minimize alcohol use, weight loss in overweight patients, treatment with a mandibular device (for mild or moderate obstructive sleep apnea), positive airway pressure device, or upper airway surgery.

Sleep-related movement disorders and alcohol use

These disorders primarily involve abnormal limb movements and consist of Restless Leg Syndrome (RLS) and Periodic Leg Movement Disorder (PLMD). The abnormal limb movements interfere with falling asleep or staying asleep through the night and some individuals with these disorders may use alcohol to self-medicate their sleep problems, although very little information exists about this relationship. Other conditions in this category of sleep disorders include sleep-related bruxism, sleep-related leg cramps, and sleep-related rhythmic movement disorder.

Restless leg syndrome

RLS is a condition that predominantly occurs in the evening or at night-time, where the individual complains of an uncomfortable and unpleasant sensation in the legs that begins or worsens during rest or inactivity. The person attempts activities such as walking or stretching to suppress these unpleasant sensations, and in trying to do so, s/he has difficulty falling asleep.

There is limited data linking alcohol consumption with RLS. In one study, alcohol consumption increased the risk of complaining about RLS symptoms by 1.5 times [37]. Another study demonstrated a lower risk of RLS symptoms with alcohol consumption of one drink a month or less when compared to higher drinking levels [84]. Some other studies have either reported a protective effect of alcohol consumption against RLS symptoms or failed to demonstrate a link between alcohol use and RLS symptoms [85,86]. These findings show that the association between RLS and alcohol consumption requires more study.

Periodic limb movement disorder

PLMD is diagnosed using overnight polysomnography and employing a criterion of >15 limb movements per hour of sleep among adults, primarily in the lower extremities. In this condition, the patient may present to the clinic with sleep disturbance and resultant impairment of functioning, which are not explained by another sleep, medical, neurologic, or psychiatric disorder [3].

Some studies have shown that alcohol consumption increases the risk of having periodic limb movements (PLMs) during sleep. One study evaluated the effect of alcohol consumption on periodic limb movements during sleep using overnight sleep studies [87]. They showed that women consuming two or more alcoholic beverages had a higher index of limb movements than those who drank fewer than two drinks per day. Although a similar trend was seen in men, the results did not reach statistical significance. Similarly, alcohol use in AUD has been linked to

periodic limb movement disorder in another study. This study showed that individuals with AUD had an elevated periodic limb movement index when compared to healthy control subjects during early recovery, and this higher PLM index increased the risk of relapse in early recovery [88]. Recommended treatments for RLS and PLMD are dopaminergic medications such as ropinirole, pramipexole, or gabapentinoids, although magnesium may benefit some patients with AUD and PLMD during early recovery [89].

Sleep-related bruxism consists of frequent or regular teeth-grinding sounds during sleep that may lead to abnormal tooth wear, jaw pain, and headaches. Alcohol consumption has been associated with self-reported complaints of bruxism and with objective activity of the jaw muscles during sleep [90–92]. The relationship between drinking and sleep-related leg cramps or sleep-related rhythmic movement disorder is unknown due to the lack of research at this interface.

In summary, alcohol consumption may increase the risk of periodic limb movement disorder and sleep-related bruxism. More research is needed to demonstrate how alcohol consumption and restless leg syndrome are linked.

Parasomnias and alcohol use

Parasomnias are defined as “undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep” resulting in disturbed sleep and include sleepwalking and sleep terrors that occur during sleep [3]. These disorders may result in psychosocial problems and place the person at risk of injury. Parasomnias may occur during either non-REM (nonrapid eye movement), REM (rapid eye movement) sleep, or during transitions to and from sleep.

NREM-related parasomnias in adults primarily include sleepwalking and sleep-related eating disorder. Sleepwalking episodes involve getting out of bed and involve movements that are usually nongoal-directed and may be complex. Sleep-related eating disorder involves recurrent episodes of dysfunctional eating, including inappropriate items such as inedible or toxic items. In pursuing these activities or their consequences, the person may place themselves at risk of harm. The relationship between alcohol and NREM-related parasomnias is unclear currently. REM-related parasomnia includes REM behavioral disorder (RBD). RBD involves repeated vocalization or complex motor behaviors in sleep and occurs during REM sleep. RBD may lead the person to act out on their dreams and usually has a chronic course. However, an acute form of RBD has been reported during acute withdrawal from alcohol and sedative-hypnotic agents. It may occur during aggravated REM sleep rebound states, characterized by more extended and pronounced REM sleep due to previous REM deprivation related to alcohol use [3].

Specific studies evaluating the association of alcohol use with parasomnias are lacking. Sleep paralysis has been associated with higher alcohol consumption in two studies, one involving college students and the other involving adults in varying professions. We acknowledge the ongoing debate about slow wave sleep, alcohol use, and parasomnias and the need for future studies, including spectral analysis scoring of overnight polysomnographic sleep data to discriminate those with sleepwalking and controls [93,94].

No specific guidelines exist for treating parasomnias, except for REM Behavior Disorder, where a low dose of clonazepam or a high dose of melatonin may be beneficial. A general recommendation is to avoid alcohol consumption in those at risk for these sleep disorders.

Other sleep-related issues associated with alcohol use

Alcohol use during pregnancy has many harmful effects on the infant. Habitual drinking by mothers may have implications for their children’s sleep. When compared to abstinent mothers, infants born to mothers with a history of binge drinking or AUD showed an increased power of their electroencephalographic activity in NREM and REM sleep. Mothers who indulged in binge drinking during the first 6 weeks of pregnancy rather than heavy drinking had a five times higher risk of having infants with sleep problems [95] whereas an increased frequency of binge drinking during these first 6 weeks of pregnancy was linked to a 6-fold higher risk of the infant having sleep-related problems [96].

In adults, some studies have evaluated the effect of alcohol on napping and narcolepsy. Napping involves a sleep episode lasting several minutes to a few hours during an individual’s expected waking period [97]. One study showed that social drinking may be correlated with fewer daytime naps [98].

In summary, risky alcohol use by the mother may increase the risk of their infants subsequently developing sleep-related problems.

Discussion

A growing body of literature is showing us that alcohol use, especially heavy drinking, has a deleterious effect on an individual’s sleep. In the context of alcohol consumption, insomnia is the most investigated sleep disorder. This relationship between alcohol use and insomnia is bidirectional, as data from multiple sources have demonstrated that the presence of one disorder (insomnia or pathological drinking) may lead to the other in the future. This bidirectional relationship directly impacts their clinical care

and needs to be kept in mind while planning or coordinating treatment. Alcohol consumption also impacts circadian rhythms, sleep duration irregularities, breathing-related sleep disorders, sleep-related movement disorders, and parasomnias. In addition to the above, maternal drinking also affects the infant's sleep. Future studies should clarify these associations.

References

- [1] Heit C, Dong H, Chen Y, Thompson DC, Deitrich RA, Vasiliou VK. The role of CYP2E1 in alcohol metabolism and sensitivity in the central nervous system. *Subcell Biochem* 2013;67:235–47. https://doi.org/10.1007/978-94-007-5881-0_8.
- [2] Francoperez J, Padilla M, Paz C. Sleep and brain monoamine changes produced by acute and chronic acetaldehyde administration in rats. *Behav Brain Res* 2006;174(1):86–92. <https://doi.org/10.1016/j.bbr.2006.07.008>.
- [3] AASM. International classification of sleep disorders - Third Edition.
- [4] Mike TB, Shaw DS, Forbes EE, Sitnick SL, Hasler BP. The hazards of bad sleep—sleep duration and quality as predictors of adolescent alcohol and cannabis use. *Drug Alcohol Depend* 2016;168:335–9. <https://doi.org/10.1016/j.drugalcdep.2016.08.009>.
- [5] Wong MM, Brower KJ, Fitzgerald HE, Zucker RA. Sleep problems in early childhood and early onset of alcohol and other drug use in adolescence. *Alcohol Clin Exp Res* 2004;28(4):578–87. <https://doi.org/10.1097/01.ALC.0000121651.75952.39>.
- [6] Wong MM, Brower KJ, Zucker RA. Childhood sleep problems, early onset of substance use and behavioral problems in adolescence. *Sleep Med* 2009;10(7):787–96. <https://doi.org/10.1016/j.sleep.2008.06.015>.
- [7] Van Reen E, Roane BM, Barker DH, McGeary JE, Borsari B, Carskadon MA. Current alcohol use is associated with sleep patterns in first-year college students. *Sleep* 2016;39(6):1321–6. <https://doi.org/10.5665/sleep.5862>.
- [8] Tachibana H, Izumi T, Honda S, Horiguchi I, Manabe E, Takemoto T. A study of the impact of occupational and domestic factors on insomnia among industrial workers of a manufacturing company in Japan. *Occup Med* 1996;46(3):221–7. <https://doi.org/10.1093/occmed/46.3.221>.
- [9] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? *J Am Med Assoc* 1989;262(11):1479–84. <https://doi.org/10.1001/jama.1989.03430110069030>.
- [10] Weissman MM, Greenwald S, Niño-Murcia G, Dement WC. The morbidity of insomnia uncomplicated by psychiatric disorders. *Gen Hosp Psychiatry* 1997;19(4):245–50. [https://doi.org/10.1016/S0163-8343\(97\)00056-X](https://doi.org/10.1016/S0163-8343(97)00056-X).
- [11] Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996;39(6):411–8. [https://doi.org/10.1016/0006-3223\(95\)00188-3](https://doi.org/10.1016/0006-3223(95)00188-3).
- [12] Currie SR, Clark S, Rimac S, Malhotra S. Comprehensive assessment of insomnia in recovering alcoholics using daily sleep diaries and ambulatory monitoring. *Alcohol Clin Exp Res* 2003;27(8):1262–9. <https://doi.org/10.1097/01.alc.0000081622.03973.57>.
- [13] Roehrs T, Papineau K, Rosenthal L, Roth T. Ethanol as a hypnotic in insomniacs: self administration and effects on sleep and mood. *Neuropsychopharmacology* 1999;20(3):279–86. [https://doi.org/10.1016/S0893-133X\(98\)00068-2](https://doi.org/10.1016/S0893-133X(98)00068-2).
- [14] Kaneita Y, Uchiyama M, Takemura S, Yokoyama E, Miyake T, Harano S, Asai T, Tsutsui T, Kaneko A, Nakamura H, Ohida T. Use of alcohol and hypnotic medication as aids to sleep among the Japanese general population. *Sleep Med* 2007;8(7–8):723–32. <https://doi.org/10.1016/j.sleep.2006.10.009>.
- [15] Johnson EO, Roehrs T, Roth T, Breslau N. Epidemiology of alcohol and medication as aids to sleep in early adulthood. *Sleep* 1998;21(2):178–86. <https://doi.org/10.1093/sleep/21.2.178>.
- [16] Vinson DC, Manning BK, Galliher JM, Dickinson LM, Pace WD, Turner BJ, Abraham A, Allen R, Austin R, Balasubrahmanyam R, Bayer WH, Benold T, Bershow R, Brull J, Bujold E, Cairney L, Church S, Curry S, Dickerman J, Farley T, Farmer J, Faulkner SE, Finnie M, Fisher L, Fortunato M, Fox C, Girmay A, Guthrie K, Hahn DL, Hammer D, Holland L, Inoue S, Johnson DS, Joshi N, Kachoria R, Krohn K, Lee WD, Longnecker S, Lopez B, Lupold C, Macken K, Mase J, McMaster S, Michel Y, Modjeski N, Narula J, Njoku C, Ocloo S, Panthangi V, Parchman ML, Patton J, Pearson T, Peterson D, Pribbenow B, Raikhel M, Rasmussen D, Reynolds W, Reynolds E, Ross D, Runkle G, Sharma H, Spector E, Stewart L, Walker L, West P, Womack G, Wu F. Alcohol and sleep problems in primary care patients: a report from the AAFP national research network. *Ann Fam Med* 2010;8(6):484–92. <https://doi.org/10.1370/afm.1175>.
- [17] Chakravorty S, Chaudhary NS, Brower KJ. Alcohol dependence and its relationship with insomnia and other sleep disorders. *Alcoholism* 2016;40(11):2271–82. <https://doi.org/10.1111/acer.13217>.
- [18] Thiele TE, Marsh DJ, Marie LS, Bernstein IL, Palmiter RD. Ethanol consumption and resistance are inversely related to neuropeptide Y levels. *Nature* 1998;396(6709):366–9. <https://doi.org/10.1038/24614>.
- [19] Comasco E, Nordquist N, Göktürk C, Åslund C, Hallman J, Oreland L, Nilsson KW. The clock gene PER2 and sleep problems: association with alcohol consumption among Swedish adolescents. *Upsala J Med Sci* 2010;115(1):41–8. <https://doi.org/10.3109/03009731003597127>.
- [20] Kovanen L, Saarikoski ST, Haukka J, Pirkola S, Aromaa A, Lonnqvist J, Partonen T. Circadian clock gene polymorphisms in alcohol use disorders and alcohol consumption. *Alcohol Alcoh* 2010;45(4):303–11. <https://doi.org/10.1093/alcalc/agq035>.
- [21] Ando H, Ushijima K, Kumazaki M, Eto T, Takamura T, Irie S, Kaneko S, Fujimura A. Associations of metabolic parameters and ethanol consumption with messenger RNA expression of clock genes in healthy men. *Chronobiol Int* 2010;27(1):194–203. <https://doi.org/10.3109/07420520903398617>.
- [22] Skarupke C, Schlack R, Lange K, Goerke M, Dueck A, Thome J, Szagun B, Cohrs S. Insomnia complaints and substance use in German adolescents: did we underestimate the role of coffee consumption? Results of the KiGGS study. *J Neural Transm* 2017;124(S1):69–78. <https://doi.org/10.1007/s00702-015-1448-7>.
- [23] Zhabenko O, Austic E, Conroy DA, Ehrlich P, Singh V, Epstein-Ngo Q, Cunningham RM, Walton MA. Substance use as a risk factor for sleep problems among adolescents presenting to the emergency department. *J Addict Med* 2016;10(5):331–8. <https://doi.org/10.1097/ADM.0000000000000243>.

- [24] Hasler BP, Casement MD, Sitnick SL, Shaw DS, Forbes EE. Eveningness among late adolescent males predicts neural reactivity to reward and alcohol dependence two years later. *Behav Brain Res* 2017;327:112–20. <https://doi.org/10.1016/j.bbr.2017.02.024>.
- [25] Fucito LM, DeMartini KS, Hanrahan TH, Yaggi HK, Heffern C, Redeker NS. Using sleep interventions to engage and treat heavy-drinking college students: a randomized pilot study. *Alcoholism* 2017;41(4):798–809. <https://doi.org/10.1111/acer.13342>.
- [26] Popovici I, French MT. Does unemployment lead to greater alcohol consumption? *Ind Relat* 2013;52(2):444–66. <https://doi.org/10.1111/irel.12019>.
- [27] Bruck D, Astbury J. Population study on the predictors of sleeping difficulties in young Australian women. *Behav Sleep Med* 2012;10(2):84–95. <https://doi.org/10.1080/15402002.2011.592888>.
- [28] Lind MJ, Hawn SE, Sheerin CM, Aggen SH, Kirkpatrick RM, Kendler KS, Amstadter AB. An examination of the etiologic overlap between the genetic and environmental influences on insomnia and common psychopathology. *Depress Anxiety* 2017;34(5):453–62. <https://doi.org/10.1002/da.22587>.
- [29] Haario P, Rahkonen O, Laaksonen M, Lahelma E, Lallukka T. Bidirectional associations between insomnia symptoms and unhealthy behaviours. *J Sleep Res* 2013;22(1):89–95. <https://doi.org/10.1111/j.1365-2869.2012.01043.x>.
- [30] Canham SL, Kaufmann CN, Mauro PM, Mojtabai R, Spira AP. Binge drinking and insomnia in middle-aged and older adults: the Health and Retirement Study. *Int J Geriatr Psychiatry* 2015;30(3):284–91. <https://doi.org/10.1002/gps.4139>.
- [31] Hussain J, Ling L, Alonso RT, Rodrigues R, Nicholson K, Stranges S, Anderson KK. Associations between sleep patterns, smoking, and alcohol use among older adults in Canada: insights from the Canadian Longitudinal Study on Aging (CLSA). *Addict Behav* 2022;132:107345. <https://doi.org/10.1016/j.addbeh.2022.107345>.
- [32] Husberg VH, Hopstock LA, Friberg O, Rosenvinge JH, Bergvik S, Rognmo K. Epidemiology of comorbid hazardous alcohol use and insomnia in 19 185 women and men attending the population-based Tromso Study. *BMC Public Health* 2015;22(1):2015.
- [33] Wang YM, Chen HG, Song M, Xu SJ, Yu LL, Wang L, Wang R, Shi L, He J, Huang YQ, Sun HQ, Pan CY, Wang XY, Lu L. Prevalence of insomnia and its risk factors in older individuals: a community-based study in four cities of Hebei Province, China. *Sleep Med* 2016;19:116–22. <https://doi.org/10.1016/j.sleep.2015.10.018>.
- [34] Taylor DJ, Pruijsma KE, Hale WJ, Kelly K, Maurer D, Peterson AL, Mintz J, Litz BT, Williamson DE. Prevalence, correlates, and predictors of insomnia in the US army prior to deployment. *Sleep* 2016;39(10):1795–806. <https://doi.org/10.5665/sleep.6156>.
- [35] Cucciare MA, Darrow M, Weingardt KR. Characterizing binge drinking among U.S. military veterans receiving a brief alcohol intervention. *Addict Behav* 2011;36(4):362–7. <https://doi.org/10.1016/j.addbeh.2010.12.014>.
- [36] Carey MG, Al-Zaiti SS, Dean GE, Sessanna L, Finnell DS. Sleep problems, depression, substance use, social bonding, and quality of life in professional firefighters. *J Occup Environ Med* 2011;53(8):928–33. <https://doi.org/10.1097/JOM.0b013e318225898f>.
- [37] Kaneita Y, Ohida T, Takemura S, Sone T, Suzuki K, Miyake T, Yokoyama E, Umeda T. Relation of smoking and drinking to sleep disturbance among Japanese pregnant women. *Prev Med* 2005;41(5–6):877–82. <https://doi.org/10.1016/j.ypmed.2005.08.009>.
- [38] Blümel JE, Cano A, Mezones-Holgún E, Barón G, Bencosme A, Benítez Z, Bravo LM, Calle A, Flores D, Espinoza MT, Gómez G, Hernández-Bueno JA, Laribeza F, Martino M, Lima S, Monterrosa A, Mostajo D, Ojeda E, Onatra W, Sánchez H, Tserotas K, Vallejo MS, Witús S, Zúñiga MC, Chedraui P. A multinational study of sleep disorders during female mid-life. *Maturitas* 2012;72(4):359–66. <https://doi.org/10.1016/j.maturitas.2012.05.011>.
- [39] Berman AH, Wennberg P, Sinadinovic K. Changes in mental and physical well-being among problematic alcohol and drug users in 12-month Internet-based intervention trials. *Psychol Addict Behav* 2015;29(1):97–105. <https://doi.org/10.1037/a0038420>.
- [40] Friedmann PD, Rose JS, Swift R, Stout RL, Millman RP, Stein MD. Trazodone for sleep disturbance after alcohol detoxification: a double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 2008;32(9):1652–60. <https://doi.org/10.1111/j.1530-0277.2008.00742.x>.
- [41] Chakravorty S, Hanlon AL, Kuna ST, Ross RJ, Kampman KM, Witte LM, Perlis ML, Oslin DW. The effects of quetiapine on sleep in recovering alcohol-dependent subjects: a pilot study. *J Clin Psychopharmacol* 2014;34(3):350–4.
- [42] Krouse RA, Morales KH, Kampman KM, Chakravorty S. The role of baseline insomnia in moderating the hypnotic properties of quetiapine. *Addict Behav* 2023;140:107622. <https://doi.org/10.1016/j.addbeh.2023.107622>.
- [43] Pandi-Perumal SR, Smits M, Spence W, Srinivasan V, Cardinali DP, Lowe AD, Kayumov L. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31(1):1–11. <https://doi.org/10.1016/j.pnpbp.2006.06.020>.
- [44] Zhou JN, Liu RY, Van Heerikhuize J, Hofman MA, Swaab DF. Alterations in the circadian rhythm of salivary melatonin begin during middle-age. *J Pineal Res* 2003;34(1):11–6. <https://doi.org/10.1034/j.1600-079X.2003.01897.x>.
- [45] Taillard J, Philip P, Chastang JF, Bioulac B. Validation of horne and ostberg morningness-eveningness questionnaire in a middle-aged population of French workers. *J Biol Rhythms* 2004;19(1):76–86. <https://doi.org/10.1177/0748730403259849>.
- [46] Paine Sarah-J, Gander PH, Travier N. The epidemiology of morningness/eveningness: influence of age, gender, ethnicity, and socioeconomic factors in adults (30–49 Years). *J Biol Rhythms* 2006;21(1):68–76. <https://doi.org/10.1177/0748730405283154>.
- [47] Pieters S, Burk WJ, Van der Vorst H, Dahl RE, Wiers RW, Engels RCME. Prospective relationships between sleep problems and substance use, internalizing and externalizing problems. *J Youth Adolesc* 2015;44(2):379–88. <https://doi.org/10.1007/s10964-014-0213-9>.
- [48] Onyper SV, Thacher PV, Gilbert JW, Gradess SG. Class start times, sleep, and academic performance in college: a path analysis. *Chronobiol Int* 2012;29(3):318–35. <https://doi.org/10.3109/07420528.2012.655868>.
- [49] Wittmann M, Paulus M, Roenneberg T. Decreased psychological well-being in late chronotypes is mediated by smoking and alcohol consumption. *Subst Use Misuse* 2010;5(1–2):15–30. <https://doi.org/10.3109/10826080903498952>.

- [50] Martin JS, Gaudreault MM, Perron M, Laberge L. Chronotype, light exposure, sleep, and daytime functioning in high school students attending morning or afternoon school shifts: an actigraphic study. *J Biol Rhythms* 2016;31(2):205–17. <https://doi.org/10.1177/0748730415625510>.
- [51] Burgess HJ, Rizvydeen M, Fogg LF, Ali K. A single dose of alcohol does not meaningfully alter circadian phase advances and phase delays to light in humans. *Am J Physiol Regul Integr Comp Physiol* 2016;310(8):R759. <https://doi.org/10.1152/ajpregu.00001.2016>.
- [52] Watson NF, Buchwald D, Paige Harden K. A twin study of genetic influences on diurnal preference and risk for alcohol use outcomes. *J Clin Sleep Med* 2013;9(12):1333–9. <https://doi.org/10.5664/jcsm.3282>.
- [53] Hasler BP, Bootzin RR, Cousins JC, Fridel K, Wenk GL. Circadian phase in sleep-disturbed adolescents with a history of substance abuse: a pilot study. *Behav Sleep Med* 2008;6(1):55–73. <https://doi.org/10.1080/15402000701796049>.
- [54] Hasler BP, Smith LJ, Cousins JC, Bootzin RR. Circadian rhythms, sleep, and substance abuse. *Sleep Med Rev* 2012;16(1):67–81. <https://doi.org/10.1016/j.smrv.2011.03.004>.
- [55] Burgess HJ, Rizvydeen M, Kikyo F, Kebbeh N, Tan M, Roecklein KA, Hasler BP, King AC, Cao D. Sleep and circadian differences between light and heavy adult alcohol drinkers. *Alcoholism* 2022;46(7):1181–91. <https://doi.org/10.1111/acer.14872>.
- [56] Hisler GC, Pedersen SL, Hasler BP. The 24-hour rhythm in alcohol craving and individual differences in sleep characteristics and alcohol use frequency. *Alcohol Clin Exp Res* 2022;46(6):1084–93. <https://doi.org/10.1111/acer.14826>.
- [57] Swanson GR, Gorenz A, Shaikh M, Desai V, Kaminsky T, van Den Berg J, Murphy T, Raeisi S, Fogg L, Vitaterna MH, Forsyth C, Turek F, Burgess HJ, Keshavarzian A. Night workers with circadian misalignment are susceptible to alcohol-induced intestinal hyperpermeability with social drinking. *Am J Physiol Gastrointest Liver Physiol* 2016;311(1):G192. <https://doi.org/10.1152/ajpgi.00087.2016>.
- [58] Dorrian J, Heath G, Sargent C, Banks S, Coates A. Alcohol use in shiftworkers. *Acc Anal Prev* 2017;99:395–400. <https://doi.org/10.1016/j.aap.2015.11.011>.
- [59] Plescia F, Cirrincione L, Martorana D, Ledda C, Rapisarda V, Castelli V, Martines F, Vinnikov D, Cannizzaro E. Alcohol abuse and insomnia disorder: focus on a group of night and day workers. *Int J Environ Res Publ Health* 2021;18(24):13196. <https://doi.org/10.3390/ijerph182413196>.
- [60] Danel T, Touitou Y. Chronobiology of alcohol: from chronokinetics to alcohol-related alterations of the circadian system. *Chronobiol Int* 2004;6:923–35. <https://doi.org/10.1081/CBI-200036886>.
- [61] Danel T, Libersa C, Touitou Y. The effect of alcohol consumption on the circadian control of human core body temperature is time dependent. *Am J Physiol Regul Integr Comp Physiol* 2001;281(1):R52. <https://doi.org/10.1152/ajpregu.2001.281.1.r52>.
- [62] Rupp TL, Acebo C, Carskadon MA. Evening alcohol suppresses salivary melatonin in young adults. *Chronobiol Int* 2007;24(3):463–70. <https://doi.org/10.1080/07420520701420675>.
- [63] Kühlwein E, Hauger RL, Irwin MR. Abnormal nocturnal melatonin secretion and disordered sleep in abstinent alcoholics. *Biol Psychiatry* 2003;54(12):1437–43. [https://doi.org/10.1016/S0006-3223\(03\)00005-2](https://doi.org/10.1016/S0006-3223(03)00005-2).
- [64] Conroy DA, Hairston IS, Arnedt JT, Hoffmann RF, Armitage R, Brower KJ. Dim light melatonin onset in alcohol-dependent men and women compared with healthy controls. *Chronobiol Int* 2012;29(1):35–42. <https://doi.org/10.3109/07420528.2011.636852>.
- [65] Boness CL, Hasler BP, Sheehan H, Pedersen SL. Associations between specific sleep and circadian characteristics and alcohol use disorder criteria and problems. *Addict Behav* 2022;132:107348. <https://doi.org/10.1016/j.addbeh.2022.107348>.
- [66] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M, Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *J Clin Sleep Med* 2015;6:591–2. <https://doi.org/10.5664/jcsm.4758>.
- [67] Schuckit MA, Bernstein LI. Sleep time and drinking history: a hypothesis. *Am J Psychiatr* 1981;138(4):528–30. <https://doi.org/10.1176/ajp.138.4.528>.
- [68] Cappuccio FP, Cooper D, Delia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011;32(12):1484–92. <https://doi.org/10.1093/euroheartj/ehr007>.
- [69] Kaneita Y, Ohida T, Uchiyama M, Takemura S, Kawahara K, Yokoyama E, Miyake T, Harano S, Suzuki K, Fujita T. The relationship between depression and sleep disturbances: a Japanese nationwide general population survey. *J Clin Psychiatry* 2006;67(2):196–203. <https://doi.org/10.4088/JCP.v67n0204>.
- [70] Palmer CD, Harrison GA, Hiorns RW. Association between smoking and drinking and sleep duration. *Ann Hum Biol* 1980;7(2):103–7. <https://doi.org/10.1080/0301446800004111>.
- [71] Chaput JP, McNeil J, Després JP, Bouchard C, Tremblay A. Short sleep duration is associated with greater alcohol consumption in adults. *Appetite* 2012;59(3):650–5. <https://doi.org/10.1016/j.appet.2012.07.012>.
- [72] Krueger PM, Friedman EM. Sleep duration in the United States: a cross-sectional population-based study. *Am J Epidemiol* 2009;169(9):1052–63. <https://doi.org/10.1093/aje/kwp023>.
- [73] Miller MB, Janssen T, Jackson KM. The prospective association between sleep and initiation of substance use in young adolescents. *J Adolesc Health* 2017;60(2):154–60. <https://doi.org/10.1016/j.jadohealth.2016.08.019>.
- [74] Miller MB, DiBello AM, Lust SA, Carey MP, Carey KB. Adequate sleep moderates the prospective association between alcohol use and consequences. *Addict Behav* 2016;63:23–8. <https://doi.org/10.1016/j.addbeh.2016.05.005>.
- [75] Iber A-I, Chesson AL, Quan SF. The AASM manual for the scoring of sleep and associated events. 2007.
- [76] Berry RB, Bonnet MH, Light RW. Effect of ethanol on the arousal response to airway occlusion during sleep in normal subjects. *Am Rev Respir Dis* 1992;2:445–52. https://doi.org/10.1164/ajrccm/145.2_pt_1445.
- [77] Issa FG, Sullivan CE. Alcohol, snoring and sleep apnea. *J Neurol Neurosurg Psychiatry* 1982;45(4):353–9. <https://doi.org/10.1136/jnnp.45.4.353>.
- [78] Mitler MM, Dawson A, Henriksen SJ, Sobers M, Bloom FE. Bedtime ethanol increases resistance of upper airways and produces sleep apneas in asymptomatic snorers. *Alcohol Clin Exp Res* 1988;12(6):801–5. <https://doi.org/10.1111/j.1530-0277.1988.tb01349.x>.

- [79] Teschler H, Berthon-Jones M, Wessendorf T, Meyer HJ, Konietzko N. Influence of moderate alcohol consumption on obstructive sleep apnoea with and without AutoSet nasal CPAP therapy. *Eur Respir J* 1996;9(11):2371–7. <https://doi.org/10.1183/09031936.96.09112371>.
- [80] Kolla BP, Foroughi M, Saeidifard F, Chakravorty S, Wang Z, Mansukhani MP. The impact of alcohol on breathing parameters during sleep: a systematic review and meta-analysis. *Sleep Med Rev* 2018;42:59–67. <https://doi.org/10.1016/j.smrv.2018.05.007>.
- [81] Le Bon O, Verbanck P, Hoffmann G, Murphy JR, Staner L, De Groote D, Mampunza S, Dulk AD, Vacher C, Kornreich C, Pelc I. Sleep in detoxified alcoholics: impairment of most standard sleep parameters and increased risk for sleep apnea, but not for myoclonias—a controlled study. *J Stud Alcohol* 1997;58(1):30–6. <https://doi.org/10.15288/jsa.1997.58.30>.
- [82] Huang YP, Chien WC, Chung CH, Huang YC, Kuo SC, Chen CY, Chen TY, Chang HA, Kao YC, Chang SY, Yeh YW, Tzeng NS. Increased incidence of alcohol use disorder and alcohol-related psychiatric disorders in patients with obstructive sleep apnea: a nationwide population-based cohort study. *Sleep Med* 2023;101:197–204. <https://doi.org/10.1016/j.sleep.2022.10.031>.
- [83] Aldrich MS, Shipley JE, Tandon R, Kroll PD, Brower KJ. Sleep-Disordered breathing in alcoholics: association with age. *Alcohol Clin Exp Res* 1993;17(6):1179–83. <https://doi.org/10.1111/j.1530-0277.1993.tb05224.x>.
- [84] Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. *Arch Int Med* 2000;160(14):2137–41. <https://doi.org/10.1001/archinte.160.14.2137>.
- [85] Winter AC, Berger K, Glynn RJ, Buring JE, Michael Gaziano J, Schürks M, Kurth T. Vascular risk factors, cardiovascular disease, and restless legs syndrome in men. *Am J Med* 2013;126(3):228. <https://doi.org/10.1016/j.amjmed.2012.06.039>.
- [86] Zhang J, Lam SP, Li SX, Li AM, Kong APS, Wing YK. Restless legs symptoms in adolescents: epidemiology, heritability, and pubertal effects. *J Psychosom Res* 2014;76(2):158–64. <https://doi.org/10.1016/j.jpsychores.2013.11.017>.
- [87] Aldrich MS, Shipley JE. Alcohol use and periodic limb movements of sleep. *Alcohol Clin Exp Res* 1993;17(1):192–6. <https://doi.org/10.1111/j.1530-0277.1993.tb00747.x>.
- [88] Brower KJ, Hall JM. Effects of age and alcoholism on sleep: a controlled study. *J Stud Alcohol* 2001;62(3):335–43. <https://doi.org/10.15288/jsa.2001.62.335>.
- [89] Hornyak M, Haas P, Veit J, Gann H, Riemann D. Magnesium treatment of primary alcohol-dependent patients during subacute withdrawal: an open pilot study with polysomnography. *Alcohol Clin Exp Res* 2004;28(11):1702–9. <https://doi.org/10.1097/alc.0000145695.52747.be>.
- [90] Rintakoski K, Kaprio J. Legal psychoactive substances as risk factors for sleep-related bruxism: a nationwide finnish twin cohort study. *Alcohol Alcohol* 2013;48(4):487–94. <https://doi.org/10.1093/alcalc/agt016>.
- [91] Ohayon MM, Li KK, Guilleminault C. Risk factors for sleep bruxism in the general population. *Chest* 2001;119(1):53–61. <https://doi.org/10.1378/chest.119.1.53>.
- [92] Hojo A, Haketa T, Baba K, Igarashi Y. Association between the amount of alcohol intake and masseter muscle activity levels recorded during sleep in healthy young women. *Int J Prosthodont* 2007;3:251–5.
- [93] Ebrahim IO, Shapiro CM, Williams AJ, Fenwick PB. Alcohol and sleep I: effects on normal sleep. *Alcoholism* 2013;37(4):539–49. <https://doi.org/10.1111/acer.12006>.
- [94] Pressman MR, Mahowald MW, Schenck CH, Bornemann MC. Alcohol-induced sleepwalking or confusional arousal as a defense to criminal behavior: a review of scientific evidence, methods and forensic considerations. *J Sleep Res* 2007;16(2):198–212. <https://doi.org/10.1111/j.1365-2869.2007.00586.x>.
- [95] Ioffe S, Chernick V. Development of the EEG between 30 and 40 weeks gestation in normal and alcohol-exposed infants. *Dev Med Child Neurol* 1988;30(6):797–807. <https://doi.org/10.1111/j.1469-8749.1988.tb14642.x>.
- [96] Alvik A, Torgersen AM, Aalen OO, Lindemann R. Binge alcohol exposure once a week in early pregnancy predicts temperament and sleeping problems in the infant. *Early Hum Dev* 2011;87(12):827–33. <https://doi.org/10.1016/j.earlhumdev.2011.06.009>.
- [97] Dhand R, Sohal H. Good sleep, bad sleep! The role of daytime naps in healthy adults. *Curr Opin Pulm Med* 2006;12(6):379–82. <https://doi.org/10.1097/01.mcp.0000245703.92311.d0>.
- [98] Furuhata R, Kaneita Y, Jike M, Ohida T, Uchiyama M. Napping and associated factors: a Japanese nationwide general population survey. *Sleep Med* 2016;20:72–9. <https://doi.org/10.1016/j.sleep.2015.12.006>.

This page intentionally left blank

Chapter 25

Improved sleep as an adjunctive treatment for smoking cessation*

Freda Patterson^a and Rebecca Ashare^b

^aDepartment of Behavioral Health and Nutrition, College of Health Sciences, University of Delaware, Newark, DE, United States; ^bPerelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States

Introduction

Despite declines in adult cigarette smoking prevalence during the past 50 years, cigarette smoking remains the leading cause of preventable death and disability in the United States. Data show that cigarette smoking and secondhand smoke exposure are accountable for at least 443,000 premature deaths and up to \$289 billion in direct health care expenditures and productivity losses each year [1]. Mortality associated with continued tobacco use is well-documented: 33% of cardiovascular and metabolic diseases, 32% of all cancers (including 87% of lung cancer), and 62% of pulmonary and respiratory diseases are attributable to cigarette smoking [2]. In spite of these adverse health effects, 15.1% of adults in the United States (~36.5 million people) are current smokers, with rates of 33%–48% reported among demographic subgroups including those who are uninsured, low-income, and low-education [3]. Data also show that adults with a mental health disorder (e.g., anxiety disorder) are twice as likely to smoke than those in the general population [4]. Thus, smoking cessation remains a public health priority.

Current FDA-approved treatments for nicotine dependence, including nicotine replacement therapies (e.g., nicotine patch, spray, gum, lozenge) and nonnicotinic treatments (e.g., bupropion, varenicline) are suboptimally effective. Whereas these treatments do double the odds of 6-month abstinence compared to placebo, less than one quarter remain abstinent [5]. *Healthy People 2020* has set the national goal of a 12% smoking prevalence rate for all demographic groups; achieving this goal will require the development of

more effective treatments for smoking cessation, as well as strategies to optimize current treatments [6]. As a common biologic function that plays a central role in metabolic regulation, emotion regulation, performance, memory consolidation, brain recuperation processes, and learning, sleep may be such an intervention target that could optimize nicotine dependence treatment response. For example, insomnia (difficulty falling and/or staying asleep) is a clinically recognized nicotine withdrawal symptom [7] that is not addressed in the clinical guidelines for nicotine dependence treatment [5]. On this basis, this chapter will first provide an overview of the epidemiology of cigarette smoking, followed by a review of the differences in sleep quality metrics in smokers versus nonsmokers. Next, a review of the effects of smoking abstinence on sleep quality and a brief overview of the possible mechanisms that may link sleep with smoking cessation outcomes will be provided. Following this, a review of evidence-based treatments for sleep disturbances will be considered with the goal of identifying sleep therapies that could be used in the context of smoking cessation. Last, future research directions needed to validate the extent to which poor sleep quality may be a viable target with which to optimize response to standard nicotine dependence treatment will be considered.

Epidemiology of cigarette smoking

Between 1965 and 2014, the United States adult smoking rate dropped from >42% to about 17% [8]. This monumental public health achievement was driven by several initiatives including enhanced public education about the adverse health effects of smoking, the development of efficacious behavioral treatments and medications, and enhanced public health policies (e.g., clean indoor air laws, cigarette taxes). However, this success appears to have plateaued—approximately one in six adults (15.1%) are current smokers, and these rates climb to about one in two (48%) in high-risk groups (i.e., low-

* Sections of Patterson F, Grandner MA, Malone SK, Rizzo A, Davey A, Edwards, DG. Sleep as a target for optimized response to smoking cessation treatment. *Nicotine and Tobacco Research*, 2017, reprinted by permission of Oxford University Press.

income, low-education, non-Caucasian) [3,9]. Because of these socioeconomic factors, culture, policies, and lack of proper healthcare, there are growing health disparities with respect to the impact of tobacco use among those living in rural areas compared to those living in urban and metropolitan areas [10]. Indeed, smoking prevalence varies widely depending on geographic region within the United States with prevalence rates of 25.4%, 24.2%, 21.3%, and 18.0% in the Midwest, South, Northeast, and West regions, respectively [11].

Despite increased awareness of the adverse health consequences, cigarette smoking remains the leading cause of preventable disease and death in the United States and accounts for 1 out of every 5 deaths [12,13]. Cigarette smoking causes 9 out of 10 lung cancers and increases the risk of other cancers, cardiovascular disease (CVD), lung disease, and infectious diseases [14]. In the context of CVDs, smokers are twice as likely to have a sudden cardiac death [15], seven times more likely to develop peripheral arterial disease [16] and more than twice as likely to have a stroke [17,18] than nonsmokers. Moreover, tobacco use costs \$170 billion in direct medical costs each year [1] representing a significant public health burden.

The increasing availability of effective treatments for nicotine dependence has contributed to the substantial decline in smoking rates. Currently, there are three FDA-approved medications for nicotine dependence: nicotine replacement therapy (NRT), which includes transdermal nicotine (TN), nasal spray, gum, and lozenges; bupropion; and varenicline. Use of these treatments significantly increases the likelihood that a quit attempt will be successful, versus no medication [19]. These medications are safe, with little evidence that serious adverse events are associated with their use [19,20], even among smokers with psychiatric [21] or medical [22] comorbidities. With respect to behavioral interventions, quit rates are generally low, ranging from 7% to 13% [23]. While recent studies suggest that novel behavioral interventions such as mindfulness treatments [24] or acceptance and commitment therapy [25] have received initial support, the majority of interventions are based on standard cognitive-behavioral and social support models [26,27]. Despite the availability of these treatments and the fact that most smokers want to quit [28], 75%–90% of smokers are unable to sustain long-term abstinence [29–31]. In order to achieve further reductions in population smoking rates, new strategies or behavioral targets are necessary to optimize current treatments. Sleep health may be such a behavioral target [32].

Sleep continuity and architecture in smokers versus nonsmokers

Overview of sleep continuity and architecture

Sleep is quantified by metrics of sleep continuity and sleep architecture. Sleep continuity refers to the timeline

of when an individual is asleep, compared to the time when they are intending to sleep. For example, key metrics within sleep continuity include the timing of sleep, the total amount of time spent in bed (time in bed, or TIB), sleep latency (time to fall asleep, or SL), number of awakenings, total time awake after sleep onset (also referred to as “wake after sleep onset” or WASO), time of final awakening, total sleep time (computed as $TST = TIB - SL - WASO$), and sleep efficiency (the proportion of time spent in bed actually asleep, computed as $[TST/TIB]*100$) [33].

Sleep architecture represents the cyclical pattern of sleep as it shifts among the various sleep stages, including non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Polysomnography (PSG) provides objective assessment of different sleep stages; the temporal and percentage of time in each of these stages are key markers of individual sleep quality. Briefly, the three NREM stages (N1, N2, N3) roughly parallel a depth-of-sleep continuum, with arousal thresholds generally lowest in N1 and highest in N3 sleep. N1 and N2 sleep stages are associated with minimal or fragmentary neuronal activity. REM sleep is characterized by heart rate, breathing rate, and brain wave activity that is similar to waking levels, compared to other stages of sleep [34]. REM sleep (as with N3) is important for cognitive tasks such as memory consolidation and information processing; dreaming predominantly occurs during REM sleep [35]. Throughout the sleep period, adults will cycle between stages of NREM and REM, spending 75%–80% of sleep time in NREM and the remainder in REM sleep [34].

Self-reported perceptions regarding sleep are also valuable metrics. Sleep disruptive events (i.e., sleep walking, night terrors) and daytime sleepiness or dysfunction (i.e., sleepiness, lack of energy, drowsiness that may prevent the completion of daytime tasks) are commonly measured characteristics of sleep [36]. A growing body of literature has compared these and other sleep variables in smokers and nonsmokers; a review of this work is provided below and summarized in Table 25.1.

Sleep architecture in smokers versus nonsmokers

Five studies were found that used PSG to examine sleep architecture in smokers and nonsmokers (Table 25.1) [37–41]. Three of the five studies found that compared to nonsmokers, smokers had a significantly higher percentage of time in N1. For example, Zang and colleagues found that among 779 smokers and 2916 never-smokers, current smokers accrued 24% more N1 sleep [37]; this would indicate shallower, more disturbed sleep. In another study of women ($N = 63$ smokers and $N = 323$ nonsmokers), the mean time in minutes in N1 was 31 for smokers and 21 for nonsmokers [38]. Similarly, smokers in these studies were

TABLE 25.1 Objective and subjective sleep metrics in smokers versus nonsmokers.

Study	Study design	N, smokers/ nonsmokers	Sleep metrics	Findings	Comments
Zang et al. [37]	Multicenter, longitudinal study; baseline PSG data	N = 779/ 2916	Sleep architecture (% time spent in each stage)	N1: smokers > non-smokers N2: smokers > non-smokers N3: smokers < non-smokers	
			Sleep onset latency	Smokers > nonsmokers	
			Total sleep time	Smokers < nonsmokers	
			Sleep efficiency	Smokers < nonsmokers	
Sahlin et al. [38]	Population-based study; PSG	N = 63/323	Sleep onset latency	Smokers > nonsmokers	
			Sleep architecture	N1: smokers > non-smokers	
			Wake after sleep onset	Smokers < nonsmokers	
Jaehne et al. [39]	Observational PSG study	N = 44/44	REM density	Smokers > nonsmokers	
			Sleep period time	Smokers < nonsmokers	Time between sleep onset and final awakening
			Sleep onset latency	Smokers > nonsmokers	
			Subjective sleep rating	Smokers > nonsmokers	Measured via PSQI; higher scores indicate more sleep problems
Soldatos et al. [40]	PSG laboratory study	N = 50/50	Sleep onset latency	Smokers > nonsmokers	
			Total time awake	Smokers > nonsmokers	
Redline et al. [41]	Prospective cohort study; PSG	N = 259/ 1256	Sleep architecture (% time spent in each stage)	N1: smokers > non-smokers N2: smokers > non-smokers N3: smokers < non-smokers	
Cohrs et al. [42]	Population-based, case-control	N = 1243/ 1071	Subjective sleep rating	Smokers > nonsmokers	Measured via PSQI; higher scores indicate more sleep problems
Branstetter et al. [43]	NHANES population-based survey	N = 2015/ 5752	Sleep duration	Smokers < non-smokers	
			Sleep onset latency	Smokers > nonsmokers	
			Early awakening	Smokers > nonsmokers	
			Nighttime awakening	Smokers > nonsmokers	

Continued

TABLE 25.1 Objective and subjective sleep metrics in smokers versus nonsmokers.—cont'd

Study	Study design	N, smokers/ nonsmokers	Sleep metrics	Findings	Comments
Phillips et al. [44]	Self-report survey	N = 77/308	Daytime sleepiness	Smokers > nonsmokers	
			Difficulty falling asleep	Smokers > nonsmokers	
			Difficulty staying asleep	Smokers > nonsmokers	
McNamara et al. [45]	NHANES population-based survey	N = 1023/2294	Difficulty falling asleep	Smokers > nonsmokers	
			Difficulty staying asleep	Smokers > nonsmokers	
			Early awakening	Smokers > nonsmokers	
			Total sleep time	Smokers < nonsmokers	
			Sleep onset latency	Smokers > nonsmokers	
Patterson et al. [46]	UK Biobank prospective cohort study; self-report	N = 34,401/405,212	Sleep duration	Smokers < nonsmokers	Smokers were also more likely to be long sleepers (≥ 9 h)
			Late chronotype	Smokers > nonsmokers	
Riedel et al. [47]	Epidemiological survey; 2 weeks sleep diaries	N = 62/606	Self-reported insomnia	Smokers > nonsmokers	Findings for light smokers (<15 cigarettes per day); no significant findings between heavier smokers and nonsmokers were found
			Time in bed	Smokers < nonsmokers	
			Total sleep time	Smokers < nonsmokers	
Grandner et al. [48]	2009 behavioral risk factor surveillance system (BRFSS)	N = 57,631/184,234	Perceived insufficient sleep	Smokers > nonsmokers	Sample includes daily and occasional smokers
Hayley et al. [49]	2012–13 National epidemiologic survey on alcohol and related conditions (NESARC-III)	N = 7265/28,912	Subjective sleep disturbance (difficulty falling/staying asleep)	smokers > nonsmokers	DSM-5 diagnosis of tobacco use disorder in the past year
			Sleep duration	Smokers < nonsmokers	

For the purpose of this table, “nonsmoker” refers to “never smokers” (i.e., smoked fewer than 100 cigarettes lifetime). For the purpose of this table, we focused on sleep metrics that differed between smokers and nonsmokers. Readers are referred to the original articles for additional measures.

PSQI, Pittsburgh sleep quality index.

McClung CA. How might circadian rhythms control mood? Let me count the ways. Biol Psychiatry 2013;74(4):242–9.

reported to have a significantly higher percentage of N2 sleep but significantly lower percentage of N3 sleep [37,41]. Jaehne and colleagues reported that in a laboratory-conducted PSG assessment of 44 smokers and 44 matched nonsmokers, smokers reported a higher REM density than their counterparts [39]. Collectively, this small body of work suggests that smokers may spend less time in deeper, more restful sleep-states than nonsmokers.

Sleep continuity in smokers versus nonsmokers

In terms of sleep onset latency, there is consensus across PSG verified studies that smokers (vs. nonsmokers) have a longer sleep onset latency [37–41], shorter sleep duration [37,39], and later sleep timing [46]. PSG verified sleep onset latency has been reported to range from 5.4 to 24.9 min [37–40] minutes longer in current versus nonsmokers. Mean total sleep time/duration has also been found to differ between smokers and nonsmokers, with smokers having shorter sleep. In one study, smokers reported 13.3 fewer minutes of total sleep time [39] and 14.0 min in another study [37]. Overall, smokers recorded significantly more time awake after sleep onset [40].

Findings from these PSG studies showing longer sleep-onset latency and shorter duration in smokers versus nonsmokers are consistent with the self-report literature. Using data from the National Health and Nutrition Examination study, Branstetter and colleagues found that current smokers took almost 25.9 (SD = 21.3) minutes to fall asleep compared to 21.5 (SD = 19.5) minutes in former smokers, and 22.1 (SD = 19.3) minutes in never smokers [43]. Other studies have found self-reported sleep latency to be significantly longer in smokers than non-smokers [42,44,45].

In terms of differences in sleep duration and sleep timing, smokers report shorter sleep duration, and later sleep timing than nonsmokers. For example, population-level data from the National Health and Nutrition Examination Survey showed that mean sleep duration in smokers is 6.6 versus 6.9 h in non/never smokers [43]. While data from the United Kingdom Biobank showed that in a sample of 34,401 smokers, 30.8% reported short sleep (≤ 6 h), and 9.3% reported long sleep (≥ 9 h) duration [46]. Several other studies found self-reported sleep duration to be significantly shorter in adult smokers than nonsmokers [45,49], with one study showing significance for light smokers (<15 cigarettes per day) versus nonsmokers, only [47]. Using data from $N = 323,047$ adult respondents of the 2009 Behavioral Risk Factor Surveillance System, Grandner and colleagues found that self-reported insufficient sleep was highest among daily current smokers and lowest among those who never smoked [48]. In terms of sleep timing, data from a national sample of adults showed that current smokers had a more than twofold

greater odds of having an evening versus intermediate timing preference [46], as well as a 40% greater odds of waking up too early [45].

When the relationship between smoking status and sleep efficiency is considered, two of the five studies that used PSG assessment reported differences. Jaehne and colleagues found that smokers had poorer sleep efficiency that was not significantly different from nonsmoker levels (87.08% vs. 89.84%, respectively) [39], whereas Redline and colleagues report that sleep efficiency was significantly lower in smokers than nonsmokers [41].

Together, these objective assessments of sleep continuity markers indicate that smokers have poorer sleep continuity than nonsmokers as suggested by longer sleep latency and shorter sleep duration. Lower sleep efficiency was indicated by some, but not all studies reviewed.

Sleep fragmentation in smokers versus nonsmokers

One PSG study of smokers and nonsmokers observed that smokers had significantly more disruptive events such as general leg movements and a higher leg movement index as compared to nonsmokers [39]. In one of the more comprehensive studies from the self-report literature examining the relationship between sleep and smoking status, a global disturbed sleep quality index was found to be significantly more prevalent in smokers versus nonsmokers (28.1% vs. 19.1%) [42]. Other data show only male smokers to have significantly greater prevalence of nightmares and disturbing dreams as compared to nonsmokers [50].

Among smokers, nocturnal awakenings to smoke are common, reported in 19%–51% of smokers [51–53]. One study showed that among night smokers, night smoking occurred on one-in-four nights (26%) and averaged two episodes per night [52]. Epidemiological evidence also suggests that current nicotine dependence is also associated with greater subjective sleep disturbance [49]. Night-time smokers are more nicotine dependent [51,52] and, following a cessation attempt, are more likely to relapse [52]. These studies indicate that smokers may be vulnerable to sleep fragmentation and disruptive events.

Daytime sleepiness in smokers versus nonsmokers

Across several longitudinal and cross-sectional studies, smokers are more likely to report daytime sleepiness than nonsmokers. In one longitudinal, observational study of 3516 adults, excessive daytime sleepiness was related to current smoking in females and not males [50]. In a study that used self-report NHANES data to examine sleep

characteristics of current ($N = 2015$), former ($N = 2741$), and never smokers ($N = 5752$), results showed that current smokers reported significantly more occurrences of feeling unrested and overly sleepy during the day as compared to the comparison groups [43]. Cross-sectional data from the Behavioral Risk Factor Surveillance System also showed that smokers reported significantly more daytime sleepiness [44].

Summary

Together, these data suggest that smokers are vulnerable to deficits in sleep continuity and architecture. From a sleep continuity perspective, smokers are more vulnerable to longer sleep latency, more awakenings, poorer sleep quality, and shorter sleep time. From a sleep architecture perspective, shorter percentage of time in slow wave sleep is more common in smokers than nonsmokers, while subjective reports indicate that smokers have more restless sleep and greater daytime drowsiness and sleepiness.

Smoking abstinence and sleep

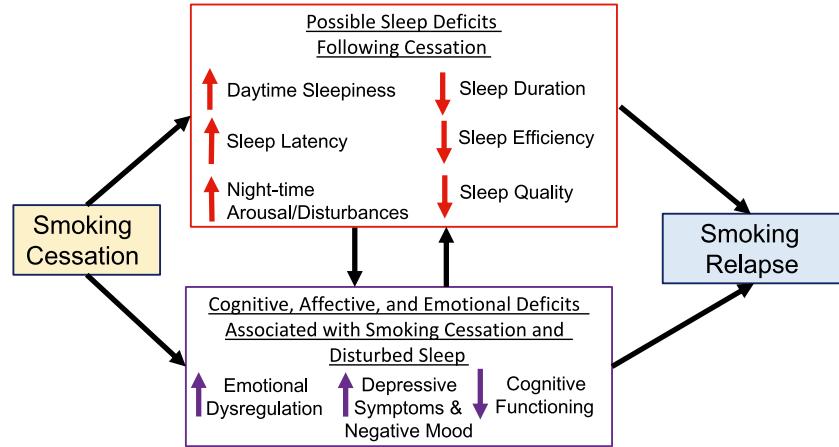
As a clinically verified symptom of nicotine withdrawal, insomnia is reported by up to 42% of abstinent smokers [54–56], while up to 80% of smokers habitually experience sleep disturbances [57] that then become exacerbated following cessation [58]. Nicotine withdrawal is a robust predictor of relapse to former smoking practices [59] and as such withdrawal symptoms are primary intervention targets. Elucidating the extent to which insomnia and other sleep deficits change following abstinence, and relate to smoking status and cessation outcome, is critical to quantifying the extent to which sleep may be a valid intervention target to promote cessation (see Fig. 25.1). Please also

see Jaehne et al. and Hayley and Downey for recent reviews [60,61].

Changes in sleep following abstinence

Three studies have objectively assessed sleep patterns (using PSG) following cessation in treatment-seeking smokers. In the larger of the two studies, 33 smokers completed a PSG assessment at baseline, 24–36 h, and 3-month following cessation [58]. Results showed a significantly increased percentage of wake time after sleep onset and night-time arousal in the first 24–36 h of quitting; no significant differences were seen at the 3-month follow-up [58]. In another study that included an analytic sample of seven treatment-seeking smokers, data showed that sleep duration and efficiency declined significantly in the first month of abstinence; however, by 1 year after cessation, sleep metrics had improved with reductions in latency to REM sleep and stage 1 (light) sleep and increases in REM (deep) sleep [62]. Wetter and colleagues reported on a double-blind randomized trial that compared sleep architecture in 34 treatment-seeking smokers who received either active or placebo nicotine patches [63]. Sleep was PSG monitored for two nights before smoking cessation and three nights afterward. The results showed that while sleep fragmentation significantly increased among placebo patch users, the active patch users did not demonstrate significant increases in sleep fragmentation following cessation [63]. Converging with these data from treatment-seeking smokers are data from a within-subject laboratory study that objectively compared the effects of smoking abstinence versus smoking as usual on sleep quality, daytime sleepiness, and mood in a sample of 18 non-treatment-seeking smokers. Results showed that as compared to smoking-as-usual, nicotine abstinence significantly increased relative arousals, sleep stage

FIGURE 25.1 Overview of sleep, cognitive, affective, and emotional deficits associated with smoking cessation and relapse.



changes, and awakenings in the first week of abstinence [64]. Collectively, these objective assessments of sleep metrics across the quitting period suggest that sleep deficits in the form of longer sleep latency and decreased sleep duration and efficiency are likely in the first weeks of quitting, but that these deficits are ameliorated 3–12 months after quitting.

Several studies have also examined self-reports of the natural history of withdrawal in abstinent smokers. Cummings and colleagues reported on a sample of 33 smokers who completed withdrawal diaries daily for a 21-day period following cessation [54]. Difficulty sleeping and daytime sleepiness in this sample did not show significant declines across the 21-day observation period as compared to the other withdrawal symptoms measured (i.e., craving, irritability). Meanwhile, heavier smokers reported significantly higher mean scores of difficulty sleeping and daytime sleepiness than light smokers [54]. By contrast, electronic diary assessment of nicotine withdrawal duration and symptom severity showed that in 214 treatment-seeking smokers, sleep disturbances did dissipate in a 21-day monitoring period after abstinence [65]. Data from these self-report studies converge with findings from studies using objective measures of sleep by showing that following nicotine abstinence, smokers experience an exacerbation of insomnia-type symptoms (i.e., longer sleep onset latency, more frequent awakenings), and shorter sleep duration and that cross time, these symptoms may dissipate.

Relationship between sleep and cessation outcome

Ten studies that explicitly examined one or more sleep metrics in relation to smoking cessation outcomes were reviewed [53,56,66–73] (Table 25.2). While the range of sleep metrics measured, the use of different tools to measure the same sleep metrics, the variability in smoking cessation treatments used, and time-period of assessment pre- and postcessation across these studies makes direct comparison challenging, some points of commentary can be raised.

First, eight studies showed that sleep metrics measured immediately before cessation and/or during cessation predicted relapse. For example, Peltier and colleagues reported that in a sample of 139 treatment-seeking smokers, increased sleep latency, reduced subjective sleep quality, and increased daytime dysfunction in the first week of quitting were predictive of relapse 4-week after treatment, while increased sleep disturbances were predictive of relapse 12-week after treatment [66]. Sleep disturbances alone did not predict relapse in a different sample of 385 treatment-seeking smokers. Instead, precessation sleep disturbances interacted with waking at night to smoke

(precessation) to predict relapse 6, 24, and 48 weeks postquitting [67].

Second, pretreatment sleep habits are relevant to smoking outcomes. Four of the studies found that precessation (vs. abstinence-induced) sleep deficits were predictive of relapse [67,69,70,73]. In a sample of 579 smokers who received a 12-week anxiety-related smoking cessation program versus a control condition, the results showed that smokers who self-reported precessation insomnia symptoms had a greater odds ($aOR = 1.11$; 95% CI = 1.01–1.22) of relapsing 3-month following cessation than those who did not have precessation insomnia symptoms. Postquit insomnia was not related to cessation outcome [69]. Likewise, in another study of 1136 smokers who received pharmacotherapy and counseling, data showed that smokers reporting more sleep disturbance pretreatment were less likely to be quit at the end of treatment ($OR = 0.79$; 95% CI = 0.67–0.93) [70]. Dorner and colleagues reported that greater nocturnal awakenings at baseline was an independent predictor of relapse 5-week following cessation in a sample of 2471 treatment-seeking smokers [73]. The remaining studies reviewed either did not have an assessment of sleep in the first week(s) of cessation [68] found that sleep patterns both before and after cessation predicted cessation outcome [66], did not report results in sufficient detail to ascertain whether sleep quality before or after cessation was related most to cessation [71], or did not find that sleep was related to cessation outcome [56].

Third, only one of the studies reviewed was designed specifically to test the efficacy of a behavioral sleep intervention on cessation outcome in a small sample of 19 smokers with a clinical diagnosis of insomnia [72]. Fucito and colleagues compared quit rates in nine participants who received a cognitive-behavioral treatment for insomnia + smoking cessation counseling + TN versus smoking cessation counseling + TN. The results of this small study showed that participants receiving the experimental insomnia treatment reported better sleep quality and efficiency; they also had more days to relapse [72].

Some of the take-home points from this literature are that sleep deficits (i.e., insomnia type symptoms of longer sleep latency, night-time awakenings, difficulty staying asleep) both before and after a quit attempt may predict relapse in treatment-seeking smokers. Importantly, not all studies found these associations, suggesting that there may be subgroups of smokers (i.e., those with higher levels of pretreatment insomnia symptoms) who may be more vulnerable to the exacerbated sleep deficits following cessation. Cognitive behavioral treatment for insomnia as an adjunctive treatment for smoking cessation may be a plausible approach to delaying relapse. The characterization or phenotype of treatment-seeking smokers most

TABLE 25.2 Review of literature examining relationship between sleep metrics and smoking cessation outcomes.

Study	Study design and sample	Assessment time points and sleep metrics measured	Treatment (pharmacotherapy, # sessions)	Comments
Foulds et al. [53]	- Cohort study analysis - 1021 smokers or recently quit smokers (59% female)	- Baseline, 4-week, and 6 month follow up - "Sometimes awaken at night to have a cigarette" (yes/no)	- Treatment that was recommended; - Six weekly sessions run by a clinical social worker, clinical psychologist, and intern - Individual counseling - FDA approved smoking cessation drugs: nicotine patch, gum, and lozenges	- At the 6 month follow up, 31.3% reported tobacco abstinence - Participants who reported waking at night to have a cigarette had a 40% increased odds of relapsing by 6-month following treatment even after adjustment for pretreatment nicotine dependence
Rapp et al. [68]	- Secondary analysis of a cluster randomized trial on smoking cessation - 500 student nurses (82% female)	- Baseline and 13-month follow-up - Average sleep duration (single item)	- Three teaching units delivered to nursing students - No pharmacotherapy	- At 13-month follow-up, 10.6% had quit - Sleep duration positively associated with cessation: Every hour of additional sleep increased the relative probability of cessation by 48% (aRR = 1.48; CI = 1.14–1.93)
Riemerth et al. [71]	- Secondary analysis of a cohort study - 2884 participants (50.3% female)	- Baseline, week 1, week 2, week 3, week 4, and week 5 were measured - Sleep-disturbing nicotine craving (NSDNC)	- Smoking cessation program with individual counseling - Nicotine replacement therapy	- While looking at NSDNC, 22.4% of patients suffer from symptoms, 77.1% awoke rarely, 9.4% awoke several times per week, 6.8% awoke most days, 6.6% awoke daily - Those with higher rate of NSDNC can be considered high dependent smokers
Okun et al. [56]	- Secondary analysis of a randomized clinical trial - 322 women	- Baseline, 1 month postquit, and 3 month follow up - Sleep disturbances, insomnia, drowsiness, and sleep quality	- Smoking cessation counseling; concerns or standard - Bupropion hydrochloride or placebo pharmacotherapy	- > 25% of women reported sleep disturbances - Smoking cessation outcomes were not related to sleep disturbance ($P = 0.54$), symptoms of insomnia ($P = 0.52$), sleep quality scores ($P = 0.42$), and drowsiness ($P = 0.14$)
Peters et al. [67]	- Double blind randomized controlled trial - 385 smokers (48% female)	- Baseline before 6-week study duration and smoking prevalence 1, 6, 24, and 48 weeks after quitting - Sleep quality and disturbances (PSQI)	- Nicotine patches (21 mg) placebo - Naltrexone and pharmacotherapy - 6-Weekly counseling	- Participants that were both poor sleepers and night smokers were significantly more likely to be smoking at 6, 24, and 48 weeks - Poor sleepers, only, compared to both poor sleep and night smoking were significantly less likely to be smoking at week 6 (OR = 0.44, CI = 0.022–0.91)

Doner et al. [73]	<ul style="list-style-type: none"> - Cohort study - 2471 participants (447-two sessions, 421-three sessions, 527-four sessions, 1076-five sessions) 	<ul style="list-style-type: none"> - Baseline then 2, 3 4, or 5 smoking cessation (depending on the amount the participant attended) - CO concentration and withdrawal symptoms measured with DSM-IV 	<ul style="list-style-type: none"> - Four groups: Two sessions, three sessions, four sessions, and five sessions - Individual or group based sessions offered - Pharmaceutical therapy 	<ul style="list-style-type: none"> - Participants that attended more sessions has a higher chance of smoking cessation from 12.1% to 61.2% ($P < .001$) - Baseline nocturnal wakening predicted lower odds of quitting ($P = .0226$)
Fucito et al. [72]	<ul style="list-style-type: none"> - Randomized trial - 19 participants (9 with CBT-I + SC and 10 with SC) 	<ul style="list-style-type: none"> - Two weeks prior to treatment (baseline), treatment times, and follow up - Sleep apnea (Berlin questionnaire), daily sleep (Pittsburgh sleep diaries), insomnia (insomnia severity index) 	<ul style="list-style-type: none"> - Two groups: (1) cognitive behavioral therapy for insomnia with smoking cessation counseling or (2) smoking cessation counseling alone - 8 sessions over 10 weeks 	<ul style="list-style-type: none"> - Smoking abstinence at the end of treatment was low (CBT-I + SC: 1/7, 14%; SC: 2/10, 20%) and follow-up (CBT-I + SC: 1/7, 14%; SC: 0/10, 0%) - Behavior intervention such as CBT-I might improve sleep for smokers that have insomnia
Ashare et al. [70]	<ul style="list-style-type: none"> - Secondary analysis of placebo controlled clinical trial - 1136 smokers (46% female) 	<ul style="list-style-type: none"> - Baseline, 1, 4, 8 weeks after target quit date, and 12 months after target quit date - Sleep disturbances calculated from sleep problems, insomnia, and abnormal dreams 	<ul style="list-style-type: none"> - Behavioral counseling through the telephone - Placebo, transdermal nicotine, or varenicline pharmacotherapy 	<ul style="list-style-type: none"> - Treatments do not lessen withdrawal related sleep disturbances. But treatments that focus on sleep disturbances could improve smoking cessation rates - Participants that reported a higher amount of sleep disturbances at baseline testing were less likely to be abstinent (OR = 0.79, CI = 0.67–0.93, $P = .004$)
Short et al. [69]	<ul style="list-style-type: none"> - Randomized control trial - 250 participants (52.8% female) 	<ul style="list-style-type: none"> - Baseline, start of quitting process, and 3 month follow up - Insomnia (single item) 	<ul style="list-style-type: none"> - Active or control group with smoking cessation program led by study staff - No pharmacotherapy 	<ul style="list-style-type: none"> - Prequit insomnia measures were indicators and predictors of smoking cessation at month 3 from the quit date - Postquit insomnia symptoms among patients did not show statistical significance with smoking status at month 3
Peltier et al. [66]	<ul style="list-style-type: none"> - Randomized control trial - 139 participants (57.6% female) 	<ul style="list-style-type: none"> - Baseline and weeks 1, 4, 12 postquit date - Sleep quality measured with WSWS and PSQI 	<ul style="list-style-type: none"> - Two groups; usual care (weekly counseling, physician visits, pharmacotherapy) and usual care plus small financial incentives - 4 weeks of weekly sessions 	<ul style="list-style-type: none"> - Participants that reported poor sleep quality the week prior to quitting and the week following the quit date had a reduced smoking cessation at weeks 4 and 12 among those of lower SES - Poor PSQI score was significantly correlated with WSWS measures assessed at quit date ($r = 0.58$, $P < .001$) and at 1 week postquit ($r = 0.48$, $P = .001$)

vulnerable to relapse because of sleep deficits, and the extent to which cognitive behavioral therapy (CBT) for insomnia increased days of abstinence in this population warrants consideration.

Effects of pharmacotherapy on sleep

Sleep disturbances are a recognized side-effect of the FDA-approved treatments for nicotine dependence including nicotine replacement therapies (patch, spray, gum, lozenge), bupropion and varenicline. One placebo-controlled trial that utilized nicotine patch and varenicline treatment arms showed that these active treatments did not ameliorate withdrawal-related sleep disturbance; thus, strategies to address sleep disturbances induced by smoking cessation pharmacologic treatments are needed to promote cessation [70]. Characterizing the sleep disturbances presented by each of the pharmacologic treatments is therefore necessary to informing the design of adjunctive nicotine dependence treatments.

Nicotine replacement therapy

Nicotine replacement therapies (NRTs; transdermal patch, gum, spray, lozenge) provide partial nicotine replacement upon cessation of smoking, and in doing so, ameliorate nicotine craving and pharmacologic withdrawal symptoms [74]. Up to 50% of treatment seeking smokers using nicotine replacement therapies report sleep disturbances that start on the day of use [75]. Disturbed sleep, vivid dreams, and daytime drowsiness are some of the more commonly reported side effects from using nicotine replacement therapies. In one study, 6.4% of participants reported disturbed sleep, 4.4% reported vivid dreams, and 1.5% reported daytime drowsiness while using NRT [76]. Meta-analytic data of 120 studies involving 177,390 individuals showed that the prevalence of insomnia among individuals using NRT for smoking cessation was 11.4% [77]. High levels of pretreatment nicotine dependence, continued cessation, and female gender were found to significantly predict sleep disturbances 4-week after quitting in a sample of 1392 treatment-seeking smokers [75]. Importantly, wearing the patch for 16 h (vs. 24 h) does not reduce its efficacy [78]. Therefore, smokers who experience sleep disruption, while using NRT may remove the patch before going to sleep.

Studies examining the trajectory of NRT sleep-related side effects suggest that sleep disturbances among NRT users may take some time to subside. In one cohort study, instances of sleep disturbance (vivid dreams, other sleep disturbances) were still being reported by up to 50% of abstinent smokers after 12-week of treatment [75]. This is consistent with another study that showed no change in reports of sleep disturbance in the 21-days following cessation [65] but inconsistent with data showing that use of TN

actually ameliorates sleep disturbances following cessation compared to placebo [63]. Collectively, these studies reporting on NRT use and sleep in smokers suggest that up to one-in-ten treatment seeking smokers can experience NRT-induced sleep disturbance following cessation that may last well into the quitting period (i.e., up to 12 weeks).

Bupropion

Sustained release bupropion (bupropion SR) is an amino-ketone antidepressant that is hypothesized to promote smoking cessation and delay relapse [79] to smoking by inhibiting dopamine reuptake in the reward center of the brain. Compared to placebo, bupropion increases the relative risk of cessation by 1.62 (95% CI = 1.49–1.76) [80].

Between 4% and 21% of treatment-seeking smokers using bupropion SR report disturbed sleep including insomnia, abnormal dreams, and daytime fatigue [81]. Some studies show that sleep disturbances associated with bupropion are significantly higher than those found in placebo and varenicline [82]. Conversely, other studies show no significant increases in sleep disturbances associated with bupropion treatment [83]. Although this evidence reporting on the increases of sleep disturbances following cessation using bupropion is mixed, that up to one-in-five bupropion users report an increase in sleep disturbances is clinically meaningful.

Varenicline

Varenicline is an $\alpha 4\beta 2$ partial agonist medication indicated for the treatment of nicotine dependence. As a $\alpha 4\beta 2$ partial agonist, varenicline stimulates sufficient dopamine to reduce craving while simultaneously acting as a partial antagonist by blocking reinforcement from smoked nicotine [84]. Double-blind, randomized trials show varenicline to outperform bupropion, NRT, and placebo in producing higher quit rates. For example, Gonzales and colleagues report that following a 12-week treatment period, varenicline quit rates were 50.3% as compared to 33.5% in the bupropion arm and 14.5% in the placebo arm [85]. Compared to placebo, meta-analytic data show bupropion to increase the odds of cessation by 1.84 and varenicline by 2.88 [86]; thus, varenicline is considered the most effective FDA-approved treatment for nicotine dependence.

Listed side effects of varenicline include insomnia, vivid, or lucid dreams and other sleep disturbances such as difficulty staying asleep. McClure and colleagues reported that 39%–46% of treatment-seeking smokers using varenicline reported difficulty sleeping, while 56%–68% reported a change in dreaming, and that these sleep disturbances were retained 21-days after cessation [87]. Meta-analysis of clinical trials that compared the efficacy of varenicline to placebo show that disturbed sleep, specifically insomnia symptoms of difficulty falling and staying asleep, as well as

the incidence of abnormal dreams were between 50% and 70% higher in varenicline recipients [88,89]. One study that prospectively evaluated changes in sleep insomnia and dreams among treatment-seeking smokers using varenicline ($N = 38$), showed that, based on daily sleep diaries over a 7-day period, participants retained excellent sleep efficiency ($>90\%$) and that while overall sleep measures did not change significantly, an increased number of awakenings and reports of dreams was observed [90]. Prospective studies suggest that insomnia-related symptoms peak in the first week of quitting and then progressively decline until pretreatment levels are achieved at 2–12 weeks [91]. Together, these studies reporting on the relationship between varenicline use and sleep disturbances show that while as many as seven-in-ten treatment-seeking smokers using varenicline report sleep symptoms, the symptoms dissipate across time.

Take home points: Relationship between sleep and cessation outcome

Poor sleep health as characterized by shorter sleep duration, difficulty falling asleep, difficulty staying asleep, early awakenings, and night-time awakenings are more common in smokers than nonsmokers. Of particular relevance to smoking-cessation efforts, sleep health deteriorates following cessation in many smokers, and this in turn is implicated in relapse. Importantly, FDA-approved treatments for nicotine dependence may also impede healthy sleep. Varenicline, the most effective smoking-cessation treatment, in particular produces insomnia symptoms and abnormal dreams as a notable side effect. These different lines of evidence converge to underscore sleep as an intervention target for treatment-seeking smokers, particularly for those using pharmacotherapy. Another question raised by this body of work is whether there are subgroups of smokers (i.e., those with higher nicotine dependence; those with poorer precessation sleep health; those with conditions associated with smoking and poor sleep health, such as depression) who are particularly vulnerable to sleep deficits and poorer sleep health following cessation and therefore might be a higher-priority for a sleep health intervention.

Possible mechanisms linking poor sleep to smoking cessation outcomes

To further understand the possible relationship between sleep and smoking cessation, it is important to consider the different mechanisms through which sleep may impact smoking behavior and vice versa. Plausible mechanisms through which tobacco use and sleep interact include cognitive, affective (i.e., mood, depressive symptoms), and emotional (i.e., emotional dysregulation) states, as well as

neurobiological mechanisms (see Fig. 25.1). A better understanding of these mechanisms may also shed light on subgroups of smokers who may be most likely to experience poor sleep during a quit attempt.

Unhealthy sleep has been associated with cognitive deficits [92–94], and cognitive impairment following smoking cessation predicts relapse [95]. Adverse changes in sleep (either substantial increases or decreases in sleep duration) have been associated with compromised cognitive function [96]. For example, short (≤ 6 h) and long (≥ 9 h) sleep has predicted poorer cognitive function [92]. Even an extra 6 h of wakefulness can produce deficits in alertness and working memory [97]. In studies of experimentally induced sleep restriction, sleep loss leads to impairments in vigilance and sustained attention [98], as well as executive function and decision-making [99], which could plausibly lead to difficulty making healthy choices. For example, Greer and colleagues [100] showed that sleep loss led to worse food-related decision-making. However, studies specifically linking sleep loss due to smoking and decision-making around smoking have not yet been conducted.

Disruption in cognitive processing is a common nicotine withdrawal symptom [55], with up to one-half of abstinent smokers reporting difficulty concentrating [101]. During abstinence, smokers experience specific deficits in sustained attention [102], working memory [103,104], and executive function [95], which are mitigated upon resumption of nicotine use [105]. Importantly, attention and concentration deficits following a quit attempt increase the risk of smoking relapse in clinical studies [106–108]. Thus, cognitive-deficits and disturbed sleep are both abstinence symptoms in habitual smokers that may interact to increase the likelihood of relapse.

Moreover, comorbid conditions associated with cognitive impairment and high smoking rates also exhibit higher prevalence of poor sleep. For instance, smoking rates among people living with HIV (PLWH) are 50%–74%—about three times higher than in the general population [109–113]. The widespread use of antiretroviral therapy (ART) has improved survival rates among PLWH [114–116], making addressing modifiable health-risk behaviors, such as tobacco use has become a critical priority. PLWH are also increasingly vulnerable to non-AIDS-related diseases including CVD, bone disease, frailty, and HIV-associated neurocognitive disorder (HAND) [117–122]. Moreover, there is evidence that poor sleep is common among PLWH, including increased sleep-onset latency and reduced N1 sleep, relative to controls [123]. PLWH who experience poor sleep, either subjectively or objectively measured, reports lower quality of life and greater daytime dysfunction [124]. While there is some evidence that certain ART regimens may contribute to poor sleep [125], high rates of tobacco use among PLWH may also exacerbate poor sleep, which may in turn, increase the

severity of HAND. These relationships are clearly complex, and more research is necessary to evaluate the unique and combined effects of tobacco use and HIV on sleep metrics and cognitive function.

Similar to cognition, there are data to suggest that depressive symptoms and emotional dysregulation are associated with smoking [126,127] and habitually poor sleep [128–130]. Poor sleep health is considered a central component of mood disorders [131], and there is growing consensus that disruption of the circadian system (sleep–wake cycle) contributes to the pathophysiology of mood disorders [131,132]. Up to 90% of depressed patients self-report difficulty falling or staying asleep [133,134]. PSG measures of sleep health including decreased REM latency (i.e., interval between sleep onset and the first REM sleep period), increased total REM sleep time and REM density (i.e., the frequency of REMs per REM period), and diminished slow wave sleep (SWS) production [135–138] predict response to depression treatment and recurrence of depression symptoms [139–141]. Moreover, sleep disturbance often precedes the onset of depression [142–144]. Even among nondepressed adults, poor sleep quality precedes a subsequent increase in depressive symptoms and negative mood [128].

Importantly, tobacco use and depression are highly comorbid. While smoking prevalence continues to decline in the general population, those with psychiatric disorders, including depression, are increasingly overrepresented among smokers [4,145–147]. Smokers have a higher prevalence of depression than nonsmokers [148,149] and upward of 43% of individuals with depression are smokers [4,146]. Smoking increases risk of first incidence, severity and recurrence of depression [150–153], and heavier smokers are at higher risk of depression [146,154]. Neuroimaging studies have revealed that abstinent smokers [155–157], depressed individuals [158,159], and individuals with sleep disorders [160] exhibit similar patterns of brain activity during difficult cognitive tasks. This complex interplay between sleep, smoking, and depressive symptomatology is likely exacerbated upon smoking cessation when abstinence from nicotine leads to increases in negative mood and insomnia symptoms [128], both of which have been shown to relate to relapse among treatment-seeking smokers [66,161]. The temporal sequence of changes in depressive symptoms and sleep health following cessation has yet to be fully understood, but such information would inform upstream intervention targets for smoking behavior.

Likewise, emotion dysregulation, or the ability to regulate emotions and control behavioral responses, has been implicated as a mechanism for how sleep may relate to smoking cognitions and quitting outcomes. From the outset, poor sleep quality has been highly correlated with emotion dysregulation in smokers. Recent evidence suggests that emotion dysregulation mediates the relationship

between insomnia symptoms and smoking variables including, negative reinforcement smoking outcome expectancies, negative reinforcement smoking motives, and negative reinforcement expectancies from smoking abstinence. Importantly these associations were adjusted for other demographic and smoking behavior variables [129]. Similarly, Fillo et al., showing that in a sample of 128 treatment-seeking smokers, greater emotion dysregulation was associated with lower self-efficacy for remaining abstinent, and a lower likelihood of having had a quit attempt of 24 h or greater [127]. This small body of work converges to suggest that emotion regulation may be an important mechanism linking sleep with cigarette smoking behaviors and quitting.

Sleep and smoking behavior also share several neurobiological mechanisms, which may partially explain these associations. For instance, the naturally occurring hormone, melatonin, which plays an essential role in sleep–wake function, has been shown to be lower among smokers compared to nonsmokers [162,163]. In preclinical models, melatonin receptor-knockout mice exhibited greater sensitivity to nicotine [164]; enhancing melatonin function may attenuate nicotine withdrawal symptoms [165] and reduce nicotine administration in mice [166]. More recently, the peptide hypocretin, which plays an important role in the sleep/wake cycle through its wake-promoting effects [167], has been shown to be associated with nicotine self-administration in rodents [168]. While there are certainly other neurotransmitters involved, melatonin and hypocretin are reviewed here to emphasize the neurobiological links between smoking and sleep that may shed light on this complex relationship.

Cognitive, affective, and emotional states present plausible pathways through which sleep and tobacco use may interact (see Fig. 25.1). This area of work is severely underdeveloped, and longitudinal studies are needed to quantify the association, and the temporal relationships, between these variables across time. Moreover, mechanistic studies are necessary to better understand the neurobiological pathways that are common and unique to sleep health and tobacco use that may lead to novel targets for interventions. Testing the extent to which improving sleep ameliorates deficits in cognitive, affective, and emotional states in smokers across the smoking cessation process will help determine if sleep improvement is a viable adjunctive therapy for smoking cessation.

Plausible adjunctive sleep therapies to promote smoking cessation

Overview

Smokers typically exhibit sleep patterns consistent with insomnia-type symptoms including difficulty falling asleep

(long sleep latency) and difficulty staying asleep (short sleep duration, frequent awakenings, and arousal during the night), that are amplified following cessation [58]. Some studies suggest that increases in disturbed sleep following cessation is attributed to the use of pharmacotherapy, whereas others suggest that disturbed sleep following cessation is attributable to nicotine-withdrawal [70]. In both scenarios, disturbed sleep before [67,69,70] and after cessation predicts relapse and, as such, warrants treatment as part of the cessation process. There are a range of behavioral and pharmacological treatments for insomnia-type symptoms that may be suitable for use in conjunction with standard nicotine dependence treatment (counseling + pharmacotherapy); an overview is provided here.

Behavioral treatments

CBT for Insomnia (CBT-I) is a first-line treatment for chronic insomnia [169] that improves sleep outcomes for up to 2 years after treatment [170] and is preferred by patients with a clinical diagnosis of insomnia to drug therapy [171]. CBT-I is comprised of two core components (stimulus control and sleep restriction therapy), as well as several optional components including cognitive therapy, sleep hygiene, and relaxation [172]. Stimulus control techniques work to strengthen the association between the bed and bedroom with sleep and to establish a consistent sleep schedule. Sleep restriction therapy is a specific approach that addresses the mismatch between sleep ability and sleep opportunity by reducing sleep opportunity to match ability and then slowly upwardly titrating sleep opportunity as long as the individual is able to maintain high sleep efficiency. Cognitive therapy seeks to identify and replace dysfunctional beliefs and attitudes about sleep and insomnia. Sleep hygiene works to address environmental factors, physiologic factors, and behavioral components (i.e., regular sleep scheduling, limiting alcohol intake). Relaxation training seeks to address the high levels of physiologic, cognitive, and/or emotional arousal, both at night and during the daytime, which is exhibited by individuals who have difficulty falling and/or staying asleep [169,173]. Deep breathing, progressive relaxation, and meditation are relaxation techniques that have been shown to lower presleep arousal (e.g., racing thoughts) and improve sleep metrics [174]. In a recent meta-analysis of 20 studies that examined the efficacy of CBT-I among patients with chronic insomnia, sleep-onset latency, WASO, total sleep time, and sleep efficiency were all significantly improved by multimodal CBT-I [174]. This is in the context of several other meta-analyses and systematic reviews of CBT-I showing that not only is it superior to placebo [173] and equivalent or superior to pharmacotherapy for insomnia [175], but it is effective even in the presence of comorbid conditions such as depression and chronic pain [176].

To date, only one study has examined the effects of a CBT-I intervention on smoking cessation outcomes [72]. Nineteen treatment-seeking smokers were randomized to receive eight sessions of CBT-I, TN patch, and smoking-cessation counseling ($N = 9$) versus TN patch and smoking cessation counseling ($N = 10$) alone. While the results showed no difference in smoking cessation rates between the groups, participants receiving the CBT-I had a longer time to relapse [72]. A fully powered examination of the effects of CBT-I on smoking cessation outcomes is warranted.

Pharmacological treatments

Benzodiazepines are a pharmacologic first-line treatment for insomnia. Currently there are five FDA-approved benzodiazepines for this indication: estazolam, flurazepam, quazepam, temazepam, and triazolam [177]. These medications act by increasing the activity of the inhibitory neurotransmitter GABA to inspire drowsiness or sedation. Consistent with this mechanism, sleep latency (time to sleep) and WASO are both significantly reduced, while sleep duration and sleep quality are significantly increased using these therapeutics in the short term. However, with increased tolerance of these pharmaceuticals, sleep improvements may be curtailed [178]. Of particular relevance to smokers, cigarette smoke contains beta-carbolines that block the actions of benzodiazepines at the GABA-A receptors [179]; thus, higher doses may be needed in smokers versus nonsmokers to observe comparable effects. In addition, benzodiazepines and other hypnotics (e.g., eszopiclone, zolpidem) often produce rebound insomnia and next-day residual effects, such as memory impairment, difficulty concentrating, or mood symptoms [180–182]—all of which may promote smoking relapse [183,184]. Nevertheless, benzodiazepines are not contraindicated with any of the FDA-approved treatments for nicotine dependence, and their role in promoting smoking cessation through improved sleep has yet to be evaluated.

Melatonin is a hormone normally secreted from the pineal gland at night that serves as the signal of darkness in the organism and as such plays a pivotal role in the physiological regulation of circadian rhythms, including sleep. Several melatonin receptor agonists have recently become available for treatment of sleep disorders: ramelteon for the treatment of insomnia characterized by difficulty with sleep onset, prolonged-release melatonin for treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over, agomelatine for the treatment of depression and associated sleep disorder, and tasimelteon for the treatment of non-24 h sleep-wake disorder in the blind [185]. Given that longer sleep latency (difficulty falling asleep) is a characteristic of smokers (vs. nonsmokers) that is exacerbated

following cessation, the reported reductions in sleep latency in ramelteon users [186] may be particularly beneficial to curbing sleep deficits following smoking cessation. Moreover, these medications have not been shown to produce the adverse next-day effects or rebound insomnia associated with hypnotics [187]. These melatonin receptor agonists are not contraindicated with the FDA-approved smoking cessation medications, and their efficacy as adjunctive smoking cessation treatments warrants investigation.

The discovery of the role of the neuropeptide, orexin, in the sleep–wake cycle is thought to be one of the major advances in sleep research in the last 2 decades [188]. This finding led to the development of several orexin receptor antagonists as potential treatments for insomnia. Suvorexant, a dual orexin 1 and orexin 2 receptor antagonist, was approved by the FDA in 2014 for insomnia and other medications that act exclusively on the orexin 2 receptor are currently being tested. These medications promote sleep by increasing REM sleep with few, if any, effects on slow wave sleep [188]. Given that smokers may spend less time in REM sleep [39], it is plausible that these medications may address this sleep deficit during a smoking cessation attempt. Indeed, the orexin system has been shown to play a role in preclinical studies of nicotine self-administration [189]. However, these medications' negative side effects similar to other hypnotics and whether they can be used in conjunction with FDA-approved smoking cessation treatments are unknown.

Directions for future research

On the basis of the research reviewed in this chapter, we suggest that sleep is an understudied and underutilized intervention target for promoting smoking cessation and preventing relapse in treatment-seeking smokers. As demonstrated, sleep deficits in terms of shorter sleep duration and insomnia symptoms (difficulty getting to sleep and staying asleep) are a sleep phenotype of smokers that may become exacerbated following cessation, both as an abstinence symptom and, as a side-effect of quit-smoking medications. As such, it could be argued that smoking-cessation practitioners have a basis from which to advise treatment-seeking smokers to strive to develop and maintain a healthy sleep schedule. A healthy sleep schedule could be defined as maximizing sleep efficiency through restricting time in bed for sleep or sex, achieving adequate sleep duration of 7–8 h, and achieving an earlier time to bed. Maintaining healthy sleep may facilitate the quitting process and increase abstinence. In addition, because standard pharmacotherapies for smoking cessation may exacerbate sleep disturbance, practitioners might discuss these potential side effects, and strategies to

mitigate them (e.g., for patients reporting sleep difficulty prior to a quit attempt, advise them to remove the nicotine patches before going to sleep).

To build the empirical basis from which to support these (and potentially other) sleep health recommendations to promote smoking-cessation treatment response, there are several directions for future work that are needed. First, the temporal relationship between smoking and sleep needs further consideration. As discussed in this review, sleep may be disrupted because of the physiological effects of nicotine and nicotine withdrawal upon abstinence. Conversely, smokers may use their smoking habit to counter the effects of daytime sleepiness because of poor sleep. Prospective, observational studies examining the temporal relationship underpinning this complex interplay between sleep and smoking are needed. Meta-analytic studies to quantify the relationship between sleep deficits with smoking behaviors and cessation outcomes would also be valuable.

Second, laboratory and clinical studies to examine the effects of pharmacological treatments for insomnia on tobacco consumption in a natural setting and as an adjunctive treatment for smoking cessation are needed. Behavioral pharmacology and laboratory studies also provide a unique opportunity to investigate mechanisms underlying this association, including neurobiological mechanisms as well as the mediating role of cognition and affect on the relationship between tobacco use and sleep.

Third, behavioral therapies for insomnia targeting treatment-seeking smokers need to be developed and evaluated in the context of smoking-cessation interventions. For example, physical activity and mindfulness-based approaches have independently been shown to reduce insomnia symptoms [190] and promote smoking abstinence [191,192]; thus, these approaches may have promise in treating smokers with higher levels of sleep deficits.

Another goal of this line of research is to elucidate the relationship between sleep, tobacco use, and cessation outcomes that will ultimately inform a sleep phenotype of risk for continued smoking. Characterizing smokers according to this phenotype will inform targeted intervention approaches to promote cessation outcomes in smokers most vulnerable to sleep deficits.

Acknowledgments

Research reported in this publication was supported by an Institutional Development Award (IDeA) Center of Biomedical Research Excellence from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM113125, by grant support from the National Institute on Drug Abuse (R21 DA040902), by the National Institute On Minority Health And Health Disparities (R01MD012734) and by the University of Delaware Research Foundation grant number 16A01366.

Conflicts of interest

Dr. Patterson receives medication free of charge from Pfizer.

References

- [1] Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending attributable to cigarette smoking: an update. *Am J Prev Med* 2015;48(3):326–33. <https://doi.org/10.1016/j.amepre.2014.10.012>.
- [2] The health consequences of smoking—50 years of progress: a report of the surgeon general. Centers for Disease Control; 2014.
- [3] Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults - United States, 2005–2015. *MMWR (Morb Mortal Wkly Rep)* 2016;65(44):1205–11. <https://doi.org/10.15585/mmwr.mm6544a2>.
- [4] Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *J Am Med Assoc* 2000;284(20):2606–10. <https://doi.org/10.1001/jama.284.20.2606>.
- [5] Fiore MC. Treating tobacco use and dependence: 2008 update: clinical practice guideline. U.S. Department of Health and Human Services . Public Health Service; 2008. p. 2008.
- [6] Carpenter MJ, Jardin BF, Burris JL, Mathew AR, Schnoll RA, Rigotti NA, Cummings KM. Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: a review of the literature. *Drugs* 2013;73(5):407–26. <https://doi.org/10.1007/s40265-013-0038-y>.
- [7] Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986;43(3):289–94. <https://doi.org/10.1001/archpsyc.1986.01800030107013>.
- [8] Centers of Disease, Control. Trends in current cigarette smoking among high school students and adults. 1965. p. 1965.
- [9] Perkett M, Robson SM, Kripalu V, Wysota C, McGarry C, Weddle D, Papas MA, Patterson F. Characterizing cardiovascular health and evaluating a low-intensity intervention to promote smoking cessation in a food-assistance population. *J Commun Health* 2017;42(3):605–11. <https://doi.org/10.1007/s10900-016-0295-2>.
- [10] AL Association. Cutting tobacco's rural roots: tobacco use in rural communities Chicago. American Lung Association; 2015. p. 2015.
- [11] Results from the 2014 National survey on drug use and health: detailed tables. Substance Abuse and Mental Health Services Administration; 2015. p. 2015.
- [12] Jamal A, Agaku IT, O'Connor E, King BA, Kenemer JB, Neff L. Current cigarette smoking among adults—United States, 2005–2013. *MMWR (Morb Mortal Wkly Rep)* 2014;63(47):1108–12.
- [13] Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *J Am Med Assoc* 2004;291(10):1238–45. <https://doi.org/10.1001/jama.291.10.1238>.
- [14] Services USDoHaH 2014 Department of Health and Human Services. Let's make the next generation Tobacco-Free: your guide to the 50th anniversary surgeon General's report on smoking and health.
- [15] Wannamethee G, Shaper AG, Macfarlane PW, Walker M. Risk factors for sudden cardiac death in middle-aged British men. *Circulation* 1995;91(6):1749–56. <https://doi.org/10.1161/01.CIR.91.6.1749>.
- [16] Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GDO, Fowkes FGR. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease. *Edinburgh Artery Study European Heart J* 1999;20(5):344–53. <https://doi.org/10.1053/euhj.1998.1194>.
- [17] Colditz GA, Bonita R, Stampfer MJ, Willett WC, Rosner B, Speizer FE, Hennekens CH. Cigarette smoking and risk of stroke in middle-aged women. *N Engl J Med* 1988;318(15):937–41. <https://doi.org/10.1056/NEJM198804143181501>.
- [18] Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH. Smoking cessation and decreased risk of stroke in women. *J Am Med Assoc* 1993;269(2):232–6. <https://doi.org/10.1001/jama.1993.03500020066033>.
- [19] Cahill K, Stevens S, Lancaster T. Pharmacological treatments for smoking cessation. *JAMA* 2014;311(2):193. <https://doi.org/10.1001/jama.2013.283787>.
- [20] Hartmann-Boyce J, Lancaster T, Stead LF. Print-based self-help interventions for smoking cessation. *Cochrane Database Syst Rev* 2014;2017(12). <https://doi.org/10.1002/14651858.CD001118.pub3>.
- [21] Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;387(10037):2507–20. [https://doi.org/10.1016/S0140-6736\(16\)30272-0](https://doi.org/10.1016/S0140-6736(16)30272-0).
- [22] Rigotti NA, Bitton A, Kelley JK, Hoeppner BB, Levy DE, Mort E. Offering population-based tobacco treatment in a healthcare setting: a randomized controlled trial. *Am J Prev Med* 2011;41(5):498–503. <https://doi.org/10.1016/j.amepre.2011.07.022>.
- [23] Patnode CD, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the U.S. preventive services task force. *Ann Intern Med* 2015;163(8):608–21. <https://doi.org/10.7326/M15-0171>.
- [24] De Souza ICW, De Barros VV, Gomide HP, Miranda TCM, De Paula Menezes V, Kozasa EH, Noto AR. Mindfulness-based interventions for the treatment of smoking: a systematic literature review. *J Alternative Compl Med* 2015;21(3):129–40. <https://doi.org/10.1089/acm.2013.0471>.
- [25] Lee EB, An W, Levin ME, Twohig MP. An initial meta-analysis of Acceptance and Commitment Therapy for treating substance use disorders. *Drug Alcohol Depend* 2015;155:1–7. <https://doi.org/10.1016/j.drugalcdep.2015.08.004>.
- [26] Stead LF, Koilpillai P, Lancaster T. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev* 2015;2015(10). <https://doi.org/10.1002/14651858.CD009670.pub3>.
- [27] Stead LF, Lancaster T. Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev* 2012;2012(12). <https://doi.org/10.1002/14651858.CD009670.pub2>.
- [28] Department Human Services. Department of Health and Human Services the health consequences of smoking—50 years of progress: a report of the surgeon general. 2014.
- [29] Schnoll RA, Lerman C. Current and emerging pharmacotherapies for treating tobacco dependence. *Expert Opin Emerg Drugs* 2006;11(3):429–44. <https://doi.org/10.1517/14728214.11.3.429>.
- [30] Kotz D, West R. Explaining the social gradient in smoking cessation: it's not in the trying, but in the succeeding. *Tob Control* 2009;18(1):43–6. <https://doi.org/10.1136/tc.2008.025981>.

- [31] Gilman SE, Martin LT, Abrams DB, Kawachi I, Kubzansky L, Loucks EB, Rende R, Rudd R, Buka SL. Educational attainment and cigarette smoking: a causal association? *Int J Epidemiol* 2008;37(3):615–24. <https://doi.org/10.1093/ije/dym250>.
- [32] Patterson F, Grandner MA, Malone SK, Rizzo A, Davey A, Edwards DG. Sleep as a target for optimized response to smoking cessation treatment. *Nicotine Tob Res* 2019;21(2):139–48. <https://doi.org/10.1093/ntxr/ntx236>.
- [33] Smith LL, Nowakowski S, Soeffing P, Orff HJ. Treating sleep disorders: principles and practice of behavioral sleep medicine. Wiley; 2003. p. 2003.
- [34] ma Carskadon WC. Dement, Principles and practice of sleep medicine. Elsevier Saunders; 2011. p. 16–26.
- [35] Chambers AM. The role of sleep in cognitive processing: focusing on memory consolidation. *WIREs Cognitive Sci* 2017;8(3). <https://doi.org/10.1002/wcs.1433>.
- [36] Krystal AD, Edinger JD. Measuring sleep quality. *Sleep Med* 2008;9(1):S10. [https://doi.org/10.1016/S1389-9457\(08\)70011-X](https://doi.org/10.1016/S1389-9457(08)70011-X).
- [37] Zhang L, Samet J, Caffo B, Punjabi NM. Cigarette smoking and nocturnal sleep architecture. *Am J Epidemiol* 2006;164(6):529–37. <https://doi.org/10.1093/aje/kwj231>.
- [38] Sahlin C, Franklin KA, Stenlund H, Lindberg E. Sleep in women: normal values for sleep stages and position and the effect of age, obesity, sleep apnea, smoking, alcohol and hypertension. *Sleep Med* 2009;10(9):1025–30. <https://doi.org/10.1016/j.sleep.2008.12.008>.
- [39] Jaehne A, Unbehauen T, Feige B, Lutz UC, Batra A, Riemann D. How smoking affects sleep: a polysomnographical analysis. *Sleep Med* 2012;13(10):1286–92. <https://doi.org/10.1016/j.sleep.2012.06.026>.
- [40] Soldatos CR, Kales JD, Scharf MB, Bixler EO, Kales A. Cigarette smoking associated with sleep difficulty. *Science* 1980;207(4430):551–3. <https://doi.org/10.1126/science.7352268>.
- [41] Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med* 2004;164(4):406–18. <https://doi.org/10.1001/archinte.164.4.406>.
- [42] Cohrs S, Rodenbeck A, Riemann D, Szagun B, Jaehne A, Brinkmeyer J, Gründer G, Wienker T, Diaz-Lacava A, Mobsacher A, Dahmen N, Thuerauf N, Kornhuber J, Kiefer F, Gallinat J, Wagner M, Kunz D, Grittner U, Winterer G. Impaired sleep quality and sleep duration in smokers—results from the German Multicenter Study on Nicotine Dependence. *Addict Biol* 2014;19(3):486–96. <https://doi.org/10.1111/j.1369-1600.2012.00487.x>.
- [43] Branstetter SA, Horton WJ, Mercincavage M, Buxton OM. Severity of nicotine addiction and disruptions in sleep mediated by early awakenings. *Nicotine Tob Res* 2016;18(12):2252–9. <https://doi.org/10.1093/ntxr/ntw179>.
- [44] Phillips BA, Danner FJ. Cigarette smoking and sleep disturbance. *Arch Intern Med* 1995;155(7):734–7. <https://doi.org/10.1001/archinte.1995.00430070088011>.
- [45] McNamara JPH, Wang J, Holiday DB, Warren JY, Parada M, Balkhi AM, Fernandez-Baca J, McCrae CS. Sleep disturbances associated with cigarette smoking. *Psychol Health Med* 2014;19(4):410–9. <https://doi.org/10.1080/13548506.2013.832782>.
- [46] Patterson F, Malone SK, Lozano A, Grandner MA, Hanlon AL. Smoking, screen-based sedentary behavior, and diet associated with habitual sleep duration and chronotype: data from the UK Biobank. *Ann Behav Med* 2016;50(5):715–26. <https://doi.org/10.1007/s12160-016-9797-5>.
- [47] Riedel BW, Durrence HH, Lichstein KL, Taylor DJ, Bush AJ. The relation between smoking and sleep: the influence of smoking level, health, and psychological variables. *Behav Sleep Med* 2004;2(1):63–78. https://doi.org/10.1207/s15402010bsm0201_6.
- [48] Grandner MA, Jackson NJ, Izci-Balserak B, Gallagher RA, Murray-Bachmann R, Williams NJ, Patel NP, Jean-Louis G. Social and behavioral determinants of perceived insufficient sleep. *Front Neurol* 2015;6(MAY). <https://doi.org/10.3389/fneur.2015.00112>.
- [49] Hayley AC, Stough C, Downey LA. DSM-5 tobacco use disorder and sleep disturbance: findings from the national epidemiologic survey on alcohol and related conditions-III (NESARC-III). *Subst Use Misuse* 2017;52(14):1859–70. <https://doi.org/10.1080/10826084.2017.1316508>.
- [50] Wetter DW, Young TB. The relation between cigarette smoking and sleep disturbance. *Prev Med* 1994;23(3):328–34. <https://doi.org/10.1006/pmed.1994.1046>.
- [51] Bover MT, Foulds J, Steinberg MB, Richardson D, Marcella SW. Waking at night to smoke as a marker for tobacco dependence: patient characteristics and relationship to treatment outcome. *Int J Clin Pract* 2008;62(2):182–90. <https://doi.org/10.1111/j.1742-1241.2007.01653.x>.
- [52] Scharf D, Dunbar M, Shiffman S. Smoking during the night: prevalence and smoker characteristics. *Nicotine Tob Res* 2008;10(1):167–78. <https://doi.org/10.1080/14622200701767787>.
- [53] Foulds J, Gandhi KK, Steinberg MB, Richardson DL, Williams JM, Burke MV, Rhoads GG. Factors associated with quitting smoking at a tobacco dependence treatment clinic. *Am J Health Behav* 2006;30(4):400–12. <https://doi.org/10.5993/AJHB.30.4.6>.
- [54] Cummings KM, Giovino G, Jaén CR, Emrich LJ. Reports of smoking withdrawal symptoms over a 21 day period of abstinence. *Addict Behav* 1985;10(4):373–81. [https://doi.org/10.1016/0306-4603\(85\)90034-6](https://doi.org/10.1016/0306-4603(85)90034-6).
- [55] Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res* 2007;9(3):315–27. <https://doi.org/10.1080/14622200701188919>.
- [56] Okun ML, Levine MD, Houck P, Perkins KA, Marcus MD. Subjective sleep disturbance during a smoking cessation program: associations with relapse. *Addict Behav* 2011;36(8):861–4. <https://doi.org/10.1016/j.addbeh.2011.03.001>.
- [57] Zhang L, Samet J, Caffo B, Bankman I, Punjabi NM. Power spectral analysis of EEG activity during sleep in cigarette smokers. *Chest* 2008;133(2):427–32. <https://doi.org/10.1378/chest.07-1190>.
- [58] Jaehne A, Unbehauen T, Feige B, Cohrs S, Rodenbeck A, Schütz A-L, Uhl V, Zober A, Riemann D. Sleep changes in smokers before, during and 3 months after nicotine withdrawal. *Addict Biol* 2015;20(4):747–55. <https://doi.org/10.1111/adb.12151>.
- [59] Al'Absi M, Hatsukami D, Davis GL, Wittmers LE. Prospective examination of effects of smoking abstinence on cortisol and withdrawal symptoms as predictors of early smoking relapse. *Drug Alcohol Depend* 2004;73(3):267–78. <https://doi.org/10.1016/j.drugalcdep.2003.10.014>.
- [60] Jaehne A, Loessl B, Bárkai Z, Riemann D, Hornyak M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. *Sleep Med Rev* 2009;13(5):363–77. <https://doi.org/10.1016/j.smrv.2008.12.003>.

- [61] Hayley AC, Downey LA. Quitters never sleep: the effect of nicotine withdrawal upon sleep. *Curr Drug Abuse Rev* 2015;8(2):73–4. <https://doi.org/10.2174/187447370802150928182458>.
- [62] Moreno-Coutiño A, Calderón-Ezquerro C, Drucker-Colín R. Long-term changes in sleep and depressive symptoms of smokers in abstinence. *Nicotine Tob Res* 2007;9(3):389–96. <https://doi.org/10.1080/14622200701188901>.
- [63] Wetter DW, Fiore MC, Baker TB, Young TB. Tobacco withdrawal and nicotine replacement influence objective measures of sleep. *J Consult Clin Psychol* 1995;63(4):658–67. <https://doi.org/10.1037/0022-006X.63.4.658>.
- [64] Prosise GL, Bonnet MH, Berry RB, Dickel MJ. Effects of abstinence from smoking on sleep and daytime sleepiness. *Chest* 1994;105(4):1136–41. <https://doi.org/10.1378/chest.105.4.1136>.
- [65] Shiffman S, Patten C, Gwaltney C, Paty J, Gnys M, Kassel J, Hickcox M, Waters A, Balabanis M. Natural history of nicotine withdrawal. *Addiction* 2006;101(12):1822–32. <https://doi.org/10.1111/j.1360-0443.2006.01635.x>.
- [66] Peltier MR, Lee J, Ma P, Businelle MS, Kendzor DE. The influence of sleep quality on smoking cessation in socioeconomically disadvantaged adults. *Addict Behav* 2017;66:7–12. <https://doi.org/10.1016/j.addbeh.2016.11.004>.
- [67] Peters EN, Fucito LM, Novosad C, Toll BA, O’Malley SS. Effect of night smoking, sleep disturbance, and their co-occurrence on smoking outcomes. *Psychol Addict Behav* 2011;25(2):312–9. <https://doi.org/10.1037/a0023128>.
- [68] Rapp K, Buechele G, Weiland SK. Sleep duration and smoking cessation in student nurses. *Addict Behav* 2007;32(7):1505–10. <https://doi.org/10.1016/j.addbeh.2006.11.005>.
- [69] Short NA, Mathes BM, Gibby B, Oglesby ME, Zvolensky MJ, Schmidt NB. Insomnia symptoms as a risk factor for cessation failure following smoking cessation treatment. *Addiction Res Theor* 2017;25(1):17–23. <https://doi.org/10.1080/16066359.2016.1190342>.
- [70] Ashare RL, Lerman C, Tyndale RF, Hawk LW, George TP, Cinciripini P, Schnoll RA. Sleep disturbance during smoking cessation: withdrawal or side effect of treatment? *J Smok Cessat* 2017;12(2):63–70. <https://doi.org/10.1017/jsc.2016.11>.
- [71] Riemerth A, Kunze U, Groman E. Nocturnal sleep-disturbing nicotine craving and accomplishment with a smoking cessation program. *Wien Med Wochenschr* 2009;159(1–2):47–52. <https://doi.org/10.1007/s10354-008-0640-x>.
- [72] Fucito LM, Redeker NS, Ball SA, Toll BA, Ikomi JT, Carroll KM. Integrating a behavioural sleep intervention into smoking cessation treatment for smokers with insomnia: a randomised pilot study. *Int Rev Red Cross* 2014;9(1):31–8. <https://doi.org/10.1017/jsc.2013.19>.
- [73] Dorner TE, Trostl A, Womastek I, Groman E. Predictors of short-term success in smoking cessation in relation to attendance at a smoking cessation program. *Nicotine Tob Res* 2011;13(11):1068–75. <https://doi.org/10.1093/ntr/ntr179>.
- [74] Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008;1. <https://doi.org/10.1002/14651858.CD000146.pub3>.
- [75] Gourlay SG, Forbes A, Marriner T, McNeil JJ. Predictors and timing of adverse experiences during transdermal nicotine therapy. *Drug Saf* 1999;20(6):545–55. <https://doi.org/10.2165/00002018-199920060-00007>.
- [76] Stapleton JA, Watson L, Spirling LI, Smith R, Milbrandt A, Ratcliffe M, Sutherland G. Varenicline in the routine treatment of tobacco dependence: a pre-post comparison with nicotine replacement therapy and an evaluation in those with mental illness. *Addiction* 2008;103(1):146–54. <https://doi.org/10.1111/j.1360-0443.2007.02083.x>.
- [77] Mills EJ, Wu P, Lockhart I, Wilson K, Ebbert JO. Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. *Tob Induc Dis* 2010;8(1). <https://doi.org/10.1186/1617-9625-8-8>.
- [78] Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012;2017(12). <https://doi.org/10.1002/14651858.CD000146.pub4>.
- [79] Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, Sachs DPL, Wolter TD, Buist AS, Johnston JA, White JD. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: a randomized, controlled trial. *Ann Intern Med* 2001;135(6):423–33. <https://doi.org/10.7326/0003-4819-135-6-200109180-00011>.
- [80] Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2014;2014(1). <https://doi.org/10.1002/14651858.CD000031.pub4>.
- [81] Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340(9):685–91. <https://doi.org/10.1056/NEJM199903043400903>.
- [82] West R, Baker CL, Cappelleri JC, Bushmakin AG. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology* 2008;197(3):371–7. <https://doi.org/10.1007/s00213-007-1041-3>.
- [83] Shiffman S, Johnston JA, Khayrallah M, Elash CA, Gwaltney CJ, Paty JA, Gnys M, Evoniuk G, DeVeau-Geiss J. The effect of bupropion on nicotine craving and withdrawal. *Psychopharmacology* 2000;148(1):33–40. <https://doi.org/10.1007/s002130050022>.
- [84] Papke RL, Heinemann SF. Partial agonist properties of cytisine on neuronal nicotinic receptors containing the $\beta 2$ subunit. *Mol Pharmacol* 1994;45(1):142–9.
- [85] Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296(1):47–55. <https://doi.org/10.1001/jama.296.1.47>.
- [86] Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* 2013;2013(5). <https://doi.org/10.1002/14651858.CD009329.pub2>.
- [87] McClure JB, Swan GE, Jack L, Catz SL, Zbikowski SM, McAfee TA, Deprey M, Richards J, Javitz H. Mood, side-effects and smoking outcomes among persons with and without probable lifetime depression taking varenicline. *J Gen Intern Med* 2009;24(5):563–9. <https://doi.org/10.1007/s11606-009-0926-8>.
- [88] Thomas KH, Martin RM, Knipe DW, Higgins JPT, Gunnell D. Risk of neuropsychiatric adverse events associated with

- varenicline: systematic review and meta-analysis. *Br Med J* 2015;350(mar12 8):h1109. <https://doi.org/10.1136/bmj.h1109>.
- [89] Drovandi AD, Chen CC, Glass BD. Adverse effects cause varenicline discontinuation: a meta-analysis. *Curr Drug Saf* 2016;11(1):78–85. <https://doi.org/10.2174/1574886311207040282>.
- [90] Polini F, Principe R, Scarpelli S, Clementi F, De Gennaro L. Use of varenicline in smokeless tobacco cessation influences sleep quality and dream recall frequency but not dream affect. *Sleep Med* 2017;30:1–6. <https://doi.org/10.1016/j.sleep.2016.11.002>.
- [91] Foulds J, Russ C, Yu CR, Zou KH, Galaznik A, Franzon M, Berg A, Hughes JR. Effect of varenicline on individual nicotine withdrawal symptoms: a combined analysis of eight randomized, placebo-controlled trials. *Nicotine Tob Res* 2013;15(11):1849–57. <https://doi.org/10.1093/ntr/ntt066>.
- [92] Xu L, Jiang CQ, Lam TH, Liu B, Jin YL, Zhu T, Zhang WS, Cheng KK, Thomas GN. Short or long sleep duration is associated with memory impairment in older Chinese: the Guangzhou Biobank cohort study. *Sleep* 2011;34(5):575–80. <https://doi.org/10.1093/sleep/34.5.575>.
- [93] Shekleton JA, Flynn-Evans EE, Miller B, Epstein LJ, Kirsch D, Brogna LA, Burke LM, Bremer E, Murray JM, Gehrman P, Lockley SW, Rajaratnam SMW. Neurobehavioral performance impairment in insomnia: relationships with self-reported sleep and daytime functioning. *Sleep* 2014;37(1):107–16. <https://doi.org/10.5665/sleep.3318>.
- [94] Goel N, Basner M, Rao H, Dinges DF. Circadian rhythms, sleep deprivation, and human performance. *Prog Molec Biol Transl Sci* 2013;119:155–90. <https://doi.org/10.1016/B978-0-12-396971-2.00007-5>.
- [95] Patterson F, Jepson C, Strasser AA, Loughead J, Perkins KA, Gur RC, Frey JM, Siegel S, Lerman C. Varenicline improves mood and cognition during smoking abstinence. *Biol Psychiatry* 2009;65(2):144–9. <https://doi.org/10.1016/j.biopsych.2008.08.028>.
- [96] Faubel R, López-García E, Guallar-Castillón P, Graciani A, Banegas JR, Rodríguez-Artalejo F. Usual sleep duration and cognitive function in older adults in Spain. *J Sleep Res* 2009;18(4):427–35. <https://doi.org/10.1111/j.1365-2869.2009.00759.x>.
- [97] Smith ME, McEvoy LK, Gevins A. The impact of moderate sleep loss on neurophysiologic signals during working-memory task performance. *Sleep* 2002;25(7):784–94. <https://doi.org/10.1093/sleep/25.7.56>.
- [98] Van Dongen HPA, Bender AM, Dinges DF. Systematic individual differences in sleep homeostatic and circadian rhythm contributions to neurobehavioral impairment during sleep deprivation. *Accid Anal Prev* 2012;45:11–6. <https://doi.org/10.1016/j.aap.2011.09.018>.
- [99] Killgore WDS, Balkin TJ, Wesensten NJ. Impaired decision making following 49 h of sleep deprivation. *J Sleep Res* 2006;15(1):7–13. <https://doi.org/10.1111/j.1365-2869.2006.00487.x>.
- [100] Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. *Nat Commun* 2013;4. <https://doi.org/10.1038/ncomms3259>.
- [101] Ward MM, Swan GE, Jack LM. Self-reported abstinence effects in the first month after smoking cessation. *Addict Behav* 2001;26(3):311–27. [https://doi.org/10.1016/S0306-4603\(00\)00107-6](https://doi.org/10.1016/S0306-4603(00)00107-6).
- [102] Myers CS. Nicotine nasal spray dose-dependently enhanced sustained attention as assessed by the continuous performance task. Society for Research on Nicotine and Tobacco; 2005. p. 2005.
- [103] Jacobsen LK, Krystal JH, Mencl WE, Westerveld M, Frost SJ, Pugh KR. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. *Biol Psychiatry* 2005;57(1):56–66. <https://doi.org/10.1016/j.biopsych.2004.10.022>.
- [104] Mendrek A, Monterosso J, Simon SL, Jarvik M, Brody A, Olmstead R, Domier CP, Cohen MS, Ernst M, London ED. Working memory in cigarette smokers: comparison to non-smokers and effects of abstinence. *Addict Behav* 2006;31(5):833–44. <https://doi.org/10.1016/j.addbeh.2005.06.009>.
- [105] Myers CS, Taylor RC, Moolchan ET, Heishman SJ. Dose-related enhancement of mood and cognition in smokers administered nicotine nasal spray. *Neuropsychopharmacology* 2008;33(3):588–98. <https://doi.org/10.1038/sj.npp.1301425>.
- [106] Dolan SL, Sacco KA, Termine A, Seyal AA, Dudas MM, Vessicchio JC, Wexler BE, George TP. Neuropsychological deficits are associated with smoking cessation treatment failure in patients with schizophrenia. *Schizophr Res* 2004;70(2–3):263–75. <https://doi.org/10.1016/j.schres.2004.01.006>.
- [107] Krishnan-Sarin S, Reynolds B, Duhig AM, Smith A, Liss T, McFetridge A, Cavallo DA, Carroll KM, Potenza MN. Behavioral impulsivity predicts treatment outcome in a smoking cessation program for adolescent smokers. *Drug Alcohol Depend* 2007;88(1):79–82. <https://doi.org/10.1016/j.drugalcdep.2006.09.006>.
- [108] Rukstalis M, Jepson C, Patterson F, Lerman C. Increases in hyperactive-impulsive symptoms predict relapse among smokers in nicotine replacement therapy. *J Subst Abuse Treat* 2005;28(4):297–304. <https://doi.org/10.1016/j.jsat.2005.02.002>.
- [109] Crothers K, Griffith TA, McGinnis KA, Rodriguez-Barradas MC, Leaf DA, Weissman S, Gilbert CL, Butt AA, Justice AC. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. *J Gen Intern Med* 2005;20(12):1142–5. <https://doi.org/10.1111/j.1525-1497.2005.0255.x>.
- [110] Feldman JG, Minkoff H, Schneider MF, Gange SJ, Cohen M, Watts DH, Gandhi M, Mochamuk RS, Anastos K. Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study. *Am J Publ Health* 2006;96(6):1060–5. <https://doi.org/10.2105/AJPH.2005.062745>.
- [111] Webb MS, Vanable PA, Carey MP, Blair DC. Cigarette smoking among HIV+ men and women: examining health, substance use, and psychosocial correlates across the smoking spectrum. *J Behav Med* 2007;30(5):371–83. <https://doi.org/10.1007/s10865-007-9112-9>.
- [112] Collins RL, Kanouse DE, Gifford AL, Senterfitt JW, Schuster MA, McCaffrey DF, Shapiro MF, Wengere NS. Changes in health-promoting behavior following diagnosis with HIV: prevalence and correlates in a national probability sample. *Health Psychol* 2001;20(5):351–60. <https://doi.org/10.1037/0278-6133.20.5.351>.
- [113] Burkhalter JE, Springer CM, Chhabra R, Ostroff JS, Rapkin BD. Tobacco use and readiness to quit smoking in low-income HIV-infected persons. *Nicotine Tob Res* 2005;7(4):511–22. <https://doi.org/10.1080/14622200500186064>.
- [114] Deeken JF, Tjen-A-Looi A, Rudek MA, Okulian C, Young M, Little RF, Dezube BJ. The rising challenge of non-AIDS-defining cancers in HIV-infected patients. *Clin Infect Dis* 2012;55(9):1228–35. <https://doi.org/10.1093/cid/cis613>.
- [115] Brugnaro P. Non-AIDS definings malignancies among human immunodeficiency virus-positive subjects: epidemiology and

- outcome after two decades of HAART era. *World J Virol* 2015;4(3):209. <https://doi.org/10.5501/wjv.v4.i3.209>.
- [116] Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;338(13):853–60. <https://doi.org/10.1056/NEJM199803263381301>.
- [117] Rubinstein PG, Aboulafia DM, Zloza A. Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges. *AIDS* 2014;28(4):453–65. <https://doi.org/10.1097/QAD.0000000000000071>.
- [118] Vaccher E, Serraino D, Carbone A, De Paoli P. The evolving scenario of non-AIDS-defining cancers: challenges and opportunities of care. *Oncologist* 2014;19(8):860–7. <https://doi.org/10.1634/theoncologist.2014-0024>.
- [119] Palella FJ, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006;43(1):27–34. <https://doi.org/10.1097/01.qai.0000233310.90484.16>.
- [120] D'Abromo A, Zingaropoli MA, Oliva A, D'Agostino C, Moghazi SAI, De Luca G, Iannetta M, d'Ettorre G, Ciardi MR, Mastroianni CM, Vullo V, Gray CM. Higher levels of osteoprotegerin and immune activation/immunosenescence markers are correlated with concomitant bone and endovascular damage in HIV-suppressed patients. *PLoS One* 2016;11(2):e0149601. <https://doi.org/10.1371/journal.pone.0149601>.
- [121] Nasi M, De Biasi S, Gibellini L, Bianchini E, Pecorini S, Bacca V, Guaraldi G, Mussini C, Pinti M, Cossarizza A. Ageing and inflammation in patients with HIV infection. *Clin Exp Immunol* 2017;187(1):44–52. <https://doi.org/10.1111/cei.12814>.
- [122] Leng SX, Margolick JB. Understanding frailty, aging, and inflammation in HIV infection. *Curr HIV AIDS Rep* 2015;12(1):25–32. <https://doi.org/10.1007/s11904-014-0247-3>.
- [123] Gamaldo CE, Spira AP, Hock RS, Salas RE, McArthur JC, David PM, Mbeo G, Smith MT. Sleep, function and HIV: a multi-method assessment. *AIDS Behav* 2013;17(8):2808–15. <https://doi.org/10.1007/s10461-012-0401-0>.
- [124] Low Y, Goforth H, Preud'Homme X, Edinger J, Krystal A. Insomnia in HIV-infected patients: pathophysiologic implications. *AIDS Rev* 2014;16(1):3–13.
- [125] Allavena C, Guimard T, Billaud E, De la Tullaye S, Reliquet V, Pineau S, Hüe H, Supiot C, Chennebault J-M, Michau C, Hitoto H, Vatan R, Raffi F. Prevalence and risk factors of sleep disturbance in a large HIV-infected adult population. *AIDS Behav* 2016;20(2):339–44. <https://doi.org/10.1007/s10461-015-1160-5>.
- [126] Cooper J, Borland R, Yong HH, Fotuhi O. The impact of quitting smoking on depressive symptoms: findings from the international tobacco control four-country survey. *Addiction* 2016;111(8):1448–56. <https://doi.org/10.1111/add.13367>.
- [127] Fillo J, Alfano CA, Paulus DJ, Smits JA, Davis ML, Rosenfield D, Marcus BH, Church TS, Powers MB, Otto MW, Baird SO, Zvolensky MJ. Emotion dysregulation explains relations between sleep disturbance and smoking quit-related cognition and behavior. *Addict Behav* 2016;57:6–12. <https://doi.org/10.1016/j.addbeh.2016.01.013>.
- [128] Michael Vanderlind W, Beevers CG, Sherman SM, Trujillo LT, McGahey JE, Matthews MD, Todd Maddox W, Schnyer DM. Sleep and sadness: exploring the relation among sleep, cognitive control, and depressive symptoms in young adults. *Sleep Med* 2014;15(1):144–9. <https://doi.org/10.1016/j.sleep.2013.10.006>.
- [129] Kauffman BY, Farris SG, Alfano CA, Zvolensky MJ. Emotion dysregulation explains the relation between insomnia symptoms and negative reinforcement smoking cognitions among daily smokers. *Addict Behav* 2017;72:33–40. <https://doi.org/10.1016/j.addbeh.2017.03.011>.
- [130] Hall FS, Der-Avakan A, Gould TJ, Markou A, Shoib M, Young JW. Negative affective states and cognitive impairments in nicotine dependence. *Neurosci Biobehav Rev* 2015;58:168–85. <https://doi.org/10.1016/j.neubiorev.2015.06.004>.
- [131] Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. *Hum Psychopharmacol* 2008;23(7):571–85. <https://doi.org/10.1002/hup.964>.
- [132] McClung CA. How might circadian rhythms control mood? Let me count the ways. *Biol Psychiatry* 2013;74(4):242–9. <https://doi.org/10.1016/j.biopsych.2013.02.019>.
- [133] Tsuno N, Berset A, Ritchie K. Sleep and depression. *J Clin Psychiatry* 2005;66(10):1254–69. <https://doi.org/10.4088/JCP.v66n1008>.
- [134] Staner L. Comorbidity of insomnia and depression. *Sleep Med Rev* 2010;14(1):35–46. <https://doi.org/10.1016/j.smrv.2009.09.003>.
- [135] Pillai V, Kalmbach DA, Ciesla JA. A meta-analysis of electroencephalographic sleep in depression: evidence for genetic biomarkers. *Biol Psychiatry* 2011;70(10):912–9. <https://doi.org/10.1016/j.biopsych.2011.07.016>.
- [136] Winkler D, Pjrek E, Praschak-Rieder N, Willeit M, Pezawas L, Konstantinidis A, Stastny J, Kasper S. Actigraphy in patients with seasonal affective disorder and healthy control subjects treated with light therapy. *Biol Psychiatry* 2005;58(4):331–6. <https://doi.org/10.1016/j.biopsych.2005.01.031>.
- [137] Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. *Dialogues Clin Neurosci* 2008;10(3):329–36. <https://doi.org/10.31887/dcn.2008.10.3dnutt>.
- [138] Armitage R, Hoffmann R, Trivedi M, Rush AJ. Slow-wave activity in NREM sleep: sex and age effects in depressed outpatients and healthy controls. *Psychiatry Res* 2000;95(3):201–13. [https://doi.org/10.1016/S0165-1781\(00\)00178-5](https://doi.org/10.1016/S0165-1781(00)00178-5).
- [139] Clark C, Dupont R, Golshan S, Gillin JC, Rapaport MH, Kelsoe JR. Preliminary evidence of an association between increased REM density and poor antidepressant response to partial sleep deprivation. *J Affect Disord* 2000;59(1):77–83. [https://doi.org/10.1016/S0165-0327\(99\)00135-4](https://doi.org/10.1016/S0165-0327(99)00135-4).
- [140] Mendlewick J. Sleep disturbances: core symptoms of major depressive disorder rather than associated or comorbid disorders. *World J Biol Psychiatr* 2009;10(4):269–75. <https://doi.org/10.3109/15622970802503086>.
- [141] Troxel WM, Kupfer DJ, Reynolds CF, Frank E, Thase ME, Miewald JM, Buysse DJ. Insomnia and objectively measured sleep disturbances predict treatment outcome in depressed patients treated with psychotherapy or psychotherapy- pharmacotherapy combinations. *J Clin Psychiatr* 2012;73(4):478–85. <https://doi.org/10.4088/JCP.11m07184>.
- [142] Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young Adults. *Biol Psychiatry* 1996;39(6):411–8. [https://doi.org/10.1016/0006-3223\(95\)00188-3](https://doi.org/10.1016/0006-3223(95)00188-3).

- [143] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? *J Am Med Assoc* 1989;262(11):1479–84. <https://doi.org/10.1001/jama.1989.03430110069030>.
- [144] Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rössler W. Prevalence, course, and comorbidity of insomnia and depression in young adults. *Sleep* 2008;31(4):473–80. <https://doi.org/10.1093/sleep/31.4.473>.
- [145] Lawrence D, Mitrou F, Zubrick SR. Smoking and mental illness: results from population surveys in Australia and the United States. *BMC Public Health* 2009;9. <https://doi.org/10.1186/1471-2458-9-285>.
- [146] Pratt LA, Brody DJ. Depression and smoking in the U.S. household population aged 20 and over, 2005–2008. *NCHS Data Brief* 2010;34:1–8.
- [147] Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry* 2004;61(11):1107–15. <https://doi.org/10.1001/archpsyc.61.11.1107>.
- [148] Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, Johnson J. Smoking, smoking cessation, and major depression. *J Am Med Assoc* 1990;264(12):1546–9. <https://doi.org/10.1001/jama.1990.03450120058029>.
- [149] Breslau N, Kilbey MM, Andreski P. Nicotine dependence, major depression, and anxiety in young adults. *Arch Gen Psychiatry* 1991;48(12):1069–74. <https://doi.org/10.1001/archpsyc.1991.01810360033005>.
- [150] Leventhal AM, Kahler CW, Ray LA, Zimmerman M. Refining the depression-nicotine dependence link: patterns of depressive symptoms in psychiatric outpatients with current, past, and no history of nicotine dependence. *Addict Behav* 2009;34(3):297–303. <https://doi.org/10.1016/j.addbeh.2008.11.008>.
- [151] Breslau N, Kilbey MM, Andreski P. Nicotine dependence and major depression: new evidence from a prospective investigation. *Arch Gen Psychiatry* 1993;50(1):31–5. <https://doi.org/10.1001/archpsyc.1993.01820130033006>.
- [152] Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking: a longitudinal investigation. *Arch Gen Psychiatry* 1998;55(2):161–6. <https://doi.org/10.1001/archpsyc.55.2.161>.
- [153] Breslau N, Novak SP, Kessler RC. Daily smoking and the subsequent onset of psychiatric disorders. *Psychol Med* 2004;34(2):323–33. <https://doi.org/10.1017/S0033291703008869>.
- [154] Colman I, Naicker K, Zeng Y, Ataullahjan A, Senthilselvan A, Patten SB. Predictors of long-term prognosis of depression. *Can Med Assoc J* 2011;183(17):1969–76. <https://doi.org/10.1503/cmaj.110676>.
- [155] Ashare RL, Valdez JN, Ruparel K, Albelda B, Hopson RD, Keefe JR, Loughead J, Lerman C. Association of abstinence-induced alterations in working memory function and COMT genotype in smokers. *Psychopharmacology* 2013;230(4):653–62. <https://doi.org/10.1007/s00213-013-3197-3>.
- [156] Falcone M, Wileyto EP, Ruparel K, Gerraty RT, Laprate L, Detre JA, Gur R, Loughead J, Lerman C. Age-related differences in working memory deficits during nicotine withdrawal. *Addict Biol* 2014;19(5):907–17. <https://doi.org/10.1111/adb.12051>.
- [157] Loughead J, Ray R, Wileyto EP, Ruparel K, Sanborn P, Siegel S, Gur RC, Lerman C. Effects of the $\alpha 4\beta 2$ partial agonist varenicline on brain activity and working memory in abstinent smokers. *Biol Psychiatry* 2010;67(8):715–21. <https://doi.org/10.1016/j.biopsych.2010.01.016>.
- [158] Harvey PO, Fossati P, Pochon JB, Levy R, LeBastard G, Lehéricy S, Allilaire JF, Dubois B. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *Neuroimage* 2005;26(3):860–9. <https://doi.org/10.1016/j.neuroimage.2005.02.048>.
- [159] Norbury R, Godlewska B, Cowen PJ. When less is more: a functional magnetic resonance imaging study of verbal working memory in remitted depressed patients. *Psychol Med* 2014;44(6):1197–203. <https://doi.org/10.1017/s0033291713001682>.
- [160] Drummond SPA, Walker M, Almklov E, Campos M, Anderson DE, Straus LD. Neural correlates of working memory performance in primary insomnia. *Sleep* 2013;36(9):1307–16. <https://doi.org/10.5665/sleep.2952>.
- [161] Cooper J, Borland R, McKee SA, Yong HH, Dugué PA. Depression motivates quit attempts but predicts relapse: differential findings for gender from the International Tobacco Control Study. *Addiction* 2016;111(8):1438–47. <https://doi.org/10.1111/add.13290>.
- [162] Nogueira LM, Sampson JN, Chu LW, Yu K, Andriole G, Church T, Stanczyk FZ, Koshiol J, Hsing AW. Individual variations in serum melatonin levels through time: implications for epidemiologic studies. *PLoS One* 2013;8(12). <https://doi.org/10.1371/journal.pone.0083208>.
- [163] Ozguner F, Koyu A, Cesur G. Active smoking causes oxidative stress and decreases blood melatonin levels. *Toxicol Ind Health* 2005;21(10):21–6. <https://doi.org/10.1191/0748233705th211oa>.
- [164] Mexal S, Horton WJ, Crouch EL, Maier SIB, Wilkinson AL, Marsolek M, Stitzel JA. Diurnal variation in nicotine sensitivity in mice: role of genetic background and melatonin. *Neuropharmacology* 2012;63(6):966–73. <https://doi.org/10.1016/j.neuropharm.2012.06.065>.
- [165] Zhdanova IV, Piotrovskaya VR. Melatonin treatment attenuates symptoms of acute nicotine withdrawal in humans. *Pharmacol Biochem Behav* 2000;67(1):131–5. [https://doi.org/10.1016/S0091-3057\(00\)00302-6](https://doi.org/10.1016/S0091-3057(00)00302-6).
- [166] Horton WJ, Gissel HJ, Saboy JE, Wright KP, Stitzel JA. Melatonin administration alters nicotine preference consumption via signaling through high-affinity melatonin receptors. *Psychopharmacology* 2015;232(14):2519–30. <https://doi.org/10.1007/s00213-015-3886-1>.
- [167] Sutcliffe JG, de Lecea L. The hypocretins: setting the arousal threshold. *Nat Rev Neurosci* 2002;3(5):339–49. <https://doi.org/10.1038/nrn808>.
- [168] Plaza-Zabala A, Maldonado R, Berrendero F. The hypocretin/orexin system: implications for drug reward and relapse. *Mol Neurobiol* 2012;45(3):424–39. <https://doi.org/10.1007/s12035-012-8255-z>.
- [169] Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Barry MJ, Boyd C, Chow RD, Fitterman N, Harris RP, Humphrey LL, Manaker S, McLean R, Mir TP, Schünemann HJ, Vijan S, Wilt T. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American college of physicians. *Ann Intern Med* 2016;165(2):125–33. <https://doi.org/10.7326/M15-2175>.
- [170] National Institutes of Health state of the science conference statement: manifestations and management of chronic insomnia in

- adults June 13–15, 2005. *Sleep* 2005;28(9). <https://doi.org/10.1093/sleep/28.9.1049>.
- [171] Vincent N, Lionberg C. Treatment preference and patient satisfaction in chronic insomnia. *Sleep* 2001;24(4):411–7. <https://doi.org/10.1093/sleep/24.4.411>.
- [172] Perlis ML, Aloia M, Kuhn B. Behavioral treatments for sleep disorders behavioral treatments for sleep disorders. United States: Elsevier Inc.; 2011. <https://doi.org/10.1016/C2009-0-62216-9>.
- [173] Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). *Sleep* 2006;29(11):1398–414. <https://doi.org/10.1093/sleep/29.11.1398>.
- [174] Trauer JM, Qian MY, Doyle JS, Rajaratnam SMW, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. *Ann Intern Med* 2015;163(3):191–204. <https://doi.org/10.7326/M14-2841>.
- [175] Smith MT, Perlis ML, Park A, Smith MS, Pennington JM, Giles DE, Buysse DJ. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatr* 2002;159(1):5–11. <https://doi.org/10.1176/appi.ajp.159.1.5>.
- [176] Xu H, Guan J, Yi H, Yin S, Wang Y. A systematic review and meta-analysis of the association between serotonergic gene polymorphisms and obstructive sleep apnea syndrome. *PLoS One* 2014;9(1):e86460. <https://doi.org/10.1371/journal.pone.0086460>.
- [177] Physician desk reference. PDR Network; 2014.
- [178] Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA* 1997;278(24):2170–7. <https://doi.org/10.1001/jama.278.24.2170>.
- [179] Cosgrove KP, McKay R, Esterlis I, Kloczynski T, Perkins E, Bois F, Pittman B, Lancaster J, Glahn DC, O’Malley S, Carson RE, Krystal JH. Tobacco smoking interferes with gabaa receptor neuroadaptations during prolonged alcohol withdrawal. *Proc Natl Acad Sci USA* 2014;111(50):18031–6. <https://doi.org/10.1073/pnas.1413947111>.
- [180] MacFarlane J, Morin CM, Montplaisir J. Hypnotics in insomnia: the experience of zolpidem. *Clin Ther* 2014;36(11):1676–701. <https://doi.org/10.1016/j.clinthera.2014.09.017>.
- [181] Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzemann J, Walsh JK, Krystal AD, Benca RM, Cohn M, Lines C, Roth T, Herring WJ. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2014;13(5):461–71. [https://doi.org/10.1016/S1474-4422\(14\)70053-5](https://doi.org/10.1016/S1474-4422(14)70053-5).
- [182] Leufkens TRM, Ramaekers JG, De Weerd AW, Riedel WJ, Vermeeren A. Residual effects of zopiclone 7.5 mg on highway driving performance in insomnia patients and healthy controls: a placebo controlled crossover study. *Psychopharmacology* 2014;231(14):2785–98. <https://doi.org/10.1007/s00213-014-3447-z>.
- [183] Loughead J, Wileyto EP, Ruparel K, Falcone M, Hopson R, Gur R, Lerman C. Working memory-related neural activity predicts future smoking relapse. *Neuropsychopharmacology* 2015;40(6):1311–20. <https://doi.org/10.1038/npp.2014.318>.
- [184] Patterson F, Jepson C, Loughead J, Perkins K, Strasser AA, Siegel S, Frey J, Gur R, Lerman C. Working memory deficits predict short-term smoking resumption following brief abstinence. *Drug Alcohol Depend* 2010;106(1):61–4. <https://doi.org/10.1016/j.drugalcdep.2009.07.020>.
- [185] Laudon M, Frydman-Marom A. Therapeutic effects of melatonin receptor agonists on sleep and comorbid disorders. *Int J Mol Sci* 2014;15(9):15924–50. <https://doi.org/10.3390/ijms150915924>.
- [186] Kohsaka M, Kanemura T, Taniguchi M, Kuwahara H, Mikami A, Kamikawa K, Uno H, Ogawa A, Murasaki M, Sugita Y. Efficacy and tolerability of ramelteon in a double-blind, placebo-controlled, crossover study in Japanese patients with chronic primary insomnia. *Expert Rev Neurother* 2011;11(10):1389–97. <https://doi.org/10.1586/ern.11.128>.
- [187] Mayer G, Wang-Weigand GS, Roth-Schechter B, Lehmann R, Staner C, Partinen M. Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. *Sleep* 2009;32(3):351–60. <https://doi.org/10.1093/sleep/32.3.351>.
- [188] Jacobson LH, Chen S, Mir S, Hoyer D. Orexin OX2 receptor antagonists as sleep aids. *Curr Topics Behav Neurosci* 2017;33:105–36. https://doi.org/10.1007/7854_2016_47.
- [189] Kenny PJ. Tobacco dependence, the insular cortex and the hypocretin connection. *Pharmacol Biochem Behav* 2011;97(4):700–7. <https://doi.org/10.1016/j.pbb.2010.08.015>.
- [190] Wong SYS, Zhang DX, Li CCK, Yip BHK, Chan DCC, Ling YM, Lo CSL, Woo DMS, Sun YY, Ma H, Mak WWS, Gao T, Lee TMC, Wing YK. Comparing the effects of mindfulness-based cognitive therapy and sleep psycho-education with exercise on chronic insomnia: a randomised controlled trial. *Psychother Psychosom* 2017;86(4):241–53. <https://doi.org/10.1159/000470847>.
- [191] Nair US, Patterson F, Rodriguez D, Collins BN. A telephone-based intervention to promote physical activity during smoking cessation: a randomized controlled proof-of-concept study. *Transl Behav Med* 2017;7(2):138–47. <https://doi.org/10.1007/s13142-016-0449-x>.
- [192] Maglione MA, Maher AR, Ewing B, Colaiaco B, Newberry S, Kandrack R, Shanman RM, Sorbero ME, Hempel S. Efficacy of mindfulness meditation for smoking cessation: a systematic review and meta-analysis. *Addict Behav* 2017;69:27–34. <https://doi.org/10.1016/j.addbeh.2017.01.022>.

This page intentionally left blank

Chapter 26

Sleep and the impact of caffeine, energy supplements, and other stimulants

Ninad S. Chaudhary^{a, b}, Priyamvada M. Pitale^c and Favel L. Mondesir^d

^aDepartment of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, United States; ^bDepartment of Neurology, University of Alabama School of Medicine, Birmingham, AL, United States; ^cDepartment of Optometry and Vision Science, School of Optometry, University of Alabama at Birmingham, Birmingham, AL, United States; ^dDivision of Cardiovascular Medicine, School of Medicine, University of Utah, Salt Lake City, UT, United States

Abbreviations

ADA	Adenosine deaminase
ADORA2A	Adenosine A2A receptor
CYP1A2	Cytochrome P450 family 1 subfamily A member 2
DSM	Diagnostic statistical manual
ED	Energy drinks
EEG	Electroencephalogram
FDA	Food and Drug Administration
GBP4	Guanylate binding protein 4
GWAS	Genome-wide association studies
ICD-9	International Classification of Diseases
IL-6	Interleukin 6
KiGGS	German Health Interview and Examination Survey for Children and Adolescents
N-REM	Nonrapid eye movement
NHANES	National Health and Nutritional Examination Survey
NHIS	National Health Interview Survey
NICHHD	National Institute of Child Health and Human Development
PRIMA1	Proline-rich membrane anchor 1
PTSD	Post-traumatic stress disorder
SNP	Single-nucleotide polymorphisms
WASO	Waking after sleep onset

Introduction

Caffeine is the most frequently used psychostimulant drug worldwide [1]. Recently, new categories of caffeine-containing products, such as energy drink supplements, have become popular and have been increasing rapidly in the past decade [2,3]. The most frequent reason people use caffeine or energy drinks is to counteract the effects of insufficient sleep or sleepiness [4,5]. The use of caffeine as a countermeasure is of grave concern, considering the prevalence of sleep problems has been on the rise in the

global population [6]. These products also have adverse effects on the cardiovascular, metabolic, and neurological systems [3]. These effects may potentially add to the existing comorbid burden due to underlying sleep disturbances. The global impact of the combined health outcomes of caffeine use and sleep problems is overarching and requires close evaluation.

The average intake of caffeine in the general population is 165 mg, an amount sufficient to interfere with sleep [1]. However, the average intake may be underestimated due to varying sources of caffeine consumed throughout the day. Caffeine is also an essential ingredient of energy drinks. In addition to caffeine, energy drinks also contain taurine, L-carnitine, vitamins, carbohydrates, herbal supplements, and other additives such as cocoa, guarana, and ginseng [2]. The current regulations do not require the inclusion of the caffeine content of these additional ingredients, which limits the information on the exact amount [7,8]. Most of the research studies examined the physiological effects of these products that improve performance; however, the associated adverse effects are still understudied [8].

There is extensive literature on the association between caffeine and sleep over the last few decades [9]. The research is mostly divided between understanding the effect of caffeine after sleep deprivation and on post-caffeine recovery sleep. The earliest reference to caffeine-sleep mechanisms is observed in a research study by Brezinova et al. [10] who reported that caffeine use is associated with stable periods of wakefulness between episodes of drowsiness that have a similar duration to any of the sleep stages. They coined the phenomenon “Caffeine-insomnia.” Subsequent research has made landslide improvements in measuring the associations between caffeine and sleep. The

research is still limited in understanding the individual variation of caffeine on sleep effects, time and dose-response relationship of these associations, establishing the causality, and interaction of caffeine, circadian rhythm, and sleep regulatory processes. The advent of energy drinks in the last decade places the importance of these associations in a new light.

This chapter focuses on the effect of caffeine, energy drinks, and other psychostimulants on the sleep of adolescents and adults. We outline the epidemiology of sleep disorders in light of caffeine and energy drink consumption, the possible underlying mechanisms and related factors, the health implications of the cumulative effect of sleep and these products, and probable recommendations.

Epidemiology

Epidemiology of sleep in caffeine

Caffeine is a by-product obtained from cocoa grown indigenously in South America and is now frequently consumed in a beverage form such as coffee, soft drinks, energy drinks, gum, or concentrated form [2]. Approximately 85% of adult Americans and 30% of American adolescents regularly consume at least one drink of caffeine each day, while only 50% consume energy drink supplements [1,11]. The use of psychostimulants is prescription-based and is not known for the civilian population. The mean caffeine intake for all adults varies from 164 to 228 mg/day primarily due to the difference in the source of consumption, which predominantly varies by age= and gender [1]. The mean daily caffeine intake was 165 ± 1 mg combined for all ages and highest for the age group of 50–64 years (226 ± 2 mg/day) [1]. The older population is more likely to consume coffee, while the younger population relies on sodas and energy drink supplements for their caffeine intake [11]. While the mean intake in men is slightly higher than women, the source of caffeine is mostly age dependent for both [9].

Caffeine use on a routine basis or sleep-deprived state improves neurobehavioral functioning in healthy individuals at a dose as low as 32 mg [12]. However, with increasing consumption or dosages, caffeine may have adverse sleep-related consequences on subsequent nights for a longer duration [4,9]. The contents of caffeine vary in these products, which determine the possible sleep disturbances based on the amount consumed [2,13] (Table 26.1). These dose-dependent adverse effects range from minor abnormalities in sleep patterns, such as poor sleep quality or reduced sleep duration, to those meeting the diagnosis of insomnia [14].

Caffeine use has primarily been researched to overcome sleep deprivation. While few studies focus on caffeine use for sleep deprivation in the general population,

most of them were concentrated in a particular community, specifically military and shift workers. Roehrs and Roth [4] reviewed anecdotal studies providing practice guidelines and recommendations for caffeine and sleep-related research. The guidelines emphasized the importance of the comprehensive assessment of dietary sources of caffeine to identify caffeine-related sleep disturbances, integrate its use in clinical evaluations of insomnia complaints, and to determine caffeine dependence in the light of insomnia for appropriate interventions. The exhaustive research in caffeine and sleep-related investigations over the past few years has led to the identification of caffeine use disorder in DSM. The DMS-IV recognizes four caffeine-related diagnoses: Caffeine intoxication, caffeine-induced anxiety disorder, caffeine-related disorder not otherwise specified, and most important from the perspective of this chapter, caffeine-induced sleep disorder (DMS-IV) [15,16]. This classification was, however, updated in DSM-V to include caffeine-induced sleep disorder under the subheading of “Other Caffeine-Induced Disorders,” and limiting the utility of caffeine use disorder as a condition for further study [17,18] (DSM V). The decision reflects the consensus of the experts that caffeine use disorder can likely be overdiagnosed since the use of caffeine is extensive worldwide [19]. These recommendations emphasize the dire need for understanding caffeine-related sleep disturbances, which are likely etiological or consequential factors of caffeine withdrawal syndrome as well as dependence.

Despite the beneficial effects of caffeine on sleep deprivation, numerous studies have observed adverse sleep-related consequences on subsequent nights [4,9]. However, the epidemiological studies quantifying these associations are limited [20–25]. The complexity of this relationship can be attributed to the nonstandardized measurements of caffeine intake or sleep disturbances, age-related differences, and individual variations in the dose-dependent effects of caffeine on sleep [9,26–28]. Here, we attempt to delineate the studies based on sleep disturbances.

One of the oldest cohorts of community-dwelling adults in the US Iowa state aged 65 years and more, reported that caffeine intake poses trouble falling asleep, which was driven by over-the-counter analgesics that contain caffeine [29]. The trends in caffeine consumption have changed drastically over the last decade, and additional sources of caffeine now influence sleep. A systematic review on the effects of caffeinated foods and beverages on cognitive functioning in the healthy adult population observed that high-dose caffeine intake of 200–400 mg more than once a week was independently associated with short sleep duration [30,31]. The interplay of caffeine consumption with sleep duration and insomnia symptoms was recently evaluated in American adults using data from the 2007–2008

TABLE 26.1 Caffeine beverages and contents.

	Caffeine content ^a	Sleep effects ^c
Coffees		
Brewed coffee	133 mg/8 oz	SSD, DFA
Instant coffee	93 mg/8 oz	SSD, frequent awakening
Espresso	320 mg/8 oz	Poor SQ, DS, changes in EEG
Soft drinks/energy drinks		
Regular or diet	35–71 mg/12 oz ^b	None to SSD
5 h Energy	215 mg/12 oz	Decreased time in bed, poor SQ, changes in EEG
Monster energy	120 mg/12 oz	DFA, DSA
Red bull	116 mg/12 oz	DFA, increased WASO, poor SS
Others	50–300 mg/8.3 oz	None to poor SQ, DS, changes in EEG
Tea and other	15–40 mg/16 oz	None

DFA, difficulty falling asleep; DFA, difficulty staying asleep; DS, daytime sleepiness; DSA, difficulty staying asleep; EEG, electroencephalograph; SQ, sleep quality; SS, sleep satisfaction; SSD, short sleep duration.

^aFDA limit.

^bFDA limit for soft drinks is 71 mg/12 oz.

^cEffects are based on the quantity of caffeine obtained from laboratory studies.

Reproduced from: Somogyi, LP. Caffeine intake by the US population. Prepared for The Food and Drug Administration and Oakridge National Laboratory; 2010; Clark I, Landolt HP. Coffee, caffeine, and sleep: a systematic review of epidemiological studies and randomized controlled trials. *Sleep Med Rev* 2017;31:70–8; Juliano LMGR. Caffeine. In: Lowinson JHRP, Millman RB, Langrod JG, editors. Substance abuse: a comprehensive textbook. Fourth ed. Baltimore: Lippincott Williams & Wilkins; 2005.

National Health and Nutrition Examination Survey (NHANES) [22]. The study provided a unique perspective that the caffeine was not only associated with insomnia symptoms of trouble falling asleep, waking after sleep onset (WASO), and daytime sleepiness but the interaction of caffeine intake and habitual sleep duration predicted nonrestorative sleep. The relationship between higher caffeine consumption with sleep duration or sleep quality was consistent in studies across the globe despite the heterogeneity in the methods of assessment of sleep duration or sleep quality [24,32–34].

There are more small-scale epidemiological studies performed in adolescents than in the adult population, owing to research recommendations in past literature and unique consumption patterns in adolescents [21,23–25]. The shortened sleep duration, excessive daytime sleepiness, dose-dependent initial insomnia, and poor sleep quality are consistent patterns observed in adolescents across these epidemiological studies. A large nationally representative school-based the National Institute of Child Health and Human Development (NICHD) study of 15,686 adolescents from grades 6 to 10 found that 75% of adolescents drank at least one soda/day, but coffee use was less prevalent with 75% having coffee less than once a week [24]. The study reported that adolescents with high caffeine intake, defined as > 1 drink/day, had almost twice the odds of reporting difficulty in sleeping or daytime

sleepiness. A similar association in a large German-based epidemiological study of 7698 adolescents (11–17 years) recognized that coffee use is an essential risk factor for insomnia at this age [35]. The dose-dependent effects of caffeine on sleep are more prominent in the early age group. Caffeine intake of as high as 77.1 mg in 12–15 years old results in shorter sleep duration, longer WASO, and longer daytime sleep on a 2-week sleep diary [25]. The sleep was more interrupted on the night after consumption in those who had 100–150 mg/dL compared to those who had 0–50 mg/day. In another study of 1522 adolescents of 13 years of age, the median caffeine intake of 22–27 mg/day via soft drinks increased the odds of shortened sleep duration such that for each 10 mg/day increase in intake there were higher odds of sleep duration 8.5 h or less [23].

The factors that dictate the relationship between caffeine and sleep are different in adolescents compared to other age groups. The short sleep duration reported in adolescents is an interactive effect of caffeine, technology, or the use of other substances, especially alcohol [21,36]. Studies observed that coffee use modifies the relationship between sleep and other substance use (alcohol, nicotine), which in turn disrupts the sleep cycle and perpetuates the cycle of sleep fragmentation and substance use [35,37–39]. These findings, however, are not always consistent across studies [40,41]. The discrepancies can be due to the

different sources of caffeine, time of intake, or duration of intake. Further, the current research has not delineated the effect of soda beverages on energy drinks, especially in young age groups who consume an excess of energy drinks. The results should not differ much, considering the main ingredient in both products is still caffeine.

The lack of objective measures of sleep disturbances or insomnia complaints has been a challenge in better understanding and generalization of these relationships from the epidemiological view. There is an overwhelming number of studies that attempted to account for the limitation of nonstandardized measures by studying insomnia symptoms, more closely related to clinical diagnosis, in a controlled environment of randomized clinical trials, laboratory-based intervention studies, or polysomnographic studies [4,9]. The exciting aspect of these studies is that they consistently found that caffeine results in reduced sleep efficiency, increased sleep latency, more episodes of WASO, and reduced sleep duration. However, these studies are limited by small sample size, restriction to younger participants, and use of nonpragmatic concentrated forms of caffeine as a part of the intervention. The randomized polysomnographic study trials, being the gold standard, will be discussed here. A double-blind crossover study on 22–25 years old and 40–60 years old observed that higher dose of caffeine (200–400 mg) was associated with dose-dependent increase in relative stage 1 sleep and reduction in absolute and relative slow-wave sleep and absolute REM movements in both age groups [42]. The younger individuals had increased absolute stage 1 sleep, while older adults had decreased absolute stage 2 sleep. Overall, the middle-aged adults are more sensitive to the high dose of caffeine [43]. A randomized controlled trial focused on understanding the sleep hygiene patterns compared the effects of 400 mg caffeine and placebo at 0, 3, and 6 h consumed before self-reported habitual bedtime. The polysomnographic findings confirmed that caffeine, compared to placebo, is associated with reduced total sleep time, delayed onset of sleep, disturbance in the sleep stages, and reduced sleep quality. These changes were prominent for a minimum of 6 h before bedtime, supporting the role of metabolic products of caffeine on sleep [44]. From the perspective of dose-dependent effects, many studies observed reduced total sleep time, duration, and sleep stages at a dose of approximately 200 mg. However, the smallest dose at which these changes are observable is still not established. One of the archival studies by Rosenthal et al. observed increased sleep latency and reduced sleep duration at a dose as low as 75 mg/day with no effects on recovery sleep [45]. Ho et al. [46] in a double-blind control group design among 20–22 years old observed that there are no changes in sleep measures at a dose of 60 mg/day x week. While the pragmatic studies will be more convincing, detailed information about these

studies provided by Clark et al. [9], Poole et al. [47], and Roehrs et al. [4] can be conclusive for some researchers.

The recovery of sleep or physiological sleep debt secondary to prolonged sleep deprivation is more common than acute sleep deprivation [48]. However, the relationship of caffeine with recovery sleep is studied less in the general population and more in those who are at work in high-risk occupation settings such as the military, medical professionals, truck drivers, pilots, and shift duty workers. Few studies conducted within the general population have shown that caffeine reduces sleep efficiency and is associated with reduced N-REM sleep EEG synchronization in daytime recovery sleep [42,49]. In addition to occupation, age is another critical demographic, as the detrimental effects of caffeine on recovery sleep are more prominent in middle-aged individuals than younger subjects [42].

Epidemiology of sleep in energy drink supplements

Even though the advent of energy drink supplements in the last decade is frequently reported to be alarming, the percentage of consumers continues to be <10% across all age groups [1,50]. The reasons for concern about these supplements are: (1) Though the consumption is <10%, caffeine intake via these supplements has increased from 0.1 to 0.3 mg/day in 2001 to 1.9–2.1 mg/day in 2010 in the US population. The data collected by Kantar World Panel provided age-specific rates which were higher in the age groups 13–17 years (5.3–6.9 mg/day) and 18–24 years (6.2–0.8 mg/day), and lower in elderly population (0.7–1.1 mg/day); (2) There is no specific nutritional information available on the contents of all these supplements which limits our knowledge on the consumption and effects of other less-known substances; (3) There is limited data on health effects of these supplements in the general population due to lack of evidence-based research. Studies related to supplements have been small and focused on young adults, college students, athletes, or military personnel. The findings from these studies are not generalizable owing to high consumption in these segmented populations, and differential comorbidity patterns compared to other age groups. The above-mentioned points are also valid for the role of these supplements in sleep disturbances.

The causal relationship between energy drinks and sleep disturbances is still debatable despite strong contemporary research. Two recent large epidemiological studies reported that short sleep duration was associated with energy drink use. A nationally representative survey based on NHANES data (2005–2014) published that short sleep duration was associated with higher intake of beverages in adults >18 years of age, and it varies with an hour of sleep lost compared to regular 7–8 h of sleep [32].

A study based on the Ontario Student Drug Use and Health Survey observed that 13% of high school students reported energy drinks use, and were more likely to report shortened sleep duration compared to nonusers, even after accounting for tobacco or alcohol use [51]. The study findings lacked cause-effect directionality, a pattern consistent in most other related investigations. The research on sleep and energy drink supplements primarily focuses on changes in work performance, cognition, or health behaviors following their consumption. In adolescents, the association focuses on academic achievement and risk-taking behavior, while in adults, it is based on a change in cognition or performance. In a small university sample, high-end energy drinks result in sleep disturbances such as later bedtimes, a harder time falling asleep, and more all-nighter episodes. The concerning factor was that the majority of students were unaware of the presence of caffeine in these supplements [52]. In another cross-sectional study of 498 random groups of college students, the researchers observed that the students consumed more than one energy drink each month on average, and 67% of them consumed energy drinks for insufficient sleep or energy to improve overall performance. However, the consumption, in general, was associated with bingeing episodes [53]. More than 58% of emergency department adolescent visitors reported ED use within the last 30 days and had trouble sleeping and work problems [54].

The military members report around three times higher daily energy drink use (27%) compared to the general population [30]. Studies on energy drink in the military population have demonstrated the association between energy drink use on sleep continuity disturbances and next-day functioning. In a 2008 Air Force Research Laboratory report, 30.8% of active-duty Air Force Personnel reported trouble falling asleep, and 10.8% reported trouble staying asleep as common adverse effects related to the consumption of energy drinks [55]. In a similar study among military volunteers of the 2007–2008 Millennium Cohort Study, energy drinks use was higher in those who reported less than the recommended 7–8 h of sleep or had trouble sleeping [56]. Energy drink use has similar reports of abnormalities of sleep duration and sleepiness among combat-deployed personnel in more contemporary studies. The personnel who had at least three or more energy drinks/day were more likely to report sleep <4 h per day, or disturbed sleep for at least half the days in a month. These personnel also reported insomnia or episodes of falling asleep during regular guard duties [57–59]. The findings require special attention considering military personnel are at constant stress from high-tempo combats, nighttime duties, personal life, illness, and frequently use these supplements for body-building, energy, improving alertness, and counteracting sleep-deprived state [60,61].

The most popular cause of sleep disturbances due to ED use is their caffeine content. However, the role of taurine and other carbohydrates has been recently explored in animal studies [62]. Tyrosine, an ingredient of some caffeinated energy drinks, was investigated in sleep-deprived healthy young males and found to have no independent association with sleep [62]. The additional nutritional information on the other ingredients is warranted for future research.

Epidemiology of sleep in other psychostimulants

Research on other psychostimulants is limited to military personnel, Air Force, and other service members owing to their extended period of sleep deprivation. The substances most frequently researched as a countermeasure to sleep deprivation are modafinil and dexamphetamine. Modafinil and dextroamphetamine improved executive function, objectively measured alertness, and psychomotor vigilance speed [63]. However, modafinil has been reported to be a more promising stimulant [64]. In the comparative efficacy of caffeine, modafinil, and dextroamphetamine, a modafinil dose of 400 mg improves performance and mood symptoms without any other adverse effects compared to other stimulants after sleep deprivation of 40 h or more. Dextroamphetamine is associated with dose-dependent impairment of sleep maintenance and decreased executive functioning, while caffeine-related adverse sleep disturbances have been discussed earlier [65]. Modafinil is also well-tolerated compared to other drugs [66,67]. In a comparison between energy drink ingredients (tyrosine, phentermine), caffeine, and dextroamphetamine after 36 h of sleep deprivation, dextroamphetamine was associated with a marked decrease in sleep drive and increased alertness on the first day recovery. Tyrosine did not affect while caffeine and phentermine had similar effects on sleep [68].

Interestingly the most common illicit stimulants used by military personnel were cocaine and amphetamines as reported by the 2005 report of Army Forensic Laboratories [69,70]. With the ongoing efforts of legislation of marijuana, the association between sleep and these stimulants may play an essential role in the general population in the future.

Relationships in specific populations

The findings from the general population may not be applicable to individuals with certain occupations such as military personnel, Air Force personnel, shift workers, emergency duty workers, and others. The daily caffeine consumption in the form of sodas and energy drinks in these high-risk occupational settings is considerably higher

than the general population owing to their work expectations even in the sleep-deprived state [30]. Second, the effect of caffeine is studied in this population from the perspective of improvement of work performance, recovery sleep, and consequences of physiological sleep debt. The risks and benefits of caffeine use in these populations can be summarized as follows:

(i) *Sleep deprivation and sleepiness:* Caffeine has been shown to be effective in maintaining cognition and performance measures even after 3–4 nights of sleep deprivation [71,72]. Compared to placebo, caffeine intake of 100–400 mg improved subjective exertion and task completion time, maintained vigilance, and maintained indices for performance and marksmanship in military personnel who are sleep deprived for 22–27 h [72,73]. These caffeine dosages are high, but caffeine can improve performance at lower doses [12]. The unique phenomenon observed in these populations is abrupt awakening from naps, which results in momentary degradation of performance known as sleep inertia. A double-blind crossover design in nonsmoking adults observed that the immediate use of caffeine gum of 100 mg post-inertia improved vigilance at 18 min post-awakening [74]. Shift workers who have fixed shifts in the evening or night are more likely to report sleepiness, insomnia symptoms, and excess caffeine consumption compared to those who have rotating shifts [75,76]. The rotating shift workers are more likely to report delayed sleep onset and improved overnight performance after caffeine use [76,77]. Caffeine also improves mood disturbances associated with sleepiness after 48 h of sleep deprivation [78,79].

However, these findings may vary depending on the pattern of consumption and activity involved. A study of pilots who were sleep-deprived for 37 h did not find any significant changes in subjective sleepiness in spite of improvement in performance [80]. Similarly, the truck drivers who were habitual coffee drinkers had no effects on sleep time after prolonged sleep deprivation [81].

(ii) *Recovery sleep:* Chronic sleep restriction is more common and concerning than acute, total sleep deprivation [48]. Individuals in these settings undergo a prolonged period of sleep deprivation, have circadian misalignment, and have a higher impact on recovery sleep. While caffeine shows sustained performance in studies measuring short-term sleep-deprived states, its effects on performance after prolonged sleep deprivation and subsequent recovery of sleep are not well-characterized. Habitual caffeine use may interfere with recovery sleep following an acute sleep-deprived state. A study of healthy civilian and active-duty military personnel observed that the effect of daily intake

of caffeine (400 mg) on subjective alertness was attenuated compared to placebo after the third night of total sleep deprivation. On the maintenance of wakefulness test, caffeine users were no longer able to maintain wakefulness after the second night of sleep deprivation and were also slower to return to baseline in the recovery period [82]. Caffeine use after 23 h of wakefulness in night shift workers was associated with increased WASO, increased stage 1 sleep, decreased slow-wave sleep, increased core body temperature, and broader distal to proximal skin temperature gradient during recovery sleep [83]. High core body temperature indicates increased alertness, which is congruent with other literature that reported no influence on performance in the period after recovery sleep [84].

(iii) *Insomnia:* The overlap of insomnia symptoms with other sleep measures limits the research of caffeine use among those with a clinical diagnosis of insomnia. Further, the treatment strategies for insomnia, including abstinence from caffeine, will influence the use of caffeine among those with insomnia. In a treatment-seeking active-duty military personnel reporting PTSD and insomnia symptoms, those who had elevated insomnia symptom severity avoided coffee use [85]. In a study of patients with primary insomnia, the use of caffeine as a treatment for sleep deprivation was associated with decreased total sleep time and increased subsequent sleep onset latency [86]. There is also a distinct overlap of insomnia symptoms with psychiatric symptoms in these populations. The contribution of psychiatric symptoms in the causation of insomnia could be more significant than the overall effect of caffeine use alone, which could potentially explain the negative association between insomnia severity and caffeine consumption across different studies [85,87]. The self-management and educational efforts to reduce caffeine in these work settings, once diagnosed with insomnia can be postulated but require further supporting evidence.

In conclusion, caffeine negatively affects sleep quality and sleep duration in these populations. However, it is of paramount importance to find the risk/benefit ratio of the use of caffeine or energy drinks for community members who are expected to maintain high performance in sleep-deprived states, which is possibly achieved by the use of these products.

Physiology of caffeine in sleep-wake homeostasis

The biological effects of caffeine and other psychostimulants on sleep are the acute or chronic reactions at a

psychological or physiological level, such as anxiety response, rewarding, or reinforcing effects. Though one of these responses is used to improve cognition, and attention span in sleep-deprived individuals, the chronic reactions or tolerance to the doses over time contribute to recovery sleep or physiological sleep debt. To understand this delayed response, we will briefly talk about these underlying biological processes. As caffeine is the essential component of energy drink supplements compared to taurine or sugar, we will limit our discussion to the physiological effects of caffeine.

Role of adenosine and caffeine in sleep-wake cycle

The biological mechanisms of caffeine involve interactions at multiple sites. Caffeine is a nonselective competitive adenosine receptor antagonist and produces its psychostimulant effects by counteracting the pulsating effects of endogenous adenosine in the central adenosine receptor [4,88]. Adenosine principally modulates the function of neurotransmitter pathways that are involved in motor activation and reward. The dopaminergic systems primarily control these pathways, as well as arousal processes involved in cholinergic, noradrenergic, histaminergic, or orexinergic systems [89]. Caffeine is structurally similar to adenosine and binds to adenosine receptors, specifically to adenosine receptors (A1 and A2A) expressed extensively in the brain.

Adenosine is a prime promoter of neural activity in sleep-wake homeostasis. Adenosine is produced from the breakdown of ATP in normal or pathological conditions due to hypoxia or ischemia [90]. The release of adenosine and subsequent mechanisms that balance the intracellular and extracellular levels of adenosine modulate the function of sleep-active neurons. Adenosine primarily causes sleep enhancement via its mechanism on the A1 receptor to inhibit the cholinergic and anticholinergic wake-responsive neurons resulting in GABAergic neuron inhibition [91]. The second most studied A2a adenosine receptor inhibits the histaminergic neurons and also directly stimulates the sleep-related active neurons in the ventrolateral preoptic nucleus, promoting sleep activity. Caffeine, an adenosine antagonist, competes with extracellular adenosine and attenuates the effect of adenosine stimulation by inhibiting the A1 and A2A receptors [89] (see Fig. 26.1). Studies in rodent models have shown that caffeine also increases the sensitivity of D2/D3 dopamine receptors, promoting wakefulness [92]. The high affinity of caffeine to these adenosine brain receptors is intertwined with physiological extracellular levels of adenosine and is mainly responsible for the motor-activating, reinforcing, and arousing properties of caffeine. Fig. 26.1 summarizes the adenosine regulation of sleep-active neurons.

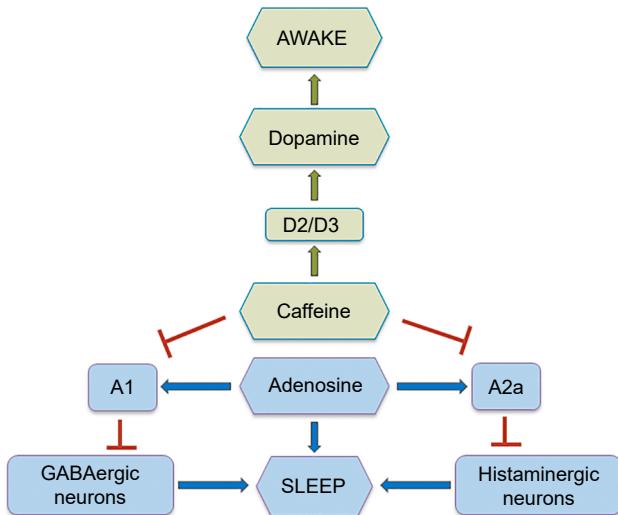


FIGURE 26.1 Schematic representation of the role of caffeine in the neurochemistry of sleep-wake homeostasis.

A1/A2a, adenosine receptors; D2/D3, dopamine receptors; Red arrows indicate inhibition. Caffeine inhibits adenosine receptors and blocks the action of extracellular levels of adenosine on these receptors. The wake pathway is activated, and the sleep pathway via adenosine is inhibited in the presence of caffeine.

Genetic factors and response to caffeine

There are pronounced individual differences in response to caffeine. Not all develop caffeine-induced sleep disturbances and insomnia [93]. These differences are secondary to the pharmacokinetic or pharmacodynamic mechanism of caffeine at the genetic level, which is further influenced by the amount of caffeine consumption or other environmental factors such as demographics, health behaviors, medical comorbidities, or comorbid substance use. The cumulative effect of these factors plays a role in determining the magnitude and duration of tolerance development or caffeine sensitivity to sleep. In this section, we will talk about genetic factors responsible for individual variation, while environmental factors will be addressed in the subsequent section.

One prominent gene polymorphism involved at the pharmacokinetic level is the *ADORA2A* gene. The gene variants modulate the subjective responses of caffeine through its effects on A2A receptors. A genome-wide association study in a community-based sample of Australian twins from the Australian Twin Registry found that the individual sensitivity of caffeine-induced insomnia depends on polymorphism in the *ADORA2A* gene (rs5751876) [94,95]. Individuals who had C/C genotypes at this SNP reported high sensitivity on the questionnaire and increased EEG beta activity on polysomnography.

Individuals with low caffeine sensitivity and no activity had the T/T genotype. The GWAS study additionally identified two specific SNPs, rs6575353 coding for *PRI-MA1* and rs521704 coding for *GBP4*, which were associated with caffeine-induced insomnia. However, the effect of *ADORA2A* polymorphism may not be similar for each insomnia symptom. A small sample size study ($n = 50$) in college students observed that the *ADORA2A* CC genotype did not moderate the effects of caffeine on WASO, even though the CC genotype was associated with WASO compared to the TT phenotype [96]. In another GWAS twin study of 3808 participants, loci at chromosome 2q and chromosome 17q were associated with caffeine-attributed sleep disturbances. The chromosome 17q is of particular interest as the genes regulating dopamine and cAMP-regulated protein pathways reside in this area, which can potentially link to caffeine-induced insomnia. However, more research is needed to validate these findings.

Another polymorphism of importance is a gene for adenosine deaminase (*ADA*), an enzyme regulating intracellular and extracellular adenosine levels. A heterozygous genotype at the gene (rs73598374) results in reduced activity of *ADA*, which increases EEG delta activity in NREM sleep. Based on this pathway, a polysomnography study of 1000 participants assessed the association between caffeine and sleep measures within both heterozygous and homozygous states [97]. Individuals with a heterozygous form of *ADA* had better sleep quality, a higher proportion of REM sleep, and fewer WASO episodes [98]. A *CYP1A2* gene polymorphism that interferes with the hepatic metabolism of caffeine can account for variability in caffeine's effect on sleep [99]. However, this mechanism affecting the bioavailability of caffeine relies first on the amount of caffeine intake, followed by *CYP1A2* gene polymorphism.

Environmental factors and response to caffeine

Currently, there are no restrictions on the amount of caffeine intake, even though the US Food and Drug Administration (FDA) lists 400 mg per day as the safe amount to ingest [1,2]. There is no standard limit for energy drinks yet. The major implication is that the individual threshold at which caffeine or energy drinks will influence sleep is not determined. It inadvertently forces us to consider individual-level variation where this relationship will be vital. We can postulate that individuals regulate their intake to achieve their primary objective of reducing sleepiness or increasing alertness, and second, to maintain within the safe dose range. While the literature has strongly focused on genetics for individual variation, the other factors should be noted.

1 Amount of intake and adverse effects: A study of US military personnel found that sleep problems are higher

in those who drink three or more energy drinks per day [57]. A similar pattern is observed in children and adolescents, where moderate-level caffeine consumers have more sleep problems [100]. These associations led to the hypothesis that caffeine or energy drink use to counter sleep deprivation may, paradoxically, worsen sleep problems. Irrespective of the directionality of the association, such a pattern will inadvertently lead to an upward trajectory of ingestion. High doses of consumption subsequently cause adverse effects, most notably seen are restlessness, nervousness, cardiovascular instability, and insomnia [100]. Caffeine results in a dose-dependent increase in anxiety, worries, and tremors compared to placebo which was partly shown to vary by individual personality [101]. In another study of healthy nonsmoking individuals, a sequential increase of caffeine dosage from none to 600 mg was associated with irritability, headache, anxiety, talkativeness, and sleepiness, but the specific threshold was not determined [79]. Caffeine withdrawal among moderate-to-high caffeine consumers also has similar symptoms. In these individuals, caffeine withdrawal was associated with a headache, impaired mood, impaired cognition, and increased blood pressure [102]. These effects are subjective, and the extent to which they are linked to the caffeine-sleep paradigm is hard to determine.

2 Chronotype/time of intake: One of the frequently reported reasons for individual variability is the time of the day when these stimulants are consumed. A Brighton Sleep Study in 20–45 years old observed that 1–4 cups per day within 6 h of bedtime was associated with shorter sleep latency, fewer awakenings, and more sleep satisfaction than heavy consumers or those who abstained from caffeine [103]. Early morning caffeine decreases the propensity for wakefulness on a subsequent night [104]. Further, evidence suggests that the evening chronotype of individuals has a significant role in the caffeine-sleep relationship. In a study of college students, those who had a circadian preference for evening time were three times more likely to consume high-dose caffeinated energy drinks and report daytime sleepiness compared to those with morning chronotype [105–107]. Adolescents are showing a slow transition to evening chronotype with increased use of electronic devices at nighttime. The use of technology at night has been associated with increased consumption of energy drinks and other caffeinated products, which cumulatively results in short sleep duration [21,36]. Few studies found no role of chronotype at the caffeine-sleep interface or observed increased WASO episodes and sleep efficiency among morning-type individuals [96,108]. Overall, the behavioral aspect of circadian preference has some role to play.

- 3 Comorbid burden of disease:** Little research has examined the effect of the comorbid burden of an individual on the sleep and use of caffeine, energy drinks, and other stimulants. In a small case-control study (134 cases, 230 controls) of diabetic participants, diabetic individuals were habitual caffeine users and reported greater daytime sleepiness after an extra cup of coffee [109]. This relationship was attributed to the presence of a highly inducible *CYP1A2* genotype in the diabetic population [110].
- 4 Sociodemographic pattern:** Another individual aspect that potentially affects both caffeine and sleep is their sociodemographic characteristics. The role of these characteristics as a risk factor for a stimulant-sleep interface is still understudied. Both energy drinks and sleep are associated with low socioeconomic status [33,111]. Energy drinks are part of government assistance programs and account for 50% of their budget, indicating high use in the low-income population [112]. Sleep also varies by socioeconomic status, and individuals with low socioeconomic status are more likely to report insomnia complaints and shorter sleep duration [111]. The consistent pattern of sleep and caffeine usage indicates a potentially stronger role of low income in addressing the outcomes of caffeine-induced sleep disturbances. Based on gender, males are three times more likely to report energy drink use than females [111]. However, in the Brazilian sample, women were reported to have a higher proportion of caffeine-induced insomnia than men [113]. There is a distinct age-related pattern in the relationship between sleep and energy drink use. A nationally representative study using NHANES data observed that caffeine intake from energy drinks and dietary supplements is higher in the age group of 19–30 years [114]. In another study using a community survey, younger respondents (<30 years) were eight times more likely to use energy drinks compared to older individuals [115]. On the other hand, sleep disturbances are an aging phenomenon, yet we are observing sleep disturbances in younger populations owing to energy drinks. The age-related changes in sleep patterns highlight the importance of monitoring caffeine-dependent sleep problems in the younger population. The NHANES study also reported that the use of energy drinks is highest among non-Hispanic White individuals, followed by Hispanic and Black respondents [114]. In contrast, the data using the NHIS study found that the consumption is highest in Black respondents [116]. The NHIS finding aligns with the racial pattern of sleep disturbances, where Blacks are more likely to have poor sleep continuity, shorter sleep duration, and less slow-wave sleep [117].
- 5 Alcohol use:** The use of alcohol mixed with caffeinated energy drinks is frequently reported and is associated with the vicious cycle of substance use and sleep

disturbances. This pattern of alcohol-mixed energy drinks is noticed commonly in the adolescent age group. A community-based study found that alcohol-mixed energy drink consumption compared to alcohol-only drinks is associated with increased chances of difficulty in falling asleep [118]. Energy drinks consumption is associated with increased alcohol use independently and also in the presence of sleep disturbances, perpetuating overall sleep problems [33,39,119,120]. Another study on college students observed that caffeinated beer improves sleep quality with no effect on sleep latency or next-day hangover symptoms, which may promote substance use [41]. In general, the combined use of alcohol and energy drinks distorts the perceptions of adaptive response to excess caffeine intake or alcohol intake, which heightens the consequences. Excess alcohol use secondary to energy drink use increases the probability of daytime sleepiness with binge drinking [121]. The role of other illegal substance use can potentially be similar to alcohol, but will not be discussed in this chapter.

The previous knowledge will help understand how caffeine interferes with the interplay between circadian and homeostatic regulatory systems to affect the periodic cycle of wakefulness and sleep.

Health implications of caffeine (stimulant) use—Sleep disturbances model

Although caffeine use and sleep disturbances have independent associations with health outcomes, the major impact of stimulant-induced insomnia on health status is sleep disturbances. These sleep disturbances are secondary to circadian misalignment, where the endogenous circadian pattern could not match the altered sleep-wake cycle owing to caffeine/energy drink consumption, resulting in deleterious effects [122]. Though not established, we will briefly discuss some of these health implications from the perspective of stimulant use resulting in, sleep disturbances, short sleep duration, and circadian misalignment. The discussion is also primarily focused on caffeine use.

- 1 Short sleep duration:** The associations of short sleep duration with chronic diseases and associated risk factors are extensively researched and are beyond the scope of this chapter. Most notable about the use of stimulants to counteract sleepiness is weight gain or obesity, glucose dysregulation, hypertension, dyslipidemia, inflammation, and hormonal dysregulation [117]. Obesity is the most immediate health outcome of concern, considering energy drinks are a part of energy supplements. Adolescents with inadequate sleep have

- poor eating behaviors, including excess consumption of caffeinated energy drinks, which are associated with higher body weight and blood pressure [123]. Community-dwelling adults and military personnel reporting caffeine or energy drink use had increased concentrations of IL-6 which is indicative of low-grade chronic inflammation in the presence of inadequate sleep leading to morbidities [50,124]. A randomized controlled trial of sleep-deprived individuals reported that caffeinated drinks adversely modulated glucose homeostasis compared to decaffeinated ones [125]. Continuous caffeine intake over a prolonged period after an extended period of sleep deprivation was associated with mental exhaustion, irritability, and mood disturbances, but not with glucose levels [126]. However, there was increased glucose response to subsequent food intake, which could be the potential mechanism of glucose dysregulation. Despite the overlap between sleep duration and sleep deprivation, short sleep duration has been shown to play a prominent role in obesity.
- 2 Nonspecific sleep disturbances:** The sleep symptoms that form a part of the ICD-9 diagnosis of insomnia but do not meet the criteria will be considered nonspecific sleep disturbances here. These symptoms include difficulty falling asleep, difficulty staying asleep, waking after sleep onset, and daytime sleepiness. There is a strong correlation between these symptoms and insomnia diagnosis and psychiatric comorbidities. Caffeine increases hyperactivity of the dopaminergic system through its inhibitory action on adenosine, which is further pressurized by sleep disturbances affecting mood, executive functioning, cognition, and behavioral disorders [127,128]. Caffeine-induced sleep disturbances increase nighttime restlessness [101]. A KiGGS German study observed that caffeine use influences the association between insomnia complaints and the use of alcohol, marijuana, and tobacco, emphasizing the role of common stimulants [35]. A case study of psychiatric patients showed that those with bipolar disorder, of which sleep disturbances are a component, had some temporal relationship between the use of energy drinks and frequent hospitalizations [129]. This finding aligns with the results of a randomized controlled trial where individuals with identified vulnerability to stress-induced sleep disturbances exhibited higher sleep reactivity to a caffeine challenge [130]. High caffeine consumption is also associated with multiple psychiatric disorders, including depression, anxiety, and substance dependence [131]. Excess consumption of energy drinks or stimulants by the military population is of special concern, considering pre-deployment sleep disturbances, or insomnia, is associated with the subsequent development of anxiety disorders, including PTSD [132]. Despite these

findings, we preclude any causal interpretation due to the cross-sectional nature of these studies as well as the lack of data on caffeine use among those who show symptoms of insomnia.

- 3 Circadian misalignment:** The sleep disturbances due to circadian rhythm misalignment occur commonly in the special populations described above. There is strong empirical evidence that excess stimulant use improves their vigilance, cognitive function, alertness, endurance performance, memory task, and reaction time. However, the benefits associated with the use of these products interfere with underlying biological sleep rhythms. These disturbed physiological processes tend to result in adverse outcomes in the physical or psychological domain. The most pertinent concerning behavior observed in shift workers, healthcare, law enforcement, and drivers is impulsive risk-taking behaviors. The caffeine response to impulsivity is secondary to a dose-dependent increase in adrenaline during the wakefulness period [133]. Accordingly, truck drivers or shift workers are likely to report impaired driving performance, commit avoidable errors, and increase the number of accidents [134–136]. These episodes are more likely to occur during daytime work when the underlying physiological response is to stay awake [137]. Studies researching the likelihood of accidents in sleep-deprived truck drivers recommend caffeine use with short naps, emphasizing the vital role of sleep in preventing accidents [138,139].

The predominant health consequences of circadian misalignment are related to cardiovascular disease and metabolic disorders. Physiological hyperarousal in the presence of chronic sleep restriction and caffeine use is associated with significant odds of hypertension [140,141]. Shift workers report higher mortality due to diabetes, cardiovascular and stroke. Rotating shift workers have increased the risk of obesity, hypertriglyceridemia, poor dietary patterns, and metabolic syndrome [122]. Bonnet and Arand, in their archival study of caffeine as a model for insomnia, observed that caffeine use causes significant metabolic changes which are associated with a decrease in sleep efficiency [14]. Chen and colleagues found that men who work long hours are twice as at risk for coronary heart disease [142]. In adolescents with different chronotypes and caffeine sensitivity, poor sleep, and situational stress are associated with cardiac changes secondary to sympathetic system activation, a phenomenon consistent with circadian disturbances. These individuals are at subsequent risk of developing insomnia and related comorbidities [143]. In summary, the burden of caffeine use as a countermeasure to sleepiness is associated with an enormous burden on health and functioning.

Recommendations

We recommend the following suggestions to improve the health and functioning of individuals:

- 1 Sleep Hygiene practices:** Insufficient sleep is a significant problem, and strict implementation of a sleep management plan to maintain sleep duration should be prioritized in all educational and workplace settings, such as schools, colleges, medical facilities, military centers, and other training facilities. Stimulant intake before bedtime should be discouraged, and daily variation should be monitored. Physical activity has been shown to alleviate the effects of caffeine use on sleep and should be recommended. A strict sleep schedule should be followed to maintain the circadian rhythm, and daytime naps should be avoided. In contrast, strategically timed short naps in conjunction with small doses of caffeine may improve mood and performance after sleep deprivation without affecting subsequent sleep patterns in specific populations and should be endorsed. However, the clinical implications of frequent napping in the general population are still preliminary and should be further investigated [144].
- 2 Better food labeling practices:** Despite the statutory FDA limit on caffeine amount, there are no strict restrictions on the contents of energy drinks and the amount of intake. The judicious use of caffeine from different sources may lead to tolerance and create a vicious cycle of insufficient sleep and habitual increasing intake of caffeine over time. This cycle will secondarily amplify health-related outcomes. The content or safety level of other ingredients in energy drinks is not even known to assess whether they show caffeine-like tolerance. The issue is further complicated for dietary supplements, which may contain adulterants. The FDA should stress the labeling options on these ingredients to inform consumers. The labels should standardize the content level of each ingredient, warnings about caffeine toxicity, and age-specific symptom-free doses [8]. Alternatively, the marketing practice for beverages should highlight the caffeine content. The marketing practices directed toward youth should be supervised. The ultimate goal is to develop a culture where caffeine intake is monitored to detect early signs of chronic use and withdrawal symptoms.
- 3 Concurrent substance use:** The concurrent use of caffeine and other substance use is discouraged. Adolescents have frequently been involved in the use of caffeine with alcohol. Their simultaneous use facilitates extended drinking sessions, interferes with executive function, and masquerades the alcohol intoxication. Such behavior is linked to risk-taking patterns such as intoxicated driving. It also has deleterious effects on

sleep maintenance and aggravates insomnia [145]. The sleep education should actively focus on this issue.

- 4 Rethinking research methodologies:** The current research on stimulant use and sleep is based on non-standardized measures. Though we have sufficient evidence on the qualitative aspect of these relationships, the quantitative parameters are still unclear. The lack of a quantitative threshold for caffeine and other ingredients has limited authorities from imposing stronger regulations. There is a distinct gap between cross-sectional population-level studies and experimental or laboratory-based studies in this area of research. The next steps in research should focus on bridging that gap. There is a need for a socioecological model, as proposed by Grandner and colleagues, that will define the temporal pathway upstream from sociodemographic and behavioral determinants of the caffeine-sleep paradigm to downstream adverse consequences of this paradigm [117]. Such a structured framework will help identify high-risk populations and plan interventions tailored to these groups. Numerous interventions that have been formulated over time have not shown improvement in the change in caffeine consumption [146]. Recently, a publicly accessible Web tool (2 B Web Alert) was used to determine the impact of sleep-wake schedule, time of day of caffeine use, and performance. Evidence-based tools like 2 B Web Alert will aid in designing effective work schedules, proposing better sleep restriction and caffeine studies, and increasing public awareness of the pattern of caffeine consumption on alertness [147].

Conclusion

In conclusion, research examining connections between sleep and caffeine, energy drinks, and other stimulants is extensive but still preliminary. Given the positive and negative effects of caffeine and energy drinks, these beverages may provide temporary relief from sleep disturbances, but their prolonged use may affect the quality of life in general. Future research should investigate the cumulative effect of sleep and stimulants on health outcomes rather than independent associations. Such investigations will provide insights to identify candidates with differential risk of sleep effects secondary to stimulant use. It will also provide guidelines to assess appropriate candidates for caffeine supplementation during sleep deprivation and derive the optimal range of caffeine dosages that may alleviate sleep deprivation without affecting subsequent recovery sleep or inducing addictive behavior. The overarching purpose of this chapter is to contribute to any policy implications in the field of sleep management of the general population.

References

- [1] Mitchell DC, Knight CA, Hockenberry J, Teplansky R, Hartman TJ. Beverage caffeine intakes in the U.S. *Food Chem Toxicol* 2014;63:136–42. <https://doi.org/10.1016/j.fct.2013.10.042>.
- [2] Somogyi LP. Caffeine intake by the US population. Prepared for the food and drug administration and Oakridge National Laboratory; 2010. p. 2010.
- [3] Seifert SM, Schaechter JL, Hershorin ER, Lipshultz SE. Health effects of energy drinks on children, adolescents, and young adults. *Pediatrics* 2011;127(3):511–28. <https://doi.org/10.1542/peds.2009-3592>.
- [4] Roehrs T, Roth T. Caffeine: sleep and daytime sleepiness. *Sleep Med Rev* 2008;12(2):153–62. <https://doi.org/10.1016/j.smrv.2007.07.004>.
- [5] De Valck E, Cluydts R. Slow-release caffeine as a countermeasure to driver sleepiness induced by partial sleep deprivation. *J Sleep Res* 2001;10(3):203–9. <https://doi.org/10.1046/j.1365-2869.2001.00260.x>.
- [6] Ohayon M, Wickwire EM, Hirshkowitz M, Albert SM, Avidan A, Daly FJ, Dauvilliers Y, Ferri R, Fung C, Gozal D, Hazen N, Krystal A, Lichstein K, Mallampalli M, Plazzi G, Rawding R, Scheer FA, Somers V, Vitiello MV. National sleep foundation's sleep quality recommendations: first report. *Sleep Health* 2017;3(1):6–19. <https://doi.org/10.1016/j.slehd.2016.11.006>.
- [7] Martyn D, Lau A, Richardson P, Roberts A. Temporal patterns of caffeine intake in the United States. *Food Chem Toxicol* 2018;111:71–83. <https://doi.org/10.1016/j.fct.2017.10.059>.
- [8] Pomeranz JL, Munsell CR, Harris JL. Energy drinks: an emerging public health hazard for youth. *J Publ Health Pol* 2013;34(2):254–71. <https://doi.org/10.1057/jphp.2013.6>.
- [9] Clark I, Landolt HP. Coffee, caffeine, and sleep: a systematic review of epidemiological studies and randomized controlled trials. *Sleep Med Rev* 2017;31:70–8. <http://www.elsevier.com/inca/publications/store/6/2/3/0/7/4/index.htm>.
- [10] Brezinova V, Oswald I, Loudon J. Two types of insomnia: too much waking or not enough sleep. *Br J Psychiatr* 1975;126(5):439–45. <https://doi.org/10.1192/bjp.126.5.439>.
- [11] Fulgoni VL, Keast DR, Lieberman HR. Trends in intake and sources of caffeine in the diets of US adults: 2001–2010. *Am J Clin Nutr* 2015;101(5):1081–7. <https://doi.org/10.3945/ajcn.113.080077>.
- [12] Lieberman HR, Wurtman RJ, Emde GG, Roberts C, Coviella ILG. The effects of low doses of caffeine on human performance and mood. *Psychopharmacology* 1987;92(3):308–12. <https://doi.org/10.1007/bf00210835>.
- [13] Juliano LMGR. Caffeine, substance abuse: a comprehensive textbook. Lippincott Williams & Wilkins; 2005. p. 2005.
- [14] Bonnet MH, Arand DL. Caffeine use as a model of acute and chronic insomnia. *Sleep* 1992;15(6):526–36.
- [15] Reid MG. Wise, DSM-IV training guide. 2014. p. 2014.
- [16] Addicott MA. Caffeine use disorder: a review of the evidence and future implications. *Curr Addict Rep* 2014;1(3):186–92. <https://doi.org/10.1007/s40429-014-0024-9>.
- [17] Ágoston C, Urbán R, Richman MJ, Demetrovics Z. Caffeine use disorder: an item-response theory analysis of proposed DSM-5 criteria. *Addict Behav* 2018;81:109–16. <https://doi.org/10.1016/j.addbeh.2018.02.012>.
- [18] Meredith SE, Juliano LM, Hughes JR, Griffiths RR. Caffeine use disorder: a comprehensive review and research agenda. *J Caffeine Res* 2013;3(3):114–30. <https://doi.org/10.1089/jcr.2013.0016>.
- [19] Moderator: Catherine Woodstock Striley, Participants, Hughes JR, Griffiths R, Juliano L, Budney AJ. A critical examination of the caffeine provisions in the diagnostic and statistical manual, 5th edition (DSM-5). *J Caffeine Res* 2013;3(3):101–7. <https://doi.org/10.1089/jcr.2013.1233>.
- [20] Bryant Ludden A, Wolfson AR. Understanding adolescent caffeine use: connecting use patterns with expectancies, reasons, and sleep. *Health Educ Behav* 2010;37(3):330–42. <https://doi.org/10.1177/1090198109341783>.
- [21] Calamaro CJ, Yang K, Ratcliffe S, Chasens ER. Wired at a young age: the effect of caffeine and technology on sleep duration and body mass index in school-aged children. *J Pediatr Health Care* 2012;26(4):276–82. <https://doi.org/10.1016/j.pedhc.2010.12.002>.
- [22] Chaudhary NS, Grandner MA, Jackson NJ, Chakravorty S. Caffeine consumption, insomnia, and sleep duration: results from a nationally representative sample. *Nutrition* 2016;32(11–12):1193–9. <https://doi.org/10.1016/j.nut.2016.04.005>.
- [23] Lodato F, Araújo J, Barros H, Lopes C, Agodi A, Barchitta M, Ramos E. Caffeine intake reduces sleep duration in adolescents. *Nutr Res* 2013;33(9):726–32. <https://doi.org/10.1016/j.nutres.2013.06.005>.
- [24] Orbeta RL, Overpeck MD, Ramcharran D, Kogan MD, Ledsky R. High caffeine intake in adolescents: associations with difficulty sleeping and feeling tired in the morning. *J Adolesc Health* 2006;38(4):451–3. <https://doi.org/10.1016/j.jadohealth.2005.05.014>.
- [25] Pollak CP, Bright D. Caffeine consumption and weekly sleep patterns in us seventh-, eighth-, and ninth-graders. *Pediatrics* 2003;111(1):42–6. <https://doi.org/10.1542/peds.111.1.42>.
- [26] Spaeth AM, Goel N, Dinges DF. Cumulative neurobehavioral and physiological effects of chronic caffeine intake: individual differences and implications for the use of caffeinated energy products. *Nutr Rev* 2014;72(1):34–47. <https://doi.org/10.1111/nure.12151>.
- [27] Loftfield E, Freedman ND, Dodd KW, Vogtmann E, Xiao Q, Sinha R, Graubard BI. Coffee drinking is widespread in the United States, but usual intake varies by key demographic and lifestyle factors. *J Nutr* 2016;146(9):1762–8. <https://doi.org/10.3945/jn.116.233940>.
- [28] Nehlig A, Alexander SPH. Interindividual differences in caffeine metabolism and factors driving caffeine consumption. *Pharmacol Rev* 2018;70(2):384–411. <https://doi.org/10.1124/pr.117.014407>.
- [29] Brown SL, Salive ME, Pahor M, Foley DJ, Corti MC, Langlois JA, Wallace RB, Harris TB. Occult caffeine as a source of sleep problems in an older population. *J Am Geriatr Soc* 1995;43(8):860–4. <https://doi.org/10.1111/j.1532-5415.1995.tb05527.x>.
- [30] Knapik JJ, Austin KG, McGraw SM, Leahy GD, Lieberman HR. Caffeine consumption among active duty United States Air Force personnel. *Food Chem Toxicol* 2017;105:377–86. <https://doi.org/10.1016/j.fct.2017.04.050>.
- [31] Ding M, Bhupathiraju SN, Chen M, Van Dam RM, Hu FB. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. *Diabetes Care* 2014;37(2):569–86. <https://doi.org/10.2337/dc13-1203UnitedStates>.
- [32] Prather AA, Leung CW, Adler NE, Ritchie L, Laraia B, Epel ES. Short and sweet: associations between self-reported sleep duration and sugar-sweetened beverage consumption among adults in the United States. *Sleep Health* 2016;2(4):272–6. <https://doi.org/10.1016/j.slehd.2016.09.007>.

- [33] Grandner MA, Knutson KL, Troxel W, Hale L, Jean-Louis G, Miller KE. Implications of sleep and energy drink use for health disparities. *Nutr Rev* 2014;72(1):14–22. <https://doi.org/10.1111/nure.12137>.
- [34] Kant AK, Graubard BI. Association of self-reported sleep duration with eating behaviors of American adults: NHANES 2005–2010. *Am J Clin Nutr* 2014;100(3):938–47. <https://doi.org/10.3945/ajcn.114.085191>.
- [35] Skarupke C, Schlack R, Lange K, Goerke M, Dueck A, Thome J, Szagun B, Cohrs S. Insomnia complaints and substance use in German adolescents: did we underestimate the role of coffee consumption? Results of the KiGGS study. *J Neural Transm* 2017;124(S1):69–78. <https://doi.org/10.1007/s00702-015-1448-7>.
- [36] Calamaro CJ, Mason TBA, Ratcliffe SJ. Adolescents living the 24/7 lifestyle: effects of caffeine and technology on sleep duration and daytime functioning. *Pediatrics* 2009;123(6). <https://doi.org/10.1542/peds.2008-3641UnitedStates>.
- [37] Jaehne A, Loessl B, Bárkai Z, Riemann D, Hornyak M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. *Sleep Med Rev* 2009;13(5):363–77. <https://doi.org/10.1016/j.smrv.2008.12.003>.
- [38] Kozak P, Paer A, Jackson N, Chakravorty MG. Alcohol, smoking, caffeine and drug use associated with sleep duration and sleep quality. *Sleep* 2011;2011.
- [39] Marmorstein NR. Interactions between energy drink consumption and sleep problems: associations with alcohol use among young adolescents. *J Caffeine Res* 2017;7(3):111–6. <https://doi.org/10.1089/jcr.2017.0007>.
- [40] Lund HG, Reider BD, Whiting AB, Prichard JR. Sleep patterns and predictors of disturbed sleep in a large population of college students. *J Adolesc Health* 2010;46(2):124–32. <https://doi.org/10.1016/j.jadohealth.2009.06.016>.
- [41] Rohsenow DJ, Howland J, Alvarez L, Nelson K, Langlois B, Verster JC, Sherrard H, Arnedt JT. Effects of caffeinated vs. non-caffeinated alcoholic beverage on next-day hangover incidence and severity, perceived sleep quality, and alertness. *Addict Behav* 2014;39(1):329–32. <https://doi.org/10.1016/j.addbeh.2013.09.008>.
- [42] Carrier J, Paquet J, Fernandez-Bolanos M, Giroard L, Roy J, Selmaoui B, Filipini D. Effects of caffeine on daytime recovery sleep: a double challenge to the sleep-wake cycle in aging. *Sleep Med* 2009;10(9):1016–24. <https://doi.org/10.1016/j.sleep.2009.01.001>.
- [43] Robillard R, Bouchard M, Cartier A, Nicolau L, Carrier J. Sleep is more sensitive to high doses of caffeine in the middle years of life. *J Psychopharmacol* 2015;29(6):688–97. <https://doi.org/10.1177/0269881115575535>.
- [44] Drake C, Roehrs T, Shambroom J, Roth T. Caffeine effects on sleep taken 0, 3, or 6 hours before going to bed. *J Clin Sleep Med* 2013;09(11):1195–200. <https://doi.org/10.5664/jcsm.3170>.
- [45] Rosenthal L, Roehrs T, Zwyghuizen-Doorenbos A, Plath D, Roth T. Alerting effects of caffeine after normal and restricted sleep. *Neuropsychopharmacology* 1991;4(2):103–8.
- [46] Ho SC, Chung JWY. The effects of caffeine abstinence on sleep: a pilot study. *Appl Nurs Res* 2013;26(2):80–4. <https://doi.org/10.1016/j.apnr.2012.08.004>.
- [47] Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ* 2017;359. <https://doi.org/10.1136/bmj.j5024>.
- [48] Basner M, Fomberstein KM, Razavi FM, Banks S, William JH, Rosa RR, Dinges DF. American time use survey: sleep time and its relationship to waking activities. *Sleep* 2007;30(9):1085–95. <https://doi.org/10.1093/sleep/30.9.1085>.
- [49] Carrier J, Fernandez-Bolanos M, Robillard R, Dumont M, Paquet J, Selmaoui B, Filipini D. Effects of caffeine are more marked on daytime recovery sleep than on nocturnal sleep. *Neuropsychopharmacology* 2007;32(4):964–72. <https://doi.org/10.1038/sj.npp.1301198>.
- [50] Manchester J, Eshel I, Marion DW. The benefits and risks of energy drinks in young adults and military service members. *Mil Med* 2017;182(7). <https://doi.org/10.7205/MILMED-D-16-00339>.
- [51] Sampasa-Kanyinga H, Hamilton HA, Chaput JP. Sleep duration and consumption of sugar-sweetened beverages and energy drinks among adolescents. *Nutrition* 2018;48:77–81. <https://doi.org/10.1016/j.nut.2017.11.013>.
- [52] Kelly CK, Roxanne Prichard J. Demographics, health, and risk behaviors of young adults who drink energy drinks and coffee beverages. *J Caffeine Res* 2016;6(2):73–81. <https://doi.org/10.1089/jcr.2015.0027>.
- [53] Malinauskas BM, Aeby VG, Overton RF, Carpenter-Aeby T, Barber-Heidal K. A survey of energy drink consumption patterns among college students. *Nutr J* 2007;6. <https://doi.org/10.1186/1475-2891-6-35>.
- [54] Jackson DAE, Cotter BV, Merchant RC, Babu KM, Baird JR, Nirenberg T, Linakis JG. Behavioral and physiologic adverse effects in adolescent and young adult emergency department patients reporting use of energy drinks and caffeine. *Clin Toxicol* 2013;51(7):557–65. <https://doi.org/10.3109/15563650.2013.820311>.
- [55] Schmidt RM, McIntire LK, Caldwell JA, Hallman C. Prevalence of energy-drink and supplement usage in a sample of air force personnel. Air Force Research Lab Wright-Patterson AFB OH Human Effectiveness Directorate; 2008. p. 2008.
- [56] Jacobson IG, Ryan MAK, Hooper TI, Smith TC, Amoroso PJ, Boyko EJ, Gackstetter GD, Wells TS, Bell NS. Alcohol use and alcohol-related problems before and after military combat deployment. *JAMA* 2008;300(6):663–75. <https://doi.org/10.1001/jama.300.6.663>.
- [57] Centers for Disease, Prevention. Energy drink consumption and its association with sleep problems among U.S. service members on a combat deployment—Afghanistan. *MMWR Morb Mortal Wkly Rep* 2010;61(44):895–2010.
- [58] McLellan TM, Riviere LA, Williams KW, McGurk D, Lieberman HR. Caffeine and energy drink use by combat arms soldiers in Afghanistan as a countermeasure for sleep loss and high operational demands. *Nutr Neurosci* 2019;22(11):768–77. <https://doi.org/10.1080/1028415X.2018.1443996>.
- [59] Waits WM, Ganz MB, Schillreff T, Dell PJ. Sleep and the use of energy products in a combat environment. *US Army Med Dep J* 2014;22–8.
- [60] Jacobson IG, Horton JL, Smith B, Wells TS, Boyko EJ, Lieberman HR, Ryan MAK, Smith TC. Bodybuilding, energy, and weight-loss supplements are associated with deployment and physical activity in U.S. Military personnel. *Ann Epidemiol* 2012;22(5):318–30. <https://doi.org/10.1016/j.annepidem.2012.02.017>.

- [61] Wesensten NJ. Legitimacy of concerns about caffeine and energy drink consumption. *Nutr Rev* 2014;72(1):78–86. <https://doi.org/10.1111/nure.12146>.
- [62] Lin FJ, Pierce MM, Sehgal A, Wu T, Skipper DC, Chabba R. Effect of taurine and caffeine on sleep-wake activity in *Drosophila melanogaster*. *Nat Sci Sleep* 2010;2:221–31. <https://doi.org/10.2147/NSS.S13034UnitedStates>.
- [63] Eliyahu U, Berlin S, Hadad E, Heled Y, Moran DS. Psychostimulants and military operations. *Mil Med* 2007;172(4):383–7. <https://doi.org/10.7205/MILMED.172.4.383>.
- [64] Buguet A, Moroz DE, Radomski MW. Modafinil-medical considerations for use in sustained operations. *Aviat Space Environ Med* 2003;74(6):659–63.
- [65] Killgore WDS, Rupp TL, Grugle NL, Reichardt RM, Lipizzi EL, Balkin TJ. Effects of dextroamphetamine, caffeine and modafinil on psychomotor vigilance test performance after 44 h of continuous wakefulness. *J Sleep Res* 2008;17(3):309–21. <https://doi.org/10.1111/j.1365-2869.2008.00654.x>.
- [66] Erman MK, Rosenberg R. Modafinil for excessive sleepiness associated with chronic shift work sleep disorder: effects on patient functioning and health-related quality of life. *Prim Care Companion J Clin Psychiatry* 2007;9(3):188–94. <https://doi.org/10.4088/pcc.v09n0304>.
- [67] Wesensten N, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. *Psychopharmacology* 2002;159(3):238–47. <https://doi.org/10.1007/s002130100916>.
- [68] Waters WF, Magill RA, Bray GA, Volaufova J, Smith SR, Lieberman HR, Rood J, Hurry M, Anderson T, Ryan DH. A comparison of tyrosine against placebo, phentermine, caffeine, and D-amphetamine during sleep deprivation. *Nutr Neurosci* 2003;6(4):221–35. <https://doi.org/10.1080/1028415031000120543>.
- [69] Grayson JK, Gibson RL, Shanklin SL, Neuhauser KM, McGhee C. Trends in positive drug tests, United States Air Force, fiscal years 1997–1999. *Mil Med* 2004;169(7):499–504. <https://doi.org/10.7205/MILMED.169.7.499>.
- [70] Lacy BW, Ditzler TF, Wilson RS, Martin TM, Ochikubo JT, Roussel RR, Pizarro-Matos JM, Vazquez R. Regional methamphetamine use among U.S. army personnel stationed in the continental United States and Hawaii: a six-year retrospective study. *Mil Med* 2008;4:353–8. <https://doi.org/10.7205/milmed.173.4.353>.
- [71] McLellan TM, Kamimori GH, Voss DM, Tate C, Smith SJR. Caffeine effects on physical and cognitive performance during sustained operations. *Aviat Space Environ Med* 2007;78(9):871–7.
- [72] McLellan TM, Kamimori GH, Bell DG, Smith IF, Johnson D, Belenky G. Caffeine maintains vigilance and marksmanship in simulated urban operations with sleep deprivation. *Aviat Space Environ Med* 2005;76(1):39–45.
- [73] McLellan TM, Bell DG, Kamimori GH. Caffeine improves physical performance during 24 h of active wakefulness. *Aviat Space Environ Med* 2004;75(8):666–72.
- [74] Newman RA, Kamimori GH, Wesensten NJ, Picchioni D, Balkin TJ. Caffeine gum minimizes sleep inertia. *Percept Mot Skills* 2013;116(1):280–93. <https://doi.org/10.2466/29.22.25.PMS.116.1.280-293UnitedStates>.
- [75] Geiger-Brown J, Rogers VE, Trinkoff AM, Kane RL, Bausell RB, Scharf SM. Sleep, sleepiness, fatigue, and performance of 12-hour-shift nurses. *Chronobiol Int* 2012;29(2):211–9. <https://doi.org/10.3109/07420528.2011.645752>.
- [76] Walia HK, Hayes AL, Przepyszny KA, Karumanchi P, Patel SR. Clinical presentation of shift workers to a sleep clinic. *Sleep Breath* 2012;16(2):543–7. <https://doi.org/10.1007/s11325-011-0540-y>.
- [77] Borland RG, Rogers AS, Nicholson AN, Pascoe PA, Spencer MB. Performance overnight in shiftworkers operating a day-night schedule. *Aviat Space Environ Med* 1986;57(3):241–9.
- [78] Kelly TL, Mitler MM, Bonnet MH. Sleep latency measures of caffeine effects during sleep deprivation. *Electroencephalogr Clin Neurophysiol* 1997;102(5):397–400. [https://doi.org/10.1016/s0921-884x\(97\)96135-x](https://doi.org/10.1016/s0921-884x(97)96135-x).
- [79] Penetar D, McCann U, Thorne D, Kamimori G, Galinski C, Sing H, Thomas M, Belenky G. Caffeine reversal of sleep deprivation effects on alertness and mood. *Psychopharmacology* 1993;112(2–3):359–65. <https://doi.org/10.1007/bf02244933>.
- [80] Lohi JJ, Huttunen KH, Lahtinen TMM, Kilpeläinen AA, Muhli AA, Leino TK. Effect of caffeine on simulator flight performance in sleep-deprived military pilot students. *Mil Med* 2007;172(9):982–7. <https://doi.org/10.7205/MILMED.172.9.982>.
- [81] Heaton K, Russell G. The effects of caffeine use on driving safety among truck drivers who are habitual caffeine users. *Workplace Health Saf* 2015;63(8):333–41. <https://doi.org/10.1177/2165079915579561>.
- [82] Doty TJ, So CJ, Bergman EM, Trach SK, Ratcliffe RH, Yarnell AM, Capaldi VF, Moon JE, Balkin TJ, Quartana PJ. Limited efficacy of caffeine and recovery costs during and following 5 days of chronic sleep restriction. *Sleep* 2017;40(12). <https://doi.org/10.1093/sleep/zsx171>.
- [83] McHill AW, Smith BJ, Wright KP. Effects of caffeine on skin and core temperatures, alertness, and recovery sleep during circadian misalignment. *J Biol Rhythms* 2014;29(2):131–43. <https://doi.org/10.1177/0748730414523078>.
- [84] Lajambe CM, Kamimori GH, Belenky G, Balkin TJ. Caffeine effects on recovery sleep following 27 h total sleep deprivation. *Aviat Space Environ Med* 2005;76(2):108–13.
- [85] McLean CP, Zandberg L, Roache JD, Fitzgerald H, Prieksma KE, Taylor DJ, Dondanville KA, Litz BT, Mintz J, Young-McCaughan S, Yarvis JS, Peterson AL, Foa EB. For the STRONG STAR consortium, caffeine use in military personnel with PTSD: prevalence and impact on sleep. *Behav Sleep Med* 2017;17(2):202–12. <https://doi.org/10.1080/15402002.2017.1326920>.
- [86] Salinapascual R, Valenciaflores M, Campos R, Castano A, Shiromani P. Caffeine challenge in insomniac patients after total sleep deprivation. *Sleep Med* 2006;7(2):141–5. <https://doi.org/10.1016/j.sleep.2005.06.008>.
- [87] Knapik J, Trone D, McGraw S, Steelman R, Austin K, Lieberman H. Caffeine use among active duty Navy and marine corps personnel. *Nutrients* 2016;8(10):620. <https://doi.org/10.3390/nu8100620>.
- [88] Landolt HP. Sleep homeostasis: a role for adenosine in humans? *Biochem Pharmacol* 2008;75(11):2070–9. <https://doi.org/10.1016/j.bcp.2008.02.024>.
- [89] Bjorness TE, Greene RW. Adenosine and sleep. *Curr Neuropharmacol* 2009;7(3):238–45. <https://doi.org/10.2174/157015909789152182UnitedStates>.

- [90] Sperlagh B, Sylvester Vizi E. The role of extracellular adenosine in chemical neurotransmission in the Hippocampus and basal Ganglia: pharmacological and clinical aspects. *Curr Top Med Chem* 2011;11(8):1034–46. <https://doi.org/10.2174/156802611795347564>.
- [91] Halassa MM, Florian C, Fellin T, Munoz JR, Lee SY, Abel T, Haydon PG, Frank MG. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. *Neuron* 2009;61(2):213–9. <https://doi.org/10.1016/j.neuron.2008.11.024>.
- [92] Volkow ND, Wang G-J, Logan J, Alexoff D, Fowler JS, Thanos PK, Wong C, Casado V, Ferre S, Tomasi D. Caffeine increases striatal dopamine D2/D3 receptor availability in the human brain. *Transl Psychiatry* 2015;5(4). <https://doi.org/10.1038/tp.2015.46>.
- [93] Bchir F, Dogui M, Ben Fradj R, Arnaud MJ, Saguen S. Differences in pharmacokinetic and electroencephalographic responses to caffeine in sleep-sensitive and non-sensitive subjects. *C R Biol* 2006;329(7):512–9. <https://doi.org/10.1016/j.crvi.2006.01.006>.
- [94] Byrne EM, Johnson J, McRae AF, Nyholt DR, Medland SE, Gehrman PR, Heath AC, Madden PAF, Montgomery GW, Chenevix-Trench G, Martin NG. A genome-wide association study of caffeine-related sleep disturbance: confirmation of a role for a common variant in the adenosine receptor. *Sleep* 2012;35(7):967–75. <https://doi.org/10.5665/sleep.1962Australia>.
- [95] Rétey JV, Adam M, Khatami R, Luhmann UFO, Jung HH, Berger W, Landolt H-P. A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. *Clin Pharmacol Ther* 2007;81(5):692–8. <https://doi.org/10.1038/sj.cpt.6100102>.
- [96] Nova P, Hernandez B, Ptolemy AS, Zeitzer JM. Modeling caffeine concentrations with the Stanford caffeine questionnaire: preliminary evidence for an interaction of chronotype with the effects of caffeine on sleep. *Sleep Med* 2012;13(4):362–7. <https://doi.org/10.1016/j.sleep.2011.11.011>.
- [97] Mazzotti DR, Guindalini C, Pellegrino R, Barrueco KF, Santos-Silva R, Bittencourt LRA, Tufik S. Effects of the adenosine deaminase polymorphism and caffeine intake on sleep parameters in a large population sample. *Sleep* 2011;34(3):399–402. <https://doi.org/10.1093/sleep/34.3.399>.
- [98] Mazzotti DR, Guindalini C, de Souza AAL, Sato JR, Santos-Silva R, Bittencourt LRA, Tufik S. Adenosine deaminase polymorphism affects sleep EEG spectral power in a large epidemiological sample. *PLoS One* 2012;7(8). <https://doi.org/10.1371/journal.pone.0044154Brazil>.
- [99] Sachse C, Brockmöller J, Bauer S, Roots I. Functional significance of a C→A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. *Br J Clin Pharmacol* 1999;47(4):445–9. <https://doi.org/10.1046/j.1365-2125.1999.00898.x>.
- [100] Temple JL, Bernard C, Lipshultz SE, Czachor JD, Westphal JA, Mestre MA. The safety of ingested caffeine: a comprehensive review. *Front Psychiatr* 2017;8. <https://doi.org/10.3389/fpsyg.2017.00080>.
- [101] Omvik S, Pallesen S, Bjorvatn B, Thayer J, Hilde Nordhus I. Night-time thoughts in high and low worriers: reaction to caffeine-induced sleeplessness. *Behav Res Ther* 2007;45(4):715–27. <https://doi.org/10.1016/j.brat.2006.06.006>.
- [102] Rogers PJ, Heatherley SV, Hayward RC, Seers HE, Hill J, Kane M. Effects of caffeine and caffeine withdrawal on mood and cognitive performance degraded by sleep restriction. *Psychopharmacology* 2005;179(4):742–52. <https://doi.org/10.1007/s00213004-2097-y>.
- [103] Mniszek DH. Brighton sleep survey: a study of sleep in 20–45-year olds. *J Int Med Res* 1988;16(1):61–5. <https://doi.org/10.1177/030006058801600107>.
- [104] Landolt HP, Werth E, Borbély AA, Dijk DJ. Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res* 1995;675(1–2):67–74. [https://doi.org/10.1016/0006-8993\(95\)00040-W](https://doi.org/10.1016/0006-8993(95)00040-W).
- [105] Suh S, Yang HC, Kim N, Yu JH, Choi S, Yun CH, Shin C. Chronotype differences in health behaviors and health-related quality of life: a population-based study among aged and older adults. *Behav Sleep Med* 2017;15(5):361–76. <https://doi.org/10.1080/15402002.2016.1141768>.
- [106] Jason T, Somrat L, Vitool L, Wipawan CP, Thanapoom R, Mahlet GT, Bizu G, Michelle AW, sleepiness D. Circadian preference, caffeine consumption and use of other stimulants among Thai college students. *J Publ Health Epidemiol* 2014;8(6):202–10. <https://doi.org/10.5897/JPHE2014.0620>.
- [107] Whittier A, Sanchez S, Castañeda B, Sanchez E, Gelaye B, Yanez D, Williams MA, Chronotype E, Sleepiness D. Caffeine consumption, and use of other stimulants among Peruvian university students. *J Caffeine Res* 2014;4(1):21–7. <https://doi.org/10.1089/jcr.2013.0029>.
- [108] Kerpershoek ML, Antypa N, Van den Berg JF. Evening use of caffeine moderates the relationship between caffeine consumption and subjective sleep quality in students. *J Sleep Res* 2018;27(5). <https://doi.org/10.1111/jsr.12670>.
- [109] Urry E, Jetter A, Holst SC, Berger W, Spinias GA, Langhans W, Landolt HP. A case-control field study on the relationships among type 2 diabetes, sleepiness and habitual caffeine intake. *J Psychopharmacol* 2017;31(2):233–42. <https://doi.org/10.1177/0269881116668595>.
- [110] Urry E, Jetter A, Landolt HP. Assessment of CYP1A2 enzyme activity in relation to type-2 diabetes and habitual caffeine intake. *Nutr Metab* 2016;13(1):1–9. <https://doi.org/10.1186/s12986-016-0126-6>.
- [111] Grandner MA, Martin JL, Patel NP, Jackson NJ, Gehrman PR, Pien G, Perlis ML, Xie D, Sha D, Weaver T, Gooneratne NS. Age and sleep disturbances among American men and women: data from the U.S. Behavioral risk factor surveillance system. *Sleep* 2012;35(3):395–406. <https://doi.org/10.5665/sleep.1704UnitedStates>.
- [112] Andreyeva T, Luedicke J, Henderson KE, Tripp AS. Grocery store beverage choices by participants in federal food assistance and nutrition programs. *Am J Prev Med* 2012;43(4):411–8. <https://doi.org/10.1016/j.amepre.2012.06.015>.
- [113] Frozi J, de Carvalho HW, Ottoni GL, Cunha RA, Lara DR. Distinct sensitivity to caffeine-induced insomnia related to age. *J Psychopharmacol* 2018;32(1):89–95. <https://doi.org/10.1177/0269881117722997>.
- [114] Bailey RL, Saldaña LG, Gahche JJ, Dwyer JT. Estimating caffeine intake from energy drinks and dietary supplements in the United States. *Nutr Rev* 2014;72(1):9–13. <https://doi.org/10.1111/nure.12138>.
- [115] Berger LK, Fendrich M, Chen HY, Arria AM, Cisler RA. Sociodemographic correlates of energy drink consumption with and

- without alcohol: results of a community survey. *Addict Behav* 2011;36(5):516–9. <https://doi.org/10.1016/j.addbeh.2010.12.027>.
- [116] Park S, Onufrek S, Blanck HM, Sherry B. Characteristics associated with consumption of sports and energy drinks among US adults: national health Interview survey, 2010. *J Acad Nutr Diet* 2013;113(1):112–9. <https://doi.org/10.1016/j.jand.2012.09.019>.
- [117] Grandner MA. Addressing sleep disturbances: an opportunity to prevent cardiometabolic disease? *Int Rev Psychiatr* 2014;26(2):155–76. <https://doi.org/10.3109/09540261.2014.911148>.
- [118] Peacock A, Bruno R, Martin FH. The subjective physiological, psychological, and behavioral risk-taking consequences of alcohol and energy drink co-ingestion. *Alcohol Clin Exp Res* 2012;36(11):2008–15. <https://doi.org/10.1111/j.1530-0277.2012.01820.x>.
- [119] Brache K, Stockwell T. Drinking patterns and risk behaviors associated with combined alcohol and energy drink consumption in college drinkers. *Addict Behav* 2011;36(12):1133–40. <https://doi.org/10.1016/j.addbeh.2011.07.003>.
- [120] Patrick ME, Griffin J, Huntley ED, Maggs JL. Energy drinks and binge drinking predict college students' sleep quantity, quality, and tiredness. *Behav Sleep Med* 2018;16(1):92–105. <https://doi.org/10.1080/15402002.2016.1173554>.
- [121] Chakravorty S, Chaudhary NS, Brower KJ. Alcohol dependence and its relationship with insomnia and other sleep disorders. *Alcohol Clin Exp Res* 2016;40(11):2271–82. <https://doi.org/10.1111/acer.13217>.
- [122] Rajaratnam SMW, Howard ME, Grunstein RR. Sleep loss and circadian disruption in shift work: health burden and management. *Med J Aust* 2013;199(8):S11. <https://doi.org/10.5694/mja13.10561>.
- [123] Quan S, Combs D, Parthasarathy S. Impact of sleep duration and weekend oversleep on body weight and blood pressure in adolescents. *Southwest J Pulp Crit Care* 2018;16(1):31–41. <https://doi.org/10.13175/swjpc150-17>.
- [124] Okun ML, Reynolds CF, Buysse DJ, Monk TH, Mazumdar S, Begley A, Hall M. Sleep variability, health-related practices, and inflammatory markers in a community dwelling sample of older adults. *Psychosom Med* 2011;73(2):142–50. <https://doi.org/10.1097/PSY.0b013e3182020d08>.
- [125] Rasaei B, Talib RA, Noor MI, Karandish M, Karim NA. Simultaneous coffee caffeine intake and sleep deprivation alter glucose homeostasis in Iranian men: a randomized crossover trial. *Asia Pac J Clin Nutr* 2016;25(4):729–39. <https://doi.org/10.6133/apcn.092015.46>.
- [126] Grant CL, Coates AM, Dorrian J, Paech GM, Pajcini M, Della Vedova C, Johnson K, Kamimori GH, Fidock J, Aidman E, Banks S. The impact of caffeine consumption during 50 hr of extended wakefulness on glucose metabolism, self-reported hunger and mood state. *J Sleep Res* 2018;27(5). <https://doi.org/10.1111/jsr.12681>.
- [127] Cauli O, Morelli M. Caffeine and the dopaminergic system. *Behav Pharmacol* 2005;16(2):63–77. <https://doi.org/10.1097/00008877-200503000-00001>.
- [128] Lara DR. Caffeine, mental health, and psychiatric disorders. *J Alzheimer's Dis* 2010;1. <https://doi.org/10.3233/JAD-2010-1378>.
- [129] Chelben J, Piccone-Sapir A, Ianco I, Shoenfeld N, Kotler M, Strous RD. Effects of amino acid energy drinks leading to hospitalization in individuals with mental illness. *Gen Hosp Psychiatry* 2008;30(2):187–9. <https://doi.org/10.1016/j.genhosppsych.2007.10.002>.
- [130] Drake CL, Jefferson C, Roehrs T, Roth T. Stress-related sleep disturbance and polysomnographic response to caffeine. *Sleep Med* 2006;7(7):567–72. <https://doi.org/10.1016/j.sleep.2006.03.019>.
- [131] Kendler Kenneth S, Myers John, Gardner Charles O. Caffeine intake, toxicity and dependence and lifetime risk for psychiatric and substance use disorders: an epidemiologic and co-twin control analysis. *Psychol Med* 2006;36(12):1717–25. <https://doi.org/10.1017/s0033291706008622>.
- [132] Gehrmann P, Seelig AD, Jacobson IG, Boyko EJ, Hooper TI, Gackstetter GD, Ulmer CS, Smith TC. Predeployment sleep duration and insomnia symptoms as risk factors for new-onset mental health disorders following military deployment. *Sleep* 2013;36(7):1009–18. <https://doi.org/10.5665/sleep.2798UnitedStates>.
- [133] Kamimori GH, Penetar DM, Headley DB, Thorne DR, Otterstetter R, Belenky G. Effect of three caffeine doses on plasma catecholamines and alertness during prolonged wakefulness. *Eur J Clin Pharmacol* 2000;56(8):537–44. <https://doi.org/10.1007/s002280000186>.
- [134] Barger LK, Lockley SW, Rajaratnam SMW, Landrigan CP. Neurobehavioral, health, and safety consequences associated with shift work in safety-sensitive professions. *Curr Neurol Neurosci Rep* 2009;9(2):155–64. <https://doi.org/10.1007/s11910-009-0024-7>.
- [135] De Mello MT, Narciso FV, Tufik S, Paiva T, Spence DW, Bahamand AS, Verster JC, Pandi-Perumal SR. Sleep disorders as a cause of motor vehicle collisions. *Int J Prevent Med* 2013;4(3):246–57.
- [136] Souza JC, Paiva T, Reimão R. Sleep habits, sleepiness and accidents among truck drivers. *Ar Neuro-Psiquiatr* 2005;63(4):925–30. <https://doi.org/10.1590/S0004-282X2005000600004>.
- [137] Akerstedt T, Fredlund P, Gillberg M, Jansson B. A prospective study of fatal occupational accidents - relationship to sleeping difficulties and occupational factors. *J Sleep Res* 2002;11(1):69–71. <https://doi.org/10.1046/j.1365-2869.2002.00287.x>.
- [138] Horne JA, Reyner LA. Counteracting driver sleepiness: effects of napping, caffeine, and placebo. *Psychophysiology* 1996;33(3):306–9. <https://doi.org/10.1111/j.1469-8986.1996.tb00428.x>.
- [139] Sharwood LN, Elkington J, Meulenens L, Ivers R, Boufous S, Stevenson M. Use of caffeinated substances and risk of crashes in long distance drivers of commercial vehicles: case-control study. *BMJ* 2013;346(mar18 3):1756–833. <https://doi.org/10.1136/bmj.f1140>.
- [140] Li Y, Vgontzas AN, Fernandez-Mendoza J, Bixler EO, Sun Y, Zhou J, Ren R, Li T, Tang X. Insomnia with physiological hyperarousal is associated with hypertension. *Hypertension* 2015;65(3):644–50. <https://doi.org/10.1161/HYPERTENSIONAHA.114.04604>.
- [141] Savoca MR, MacKey ML, Evans CD, Wilson M, Ludwig DA, Harshfield GA. Association of ambulatory blood pressure and dietary caffeine in adolescents. *Am J Hypertens* 2005;18(1):116–20. <https://doi.org/10.1016/j.amjhyper.2004.08.011>.
- [142] Cheng LD, Hwang JJ, Chen, Chen MF, Su TC. Working hours, sleep duration and the risk of acute coronary heart disease: a case-control study of middle-aged men in Taiwan. *Int J Cardiol* 2003;171(3):1029–36.
- [143] Bonnet MH, Arand DL. Situational insomnia: consistency, predictors, and outcomes. *Sleep* 2003;26(8):1029–36.
- [144] McCrae CS, Rowe MA, Dautovich ND, Lichstein KL, Durrence HH, Riedel BW, Taylor DJ, Bush AJ. Sleep hygiene practices in two community dwelling samples of older adults. *Sleep* 2006;29(12):1551–60. <https://doi.org/10.1093/sleep/29.12.1551>.

- [145] Bonnet MH, Balkin TJ, Dinges DF, Roehrs T, Rogers NL, Wesensten NJ. The use of stimulants to modify performance during sleep loss: a review by the sleep deprivation and stimulant task force of the American academy of sleep medicine. *Sleep* 2005;28(9):1163–87. <https://doi.org/10.1093/sleep/28.9.1163>.
- [146] Mindell JA, Sedmak R, Boyle JT, Butler R, Williamson AA. Sleep Well!: a pilot study of an education campaign to improve sleep of socioeconomically disadvantaged children. *J Clin Sleep Med* 2016;12(12):1593–9. <https://doi.org/10.5664/jcsm.6338>.
- [147] Reifman J, Kumar K, Wesensten NJ, Tountas NA, Balkin TJ, Ramakrishnan S. 2B-alert web: an open-access tool for predicting the effects of sleep/wake schedules and caffeine consumption on neurobehavioral performance. *Sleep* 2016;39(12):2157–9. <https://doi.org/10.5665/sleep.6318>.

This page intentionally left blank

Chapter 27

Sleep, stress, and immunity

Aric A. Prather

Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA, United States

Introduction

Sleep is a biological imperative, conserved across species, that plays a fundamental role in promoting health and well-being [1,2]. Epidemiologic evidence consistently links poor sleep, characterized by short sleep duration, poor sleep continuity, and poor subjective sleep quality, with increased rates of a number of age-related conditions, including cardiovascular disease and metabolic conditions, as well as, premature mortality [3–6]; however, the biological mechanisms that underlie these associations are not well understood. The immune system has emerged as one promising pathway [7]. Over the past several decades, researchers have been investigating the sleep-immune connection in humans. As will be summarized below, there is now a compelling literature supporting the role of sleep and sleep loss on immune functioning and risk for immune-related conditions. Moreover, there is growing appreciation that sleep may serve as a predictor of how quickly the immune system ages.

The influence of sleep on physical health cannot be overstated, but it would be a mistake to focus on sleep in isolation. Sleep is malleable, always susceptible to the perturbations of the prior day. Energy expenditure, substances consumed (e.g., caffeine, nutrition), and one's psychological stress acutely affect the duration, continuity, and quality of sleep. Conversely, sleep the night prior can have dramatic effects on how someone thinks and feels the following day. Indeed, data suggest that sleep and stress are reciprocally connected. This is particularly relevant when considering sleep's influence on the immune system because there is a complementary literature demonstrating that psychological stress modulates many of the same immunologic pathways observed in sleep research [8]. Unfortunately, few studies have examined the independent and synergistic roles of sleep and psychological stress on immunity.

The goal of this chapter is to provide a review of the scientific human literature linking sleep and the immune

system, including the acquired and innate immune system as well as markers of immune cell aging (i.e., immunosenescence). Next, parallels will be drawn using the psychological stress and immune system literature, which will be followed by a discussion of the reciprocal links between sleep and psychological stress and the pathways through which they can influence immune function. Finally, a review of the limited research examining the synergistic influences of sleep and psychological stress will be presented. First, however, a brief overview of the immune system is provided to help orient the reader.

Overview of the immune system

The immune system comprises cells and soluble molecules that work together to protect the body (i.e., self) from the foreign antigens such as viruses and bacteria (i.e., nonself). Though exquisitely dependent on one another, the immune system is typically separated into two distinct arms: the acquired and innate immune system.

Acquired immune system

The acquired immune system, as the name suggests, develops over time in response to antigen exposure. This arm is slow acting, often requiring days to weeks to produce the intended immune response, and is comprised of various lymphocytes (e.g., helper ($CD4^+$) and cytotoxic ($CD8^+$) T-cells and B ($CD19^+$) cells) that have receptors on their cell surfaces that respond to one and only one antigen. In response to an infectious challenge, the antigen is taken up by antigen presenting cells (APCs), such as dendritic cells or macrophages, that then migrate to lymphoid organs (e.g., lymph nodes). The APCs present the antigen to helper T-cells. Once activated, these begin to divide and proliferate to mount an immune cell army whose role is to clear the body of the invader (i.e., antigen). The primary role of helper T-cells is to produce and release cytokines that modulate the rest of the immune system. The role of

cytotoxic T-cells is to seek out and lyse infected cells (e.g., virally infected cells), while B-cells produce antibodies, which are soluble proteins critical in neutralizing bacterial toxins and flagging free-floating viruses and infected cells so as to communicate the need for destruction to the innate arm of the immune system. Antibody levels are clinically meaningful as they are the end product of vaccinations. Activated T-and B-cells maintain immunological memory and can circulate in the blood for years to provide a rapid response if challenged by the same antigen once again.

Innate immune system

The innate immune system is functional at birth and is activated quickly (e.g., minutes to hours). It is the body's first line of immune defense and includes physical and anatomical barriers such as the skin and, unlike the acquired immune system, is made up of specialized cells that do not require specific recognition of an antigen to become activated [9]. Examples of these cells include natural killer (NK) cells, granulocytes (e.g., neutrophils), and macrophages. NK cells play an important role in halting the early phases of viral infections and attacking cells that are malignant. NK cells release a toxic substance to lyse unwanted cells. Macrophages, in contrast, are phagocytic, meaning that they eat their targets (i.e., unwanted invaders). They also release cytokines, which are proteins that facilitate inflammation. During an inflammatory response, immune cells congregate at the site of injury, such as a wound, releasing toxic molecules, and signaling proteins to neutralize the threat and call other surrounding immune cells to their aid. The inflammatory response is critical to survival; however, prolonged or unregulated inflammation can contribute to inflammatory-related diseases, including autoimmune conditions and cardiovascular disease, among others. Key proinflammatory cytokines include interleukin (IL)-6, tumor necrosis factor (TNF)- α , and IL-1 β . Additionally, C-reactive protein, which is an acute phase protein produced by the liver in response to increasing levels of IL-6, has emerged as a measure of chronic systemic inflammation and is a clinical risk factor for cardiovascular disease [10].

The aging immune system

There are several well-recognized changes that occur as the immune system ages. These changes include involution of the thymus, which causes diminution of T-cell diversity and increases in low grade systemic inflammation, known as inflammaging [11]. There is also an accumulation of aged immune cells that are characterized by cellular senescence. Cellular senescence is a state of cell cycle arrest that is marked by an inability to effectively replicate. One pathway to cell cycle arrest that has been studied by a

number of sleep researchers is telomere attrition. Telomeres are DNA protein complexes at the ends of chromosomes of eukaryotic cells that protect the DNA that encodes genetic information from genomic instability and damage. Telomeres shorten with each cellular division, and if not replaced by the enzyme telomerase, critically short telomeres will send the cell into either apoptosis or cell cycle arrest. With advancing age, the shortening of telomeres primarily occurs in cytotoxic T-cells (CD8 $^{+}$), particularly those who have lost CD28 expression. CD28 is a co-stimulatory molecule on the cell surface important for facilitating proliferative capacity.

Beyond an inability to replicate, senescent cells are also characterized by a unique secretory pattern known as the senescence associated secretory phenotype (SASP), which is marked by increased proinflammatory and chemokine activity (e.g., IL-6, IL-8, monocyte chemotactic protein (MCP)-2 and MCP-4, as well as intracellular adhesion molecule (ICAM)-1, among other molecules). Prior work in animals demonstrates the removal of senescent cells reduces age-related pathology [12], potentially due to the reduction in SASP.

Variability is inherent in all of the immune parameters described above. As such, there has been growing interest among sleep researchers to determine whether different aspects of sleep may account for significant levels of variability in these markers, which may illuminate why poor sleep is associated with susceptibility to infectious illness and age-related medical conditions.

Sleep, acquired immunity, and infectious disease risk

Animal and human studies demonstrate that poor sleep is associated with alterations in aspects of acquired immunity with implications for infectious disease risk [13]. This is certainly consistent with anecdotal experiences where prolonged periods of insufficient sleep tracks with one's increased risk of "catching a cold." However, there is now strong empirical evidence to support this common belief. For example, in a sample taken from the National Health and Nutritional Examinations Surveys spanning from 2005 to 2012, self-reported short sleep duration (≤ 5 h per night), endorsing a physician diagnosis of a sleep disorder, and having told a physician about having a sleep disturbance were associated with increased rates of head and chest colds as well as infection compared to better sleepers [14].

The cross-sectional nature of these data limits inferences regarding the directionality of these associations. However, prospective evidence showed that self-reported short sleep duration (≤ 5 h per night) and long sleep duration (≥ 9 h per night) predicted increased incidence of physician diagnosed pneumonia compared to normal

sleepers (8 h sleepers) [15]. This study, though intriguing, was limited by a number of factors that typically plague the sleep and health literature, including use of single retrospective self-report item to assess typical sleep duration. In addition, exposure to the pneumococcal virus was not controlled, raising concerns about possible unmeasured, confounding variables that predict likelihood of exposure rather than response to the virus.

The strongest human evidence demonstrating that poor sleep is associated with increased susceptibility to infectious illness comes from a series of experimental studies in which healthy participants are exposed to a known quantity of rhinovirus—the virus responsible for producing an upper respiratory infection [16–18]. The general design of these studies is as follows: participants are quarantined in a hotel throughout the course of the study, which begins 1–2 days prior to being inoculated with the live virus and spans an additional 5–7 days of monitoring. On the days prior to inoculation, participants undergo a nasal wash to ensure that they have no baseline infection and have their blood drawn to assess any preexisting antibodies to the virus. On the third day of quarantine, the participants receive known quantities of the virus, administered intranasally. Subsequent to this, participants are then monitored for subjective and objective signs of illness. In order to verify the presence of infection, daily nasal washings are conducted and assayed for evidence of viral shedding (i.e., replication of the virus). In addition, viral-specific antibody titers are obtained 21–28 days after inoculation. Individuals are deemed infected if (1) they show evidence of viral shedding or (2) demonstrate a twofold increase over their baseline levels in the virus-specific antibody titers. Importantly, not all participants infected go on to show signs of objective illness. Physical examinations are carried out each day to monitor signs of objective illness. Specifically, nasal congestion is quantified by measuring the time required for a dye administered in the nose to reach the nasopharynx [19]. Daily mucus secretion is quantified by weighing tissues used throughout the day, subtracting the weight of the tissue. Typically, a baseline adjusted nasal clearance time of >7 min and/or a total adjusted mucus weight of at least 10 g is used as the threshold for the presence of clinical illness in participants who show evidence of infection [20].

This paradigm provides the unique opportunity to prospectively test whether sleep prior to viral exposure predicts who is susceptible to becoming infected and developing a biologically verified cold. In this regard, Cohen and colleagues found that shorter sleep duration and poorer sleep efficiency assessed by 14-night sleep diary significantly predicted increased likelihood for developing a biologically verified cold [16]. Similarly, in a separate sample, Prather and colleagues demonstrated that shorter sleep duration, this time measured by seven nights of wrist

actigraphy, predicted increased likelihood of developing a cold [18]. As displayed in Fig. 27.1, they found that participants who obtained 6 or fewer hours of sleep on average were four times more likely to develop a cold compared to those who obtained >7 h per night. Importantly, these findings were independent of a bevy of potential confounders, including baseline antibody titers, sociodemographic factors, health behaviors, and psychological processes, such as levels of psychological stress. Furthermore, neither study found that sleep predicted susceptibility to infection.

This experimental paradigm provides important objective, empirical evidence that insufficient sleep confers risk for infectious illness. Another clinically relevant model used to assess the role of sleep on infectious disease risk is through the use of vaccinations. Prophylactic vaccination is used to simulate infection and induce the formation of memory T- and B-cells with antibodies to the specific targeted pathogen. Several experimental studies employing total or partial sleep restriction following vaccination suggest that acute sleep loss can impair, albeit transiently, antibody responses compared to undisturbed sleep [21–24]. For example, Spiegel and colleagues examined the effects of partial sleep restriction (i.e., reducing sleep opportunity in the lab from 8 to 4 h per night for six consecutive nights) compared to undisturbed sleepers on response to the influenza vaccination. Antibody titers to the influenza vaccine were measured at baseline, 10-days

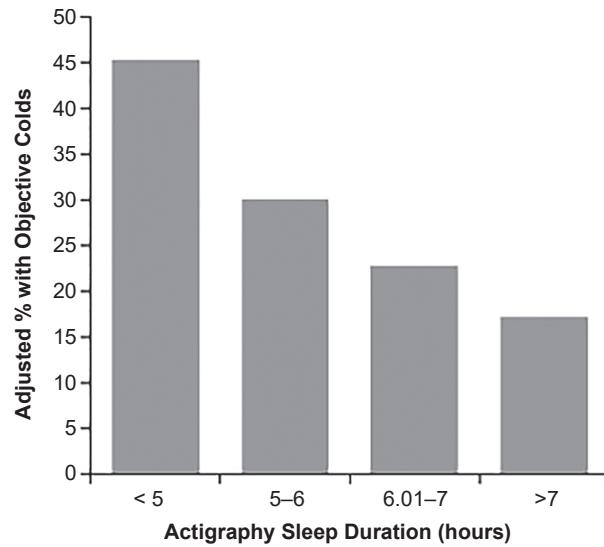


FIGURE 27.1 Sleep duration, averaged over seven nights of wrist actigraphy and measured prior to virus exposure, is associated with percentage of participants who subsequently developed a biologically verified cold. The percentage of colds is based on predicted values (adjusted for age and prechallenge viral specific antibody levels). From Prather AA, Janicki-Deverts D, Hall MH, Cohen S. Behaviorally assessed sleep and susceptibility to the common cold. *Sleep* 2015;38(9):1353–9. <https://doi.org/10.5665/sleep.4968>, used with permission.

postvaccination, and between 21 and 30 days post-vaccination. Analyses revealed that 10 days after the vaccination, those who were randomized to the sleep restriction condition mounted a response half that of the undisturbed sleepers; however, by the later measurement time point, there were no group differences.

It is possible that the modest and transient effects of experimental sleep loss may be more substantial among those who experience chronically short sleep. In this regard, Prather and colleagues examined the prospective associations between sleep measures, obtained via wrist actigraphy and averaged over time, and vaccination response to the hepatitis B vaccination series in a sample of healthy midlife adults [25]. Analyses revealed that shorter average sleep duration was associated with fewer viral specific antibodies to the vaccination, such that for every additional hour of sleep, participants experienced a 56% increase in antibody production. This study also attempted to examine whether the reduction in antibody responses carried any clinical relevance. Using CDC guidelines for determining the threshold for “protection” conferred by the hepatitis B vaccination series, analyses revealed that short sleepers (i.e., those sleeping <6 h per night) were nearly 12 times more likely to be left unprotected 6 months after the vaccination series compared to participants who slept >7 h per night.

To date, only one study has examined whether insomnia serves as a risk factor for impaired vaccination response. Taylor and colleagues examined whether participants with insomnia disorder, assessed by structured clinical interview, showed impaired response to the influenza vaccine as compared to noninsomniac participants [26]. Overall, participants with insomnia showed fewer antibodies to the influenza vaccine compared to controls both before and after the vaccination, suggesting that while the magnitude of the response to the vaccination was similar between those with and without insomnia, antibody titers produced by insomnia participants were lower overall.

What are the underlying immune mechanisms through which poor sleep is linked to infectious disease risk? Studies employing experimental sleep loss support reliable alterations in immune parameters that are thought to underlie host resistance. For example, acute sleep loss is associated with redistribution of T- and B-cells in peripheral circulation [27–30]. Circulating T-and B-cells peak early in the evening and then migrate to the lymphoid organs where they may come in contact with antigens, such as viruses. As such, sleep loss may impact the ability of these immune cells to be in the “right place at the right time” [31]. In addition, sleep loss is associated with impaired T-cell functioning, including diminished antigen-specific response by helper T-cells [22], as well as a decline in the production of IL-12 [32], a cytokine central

to T-cell maturation. Finally, sleep loss is associated with impaired proliferative capacity (i.e., cellular replication) of T-cells when stimulated in vitro and modulation of the function of APCs, which may affect how well these cells present viruses to the rest of the immune system [27,32].

Summary. Experimental and observational data support the notion that poor sleep can impair acquired immunity, with clinical implications related to susceptibility to the common cold and vaccination efficacy. While laboratory studies have identified which aspects of the acquired immune response are altered during disturbed sleep, there is still a need for researchers to test sleep interventions to determine whether improvements in sleep can enhance vaccination responses and otherwise protect populations whose acquired immune system is suboptimal, such as the elderly or individuals who are HIV⁺.

Sleep, innate immunity, and inflammatory disease risk

The innate immune system is regulated by both sleep and circadian processes. For example, there are nocturnal increases in NK cell number and function during sleep that are markedly impaired under periods of sleep loss [33,34]. In a small study of healthy volunteers, NK cell cytotoxicity was significantly lower in response to a night of partial sleep restriction (i.e., deprived of sleep from 3 to 7:00 a.m.) compared to an undisturbed night of sleep [33]. Inflammatory cytokines increase across the night, which is partially due to circadian rhythmicity; however, there is a substantial literature that shows that sleep also modulates inflammatory activity. This is not surprising given that inflammation appears to be a central pathway in the pathogenesis of several chronic diseases where sleep plays a role, such as cardiovascular disease [35]. Irwin and colleagues recently published a comprehensive meta-analytic review on the associations between measures of sleep and inflammation [36]. In an analysis of 72 studies, greater sleep disturbances, assessed by questionnaires, were associated with higher levels of circulating IL-6 and CRP but not TNF- α . Shorter sleep duration, when measured subjectively by self-report, was unrelated to IL-6 or CRP levels, though when measured objectively, shorter sleep duration was significantly related to higher IL-6. In addition, longer sleep duration was associated with higher CRP and IL-6 but not TNF- α , highlighting the curvilinear risk conferred by both long and short sleep.

There is a large experimental literature examining the effects of partial and total sleep restriction on markers of inflammation. For example, several studies have found that multiple nights of partial sleep restriction (e.g., reducing sleep opportunity from 8 to 4 h per night) is associated with elevated levels of CRP and IL-6; however, other

studies have failed to find such effects. In fact, in the most recent meta-analysis, Irwin and colleagues failed to observe an aggregated effect of sleep restriction on next day levels of CRP, IL-6, or TNF- α (nonsignificant effect sizes ranging from -0.43 to 0.61) [36].

The effects of sleep restriction on inflammation have been more consistent when researchers have focused on genomic and cellular measures of the inflammatory response as opposed to protein levels in systemic circulation. The inflammatory response is initiated when an antigen (such as a lipopolysaccharide [LPS], which is an endotoxin that is a major component of the outer membrane of Gram-negative bacteria) binds to a toll-like receptor found on the cell surfaces of macrophages. This initiates a signaling cascade characterized by the activation of intracellular transcriptional factors nuclear factor kB and activator protein 1. Activation of these transcriptional factors leads to the transcription of inflammatory response genes within the nucleus of the cell, including *TNF* and *IL1*. Studies examining the influence of sleep loss on inflammatory gene expression, transcriptional pathways, and the intracellular production of inflammatory proteins tend to demonstrate that acute sleep loss results in an upregulation in inflammatory activity [37–40]. For example, in a sample of 30 healthy adults, a night of partial sleep loss (i.e., sleep opportunity from 3 to 7:00 a.m.) was associated with a threefold increase in transcription of IL-6 messenger RNA and a twofold increase in transcription TNF- α RNA the following morning compared to a baseline period [37].

Like was the case for outcomes within the acquired immune system, few studies have examined the associations between inflammation and insomnia. One exception is a study of 22 participants, half of whom were diagnosed with insomnia. Nocturnal levels of IL-6 were sampled across a single night in the sleep laboratory, and it was observed that patients with insomnia had significantly higher levels of circulating IL-6 [41]. Three other studies have examined the association between insomnia diagnosis and systemic levels of IL-6 with mixed results [42–44]. As such, when examined in aggregate, insomnia diagnosis does not appear to be associated with higher levels of inflammation relative to patients without insomnia [36]. One explanation for these mixed findings may be that some participants with insomnia also experience short sleep duration, while others do not. Insomnia with short sleep duration has emerged as a more severe biological phenotype [45]. In this regard, in an adolescent sample, shorter sleepers (≤ 7 h per night) with symptoms of insomnia showed higher levels of circulating CRP compared to those with insomnia but sleep >7 h per night [46].

While current data suggest that overall clinical insomnia does not appear to be strongly associated with inflammatory activity, there is intriguing evidence that treating insomnia may result in related regulation of

inflammation. In this regard, a recent randomized controlled study examined the effects of cognitive behavioral therapy for insomnia (CBTI), Tai Chi Chih (TCC), and a sleep seminar control condition on cellular and genomic markers of inflammation in an older adult sample with insomnia. Over the course of the 4-month study and 16-month follow-up, CBTI produced a significant decrease in levels of CRP compared to the control condition. The TCC condition also produced an initial reduction in CRP, though this was lost by the 16-month follow up period. CBTI also produced a reduction in inflammatory gene expression over the course of the study, as did the TCC condition [47]. Notably, TCC has also been shown to reduce inflammation in breast cancer patients with insomnia [48]. More intervention research is needed to assess whether behavioral treatments for individuals with sleep disturbances can produce robust, clinically meaningful improvements in aspects of innate immune function.

Summary. Poor sleep is associated with impairment in some aspects of innate immunity (e.g., NK cell cytotoxicity) and enhancement in inflammatory activity. Overall, observational studies demonstrate that systemic inflammation is elevated in individuals reporting sleep disturbances, and those who report (or demonstrate via more objective methods) short and long sleep duration. In contrast, experimental studies of sleep restriction do not support a consistent increase in protein levels of proinflammatory cytokines; however, there are differences in study design that may contribute to heterogeneity in these effects. Moreover, sleep loss is associated with alterations in transcriptional pathways responsible for inflammatory activity, suggesting that acute sleep loss affect cellular processes. Finally, recent intervention data show that in some instances (e.g., in patients with insomnia in late life), behavioral strategies aimed at improving sleep can produce changes in markers of inflammation; however, more work in this area is needed.

Sleep and immunological aging

Research demonstrating that poor sleep is predictive of disease, and premature mortality has raised the possibility that sleep may play a role in the rate at which the immune system ages. As noted above, poor sleep, in some but not all studies, is associated with elevated levels of systemic inflammation, which is one aspect of immune system aging. Similarly, short sleep duration is associated with impaired vaccination efficacy—yet another aspect of the immune system that degrades from mid to late life. In addition, a growing body of research has focused on associations between sleep and telomere length, a recognized marker of immunosenescence.

The first evidence supporting an association between sleep and telomere length came from a study of 245

women aged 49–66 years [49]. Here, researchers found poorer subjective sleep quality was significantly associated with shorter immune cell telomere length, independent of chronological age, race, body mass index, and income. This association was strongest among participants who endorsed that their reports of poor sleep reflected a more chronic problem, which is consistent with the notion that prolonged poor sleep may promote a “wear and tear” on the immune system. Since this initial finding, several other studies have found that poor subjective quality and short sleep duration, measured both subjectively and by actigraphy, were associated with shorter immune cell telomere length [50–53].

Sleep disorders, such as obstructive sleep apnea (OSA) and insomnia, have also been examined in the context of telomere length. Indeed, a recent meta-analytic review supported a significant association between diagnosis of OSA and shorter telomeres [54]. Unfortunately, only eight studies were available for review, which indicates a need for more rigorous research in this area. Relatedly, it remains unclear if effective treatment of OSA can slow cellular aging. Only two studies have examined the association between insomnia and telomere length. In one study of women with a prior diagnosis of breast cancer, those who were experiencing insomnia had shorter telomeres than women without insomnia, though this difference was not statistically significant [55]. In a second sample, insomnia status interacted with chronological age to predict immune cell telomere length such that insomnia was associated with shorter telomeres in older participants (aged 70–88 years) but not younger participants (aged 60–69 years) [56].

The majority of studies that have investigated links between sleep and immune cell telomere length relied on telomere samples from either whole blood or peripheral blood mononuclear cells (PBMCs). In either case, the blood sample is comprised of several different immune cell subsets (e.g., B and T cells, monocytes, granulocytes), all of which may have telomeres of differing lengths [57,58]. This poses a challenge for understanding the extent to which poor sleep promotes accelerated immunosenescence in particular cell types, given that the accrual of senescent immune cells (often driven by short telomere length) occurs disproportionately in CD8 + T-cells. To date, only one study has investigated associations between sleep and telomere length in sorted immune cells [59]. In this regard, in a study of 87 obese women, poorer overall sleep quality, as measured using the Pittsburgh Sleep Quality Index, was significantly associated with shorter immune cell telomere length in CD8 + and CD4 + T-cells, but not in B-cells or granulocytes. Self-reported sleep duration, obtained by sleep diary, was not associated with telomere length in any immune cell subset.

Finally, one study has examined the influence of sleep loss on signaling pathways active within senescent immune cells, including the transcription of the SASP pathway and the expression of p16^{INK4a}, a marker of cellular senescence. Here, Carroll and colleagues found that a night of partial sleep deprivation (i.e., sleep opportunity from 3 to 7:00 a.m.) was associated with an upregulation in gene expression of SASP genes and senescent marker p16^{INK4a} in PBMCs compared to an undisturbed night of sleep [60]. These data raise the possibility that acute sleep loss may drive immune cells toward senescence, though this needs to be examined more comprehensively.

Summary. Accumulating evidence points to the role of sleep in the development and progression of age-related diseases, many of which include alterations in immune functioning. As such, it should not be surprising that poor sleep is associated with markers of immunosenescence. Short sleep duration and poor sleep quality predict shorter immune cell telomere length in several studies. The same can be said for sleep disorders like OSA and insomnia. To date, however, studies of sleep and telomere length have been cross-sectional and prospective designs are needed to determine whether poor sleep promotes accelerated telomere attrition. It should be noted that senescent cells, by their very nature, are inflammatory and also implicated in compromised acquired immunity (e.g., vaccination efficacy), which raises the possibility that accelerated immunosenescence may serve as a pathway through which poor sleep may contribute to inflammatory and infectious immune-related outcomes.

Beyond sleep: Does stress influence immunity?

As will be reviewed below, sleep and stress are bidirectionally linked. Moreover, stress is associated with alterations in immunity. While a comprehensive review of the stress-immunity literature is beyond the scope of this chapter, what is striking is that many of the findings replete in the psychological stress-immunity literature parallel those observed studies of habitual short sleep duration, sleep disturbance, and laboratory studies employing acute sleep loss [8]. With regards to acquired immunity, higher perceptions of psychological stress as well as a greater number of stressful life events (i.e., exposures to stress) have been associated with increased susceptibility to infectious illness using the same experimental viral challenge paradigm described above [61,62]. Moreover, higher levels of stress, particularly when it is chronic, are associated with impaired vaccination response [63,64]. Higher stress is also associated with increased likelihood of reactivation of latent viruses (e.g., herpes), which is typically attributed to an inability of the acquired immune system to keep the

virus dormant, as well as impaired wound healing [65]. Laboratory paradigms that employ acute stress exposure, such as having a participant give a speech in front of harsh evaluators, provides an ideal context to investigate how acute bouts of stress modulate immunity. Again, similar to what is seen under periods of sleep loss, acute laboratory stress results in redistribution of immune cells in peripheral circulation as well as an impairment in the ability of T-cells to proliferate when challenged [66,67].

The innate immune system is also affected by stress. For instance, chronic stress has been associated with enhanced levels of inflammation and impairments in NK cell activity [68,69]. There is also consistent evidence that chronic stress, such as serving as a caregiver, is associated with an upregulation in inflammatory genes as well as a downregulation in neuroendocrine pathways that regulate inflammatory activity [70]. Moreover, a recent meta-analysis demonstrated that acute laboratory stress produces consistent stress-related increases in cellular production and circulating levels of several markers of systemic inflammation, including IL-6, TNF- α , and IL-1 β [71].

Finally, in contrast to the limited data on sleep and markers of immunological aging, much more work has been done on the influence of psychological stress. For example, Epel and colleagues provided the first evidence that greater perceptions of stress were associated with shorter immune cell telomere length [72]. Since this seminal study, several meta-analytic reviews have supported that higher levels of psychological stress are associated with shorter telomere length [73]. In addition, there is some compelling evidence that stress exposures, in both early life and adulthood, can predict accelerated telomere attrition over time [74,75].

Summary. The influence of psychological stress on the immune system is well documented, with many of the findings mirroring those observed in the sleep literature, including impairments in acquired (e.g., vaccination efficacy) and innate (e.g., NK cell cytotoxicity) immunity, as well as an upregulation in inflammation.

Sleep and psychological stress: Reciprocal processes

Sleep and psychological stress are bidirectionally linked, where daytime stressors affect one's ability to sleep soundly and poor sleep affects how one responds to the hassles of the day. With respect to the former (i.e., stress affecting sleep), this is no better example than when one considers insomnia. Indeed, stressful life events are routinely identified as precipitating factors in 3P model of insomnia [76], and there is strong evidence that stress exposures often precede insomnia onset [77]. For example,

Drake and colleagues prospectively examined whether presence of stressful life events over the past year predicted incidence of insomnia 1-year later in a sample of >2000 participants free of insomnia and other comorbid psychiatric illnesses at baseline. Analyses revealed that more stressful life events predicted greater likelihood of insomnia, with a 13% increase risk of insomnia for every additional stressor reported [78]. Notably, stressors do not always lead to insomnia but may be more likely among those who tend to experience hyperarousal or vigilance in response to stress. In this regard, in the same study described above, Drake and colleagues found that participants who had a propensity for sleep disturbance in response to stress (known as sleep reactivity) were more likely to experience insomnia in the future, and this was particularly true among participants who also reported more stress exposures.

In contrast to research examining the role of stress in promoting poor sleep, literature on how poor sleep influences an individual's perception and response to stress is less well developed [79]. One of the challenges inherent in incorporating stress into sleep research is the variability in which the term "stress" is used across disciplines [80]. In an effort to provide a model for testing how sleep influences the experience of stress (Table 27.1), it is important to first separate the stress process from the stress exposure (i.e., a stressor). The stress process can be further partitioned into (1) psychological appraisal of the stressor (i.e., evaluation of whether the stressor is demanding and beyond one's ability to effectively cope [81]), (2) response, including one's affective (i.e., emotional) and physiological reactivity to the stressor, and (3) recovery, including how long one's affective or physiological response lasts following the cessation of the stressor. Though not part of the stress process per se, it is likely that sleep can influences one's situation selection (i.e., the tendency to select into situations where a stressor is more likely to occur).

What is the evidence that sleep can influence the stress process? First starting with situation selection, Gordon and Chen provide some intriguing evidence using romantic couples. In this regard, they found that a poor night of sleep increased the likelihood of an interpersonal conflict (e.g., a stress exposure) within the couple the following day [82]. With respect to the stress process, much of the evidence comes from experimental studies of sleep loss. For example, Dinges and colleagues demonstrated that a night of sleep loss led participants to subjectively report more perceived stress in response to a task than under non-sleep-deprived conditions [83]. This raises the possibility that sleep loss may lower one's threshold for what is perceived as stressful (i.e., appraisal). There is also compelling evidence when it comes to physiological responses to stress. In a seminal study, Walker and colleagues reported that a

TABLE 27.1 Proposed ways in which poor sleep can affect experiences of daily stress.

	Stress process		
Situation selection	Appraisal	Reactivity	Recovery
<ul style="list-style-type: none"> Increased likelihood of stress exposure (e.g., interpersonal stress, accident) 	<ul style="list-style-type: none"> Increase allocation of attention to negative stimuli/threat Tendency to appraise exposure as more threatening/stressful 	<ul style="list-style-type: none"> Greater affective and physiologic reactivity to stress exposure 	<ul style="list-style-type: none"> Prolonged physiologic arousal Tendency toward maladaptive cognitive strategies (e.g., rumination)

night of sleep loss produced greater amygdala activity in response to threatening stimuli compared to an undisturbed sleep control condition [84]. Similarly, Franzen and colleagues found that compared to undisturbed sleep, a night of sleep loss produced greater blood pressure reactivity to a standardized acute laboratory stressor [85].

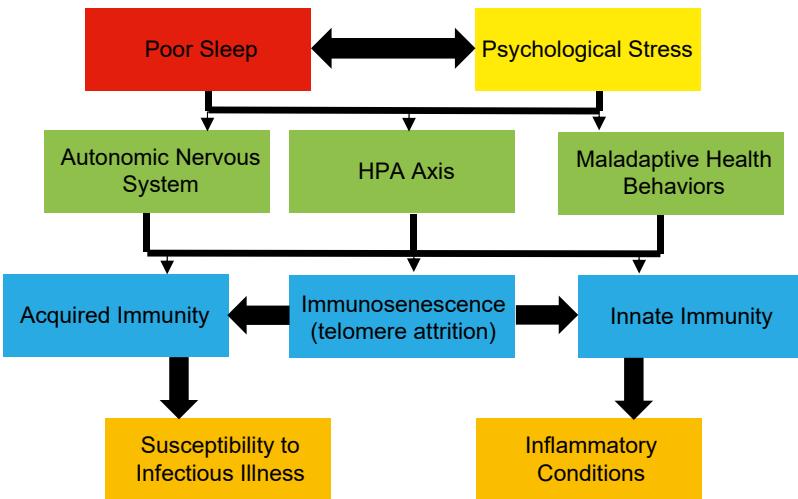
How does poor sleep and psychological stress affect immunity?

As displayed in Fig. 27.2, there are a number of pathways through which poor sleep and psychological stress can affect immunity. The immune system is strongly regulated by outputs from the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. The ANS is composed of the sympathetic (SNS), parasympathetic (PNS), and enteric nervous system, though much of the research on ANS and immunity in humans has focused exclusively on the SNS and PNS. Catecholamines, norepinephrine and epinephrine, bind to adrenergic receptors on immune cells to influence function. In addition, sympathetic nerve fibers directly innervate lymphoid

organs, modulating immunity. Sympathetic activation is routinely observed with acute bouts of stress, while decreases in SNS and a related increase in PNS are observed during sleep. In disrupted sleep, there is evidence of increased SNS activity. For instance, patients with insomnia are often characterized by hypervigilance, including enhanced SNS activation. Similarly, even short bouts of sleep loss are associated with increased SNS in some but not all studies [86]. As such, immune changes observed during stress and sleep may be due in part to alterations in SNS activity. There is growing evidence that the PNS, and its substrate acetylcholine, play an important role in regulating inflammatory activity [87,88]. PNS activity is reduced both under stress and poor sleep, suggesting that inflammatory activity may be dysregulated in part due to alterations in both SNS and PNS.

The HPA axis is another canonical biological pathway engaged by acute psychological stress and often disturbed by poor sleep. The primary output of the HPA axis is the hormone cortisol, which is a glucocorticoid that plays a central role in modulating acquired and innate immunity. In particular, cortisol regulates inflammation by

FIGURE 27.2 Pathways through which poor sleep and psychological stress may increase one's susceptibility to infectious illness and inflammatory conditions.



downregulating inflammatory gene expression within the cell. However, under chronic stress, immune cells become resistant to the antiinflammatory effects of cortisol, rendering inflammatory functioning unchecked [89]. It is unclear whether prolonged sleep disturbance promotes a similar phenomenon but is certainly an area of worthy investigation. Insomnia has been shown to be related to elevated levels of cortisol [86,90], which may accumulate over the 24-h period [44]. In addition, patients with insomnia show alterations in the diurnal rhythm of cortisol compared to participants without insomnia [91]. Cortisol is also implicated in regulating nocturnal immunity, including the movement of immune cells from the bone marrow into circulation and on into lymphoid organs [31]. Thus, nocturnal immunity, and possibly host resistance to infection, could be altered to the extent that sleep disruption alters cortisol rhythms. Finally, there is some basic science data to suggest that cortisol also plays a role in accelerating telomere attrition. Indeed, T-cells treated *in vitro* with cortisol show a downregulation in telomerase activity, which is the enzyme charged with maintaining telomere integrity [92].

In addition to biological mechanisms, maladaptive health behaviors, such as tobacco smoke exposure, insufficient physical activity, excess alcohol consumption, illicit drug use, and poor nutrition can be pathways toward impaired immune functioning. The engagement in such behaviors may serve as coping mechanisms for individuals under prolonged stress or sleep loss. Furthermore, many of these behaviors (e.g., excess alcohol consumption [93]) can directly impair sleep quality, thus perpetuating the cycle between sleep and stress.

Stress–sleep connection and immunity

The parallels between poor sleep and stress on immunity beg the question of whether there may be synergistic effects worth investigation. To date, research in this area has been limited, which is unfortunate because the sleep–stress connection presents important intervention opportunities. For example, sleep interventions such as sleep extension or behavioral treatments for insomnia (e.g., CBTI) may not only lead to better sleep but could have “spillover” effects on one’s capacity to better regulate negative emotions in response to stress exposure. Similarly, stress reduction programs (e.g., mindfulness-based stress reduction) may not only improve one’s experiences of stress but also lead to more restful, consolidated sleep. Moreover, either target (stress or sleep) may confer salubrious effects on immunity.

Though interventions have not been tested to date, the few studies that have examined the synergistic effects of sleep and stress on immunity are promising. In this regard,

two studies have examined whether global sleep quality modulated increases in circulating levels of IL-6 in response in healthy adults exposed to an acute laboratory stressor [94,95]. In both cases, poorer overall sleep quality was associated with stronger inflammatory responses to the acute stressors. Synergistic effects have also been observed in the context of infectious disease risk. Prather and colleagues, using the cold study paradigm described above, found in a sample of over 700 participants that shorter self-reported sleep duration predicted who went on to develop a biologically verified cold following inoculation with the cold virus. However, this association was only true among individuals who reported average or below average subjective socioeconomic status (SES) [17]. While not a commonly used measure of psychological stress, subjective SES may reflect the chronic burden of feeling “lesser” compared to others. This is speculative but is consistent with other literature that finds that lower subjective SES predicts increased rates of diseases routinely observed at higher rates among those experiencing elevated levels of stress [96,97]. Finally, one study reported an interaction between global sleep quality and perceived stress in predicting immune cell telomere length, such that the relationship between poorer overall sleep and shorter telomere length was significantly stronger participants who also reported higher levels psychological stress. Moreover, sleep quality was unrelated to telomere length in participants reporting lower levels of psychological stress [59].

Conclusion

Poor sleep and psychological stress are associated with alterations in immune system functioning that can have important implications for the development and progression of many age-related conditions. While efforts within the areas of basic and translational science have focused on the independent effects of sleep and stress on immunity, there is a significant gap in our understanding of the interactions between the two. As was highlighted above, there are parallels regarding the influence of sleep and stress on immunity as well as obvious shared biological and behavioral pathways. Furthermore, there are exciting opportunities for employing interventions that may take advantage of the reciprocal links between sleep and stress and produce important benefits for immune health. From a population health perspective, it is clear that stress exposures and sleep disturbances are not evenly distributed across the population. As such, there is a pressing need to better understand these bidirectional processes so that more appropriate interventions can help those at greatest risk for infectious and inflammatory conditions as well as diseases associated with immunosenescence.

References

- [1] Buysse DJ. Sleep health: can we define it? Does it matter? *Sleep* 2014;37(1):9–17. <https://doi.org/10.5665/sleep.3298>.
- [2] Luyster FS, Strollo PJ, Zee PC, Walsh JK. Sleep: a health imperative. *Sleep* 2012;35(6):727–34. <https://doi.org/10.5665/sleep.1846>.
- [3] Cappuccio FP, Cooper D, Delia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011;32(12):1484–92. <https://doi.org/10.1093/euroheartj/ehr007>.
- [4] Cappuccio FP, D’Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep* 2010;33(5):585–92. <https://doi.org/10.1093/sleep/33.5.585>.
- [5] Cappuccio FP, D’Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33(2):414–20. <https://doi.org/10.2337/dc09-1124>.
- [6] Watson NF, et al. Recommended amount of sleep for a healthy adult: A joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep* 2015;38(6):843–4. <https://doi.org/10.5665/sleep.4716.15509109>.
- [7] Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. *Annu Rev Psychol* 2015;66:143–72. <https://doi.org/10.1146/annurev-psych-010213-115205>.
- [8] Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004;130(4):601–30. <https://doi.org/10.1037/0033-2959.130.4.601>.
- [9] Medzhitov R. Toll-like receptors and innate immunity. *Nat Rev Immunol* 2001;1(2):135–45. <https://doi.org/10.1038/35100529>.
- [10] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association. *Circulation* 2003;107(3):499–511. <https://doi.org/10.1161/01.CIR.0000052939.59093.45>.
- [11] Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol Series A: Biol Sci Med Sci* 2014;69(Suppl. 1):S4. <https://doi.org/10.1093/gerona/glu057>.
- [12] Baker DJ, Wijshake T, Tchkonia T, Lebrasseur NK, Childs BG, Van De Sluis B, Kirkland JL, Van Deursen JM. Clearance of p16 Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* 2011;479(7372):232–6. <https://doi.org/10.1038/nature10600>.
- [13] Opp MR, Born J, Irwin MR. Sleep and the immune system. *Psychoneuroimmunology* 2007;1:579–618. <https://doi.org/10.1016/B978-012088576-3/50034-4>.
- [14] Prather AA, Leung CW. Association of insufficient sleep with respiratory infection among adults in the United States. *JAMA Intern Med* 2016;176(6):850–2. <https://doi.org/10.1001/jamainternmed.2016.0787>.
- [15] Patel SR, Malhotra A, Gao X, Hu FB, Neuman MI, Fawzi WW. A prospective study of sleep duration and pneumonia risk in women. *Sleep* 2012;35(1):97–101. <https://doi.org/10.5665/sleep.1594>.
- [16] Cohen S, Doyle WJ, Alper CM, Janicki-Deverts D, Turner RB. Sleep habits and susceptibility to the common cold. *Arch Intern Med* 2009;169(1):62–7. <https://doi.org/10.1001/archinternmed.2008.505>.
- [17] Prather AA, Janicki-Deverts D, Adler NE, Hall M, Cohen S. Sleep habits and susceptibility to upper respiratory illness: the moderating role of subjective socioeconomic status. *Ann Behav Med* 2017;51(1):137–46. <https://doi.org/10.1007/s12160-016-9835-3>.
- [18] Prather AA, Janicki-Deverts D, Hall MH, Cohen S. Behaviorally assessed sleep and susceptibility to the common cold. *Sleep* 2015;38(9):1353–9. <https://doi.org/10.5665/sleep.4968>.
- [19] Doyle WJ, McBride TP, Skoner DP, Maddern BR, Gwaltney JM, Uhrin M. A double-blind, placebo-controlled clinical trial of the effect of chlorpheniramine on the response of the nasal airway, middle ear and eustachian tube to provocative rhinovirus challenge. *Pediatr Infect Dis J* 1988;7(3):229–38. <https://doi.org/10.1097/00006454-198803000-00033>.
- [20] Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Social ties and susceptibility to the common cold. *JAMA* 1997;277(24):1940–4. <https://doi.org/10.1001/jama.277.24.1940>.
- [21] Benedict C, Brytting M, Markström A, Broman JE, Schiöth HB. Acute sleep deprivation has no lasting effects on the human antibody titer response following a novel influenza A H1N1 virus vaccination. *BMC Immunol* 2012;13. <https://doi.org/10.1186/1471-2172-13-1Sweden>.
- [22] Lange T, Dimitrov S, Bollinger T, Diekelmann S, Born J. Sleep after vaccination boosts immunological memory. *J Immunol* 2011;187(1):283–90. <https://doi.org/10.4049/jimmunol.1100015>.
- [23] Lange T, Perras B, Fehm HL, Born J. Sleep enhances the human antibody response to hepatitis A vaccination. *Psychosom Med* 2003;65(5):831–5. <https://doi.org/10.1097/01.PSY.0000091382.61178.F1>.
- [24] Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. *JAMA* 2002;288(12):1471–2. <https://doi.org/10.1001/jama.288.12.1469>.
- [25] Prather AA, Hall M, Fury JM, Ross DC, Muldoon MF, Cohen S, Marsland AL. Sleep and antibody response to hepatitis B vaccination. *Sleep* 2012;35(8):1063–9. <https://doi.org/10.5665/sleep.1990>.
- [26] Taylor DJ, Kelly K, Kohut ML, Song KS. Is insomnia a risk factor for decreased influenza vaccine response? *Behav Sleep Med* 2017;15(4):270–87. <https://doi.org/10.1080/15402002.2015.1126596>.
- [27] Bollinger T, Bollinger A, Skrum L, Dimitrov S, Lange T, Solbach W. Sleep-dependent activity of T cells and regulatory T cells. *Clin Exp Immunol* 2009;155(2):231–8. <https://doi.org/10.1111/j.1365-2249.2008.03822.x>.
- [28] Besedovsky L, Lange T, Born J. Sleep and immune function. *Pflueg Arch Eur J Physiol* 2012;463(1):121–37. <https://doi.org/10.1007/s00424-011-1044-0>.
- [29] Born J, Lange T, Hansen K, Mölle M, L Fehm H. Effects of sleep and circadian rhythm on human circulating immune cells. *J Immunol* 1997;158(9):4454–64. <https://doi.org/10.4049/jimmunol.158.9.4454>.
- [30] Born J, Uthgenannt D, Dodt C, Nünninghoff D, Ringvolt E, Wagner T, Fehm H-L. Cytokine production and lymphocyte subpopulations in aged humans. An assessment during nocturnal sleep. *Mech Ageing Dev* 1995;84(2):113–26. [https://doi.org/10.1016/0047-6374\(95\)01638-4](https://doi.org/10.1016/0047-6374(95)01638-4).
- [31] Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. *Ann N Y Acad Sci* 2010;1193(1):48–59. <https://doi.org/10.1111/j.1749-6632.2009.05300.x>.
- [32] Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating human antigen presenting cells regulated by sleep. *Sleep* 2007;30(4):401–11. <https://doi.org/10.1093/sleep/30.4.401>.

- [33] Irwin M, Mascovich A, C Gillin J, Willoughby R, Pike J, L Smith T. Partial sleep deprivation reduces natural killer cell activity in humans. *Psychosom Med* 1994;56(6):493–8. <https://doi.org/10.1097/00006842-199411000-00004>.
- [34] Irwin M, Mcclintick J, Costlow C, Fortner M, White J, Christian Gillin J. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *FASEB (Fed Am Soc Exp Biol) J* 1996;10(5):643–53. <https://doi.org/10.1096/fasebj.10.5.8621064>.
- [35] Medzhitov R. Origin and physiological roles of inflammation. *Nature* 2008;454(7203):428–35. <https://doi.org/10.1038/nature07201>.
- [36] Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry* 2016;80(1):40–52. <https://doi.org/10.1016/j.biopsych.2015.05.014>.
- [37] Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med* 2006;166(16):1756–62. <https://doi.org/10.1001/archinte.166.16.1756>.
- [38] Irwin MR, Carrillo C, Olmstead R. Sleep loss activates cellular markers of inflammation: sex differences. *Brain Behav Immun* 2010;24(1):54–7. <https://doi.org/10.1016/j.bbi.2009.06.001>.
- [39] Irwin MR, Wang M, Ribeiro D, Cho HJ, Olmstead R, Breen EC, Martinez-Maza O, Cole S. Sleep loss activates cellular inflammatory signaling. *Biol Psychiatry* 2008;64(6):538–40. <https://doi.org/10.1016/j.biopsych.2008.05.004>.
- [40] Irwin MR, Witarama T, Caudill M, Olmstead R, Breen EC. Sleep loss activates cellular inflammation and signal transducer and activator of transcription (STAT) family proteins in humans. *Brain Behav Immun* 2015;47:86–92. <https://doi.org/10.1016/j.bbi.2014.09.017>.
- [41] Burgos I, Richter L, Klein T, Fiebich B, Feige B, Lieb K, Voderholzer U, Riemann D. Increased nocturnal interleukin-6 excretion in patients with primary insomnia: a pilot study. *Brain Behav Immun* 2006;20(3):246–53. <https://doi.org/10.1016/j.bbi.2005.06.007>.
- [42] Song C, et al. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J Affect Disord* 1998;49(3):211–9. [https://doi.org/10.1016/s0165-0327\(98\)00025-1](https://doi.org/10.1016/s0165-0327(98)00025-1).
- [43] Okun ML, Reynolds CF, Buysse DJ, Monk TH, Mazumdar S, Begley A, Hall M. Sleep variability, health-related practices, and inflammatory markers in a community dwelling sample of older adults. *Psychosom Med* 2011;73(2):142–50. <https://doi.org/10.1097/PSY.0b013e3182020d08>.
- [44] Vgontzas AN, Tsigos C, Bixler EO, Stratakis CA, Zachman K, Kales A, Vela-Bueno A, Chrousos GP. Chronic insomnia and activity of the stress system: a preliminary study. *J Psychosom Res* 1998;45(1):21–31. [https://doi.org/10.1016/S0022-3999\(97\)00302-4](https://doi.org/10.1016/S0022-3999(97)00302-4).
- [45] Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev* 2013;17(4):241–54. <https://doi.org/10.1016/j.smrv.2012.09.005>.
- [46] Fernandez-Mendoza J, Baker JH, Vgontzas AN, Gaines J, Liao D, Bixler EO. Insomnia symptoms with objective short sleep duration are associated with systemic inflammation in adolescents. *Brain Behav Immun* 2017;61:110–6. <https://doi.org/10.1016/j.bbi.2016.12.026>.
- [47] Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Breen EC, Witarama T, Yokomizo M, Lavretsky H, Carroll JE, Motivala SJ, Bootzin R, Nicassio P. Cognitive behavioral therapy vs. Tai Chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. *Sleep* 2014;37(9):1543–52. <https://doi.org/10.5665/sleep.4008>.
- [48] Irwin MR, Olmstead R, Breen EC, Witarama T, Carrillo C, Sadeghi N, Arevalo JMG, Ma J, Nicassio P, Ganz PA, Bower JE, Cole S, Chi Tai. Cellular inflammation, and transcriptome dynamics in breast cancer survivors with insomnia: a randomized controlled trial. *J Nat Cancer Inst Monogr* 2014;2014(50):295–301. <https://doi.org/10.1093/jncimonographs/lgu028>.
- [49] Prather AA, Puterman E, Lin J, O'Donovan A, Krauss J, Tomiyama AJ, Epel ES, Blackburn EH. Shorter leukocyte telomere length in midlife women with poor sleep quality. *J Aging Res* 2011;2011. <https://doi.org/10.4061/2011/721390>.
- [50] Lee KA, Gay C, Humphreys J, Portillo CJ, Pullinger CR, Aouizerat BE. Telomere length is associated with sleep duration but not sleep quality in adults with human immunodeficiency virus. *Sleep* 2014;37(1):157–66. <https://doi.org/10.5665/sleep.3328>.
- [51] Liang G, et al. Associations between rotating night shifts, sleep duration, and telomere length in women. *PLoS One* 2011;6(8):e23462. <https://doi.org/10.1371/journal.pone.0023462>.
- [52] Jackowska M, et al. Short sleep duration is associated with shorter telomere length in healthy men: findings from the whitehall II cohort study. *PLoS One* 2012;7(10):e47292. <https://doi.org/10.1371/journal.pone.0047292>.
- [53] Tempaku PF, Mazzotti DR, Tufik S. Telomere length as a marker of sleep loss and sleep disturbances: a potential link between sleep and cellular senescence. *Sleep Med* 2015;16(5):559–63. <https://doi.org/10.1016/j.sleep.2015.02.519>.
- [54] Huang P, et al. The association between obstructive sleep apnea and shortened telomere length: a systematic review and meta-analysis. *Sleep Med* 2018;48:107–12. <https://doi.org/10.1016/j.sleep.2017.09.034>.
- [55] Garland SN, Palmer C, Donelson M, Gehrmann P, Johnson FB, Mao JJ. A nested case-controlled comparison of telomere length and psychological functioning in breast cancer survivors with and without insomnia symptoms. *Rejuvenation Res* 2014;17(5):453–7. <https://doi.org/10.1089/rej.2014.1586>.
- [56] Carroll JE, Esquivel S, Goldberg A, Seeman TE, Effros RB, Dock J, Olmstead R, Breen EC, Irwin MR. Insomnia and telomere length in older adults. *Sleep* 2016;39(3):559–64. <https://doi.org/10.5665/sleep.5526>.
- [57] Lin J, Epel E, et al. Analyses and comparisons of telomerase activity and telomere length in human T and B cells: insights for epidemiology of telomere maintenance. *J Immunol Methods* 2010;352(1–2):71–80. <https://doi.org/10.1016/j.jim.2009.09.012>.
- [58] Lin J, et al. Systematic and cell type-specific telomere length changes in subsets of lymphocytes. *J Immunol Res* 2016;2016:1–9. <https://doi.org/10.1155/2016/5371050>.
- [59] Prather AA, Gurfein B, Moran P, Daubenmier J, Acree M, Bacchetti P, Sinclair E, Lin J, Blackburn E, Hecht FM, Epel ES. Tired telomeres: poor global sleep quality, perceived stress, and telomere length in immune cell subsets in obese men and women. *Brain Behavior Immunity* 2015;47:155–62. <https://doi.org/10.1016/j.bbi.2014.12.011>.

- [60] Carroll JE, Cole SW, Seeman TE, Breen EC, Witarama T, Arevalo JMG, Ma J, Irwin MR. Partial sleep deprivation activates the DNA damage response (DDR) and the senescence-associated secretory phenotype (SASP) in aged adult humans. *Brain Behav Immun* 2016;51:223–9. <https://doi.org/10.1016/j.bbi.2015.08.024>.
- [61] Cohen S, Doyle WJ, Skoner DP, Frank E, Rabin BS, Gwaltney JM. Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychol* 1998;17(3):214–23. <https://doi.org/10.1037/0278-6133.17.3.214>.
- [62] Cohen S, Williamson GM. Stress and infectious disease in humans. *Psychol Bull* 1991;109(1):5–24. <https://doi.org/10.1037/0033-2909.109.1.5>.
- [63] Burns VE, Carroll D, Ring C, Drayson M. Antibody response to vaccination and psychosocial stress in humans: relationships and mechanisms. *Vaccine* 2003;21(19–20):2523–34. [https://doi.org/10.1016/S0264-410X\(03\)00041-0](https://doi.org/10.1016/S0264-410X(03)00041-0).
- [64] Cohen S, Miller GE, Rabin BS. Psychological stress and antibody response to immunization: a critical review of the human literature. *Psychosom Med* 2001;63(1):7–18. <https://doi.org/10.1097/00006842-200101000-00002>.
- [65] Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. *Nat Rev Immunol* 2005;5(3):243–51. <https://doi.org/10.1038/nri1571>.
- [66] Marsland AL, Muldoon MF, Cohen S, Herbert TB, Bachen EA, Patterson S, Rabin B, Manuck SB. Lymphocyte subset redistribution during acute laboratory stress in young adults: mediating effects of hemoconcentration. *Health Psychol* 1997;16(4):341–8. <https://doi.org/10.1037/0278-6133.16.4.341>.
- [67] Marsland AL, Kuan DCH, Sheu LK, Krajina K, Kraynak TE, Manuck SB, Gianaros PJ. Systemic inflammation and resting state connectivity of the default mode network. *Brain Behav Immun* 2017;62:162–70. <https://doi.org/10.1016/j.bbi.2017.01.013>.
- [68] Wyman PA, Moynihan J, Eberly S, Cox C, Cross W, Jin X, Caserta MT. Association of family stress with natural killer cell activity and the frequency of illnesses in children. *Arch Pediatr Adolesc Med* 2007;161(3):228–34. <https://doi.org/10.1001/archpedi.161.3.228>.
- [69] Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U.S.A* 2003;100(15):9090–5. <https://doi.org/10.1073/pnas.1531903100>.
- [70] Miller GE, Chen E, Sze J, Marin T, Arevalo JMG, Doll R, Ma R, Cole SW. A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-κB signaling. *Biol Psychiatry* 2008;64(4):266–72. <https://doi.org/10.1016/j.biopsych.2008.03.017>.
- [71] Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. *Brain Behav Immun* 2017;64:208–19. <https://doi.org/10.1016/j.bbi.2017.01.011>.
- [72] Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci USA* 2004;101(49):17312–5. <https://doi.org/10.1073/pnas.0407162101>.
- [73] Mathur MB, Epel E, Kind S, Desai M, Parks CG, Sandler DP, Khazeni N. Perceived stress and telomere length: a systematic review, meta-analysis, and methodologic considerations for advancing the field. *Brain Behav Immun* 2016;54:158–69. <https://doi.org/10.1016/j.bbi.2016.02.002>.
- [74] Shalev I, Entringer S, Wadhwa PD, Wolkowitz OM, Puterman E, Lin J, Epel ES. Stress and telomere biology: a lifespan perspective. *Psychoneuroendocrinology* 2013;38(9):1835–42. <https://doi.org/10.1016/j.psyneuen.2013.03.010>.
- [75] Puterman E, Gemmill A, Karasek D, Weir D, Adler NE, Prather AA, Epel ES. Lifespan adversity and later adulthood telomere length in the nationally representative US Health and Retirement Study. *Proc Natl Acad Sci USA* 2016;113(42):E6335. <https://doi.org/10.1073/pnas.1525602113>.
- [76] Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. *Psychiatr Clin* 1987;10(4):541–53. [https://doi.org/10.1016/s0193-953x\(18\)30532-x](https://doi.org/10.1016/s0193-953x(18)30532-x).
- [77] Drake CL, Roehrs T, Roth T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiety* 2003;18(4):163–76. <https://doi.org/10.1002/da.10151>.
- [78] Drake CL, Pillai V, Roth T. Stress and sleep reactivity: a prospective investigation of the stress-diathesis model of insomnia. *Sleep* 2014;37(8):1295–304. <https://doi.org/10.5665/sleep.3916>.
- [79] Gordon AM, Mendes WB, Prather AA. The social side of sleep: elucidating the links between sleep and social processes. *Curr Dir Psychol Sci* 2017;26(5):470–5. <https://doi.org/10.1177/0963721417712269>.
- [80] Epel ES, Crosswell AD, Mayer SE, Prather AA, Slavich GM, Puterman E, Mendes WB. More than a feeling: a unified view of stress measurement for population science. *Front Neuroendocrinol* 2018;49:146–69. <https://doi.org/10.1016/j.yfrne.2018.03.001>.
- [81] Lazarus FS. Stress, appraisal and coping. Springer; 1984. p. 1984.
- [82] Gordon AM, Chen S. The role of sleep in interpersonal conflict: do sleepless nights mean worse fights? *Soc Psychol Personal Sci* 2014;5(2):168–75. <https://doi.org/10.1177/1948550613488952>.
- [83] Minkel JD, Banks S, Htaik O, Moreta MC, Jones CW, McGlinchey EL, Simpson NS, Dinges DF. Sleep deprivation and stressors: evidence for elevated negative affect in response to mild stressors when sleep deprived. *Emotion* 2012;12(5):1015–20. <https://doi.org/10.1037/a0026871>.
- [84] Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep - a prefrontal amygdala disconnect. *Curr Biol* 2007;17(20):R877. <https://doi.org/10.1016/j.cub.2007.08.007>.
- [85] Franzen PL, Gianaros PJ, Marsland AL, Hall MH, Siegle GJ, Dahl RE, Buysse DJ. Cardiovascular reactivity to acute psychological stress following sleep deprivation. *Psychosom Med* 2011;73(8):679–82. <https://doi.org/10.1097/PSY.0b013e31822ff440>.
- [86] Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Med Rev* 2008;12(3):197–210. <https://doi.org/10.1016/j.smrv.2007.07.007>.
- [87] Pavlov VA, Tracey KJ. Neural regulators of innate immune responses and inflammation. *Cell Mol Life Sci* 2004;61(18):2322–31. <https://doi.org/10.1007/s00018-004-4102-3>.
- [88] Tracey KJ. The inflammatory reflex. *Nature* 2002;420(6917):853–9. <https://doi.org/10.1038/nature01321>.
- [89] Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychol* 2002;21(6):531–41. <https://doi.org/10.1037/0278-6133.21.6.531>.

- [90] Meerlo P, Koehl M, Van Der Borght K, Turek FW. Sleep restriction alters the hypothalamic-pituitary-adrenal response to stress. *J Neuroendocrinol* 2002;14(5):397–402. <https://doi.org/10.1046/j.0007-1331.2002.00790.x>.
- [91] Backhaus J, Junghanns Klaus, Hohagen Fritz. Sleep disturbances are correlated with decreased morning awakening salivary cortisol. *Psychoneuroendocrinology* 2004;29(9):1184–91. <https://doi.org/10.1016/j.psyneuen.2004.01.010>.
- [92] Choi J, Fauci SR, Effros RB. Reduced telomerase activity in human T lymphocytes exposed to cortisol. *Brain Behav Immun* 2008;22(4):600–5. <https://doi.org/10.1016/j.bbi.2007.12.004>.
- [93] Redwine L, Dang J, Hall M, Irwin M. Disordered sleep, nocturnal cytokines, and immunity in alcoholics. *Psychosom Med* 2003;65(1):75–85. <https://doi.org/10.1097/01.psy.0000038943.33335.d2>.
- [94] Heffner KL, Ng HM, Suhr JA, France CR, Marshall GD, Pigeon WR, Moynihan JA. Sleep disturbance and older adults' inflammatory responses to acute stress. *Am J Geriatr Psychiatr* 2012;20(9):744–52. <https://doi.org/10.1097/JGP.0b013e31824361de>.
- [95] Prather AA, Puterman E, Epel ES, Dhabhar FS. Poor sleep quality potentiates stress-induced cytokine reactivity in postmenopausal women with high visceral abdominal adiposity. *Brain Behav Immun* 2014;35:155–62. <https://doi.org/10.1016/j.bbi.2013.09.010>.
- [96] Adler NE, Boyce T, Chesney MA, Cohen S, Folkman S, Kahn RL, Syme SL. Socioeconomic status and health: the challenge of the gradient. *Am Psychol* 1994;49(1):15–24. <https://doi.org/10.1037/003-066X.49.1.15>.
- [97] Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. *JAMA* 2007;298(14):1685–7. <https://doi.org/10.1001/jama.298.14.1685>.

This page intentionally left blank

Part VI

Sleep and brain health

This page intentionally left blank

Chapter 28

Sleep loss and impaired vigilant attention

Mathias Basner

Unit for Experimental Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States

Sleep is found widely throughout the animal kingdom [1]. Although its functions are not fully understood, there is substantial evidence that sleep of sufficient duration and quality is necessary to ensure high levels of waking alertness, attention, and cognitive performance [2–4] and to avoid predisposing humans to adverse health outcomes [5,6]. Despite growing awareness of these negative outcomes [7], surveys indicate that 35%–40% of the adult US population chronically curtail their sleep to < 7 h on weekday nights [8,9], primarily for lifestyle reasons [10,11].

Neurobehavioral consequences of acute and chronic sleep loss

Both acute total deprivation (i.e., a period without any sleep beyond the typical 16 h awake) and chronic partial sleep restriction (i.e., multiple days with reduced sleep duration per 24 h) induce neurobehavioral changes in humans beyond subjective sleepiness, despite motivation to prevent these effects. The most reliable changes include increased lapses of sustained attention (i.e., errors of omission) and compensatory response disinhibition (i.e., errors of commission); psychomotor and cognitive slowing; working memory deficits; slow eyelid closures; and reduced sleep latency [3,4]. Recent publications [12,13] have challenged the claim that sleep loss primarily impairs executive functions and reasoning. High-order cognitive functions can be affected by sleep loss, but these effects are likely mediated by deficits in the ability to sustain wakefulness and attention and to accurately respond in a timely manner. The most sensitive indicators of sleep loss seem to be those that precisely track moment-to-moment changes in neural indicators of state (especially EEG and fMRI) or behavioral markers of the stability of sustained attention, such as the psychomotor vigilance test (PVT).

Studies on the effects of chronic partial sleep restriction and recovery indicate that the mechanisms underlying the dynamic neurobehavioral changes induced by chronic sleep restriction may be fundamentally different from those associated with acute total sleep deprivation [14]. Sleep-dose-response experiments found that chronic restriction of sleep between 3 and 7 h time in bed per 24 h resulted in sleep dose-dependent, near-linear declines in vigilant attention across 7–14 days of sleep restriction, reaching levels that were comparable to 2–3 nights without any sleep [15,16]. The neurobehavioral effects of chronic sleep restriction are modulated by endogenous circadian phase—with the greatest deficits during the circadian night [17–19]. Also, several experiments demonstrate that subjects frequently underestimate sleep loss-related decrements in neurobehavioral performance, especially during the biological night [16,20].

Differential vulnerability to sleep loss

Several studies found trait-like individual differences in the magnitude of neurobehavioral consequences to both acute total [21,22] and to chronic partial sleep deprivation [16,23–25] that were highly replicable, suggesting a polygenic trait. Numerous factors have been investigated as potential predictors of phenotypic vulnerability to sleep loss, but none fully accounts for this phenomenon [26]. A few small studies do suggest that those vulnerable to acute total sleep deprivation may also be vulnerable to chronic partial sleep loss [12,27–30].

Effects of sleep loss on vigilant attention

As mentioned above, there is extensive evidence that the neurobehavioral consequences of sleep loss can be measured in certain aspects of cognitive functioning

[3,4,31]. Among the most reliable effects of sleep deprivation is degradation of attention [3,13], especially vigilant attention as measured by the PVT [2,32]. The effects of sleep loss on PVT performance appear to be due to variability in maintenance of the alert state (i.e., alerting network) [2] and can include deficits in endogenous selective attention [33,34], but they may also occur in attention involved in orienting to sensory events (i.e., orienting network) and attention central to regulating thoughts and behaviors (i.e., executive network) [35–37]. These multidimensional features of attention suggest it has a fundamental role in a wide range of cognitive functions, which may be the mechanisms by which sleep loss affects a range of performances, although it remains controversial whether impairment due to sleep deprivation is generic to all cognitive processes subserved by attentional processes [38].

The psychomotor vigilance test

The PVT [2,39–41] has become arguably the most widely used measure of behavioral alertness owing in large part to the combination of its high sensitivity to sleep deprivation [2,32] and its psychometric advantages over other cognitive tests. The standard 10 min PVT measures sustained or vigilant attention by recording response times (RT) to visual (or auditory) stimuli that occur at random interstimulus intervals (ISI, 2–10 s in the standard 10 min PVT, including a 1 s feedback period during which the RT to the last stimulus is displayed) [32,39,42,43]. It is not entirely accurate to describe the PVT as merely simple RT. The latter is a generic phrase historically used to refer to the measurement of the time it takes to respond to a stimulus with one type of response (in contrast a complex RT task can require different responses to different stimuli). A simple RT test assumes no specific number of RTs—in fact, it can be based on a single RT. Similar to simple RT, the PVT relies on a stimulus (typically visual) and an RT (typically a button press), but it also relies on sampling many responses to stimuli that appear at a random ISI within a prespecified ISI range and that therefore occur over a period of time (i.e., 10 min in terms of the most commonly used PVT). Therefore, time on task and ISI parameterization instantiate the “vigilance” aspect of the PVT. Response time to stimuli attended to has been used since the late 19th century in sleep deprivation research [42,44,45] because it offers a simple way to track changes in behavioral alertness caused by inadequate sleep, without the confounding effects of aptitude and learning [2,32,41,46]. Moreover, the 10 min PVT [39] has been shown to be highly reliable, with intraclass correlations for key metrics such as lapses measuring test-retest reliability above 0.8 [32].

PVT performance also has ecological validity in that it can reflect real-world risks because deficits in sustained

attention and timely reactions adversely affect many applied tasks, especially those in which work-paced or timely responses are essential (e.g., stable vigilant attention is critical for safe performance in all transportation modes, many security-related tasks, and a wide range of industrial tasks). Lapses in attention as measured by the PVT can occur when fatigue is caused by either sleep loss or time on task [42,47,48], which are the two factors that make up virtually all theoretical models of fatigue in real-world performance. There is a large body of literature on attentional deficits having serious consequences in applied settings [49–52].

Sleep deprivation (SD) induces reliable changes in PVT performance, causing an overall slowing of response times, a steady increase in the number of errors of omission (i.e., lapses of attention, historically defined as RTs \geq twice the mean RT or 500 ms), and a more modest increase in errors of commission (i.e., responses without a stimulus, or false starts) [16,53]. These effects can increase as task duration increases (so-called time-on-task effect or vigilance decrement) [54], and they form the basis of the state instability theory (Fig. 28.1) [2,32,39–41,44]. According to this theory, several competing systems influence behavior during periods of sleep loss, two of the most important being the involuntary drive to fall asleep and a counteracting top-down drive to sustain alertness [2]. The interaction of these sleep-initiating and wake-maintaining systems leads to unstable sustained attention as manifested in longer RTs occurring stochastically throughout each PVT performance bout [2,41]. Neuroimaging studies reveal that slowed responses on visual attention tasks—including the PVT—during sleep deprivation are associated with changes in neural activity in distributed brain regions that can include frontal and parietal control regions, visual and insular cortices, cingulate gyrus, and the thalamus [34,55–58].

The 10 min PVT [2,32,39] has been shown to be sensitive to both acute total sleep deprivation (TSD) [16,41,59] and chronic partial sleep deprivation (PSD) [15,16,40,59–61]; to be affected both by sleep homeostatic and circadian drives [62,63]; to reveal large intersubject variability in the response to sleep loss [21,23,64]; to demonstrate the effects of jet lag and shift work [65]; and to reveal improvements in alertness after wake-promoting interventions [66–68] and recovery from sleep loss [69,70] and after initiation of CPAP treatment in patients with obstructive sleep apnea (OSA) [71]. The PVT is often used as a “gold-standard” measure for the neurobehavioral effects of sleep loss, against which other biomarkers or fatigue detection technologies are compared [72,73].

However, despite its simplicity, the complexity of developing a valid and reliable PVT is often underestimated. In contrast to most other cognitive tests, RT shifts of a few milliseconds can be meaningful on the PVT,

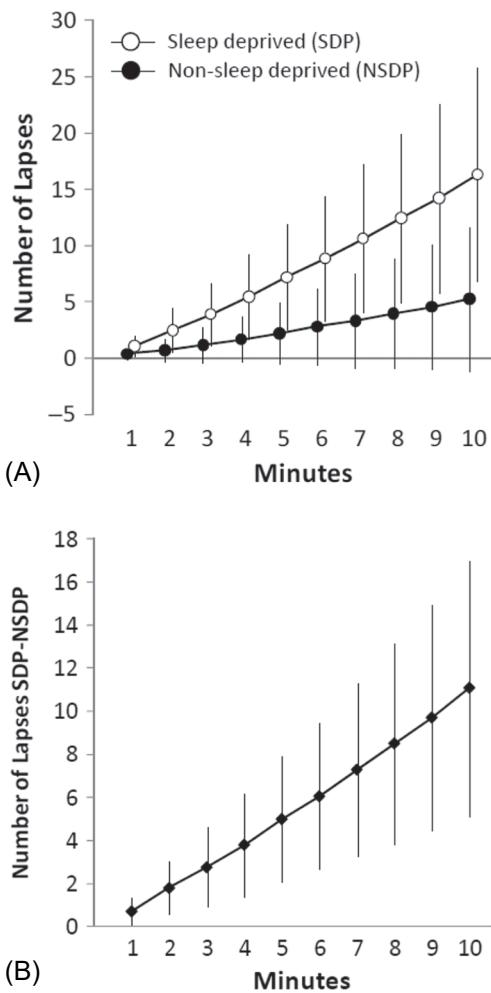


FIGURE 28.1 The analyses shown in (A) and (B) were restricted to the first 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 min of the 10 min PVT (abscissa). (A) The number of lapses and their standard deviation are shown for the sleep deprived and the non-sleep-deprived state. (B) The within-subject differences between sleep deprived and non-sleep-deprived states of the number of lapses, and their standard deviations are shown. Adapted from Basner M, Dinges DF. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. *Sleep* 2011;34(5):581–91.

and it is therefore important to use calibrated software and hardware. This and other caveats are discussed in greater detail below.

PVT software and hardware

Numerous versions of the PVT are available, either commercially or for free, across several hardware platforms. Researchers also frequently program their own version of the PVT. It is therefore unclear how data produced on different versions of the PVT compare across studies. This is especially true for PC-based PVTs [74,75] (that often use a mouse or a keyboard for response input) relative to platforms that use a touchscreen for input (e.g., tablets and

smartphones). For example, both the orientation of a smartphone and the input method (e.g., tapping the screen vs. swiping) have been shown to influence response times [76,77]. Also, each system has a certain response latency, that is, the time it takes for a response (e.g., pushing down the spacebar) to be registered by the system. During calibration, the average response latency is typically determined and then subtracted from response times registered by the system. However, the system latency is typically the result of several serial processes that may sample at different frequencies. Therefore, the variability of response latencies is also critical for the validity of the PVT and should be small [78]. Our research group ran into a problem when switching from a fourth-generation iPad to the iPad Air. With the new hardware iteration, Apple had introduced a new power saving feature. The touchscreen polling rate decreased to $60\text{ Hz} < 2\text{ s}$ after the last touch. This led to a response time binning on the PVT with a bin size of $\sim 17\text{ ms}$. Although dedicated hardware versions like the PVT-192 exist, both bulkiness and the high price are likely prohibitive for their use in large-scale studies. Valid and reliable smartphone versions of the PVT are urgently needed to facilitate these studies [77], acknowledging that smartphones are not built to be precise measurement tools for capturing reaction times with millisecond accuracy.

Another factor affecting cross-study comparability of the PVT is poor standardization of both test parameters (e.g., inclusion of the 1 s feedback interval in the ISI or not?) and outcome variables (e.g., inclusion of timeouts in calculation of average response times?). These parameters can greatly affect PVT performance, and it is important that the field uses the same instrument to assess vigilant attention. In an effort to increase standardization across studies, Basner and Dinges published and encouraged to adopt definitions of test parameters and outcomes variables for the PVT [79].

PVT duration

For many applied settings, the standard 10 min version of the PVT is too long. Therefore, several groups have developed 5 min [76,80–84] and 3 min [85] versions of the PVT. As mentioned above, PVT performance deteriorates with time-on-task, and sleep-deprived subjects performing the PVT can likely compensate for brief periods of time. Thus, there is a trade-off between test duration and sensitivity (as shown by Basner et al. [85]), and it is likely not feasible to develop very short versions of the PVT that remain sensitive. Accordingly, both 2-min [80] and 90 s [82] versions of the PVT were deemed to be too insensitive to be used as valid tools for the detection of neurobehavioral effects of fatigue. Obviously, data generated with different duration versions of the PVT are not directly

comparable, especially if parameters affecting data sampling and analysis are not changed. In an effort to increase comparability between the 10 min and a 3 min version of the PVT, ISIs were shortened from 2–10 s to 1–4 s (a newer iteration [46] uses 2–5 s), and the lapse threshold was decreased from 500 to 355 ms. Shorter ISIs have been shown to be associated with longer RTs [86]. This 3 min version has been successfully implemented in large-scale field studies and was shown to be sensitive to, for example, the effects of sleep loss [87] and sleep medication use [88].

Yet another approach to decrease PVT duration was introduced by Basner and Dinges in 2012. They proposed an adaptive duration PVT (PVT-A). The PVT-A algorithm samples data until a certain decision threshold is exceeded, at which point the test determines to have gathered enough information and stop administration. With this approach, it was possible to decrease average test duration from 10 min to <6.5 min, with a minimal test duration of <30 s. The adaptive duration strategy may be superior to a simple reduction of PVT duration where the fixed test duration may be too short to identify subjects with moderate impairment (showing deficits only later during the test) but unnecessarily long for those who are either fully alert or severely impaired. Recently, an adaptive duration 3-min version of the PVT was developed and validated (PVT-BA) [89]. Here, test duration averaged 1 min and 43 s, with a minimal duration of 16.4 s. This version is thus suitable for most applied settings.

PVT outcome metric

Based on the time series of RTs, a number of outcome metrics can be produced for the PVT, including average and median RT, reciprocal transforms of RT (i.e., 1/RT or response speed), the number of lapses (i.e., errors of omission; typically RTs ≥ 500 ms), false starts (i.e., errors of commission; typically RTs < 100 ms), the fastest or slowest 10% of RT or 1/RT, and the standard deviation of RT, to only name a few. All of these outcome variables are in use but inconsistently reported across studies. Also, it is sometimes unclear whether a primary PVT outcome metric was defined a priori, or whether the researcher engaged in a fishing expedition among available PVT outcomes (often without proper correction for multiple testing). In an effort to determine the most sensitive PVT outcomes, Basner and Dinges compared effect sizes of 10 frequently used PVT outcomes, and suggested that response speed and lapses should be considered as primary PVT outcomes [79]. Several investigators have suggested new and more sensitive PVT outcomes (e.g., Rajaraman et al. [90], Basner et al. [91], Chavali et al. [92]), but it remains to be seen to what degree they will be accepted and used by the research community. Importantly, Basner et al. [91] found that the

sensitivity of response speed was comparable to their new PVT metric and thus corroborates the superiority of response speed as a primary outcome for the PVT.

Research agenda

Further studies are needed to shed light on the biological mechanisms underlying the changes in vigilant attention induced by acute total and chronic partial sleep loss and the changes observed during recovery from sleep loss. Also, we know very little about the effects of chronic sleep restriction on vigilant attention beyond three consecutive weeks, stressing the need for a low-cost but yet valid and reliable version of the PVT that can easily be deployed in large-scale field studies. The application of the PVT and adaptive versions of the PVT for fitness-for-duty or readiness-to-perform assessments also warrants further investigation.

References

- [1] Siegel JM. Sleep viewed as a state of adaptive inactivity. *Nat Rev Neurosci* 2009;10(10):747–53. <https://doi.org/10.1038/nrn2697>.
- [2] Lim J, Dinges DF. Blackwell publishing Inc. United states sleep deprivation and vigilant attention. *Ann N Y Acad Sci* 2008;1129:305–22. <https://doi.org/10.1196/annals.1417.002>.
- [3] Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol* 2009;29(4):320–39. <https://doi.org/10.1055/s-0029-1237117>.
- [4] Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med* 2007;3(5):519–28. <https://doi.org/10.5664/jcsm.26918>.
- [5] Buxton OM, Cain SW, O'Connor SP, Porter JH, Duffy JF, Wang W, Czeisler CA, Shea SA. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. *Sci Transl Med* 2012;4(129). <https://doi.org/10.1126/scitranslmed.3003200>.
- [6] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M, Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL. Joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. *Sleep* 2015;38(8):1161–83. <https://doi.org/10.5665/sleep.4886>.
- [7] Basner M, Dinges DF. Sleep duration in the United States 2003–2016: first signs of success in the fight against sleep deficiency? *Sleep* 2018;41(4):1–16. <https://doi.org/10.1093/sleep/zsy012>.
- [8] Centers for Disease, Prevention. Effect of short sleep duration on daily activities—United States. *MMWR Morb Mortal Wkly Rep* 2005;60(8):239–42.
- [9] Pankowska MM, Lu H, Wheaton AG, Liu Y, Lee B, Greenlund KJ, et al. Prevalence and geographic patterns of self-reported short sleep duration among US adults, 2020. *Prev Chronic Dis* 2023;20:E53.
- [10] Basner M, Fomberstein KM, Razavi FM, Banks S, William JH, Rosa RR, Dinges DF. American time use survey: sleep time and its

- relationship to waking activities. *Sleep* 2007;30(9):1085–95. <https://doi.org/10.1093/sleep/30.9.1085>.
- [11] Basner M, Spaeth AM, Dinges DF. Sociodemographic Characteristics and Waking Activities and their role in the timing and duration of sleep. *Sleep* 2014;37(12):1889–906. <https://doi.org/10.5665/sleep.4238>.
- [12] Lo JC, Groeger JA, Santhi N, Arbon EL, Lazar AS, Hasan S, von Schantz M, Archer SN, Dijk DJ, Yamazaki S. Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase. *PLoS One* 2012;7(9):e45987. <https://doi.org/10.1371/journal.pone.0045987>.
- [13] Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol Bull* 2010;136(3):375–89. <https://doi.org/10.1037/a0018883>.
- [14] Basner M, Rao H, Goel N, Dinges DF. Sleep deprivation and neurobehavioral dynamics. *Curr Opin Neurobiol* 2013;23(5):854–63. <https://doi.org/10.1016/j.conb.2013.02.008>.
- [15] Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res* 2003;12(1):1–12. <https://doi.org/10.1046/j.1365-2869.2003.00337.x>.
- [16] Van Dongen HPA, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26(2):117–26. <https://doi.org/10.1093/sleep/26.2.117>.
- [17] Cohen DA, Wang W, Wyatt JK, Kronauer RE, Dijk DJ, Czeisler CA, Klerman EB. Uncovering residual effects of chronic sleep loss on human performance. *Sci Transl Med* 2010;2(14):14. <https://doi.org/10.1126/scitranslmed.3000458>.
- [18] Zhou X, Ferguson SA, Matthews RW, Sargent C, Darwent D, Kennaway DJ, Roach GD. Sleep, wake and phase dependent changes in neurobehavioral function under forced desynchrony. *Sleep* 2011;34(7):931–41. <https://doi.org/10.5665/SLEEP.1130Australia>.
- [19] Mollicone DJ, Van Dongen HPA, Rogers NL, Banks S, Dinges DF. Time of day effects on neurobehavioral performance during chronic sleep restriction. *Aviat Space Environ Med* 2010;81(8):735–44. <https://doi.org/10.3357/ASEM.2756.2010>.
- [20] Zhou X, Ferguson SA, Matthews RW, Sargent C, Darwent D, Kennaway DJ, Roach GD. Mismatch between subjective alertness and objective performance under sleep restriction is greatest during the biological night. *J Sleep Res* 2012;21(1):40–9. <https://doi.org/10.1111/j.1365-2869.2011.00924.x>.
- [21] Van Dongen HPA, Baynard MD, Maislin G, Dinges DF. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep* 2004;27(3):423–33.
- [22] Dongen, Maislin G, Dinges DF. Dealing with inter-individual differences in the temporal dynamics of fatigue and performance: importance and techniques. *Aviat Space Environ Med* 2004;75:147–54.
- [23] Goel N, Banks S, Mignot E, Dinges DF, Bartell PA. PER3 polymorphism predicts cumulative sleep homeostatic but not neurobehavioral changes to chronic partial sleep deprivation. *PLoS One* 2009;4(6):e5874. <https://doi.org/10.1371/journal.pone.0005874>.
- [24] Goel N, Banks S, Mignot E, Dinges DF. DQB1*0602 predicts interindividual differences in physiologic sleep, sleepiness, and fatigue. *Neurology* 2010;75(17):1509–19. <https://doi.org/10.1212/WNL.0b013e3181f9615d>.
- [25] Goel N, Banks S, Lin L, Mignot E, Dinges DF, Uddin M. Catechol-O-Methyltransferase Val158Met polymorphism associates with individual differences in sleep physiologic responses to chronic sleep loss. *PLoS One* 2011;6(12):e29283. <https://doi.org/10.1371/journal.pone.0029283>.
- [26] Tkachenko O, Dinges DF. Interindividual variability in neurobehavioral response to sleep loss: a comprehensive review. *Neurosci Biobehav Rev* 2018;89:29–48. <https://doi.org/10.1016/j.neubiorev.2018.03.017>.
- [27] Tassi P, Schimchowitz S, Rohmer O, Elbaz M, Bonnefond A, Sagaspe P, Taillard J, Léger D, Philip P. Effects of acute and chronic sleep deprivation on daytime alertness and cognitive performance of healthy snorers and non-snorers. *Sleep Med* 2012;13(1):29–35. <https://doi.org/10.1016/j.sleep.2011.06.017>.
- [28] Philip P, Sagaspe P, Prague M, Tassi P, Capelli A, Bioulac B, Commenges D, Taillard J. Acute versus chronic partial sleep deprivation in middle-aged people: differential effect on performance and sleepiness. *Sleep* 2012;35(7):997–1002. <https://doi.org/10.5665/sleep.1968>.
- [29] Drake CL, Roehrs TA, Burduvali E, Bonahoom A, Rosekind M, Roth T. Effects of rapid versus slow accumulation of eight hours of sleep loss. *Psychophysiology* 2001;38(6):979–87. <https://doi.org/10.1111/1469-8986.3860979>.
- [30] Rupp TL, Wesensten NJ, Balkin TJ. Trait-like vulnerability to total and partial sleep loss. *Sleep* 2012;35(8):1163–72. <https://doi.org/10.5665/sleep.2010>.
- [31] Van Dongen HPA, Vitellaro KM, Dinges DF. Individual differences in adult human sleep and wakefulness: leitmotif for a research agenda. *Sleep* 2005;28(4):479–96. <https://doi.org/10.1093/sleep/28.4.479>.
- [32] Dorrian J, Rogers NL, Dinges DF. Psychomotor vigilance performance: neurocognitive assay sensitive to sleep loss. Informa UK Limited; 2004. p. 39–70. <https://doi.org/10.3109/9780203998007-4>.
- [33] Córdova CA, Said BO, McCarley RW, Baxter MG, Chiba AA, Strecker RE. Sleep deprivation in rats produces attentional impairments on a 5-choice serial reaction time task. *Sleep* 2006;29(1):69–76.
- [34] Lim J, Tan JC, Parimal S, Dinges DF, Chee MWL. Sleep deprivation impairs object-selective attention: a view from the ventral visual cortex. *PLoS One* 2010;5(2). <https://doi.org/10.1371/journal.pone.0009087Singapore>.
- [35] Posner MI. Measuring alertness. *Ann N Y Acad Sci* 2008;1129:193–9. <https://doi.org/10.1196/annals.1417.011>.
- [36] Trujillo LT, Kornguth S, Schnyer DM. An ERP examination of the different effects of sleep deprivation on exogenously cued and endogenously cued attention. *Sleep* 2009;32(10):1285–97. <https://doi.org/10.1093/sleep/32.10.1285>.
- [37] Anderson C, Horne JA. Sleepiness enhances distraction during a monotonous task. *Sleep* 2006;29(4):573–6. <https://doi.org/10.1093/sleep/29.4.573>.
- [38] Tucker AM, Whitney P, Belenky G, Hinson JM, Van Dongen HPA. Effects of sleep deprivation on dissociated components of executive functioning. *Sleep* 2010;33(1):47–57. <https://doi.org/10.1093/sleep/33.1.47>.
- [39] Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav*

- Res Methods Instrum Comput 1985;17(6):652–5. <https://doi.org/10.3758/BF03200977>.
- [40] Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, Aptowicz C, Pack AI. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep* 1997;20(4):267–77.
- [41] Doran SM, Van Dongen HPA, Dinges DF. Sustained attention performance during sleep deprivation: evidence of state instability. *Arch Ital Biol* 2001;139(3):253–67.
- [42] Dinges NB, Kribbs. Performing while sleepy: effects of experimentally-induced sleepiness. John Wiley and Sons; 1991. p. 97–128.
- [43] Warm JS, Parasuraman R, Matthews G. Vigilance requires hard mental work and is stressful. *Hum Factors* 2008;50(3):433–41. <https://doi.org/10.1518/001872008X312152>.
- [44] Patrick GTW, Allen Gilbert J. Studies from the psychological laboratory of the University of Iowa: on the effects of loss of sleep. *Psychol Rev* 1896;3(5):469–83. <https://doi.org/10.1037/h0075739>.
- [45] Dinges DF. Probing the limits of functional capability: the effects of sleep loss on short-duration tasks. *Sleep Arousal Perform* 1992;177:88.
- [46] Basner M, Hermosillo E, Nasrini J, McGuire S, Saxena S, Moore TM, Gur RC, Dinges DF. Repeated administration effects on psychomotor vigilance test performance. *Sleep* 2018;41(1). <https://doi.org/10.1093/sleep/zsx187>.
- [47] Lim J, Wu WC, Wang J, Detre JA, Dinges DF, Rao H. Imaging brain fatigue from sustained mental workload: an ASL perfusion study of the time-on-task effect. *Neuroimage* 2010;49(4):3426–35. <https://doi.org/10.1016/j.neuroimage.2009.11.020>.
- [48] Davies DR, Parasuraman R. The psychology of vigilance. Academic Press; 1982.
- [49] Philip P, Akerstedt T. Transport and industrial safety, how are they affected by sleepiness and sleep restriction? *Sleep Med Rev* 2006;10(5):347–56. <https://doi.org/10.1016/j.smrv.2006.04.002>.
- [50] Dinges DF. An overview of sleepiness and accidents. *J Sleep Res* 1995;4:4–14. <https://doi.org/10.1111/j.1365-2869.1995.tb00220.x>.
- [51] Van Dongen HPA, Dinges DF. Sleep, circadian rhythms, and psychomotor vigilance. *Clin Sports Med* 2005;24(2):237–49. <https://doi.org/10.1016/j.csm.2004.12.007>.
- [52] Gunzelmann G, Moore LR, Gluck, Dongen, Dinges DF. Cognitive Science Society Individual differences in sustained vigilant attention: insights from computational cognitive modeling. In: 30th Annual Meeting of the Cognitive Science Society; 2008.
- [53] Dinges DF, Mallis MM. Managing fatigue by drowsiness detection. Elsevier BV; 1998. p. 209–29. <https://doi.org/10.1016/b978-008043357-8/50012-1>.
- [54] Gunzelmann, Moore LR, Gluck A, Dongen, Dinges DF. Cognitive fatigue: multidisciplinary perspectives on current research and future applications. American Psychological Association; 2010. p. 83–101.
- [55] Chee MWL, Tan JC, Zheng H, Parimal S, Weissman DH, Zagorodnov V, Dinges DF. Lapsing during sleep deprivation is associated with distributed changes in brain activation. *J Neurosci* 2008;28(21):5519–28. <https://doi.org/10.1523/jneurosci.0733-08.2008>.
- [56] Drummond SPA, Bischoff-Grethe A, Dinges DF, Ayalon L, Mednick SC, Meloy MJ. The neural basis of the psychomotor vigilance task. *Sleep* 2005;28(9):1059–68.
- [57] Tomasi D, Wang RL, Telang F, Boronikolas V, Jayne MC, Wang GJ, Fowler JS, Volkow ND. Impairment of attentional networks after 1 night of sleep deprivation. *Cerebr Cortex* 2009;19(1):233–40. <https://doi.org/10.1093/cercor/bhn073>.
- [58] Ma N, Dinges DF, Basner M, Rao H. How acute total sleep loss affects the attending brain: a meta-analysis of neuroimaging studies. *Sleep* 2015;38(2):233–40. <https://doi.org/10.5665/sleep.4404>.
- [59] Jewett ME, Dijk DJ, Kronauer RE, Dinges DF. Dose-response relationship between sleep duration and human psychomotor vigilance and subjective alertness. *Sleep* 1999;22(2):171–9. <https://doi.org/10.1093/sleep/22.2.171>.
- [60] Balkin TJ, Bliese PD, Belenkay G, Sing H, Thorne DR, Thomas M, Redmond DP, Russo M, Wesensten NJ. Comparative utility of instruments for monitoring sleepiness-related performance decrements in the operational environment. *J Sleep Res* 2004;13(3):219–27. <https://doi.org/10.1111/j.1365-2869.2004.00407.x>.
- [61] Mollicone DJ, Van Dongen HPA, Rogers NL, Dinges DF. Response surface mapping of neurobehavioral performance: testing the feasibility of split sleep schedules for space operations. *Acta Astronaut* 2008;63(7–10):833–40. <https://doi.org/10.1016/j.actaastro.2007.12.005>.
- [62] Wyatt JK, Ritz-De Cecco A, Czeisler CA, Dijk DJ. Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. *Am J Physiol Regul Integr Comp Physiol* 1999;277(4):R1152. <https://doi.org/10.1152/ajpregu.1999.277.4.r1152>.
- [63] Graw P, Kräuchi K, Knoblauch V, Wirz-Justice A, Cajochen C. Circadian and wake-dependent modulation of fastest and slowest reaction times during the psychomotor vigilance task. *Physiol Behav* 2004;80(5):695–701. <https://doi.org/10.1016/j.physbeh.2003.12.004>.
- [64] Killgore WDS, Grugle NL, Reichardt RM, Killgore DB, Balkin TJ. Executive functions and the ability to sustain vigilance during sleep loss. *Aviat Space Environ Med* 2009;80(2):81–7. <https://doi.org/10.3357/ASEM.2396.2009>.
- [65] Neri DF, Oyung RL, Colletti LM, Mallis MM, Tam PY, Dinges DF. Controlled breaks as a fatigue countermeasure on the flight deck. *Aviat Space Environ Med* 2002;73(7):654–64.
- [66] Dinges DF, Orne MT, Whitehouse WG, Orne EC. Temporal placement of a nap for alertness: contributions of circadian phase and prior wakefulness. *Sleep* 1987;10(4):313–29.
- [67] Van Dongen HPA, Price NJ, Mullington JM, Szuba MP, Kapoor SC, Dinges DF. Caffeine eliminates psychomotor vigilance deficits from sleep inertia. *Sleep* 2001;24(7):813–9. <https://doi.org/10.1093/sleep/24.7.813>.
- [68] Czeisler CA, Walsh JK, Roth T, Hughes RJ, Wright KP, Kingsbury L, Arora S, Schwartz JRL, Niebler GE, Dinges DF. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med* 2005;353(5):476–86. <https://doi.org/10.1056/NEJMoa041292>.
- [69] Rupp TL, Wesensten NJ, Bliese PD, Balkin TJ. Banking sleep: realization of benefits during subsequent sleep restriction and recovery. *Sleep* 2009;32(3):311–21. <https://doi.org/10.1093/sleep/32.3.311>.
- [70] Banks S, Van Dongen HPA, Maislin G, Dinges DF. Neurobehavioral dynamics following chronic sleep restriction: dose-response effects of one night for recovery. *Sleep* 2010;33(8):1013–26. <https://doi.org/10.1093/sleep/33.8.1013>.

- [71] Kribbs NB, Pack AI, Kline LR, Getsy JE, Schuett JS, Henry JN, Maislin G, Dinges DF. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;147(5):1162–8. <https://doi.org/10.1164/ajrccm/147.5.1162>.
- [72] Dawson D, Searle AK, Paterson JL. Look before you (s)leep: evaluating the use of fatigue detection technologies within a fatigue risk management system for the road transport industry. *Sleep Med Rev* 2014;18(2):141–52. <https://doi.org/10.1016/j.smrv.2013.03.003>.
- [73] Chua ECP, Tan WQ, Yeo SC, Lau P, Lee I, Mien IH, Puvanendran K, Gooley JJ. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. *Sleep* 2012;35(3):325–34. <https://doi.org/10.5665/sleep.1688singapore>.
- [74] Reifman J, Kumar K, Khitrov MY, Liu J, Ramakrishnan S. PC-PVT 2.0: an updated platform for psychomotor vigilance task testing, analysis, prediction, and visualization. *J Neurosci Methods* 2018;304:39–45. <https://doi.org/10.1016/j.jneumeth.2018.04.007>.
- [75] Basner M, Savitt A, Moore TM, Port AM, McGuire S, Ecker AJ, Nasrini J, Mollicone DJ, Mott CM, McCann T, Dinges DF, Gur RC. Development and validation of the Cognition test battery for spaceflight. *Aerospace Med Human Performance* 2015;86(11):942–52. <https://doi.org/10.3357/AMHP.4343.2015>.
- [76] Arsintescu L, Mulligan JB, Flynn-Evans EE. Evaluation of a psychomotor vigilance task for touch screen devices. *Hum Factors* 2017;59(4):661–70. <https://doi.org/10.1177/0018720816688394>.
- [77] Grandner MA, Watson NF, Kay M, Ocaño D, Kientz JA. Addressing the need for validation of a touchscreen psychomotor vigilance task: important considerations for sleep health research. *Sleep Health* 2018;4(5):387–9. <https://doi.org/10.1016/j.slehd.2018.08.003>.
- [78] Basner M, Moore TM, Nasrini J, Gur RC, Dinges DF. Response speed measurements on the psychomotor vigilance test: how precise is precise enough? *Sleep* 2021;44(1):zsaa121.
- [79] Basner M, Dinges DF. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. *Sleep* 2011;34(5):581–91. <https://doi.org/10.1093/sleep/34.5.581>.
- [80] Loh S, Lamond N, Dorrian J, Roach G, Dawson D. The validity of psychomotor vigilance tasks of less than 10-minute duration. *Behav Res Methods Instrum Comput* 2004;36(2):339–46. <https://doi.org/10.3758/bf03195580>.
- [81] Lamond N, Jay SM, Dorrian J, Ferguson SA, Roach GD, Dawson D. The sensitivity of a palm-based psychomotor vigilance task to severe sleep loss. *Behav Res Methods* 2008;40(1):347–52. <https://doi.org/10.3758/BRM.40.1.347>.
- [82] Roach GD, Dawson D, Lamond N. Australia Can a shorter psychomotor vigilance task be used as a reasonable substitute for the ten-minute psychomotor vigilance task? *Chronobiol Int* 2006;23(6):1379–87. <https://doi.org/10.1080/07420520601067931>.
- [83] Lamond N, Dawson D, Roach GD. Fatigue assessment in the field: validation of a hand-held electronic psychomotor vigilance task. *Aviat Space Environ Med* 2005;76(5):486–9.
- [84] Thorne DR, Johnson DE, Redmond DP, Sing HC, Belenky G, Shapiro JM. The Walter Reed palm-held psychomotor vigilance test. *Behav Res Methods* 2005;37(1):111–8. <https://doi.org/10.3758/BF03206404>.
- [85] Basner M, Mollicone D, Dinges DF. Validity and sensitivity of a brief psychomotor vigilance test (PVT-B) to total and partial sleep deprivation. *Acta Astronaut* 2011;69(11–12):949–59. <https://doi.org/10.1016/j.actaastro.2011.07.015>.
- [86] Yang FN, Xu S, Chai Y, Basner M, Dinges DF, Rao H. Sleep deprivation enhances inter-stimulus interval effect on vigilant attention performance. *Sleep* 2018;1–12.
- [87] Basner M, Dinges DF, Shea JA, Small DS, Zhu J, Norton L, Ecker AJ, Novak C, Bellini LM, Volpp KG. Sleep and alertness in medical interns and residents: an observational study on the role of extended shifts. *Sleep*. 2017;40(4). <https://doi.org/10.1093/sleep/zsx027>.
- [88] Dinges DF, Basner M, Ecker AJ, Baskin P, Johnston SL. Effects of zolpidem and zaleplon on cognitive performance after emergent morning awakenings at Tmax: a randomized placebo-controlled trial. *Sleep*. 2019;42(3). <https://doi.org/10.1093/sleep/zsy258>.
- [89] Basner M. Ultra-short objective alertness assessment: an adaptive duration version of the 3 minute PVT (PVT-BA) accurately tracks changes in psychomotor vigilance induced by sleep restriction. *Sleep Adv* 2022;3(1):zpac038.
- [90] Rajaraman S, Ramakrishnan S, Thorsley D, Wesensten NJ, Balkin TJ, Reifman J. A new metric for quantifying performance impairment on the psychomotor vigilance test. *J Sleep Res* 2012;21(6):659–74. <https://doi.org/10.1111/j.1365-2869.2012.01008.x>.
- [91] Basner M, McGuire S, Goel N, Rao H, Dinges DF. A new likelihood ratio metric for the psychomotor vigilance test and its sensitivity to sleep loss. *J Sleep Res* 2015;24(6):702–13. <https://doi.org/10.1111/jsr.12322>.
- [92] Chavali VP, Riedy SM, Van Dongen HPA. Signal-to-noise ratio in PVT performance as a cognitive measure of the effect of sleep deprivation on the fidelity of information processing. *Sleep*. 2017;40(3). <https://doi.org/10.1093/sleep/zsx016>.

This page intentionally left blank

Chapter 29

Sleep loss, decision-making, and executive function

Sofia K. Fluke¹, Brieann C. Satterfield^{1, a} and William D. Scott Killgore^{2, a}

¹Sleep and Performance Research Center, Department of Translational Medicine and Physiology, Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, United States; ²Social, Cognitive, and Affective Neuroscience (SCAN) Laboratory, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, United States

Abbreviations

ACC	Anterior cingulate cortex
ADA	Adenosine deaminase
ADORA2A	Adenosine A2A receptor
AQP4	Aquaporin-4
BART	Balloon risk analog test
BDNF	Brain derived neurotrophic factor
CSF	Cerebrospinal fluid
DAT1	Dopamine transporter
DRD2	Dopamine D2 receptor
DTI	Diffusion tensor imaging
h	Hour
IGT	Iowa gambling task
mg	Milligram
min	Minute
OFC	Orbitofrontal cortex
PER3	PERIOD3
PFC	Prefrontal cortex
PVT	Psychomotor vigilance test
RT	Response time
SD	Standard deviation
SE	Standard error
sec	Second
TNF α	Tumor necrosis factor alpha
VWM	Visual working memory
WCST	Wisconsin card sorting task

Introduction

Modern society operates around the clock, often at the expense of adequate sleep. Insufficient sleep has emerged as a widespread public health concern that is frequently underestimated in its seriousness [1]. While the National

Sleep Foundation recommends adults sleep >7 h per night [2], 35% of adults in the United States sleep less [3]. Most people have suffered from sleep loss, either chronic or acute, at some point in their lives whether it be due to a new baby, stress, studying for an exam, or other circumstances. However, many people fail to realize the negative impact sleep loss has on cognitive functioning and how this has far-reaching real-world implications. In fact, insufficient sleep is common in several safety-critical occupations, including medical professionals, military personnel, airline pilots, and truck drivers, just to name a few. Thus, it is important to understand how sleep loss impacts various aspects of cognition.

The present chapter provides an overview of the effects of sleep loss on several major cognitive domains. First, it is important to discuss the underlying neurobiological mechanisms that regulate sleep and wake, and thus modulate cognitive performance. We must also appreciate that human cognitive capacities are complex, with higher-order processes (e.g., executive functions, decision-making) building upon a foundation of elementary processes (e.g., attention). Therefore, this chapter will offer a discussion of how sleep loss impairs alertness, sustained attention, and vigilance. In addition, we will discuss the importance of considering how interindividual differences are related to relative resistance or vulnerability to cognitive impairment. We will then build upon these elementary capacities and focus on the consequences that sleep loss has on several complex executive function domains including working memory, inhibitory control, cognitive control, problem solving, risk-taking, and decision-making.

a Equally contributed.

Neurobiology of sleep and fatigue

There are two fundamental neurobiological processes that drive fatigue and alertness: the *homeostatic process* (Process S) and the *circadian process* (Process C) [4,5]. The homeostatic process keeps track of prior amounts of sleep and wakefulness, and is conceptualized as an accumulating pressure for sleep with increasing time spent awake. This pressure is then dissipated over the course of a sleep period. The circadian process is the body's natural 24-h rhythm that keeps track of time of day. This process, modulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, also referred to as the central biological clock, oscillates throughout a 24-h period to drive daytime alertness and nighttime sleepiness. During daytime hours, homeostatic sleep pressure accumulates with each hour awake, but is counteracted by the circadian drive for alertness. This interaction between the homeostatic and circadian pressures allows us to maintain normal daytime functioning at a fairly constant level. During nighttime hours, the homeostatic pressure for sleep is high and the circadian drive for alertness is low, promoting the onset and maintenance of sleep. Thus, waking performance is optimal during daytime hours and worst during nighttime hours (Fig. 29.1) [5,6]. However, perturbations to this system (i.e., shift work, mistimed sleep, travel across time zones) can result in impaired neurobehavioral functioning. For example, the homeostatic and circadian processes become misaligned when an individual works during the night and sleeps during the day. In such a case, the homeostatic pressure for sleep mounts over the course of nighttime waking hours, but the circadian drive for alertness decreases, and hits the nadir during the early morning

hours (Fig. 29.1). The net effect of this misalignment is increased fatigue, which can lead to cognitive performance impairment. Further, sleeping during the day is often difficult for a nightshift worker. This is because the circadian process increases the pressure for wakefulness throughout the day, forcing an individual to awaken before the homeostatic pressure is fully dissipated. This type of sleep curtailment can lead to a net accumulation of sleep debt [6].

Alertness, sustained attention, and vigilance

In our day-to-day lives, the ability to maintain focus and attention is essential for effectively completing the task at hand and solving problems that require complex cognitive processing. Our ability to maintain attention and alertness fluctuates throughout the day as a function of the circadian and homeostatic processes, often without notice. However, when these two processes become misaligned due to extended wakefulness or mistimed sleep, attention begins to degrade. When wake is extended beyond 16 h or restricted to <6 h per night, individuals tend to show consistent and profound impairment in sustained attention.

Psychomotor vigilance

Sustained attention is typically measured using the psychomotor vigilance test (PVT) [7,8]. The PVT is a simple computerized reaction time task that is considered to be the gold standard measure of behavioral alertness. It is sensitive to sleep loss and does not show an appreciable learning effect [9,10]. In the standard version of the task, a visual

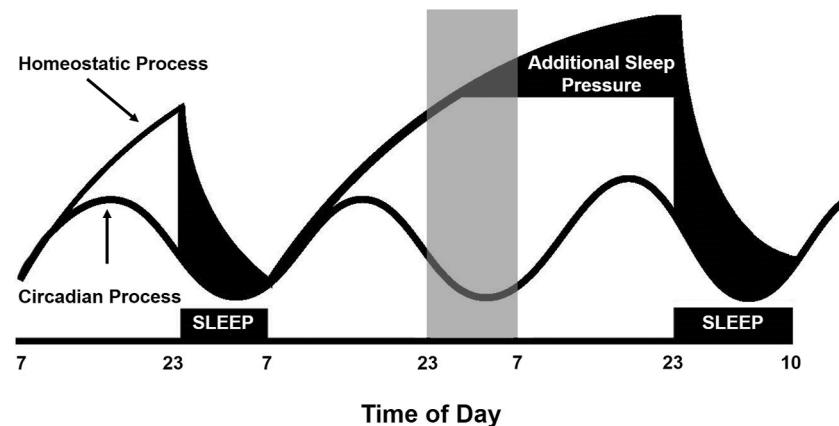


FIGURE 29.1 The two process model of sleep regulation. The homeostatic process (S) and circadian process (C) interact to drive daytime alertness and nighttime sleepiness. Homeostatic pressure for sleep increases as a function of time spent awake and dissipates with time spent asleep. At the same time, circadian pressure oscillates across a 24-h period, with pressure for alertness highest in the early evening and lowest during the early morning hours. However, when an individual skips a night of sleep (shaded area) homeostatic pressure continues to build, while the circadian process continues to drive sleepiness during the earlier morning hours. At this point, the net effect of high homeostatic pressure and low circadian pressure is reduced alertness and increased fatigue, resulting in impaired cognitive functioning. Once an individual goes to sleep, homeostatic pressure decreases, and often results in increased sleep duration that is required to fully dissipate the homeostatic buildup. Modified from File: Two-process model of sleep regulation. WikiMedia; 2007. https://en.wikipedia.org/wiki/File:Two-process_model_of_sleep_regulation.jpg.

stimulus is presented on the screen at random intervals between 2 and 10 s for a total of 10 min in duration. When the stimulus appears, the examinee presses a response button as quickly as possible, while avoiding false starts. Lim and Dinges [11] identified several distinct impacts that sleep deprivation has on PVT performance: (1) slowing of response times (RTs), (2) increases in attentional lapses, (3) exaggerated time-on-task effects, and (4) sensitivity to homeostatic and circadian influences.

In a typical sleep deprivation study, PVT RTs begin to slow around 16 h of wakefulness and degrade further across the night, with impairment being the most prominent during the early morning hours (i.e., the circadian nadir). *Slower responses* on the PVT are associated with reduced activation in the default mode network, a cortical system that includes the medial frontal and posterior cingulate cortex, regions that are most active when the brain is idle and not involved in complex cognitive processing [12]. While the average RT across trials increases during periods of sleep deprivation, there is also a significant slowing of both the fastest 10% and slowest 10% of RTs on the PVT. Albeit, the slowest RTs are disproportionately affected compared to the fastest 10% RTs (Fig. 29.2) [8,10,13,14]. This indicates that sleep loss impacts not only the typical response, but also the best and worst performance. Decrement in PVT performance are not limited to conditions of total sleep deprivation. PVT

performance is also substantially degraded when sleep is restricted by only a few hours each night. Belenky et al. demonstrated that when sleep is restricted to either 7, 5, or 3 h per night over the course of 1 week, response speeds ($1/RT \times 1000$) slowed in a cumulative manner across days [15]. Even when participants were allowed three 8 h nighttime recovery sleep periods, performance did not return to baseline levels (Fig. 29.3) [15].

Another characteristic of sleep loss is the increased frequency and duration of *attentional lapses* (RTs ≥ 500 ms) that occur within a single PVT bout, which are also accompanied by increases in errors of commission or false alarms (i.e., responding when no stimulus is present). Van Dongen et al. demonstrated that when sleep is restricted to either 6, 4, or 8 h over the course of 2 weeks the number of attentional lapses increases in a cumulative and dose-dependent manner [16]. In fact, when sleep restriction was most severe (i.e., 4 h per night), the average number of lapses at the end of the 2 weeks was similar to the average number of lapses seen at the end of an 88 h sleep deprivation period [16]. Neuroimaging findings suggest that attentional lapses during sleep deprivation are related to reduced neural activation within the frontal, parietal and occipital regions, as well as the thalamus [17]. Together, imaging and behavioral studies have demonstrated how sleep loss disrupts normal functioning within the vigilant attention network, in turn hindering the ability to sustain attention.

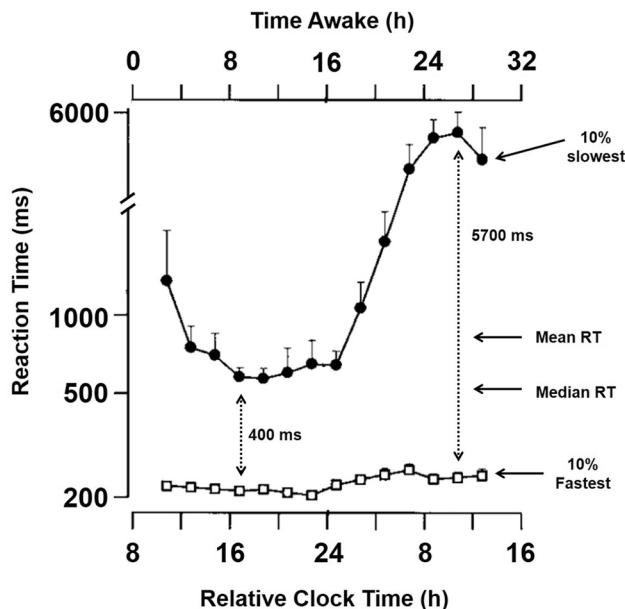


FIGURE 29.2 Time course of PVT mean RTs across 32 h of sleep deprivation. PVT performance remained relatively stable until 16 h wake. Up until this point, only 400 ms separated the average 10% slowest (black circles) and 10% fastest (white squares) RTs. However, with increased time awake, RTs slowed dramatically. Just after 24 h wake, approximately 5700 ms separated the fastest and slowest 10% of RTs. While not displayed in this figure, mean and median RTs are also significantly impacted by sleep loss and fall between the fastest and slowest curves shown here. Modified from Cajochen C, Khalsa SB, Wyatt JK, Czeisler CA, Dijk DJ. EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *Am J Physiol* 1999;277:R640–9.

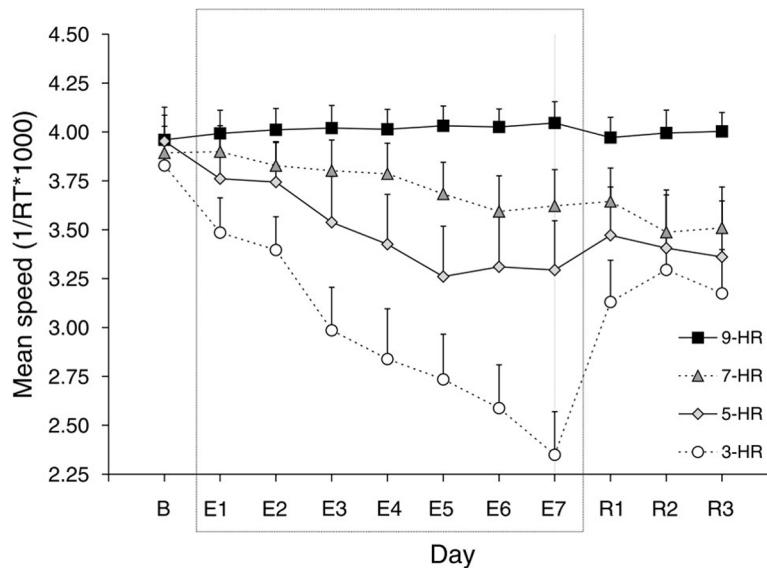


FIGURE 29.3 Mean response speed ($1/RT^*1000$) on the PVT over the course of a 7 day sleep restriction protocol as a function of sleep condition group. All groups had similar PVT performance at baseline (B). In the 9 h sleep group, PVT performance remained stable across sleep restriction days (E1–E7) and into the recovery days (R1–R3). When sleep was restricted to either 7, 5, or 3 h, there was a steady decline in PVT mean speed as days progressed. This decline was more pronounced in the 3 h sleep condition compared to the 7 h sleep condition. In addition, 8 h sleep for three nights (recovery) was not sufficient to return PVT performance back to baseline levels. Reproduced from Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res* 2003;12(1):1–12, with permission from John Wiley and Sons.

The *time-on-task effect* is a phenomenon in which performance degrades as a function of time spent performing a cognitive task. That is, performance progressively declines the longer an individual is required to sustain attention necessary to perform the task [18]. This results in increased performance variability [19]. The time-on-task effect is apparent on several different types of cognitive tasks, however it is especially noticeable on tasks of vigilant attention, like the PVT [20]. On the PVT, the time-on-task effect manifests as a steady increase in the standard deviation of RTs across the task duration [10]. This phenomenon is present even under well-rested baseline conditions. Variability in PVT RTs is also a distinct characteristic of how vigilant attention is affected by sleep loss. Interestingly, the time-on-task effect interacts with sleep loss to amplify performance impairments when homeostatic pressure is high [8,10,21]. When faced with sleep loss, the time-on-task effect can be mediated by taking short breaks or switching tasks [6,22,23].

Last, PVT performance is sensitive to *homeostatic and circadian influences* [8,24]. Fig. 29.4 shows the dynamic influence that the two neurobiological processes exert on performance. As described above, homeostatic pressure increases across hours awake, while the circadian process waxes and wanes across a 24-h period (Fig. 29.4, left). When these processes are considered in interaction, the sum of the two processes modulates PVT performance in a distinct manner. Fig. 29.4 (right) shows how the net effect

of the two neurobiological processes impact PVT performance during 62 h of total sleep deprivation. Not only does PVT impairment increase with time spent awake, it also oscillates with the circadian process. Performance slightly improves during the early evening hours when the circadian pressure for wake is high, but further deteriorates after the circadian nadir and with mounting homeostatic pressure [25].

Wake state instability

Several aspects of PVT performance impairment, as described above, have been summarized into a single theory: the wake state instability hypothesis [10]. Sleep loss leads to a decrease in RTs, increase in attentional lapses and errors, and an increase in the time-on-task effect, all of which are influenced by mounting homeostatic pressure and manifesting as performance instability [8]. These moment-to-moment variations in performance are not gradual, linear, or predictable, but rather stochastic in nature. For example, Fig. 29.5 shows PVT responses from a single subject throughout the course of a 62 h sleep deprivation period. In the early afternoon when the subject has only been awake for 5 h, PVT performance is stable, with minimal variability in RTs and no attentional lapses. However, a different picture emerges 24 h later when the subject has been awake for 29 consecutive hours (Fig. 29.5, middle). At this point, there is moderate

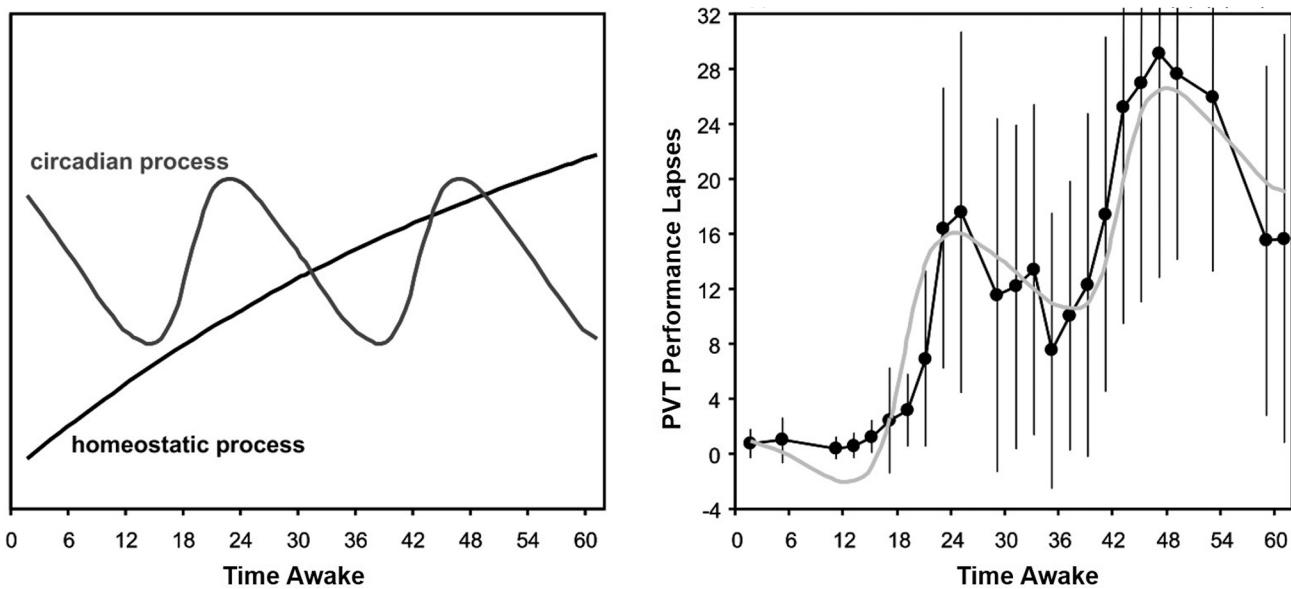


FIGURE 29.4 The influence of the homeostatic and circadian processes on PVT performance during 62 h of extended wakefulness. The left panel shows the steady increase in homeostatic pressure across the sleep deprivation period in interaction with the waxing and waning of the circadian process. The right panel shows a mathematical derivation of the sum of the homeostatic and circadian processes (gray curve) overlaid on mean PVT lapses (\pm SD; black curve) collected from 12 healthy adults. Reproduced from Van Dongen HPA, Belenky G. Individual differences in vulnerability to sleep loss in the work environment. *Ind Health* 2009; 47(5):518–26, with permission.

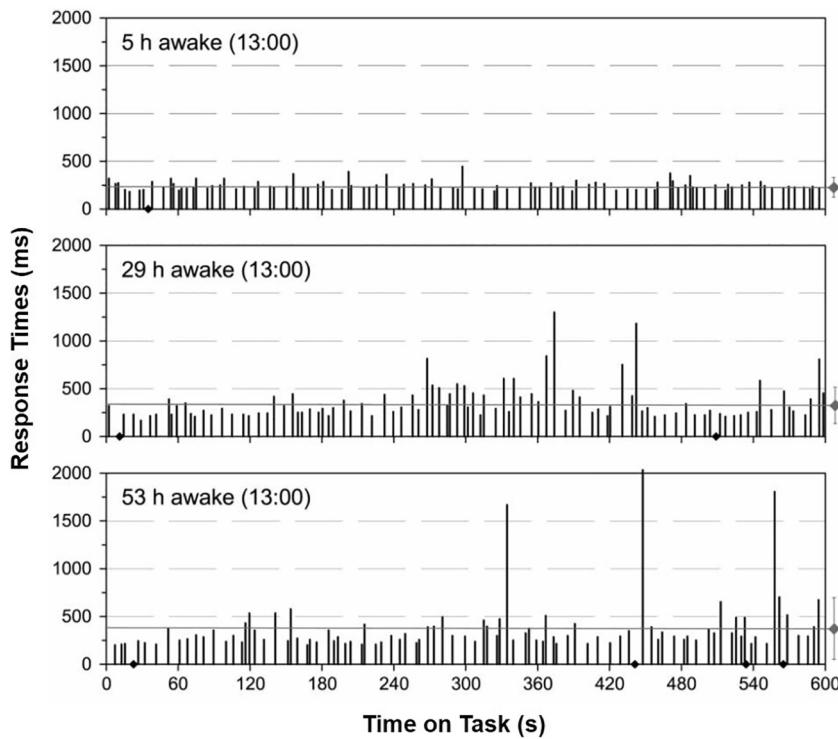


FIGURE 29.5 Raw PVT RTs from a single subject collected over the course of a 62 h sleep deprivation period. RTs are plotted against time-on-task. PVT performance is shown at 5 h wakefulness (top panel), again 24 h later (middle panel), and another 24 h later (bottom panel). RTs become longer and more variable as a function of both time-on-task and time awake. Additionally, false starts (black diamonds) also increase. Gray diamonds: Mean RT \pm SD. Reproduced from Satterfield BC, Van Dongen HPA. Occupational fatigue, underlying sleep and circadian mechanisms, and approaches to fatigue risk management. *Fatigue Biomed Heal Behav* 2013;246(3):118–36, with permission of Taylor & Francis Ltd. (<http://www.informaworld.com>).

variability in RTs as time-on-task increases, and the occasional response exceeds the 500 ms attentional lapse threshold. Another 24 h later (Fig. 29.5, bottom), performance variability is further increased. At 53 h awake, attentional lapses become more frequent, RTs become longer, more errors are made, and the time-on-task effect is amplified. Together, these data illustrate that performance instability is a hallmark of sleep loss [6,18,23]. It is this unstable and unpredictable nature that makes fatigue so dangerous, especially in safety-critical operations. It has been posited that the stochastic nature of performance instability is the result of neuronal groups involved in the task expressing a local, use-dependent sleep-like state. The local sleep theory suggests that activity from sustained use during a performance task and extended wakefulness pushes local neuronal groups to fall asleep. In turn, information processing in the task-specific pathway is interrupted, causing performance instability and increased attentional lapses [18,26].

Individual differences

Research has shown that there are varying degrees of cognitive impairment during sleep loss across individuals. That is, not all individuals respond to sleep loss in the same manner [27–30]. These interindividual differences are substantial and robust across a variety of manipulations,

and constitute a trait [21,31,32]. As demonstrated by Van Dongen et al. [32], there are individuals who are resilient to the effects that sleep deprivation exerts on cognitive performance and individuals who are incredibly vulnerable. Fig. 29.6 shows that resilient individuals (*triangles*) are able to maintain stable performance across a 40 h sleep deprivation period, while vulnerable individuals (*circles*) show substantial impairment as wake extends past 16 h [33]. Due to the stable, trait nature of interindividual differences, a number of biomarkers have been assessed to predict which individuals may be more or less susceptible to cognitive impairment due to sleep loss. These include personality and sensory markers [34,35], neural markers [36], and genetic markers [37].

Several neuroimaging studies have sought to identify neural predictors of interindividual differences in cognitive performance by assessing functional activation while performing a cognitive task [17,38–40], functional connectivity between brain regions [41], and white matter microstructure [42]. Chee and Tan found that sleep loss was associated with lower fronto-parietal activation compared to the rested state, and individuals most vulnerable to impaired selective attention had reduced activation in top-down cognitive bias regions (i.e., frontal and parietal cortices) [17]. In addition to measuring changes in neural activation, individual differences in neuroanatomical connectivity and structure have been

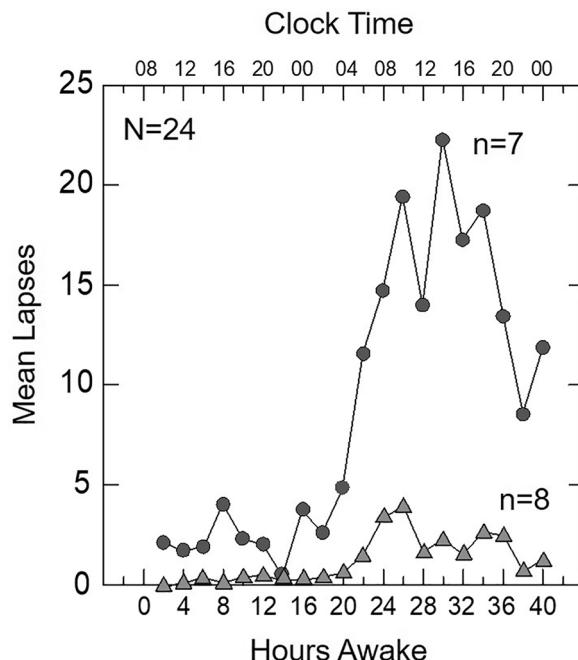


FIGURE 29.6 Mean PVT lapses collected from 24 individuals during 40 h of total sleep deprivation. The number of PVT lapses remains low until about 16 h awake. At this point, the number of PVT lapses increases significantly for those most vulnerable ($n = 7$) to impairment (*circles*). In contrast, the number of PVT lapses remains relatively stable for those most resilient ($n = 8$) to impairment (*triangles*). Performance for the remaining nine individuals falls between these curves. Modified from Van Dongen HPA, Maislin G, Dinges DF. Dealing with inter-individual differences in the temporal dynamics of fatigue and performance: Importance and techniques. *Aviat Space Environ Med* 2004;75(Suppl 3):A147–54, with permission.

identified. For example, our lab used diffusion tensor imaging (DTI) to assess the association between microstructure of the fronto-parietal attention system and PVT performance during a single night of sleep deprivation. We found that indirect measures of higher white matter integrity and higher myelination in the fiber pathways connecting the left frontal and left parietal regions were significantly correlated with resistance to PVT impairment [42]. Neural markers have the potential to help identify those individuals most vulnerable and those most resistant to impaired cognitive performance without having to expose them to any sleep loss paradigm. This affords us with a better understanding of the neural mechanisms underlying sleep loss related cognitive impairment.

Identifying genetic markers of interindividual differences to performance impairments has become a large area of research in the last several years. Often, genetic polymorphisms are used as a tool to investigate how the functional differences brought about by the polymorphisms influence inter-individual differences in cognitive performance [43]. These studies have focused on polymorphisms associated with circadian pathways, adenosine (a marker of homeostatic pressure) pathways, neurotransmitters, neural signaling pathways, and immune responses [43]. Genetic polymorphisms can also indicate a predisposition to neurodegeneration, predicting cognitive decline, and contribute to individual differences in sleep architecture and response to sleep loss. For example, the astrocytic water channel aquaporin 4 (AQP4) controls the flow of cerebrospinal fluid (CSF) through the parenchyma of the

brain, contributing to waste clearance [44]. A haplotype of the AQP4 gene (HiMi minor allele) that contributes to an increased pre-disposition to neurodegeneration due to a decrease in CSF clearance (typically referred to as the “glymphatic system”) is associated with decreased amounts of slow wave sleep, increased subjective sleepiness during extended wakefulness, and worse performance on attentional tasks during sleep deprivation [44].

PVT performance during sleep deprivation is mediated by several genetic variants, including those of the adenosine A_{2A} receptor (ADORA2A) gene [45], adenosine deaminase (ADA) gene, dopamine transporter (DAT1) gene [46,47], and the tumor necrosis factor alpha (TNF α) gene [48]. For example, it was recently found that a variant of DAT1 mediates the time-on-task effect during sleep deprivation [46]. Study participants performed the PVT every 2 h over the course of a 38 h sleep deprivation period. Subjects homozygous for the 10-repeat variant of DAT1 were resilient to the time-on-task effect compared to subjects with the 9-repeat variant of the same gene. As Fig. 29.7 shows, performance between the two DAT1 genotype groups diverged as sleep deprivation progressed, with the most resilient individuals (i.e., the 10/10 group) maintaining stable performance with very little time-on-task effect [46]. Holst et al. also found that DAT1 genotype modulates PVT performance, specifically PVT lapses [47]. Genetic markers have also been found to influence performance on a variety of other cognitive tasks and will be discussed throughout the remainder of the chapter.

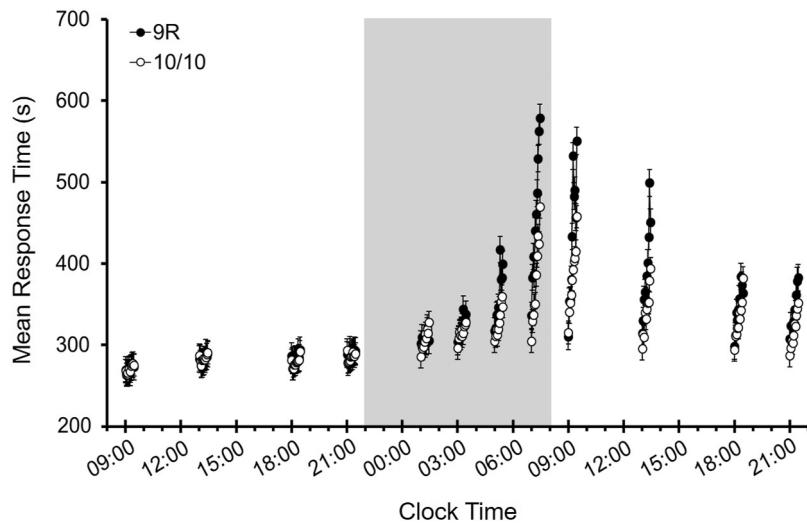


FIGURE 29.7 Time-on-task performance for the DAT1 genotype groups across 38 h of total sleep deprivation. Mean RTs (\pm standard error) from 12 individual test bouts are plotted in 1-min bins for the 10-min PVT. Individuals carrying the 9-repeat allele, as either heterozygous or homozygous, were grouped together (9R). Data are plotted against the start time of the PVT test bout. As sleep deprivation progressed, time-on-task performance diverged between the 9R and 10/10 DAT1 genotype groups, such that those homozygous (10/10) for the DAT1 10-repeat allele were protected against severe time-on-task impairment. Shaded area: Nighttime test bouts. Modified from Satterfield BC, Wisor JP, Schmidt MA, Van Dongen HPA. Time-on-task effect during sleep deprivation in healthy young adults is modulated by dopamine transporter genotype. *Sleep* 2017;40(12):zsx167, with permission from Oxford University Press.

Executive functions

The term “executive function” is used to describe a group of higher order cognitive processes that are necessary to coordinate and control deliberate actions toward future goals [49]. The term encompasses several cognitive processes including the ability to sustain attention while suppressing distractors, inhibit inappropriate actions, switch tasks, shift mental sets, think flexibly, plan and sequence events, and make appropriate and low-risk decisions, to name a few (Fig. 29.8). While these complex cognitive processes are mediated by several interacting cortical and subcortical regions, they rely heavily on the prefrontal cortex (PFC) which is sensitive to the effects of sleep loss [50]. Notably, the PFC shows reduced glucose metabolism

following sleep deprivation (Fig. 29.9) [51], which is not fully reversed following a single night of recovery sleep [52]. This decline in prefrontal metabolic activity is thought to underlie some of the cognitive impairments seen during sleep loss.

To further complicate matters, not only are there interindividual differences in cognitive performance as discussed in the previous section, these differences are also task-dependent [53], meaning that those most vulnerable to impairment on one task are not necessarily vulnerable to performance impairment on a different task. This is because cognitive performance, including executive functioning, is not a unitary concept. Most tasks designed to measure executive functions involve several integrated processes that are differentially impacted by sleep loss

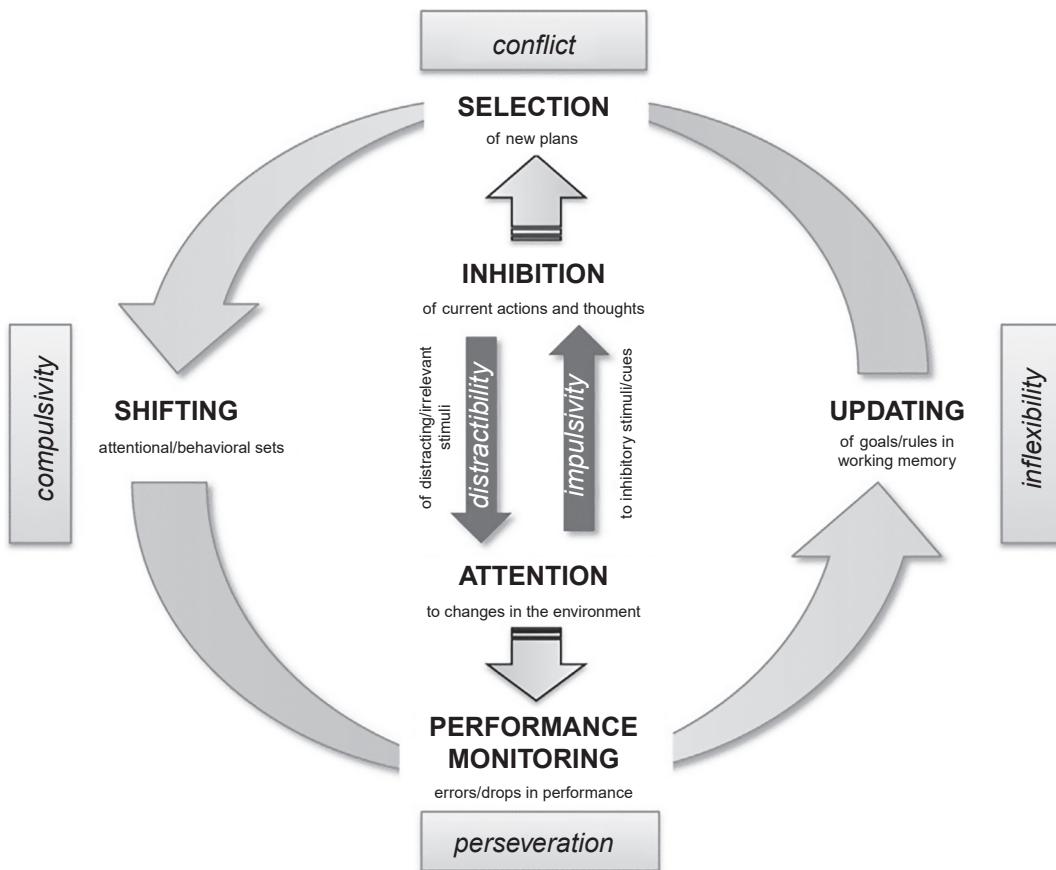


FIGURE 29.8 A simplified schematic of the hypothesized relationship between the different executive functions. The ability to sustain attention and inhibit inappropriate responses are thought to be central components of executive function. A well-rested individual will pay *attention* to incoming information in order to respond appropriately to incoming stimuli, such as *inhibiting* the current course of action if needed. At the same time, the brain *monitors performance* based on internal and external feedback and triggers a signal that a new plan of action is required if performance levels drop and the number of errors increase. Then, behaviors are updated to reflect a change in goals and a new plan is *selected*. With the implementation of a new course of action, an individual must then *shift* both behavioral and attentional resources to continue with the new plan. However, sleep loss disrupts several points in this cycle leading to unfavorable actions and outcomes. For example, impairments in attention and inhibition may lead to distractibility and impulsivity, respectively. Further, impaired attention can lead to perseveration, or over focused behavior. In turn, relevant goals and rules are unable to be updated, resulting in inflexibility. Inflexible behavior does not allow for an individual to select a new course of action and could lead to compulsive behavior. Thus, one must be able to effectively integrate attention, inhibition, and flexibility in order to monitor performance and accurately update goals in response to environmental changes. *Reproduced from Bari A, Robbins TW. Inhibition and impulsivity: Behavioral and neural basis of response control. Prog Neurobiol 2013;108:44–79, with permission from Elsevier.*

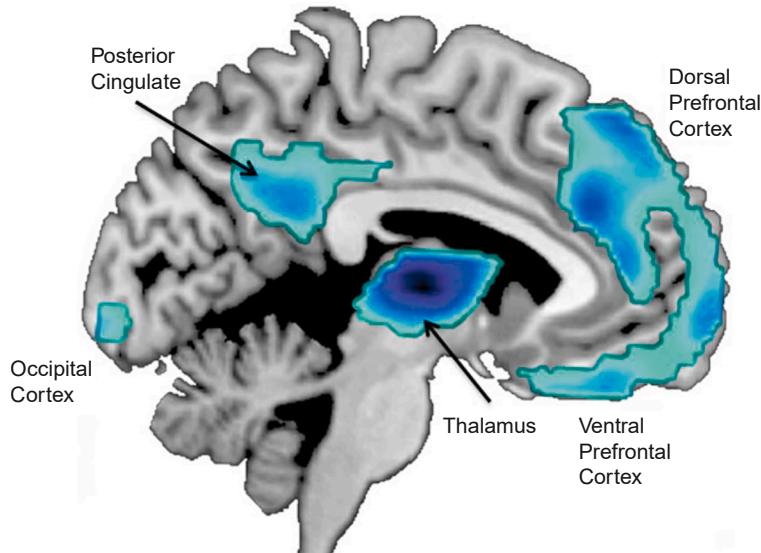


FIGURE 29.9 A positron emission tomography (PET) image of regional cerebral glucose metabolism following 24 h of sleep deprivation. Sleep deprivation results in decreased glucose metabolism in areas of the prefrontal cortex, thalamus, and posterior cingulate. Reduced metabolism in these areas is thought to subserve some of the sleep loss induced impairments in cognitive performance we often see. Reproduced from Killgore WDS, Weber M. *Sleep deprivation and cognitive performance*. In: Bianchi MT, editor. *Sleep deprivation and disease: effects on the body, brain, and behavior*. New York: Springer; 2014. p. 209–29.

[54]. The complexity and multiple cognitive processes involved in many executive function tasks introduces a “task impurity problem.” As Tucker et al. have demonstrated, performance on executive function tasks may not be attributable to global task impairments, but rather impairments in specific cognitive components of the task [55]. Thus, caution should be taken when administering and interpreting performance data from complex executive function tasks.

Working memory

Working memory can be described as the capacity to maintain and manipulate information in immediate memory, and underlies most executive functions. Working memory is conceptualized as having four components that include the storage of information, integration of information, regulation of information, and manipulation of information [56–58]. Working memory is distinct from short-term memory in that it requires both short-term storage of information *and* manipulation of that information [56]. There are several cognitive tasks that are used to measure various aspects of working memory, including digit span, word recall, number generation, serial addition, Sternberg, and *N*-back tasks [57].

In a meta-analysis, Lim and Dinges found that sleep loss impacts working memory performance with moderate effect sizes. Specifically, they found that both accuracy and RTs are impaired on these tasks [11]. Chee et al. conducted a series of studies using two different working

memory tasks to investigate how sleep loss disrupts neural signaling specific to maintenance and manipulation of information. Following either 24 or 35 h of total sleep deprivation, both tasks showed reduced functional activation within bilateral parietal regions [59,60], a common finding in studies of working memory and sleep loss [39,61,62]. However, Chee et al. [59,60] found conflicting results in regard to activity within the PFC. In the latter study of the series [60], activity in the left PFC was *reduced* after sleep loss, while the first study [59] found that activation in the left PFC actually *increased* after 24 h of sleep deprivation. The increase in neural responsiveness of the PFC following sleep loss may reflect the initiation of compensatory mechanisms that are required to maintain stable performance. The compensatory recruitment hypothesis suggests that some individuals are able to sustain cognitive performance during sleep loss by recruiting areas of the cortex that are typically not engaged by the same task during rested wakefulness [63].

Working memory performance during sleep loss appears to also be mediated by a genetic polymorphism of the circadian clock gene PERIOD3 (PER3). Individuals with the 5-repeat allele for PER3 had better working memory performance on an *N*-back task than those with the 4-repeat allele. The difference in performance was significant only at the circadian nadir in the early morning hours [64]. Taken together, findings from neuroimaging studies show that sleep deprivation influences working memory through disruption to fronto-parietal networks, and performance is mediated by genetic polymorphisms of the circadian system.

While imaging studies have been able to identify brain regions involved in working memory performance during sleep loss, behavioral studies have found that sleep loss differentially impacts specific aspects of working memory performance [55,60,65], and in a sex-dependent manner [66,67]. For example, Chee and Chuah found that sleep deprivation impairs general visual working memory (VWM) capacity, possibly due to degraded perceptual processing [68]. However, others have found that sleep loss does not impair VWM capacity, but rather impairs the ability to filter out VWM distractors [65]. Tucker et al. [55] also demonstrated that while sleep loss may show global decrements in working memory, the impairment is driven by specific working memory components. When dissociating a working memory task into “executive” and “nonexecutive” components, the nonexecutive working memory components (i.e., RTs) were the only elements impacted. “Executive” working memory scanning efficiency and resistance to proactive interference remained intact [55].

Rångtell and colleagues [66] administered a sequence-type working memory task following a single night of sleep loss, or 8 h sleep, which study participants performed in silence or with an auditory distraction. They were then asked to rate how confident they were in their performance. Overall, sleep loss impaired working memory performance in women, but not in men. Neither sex reported differences in subjective working memory performance. The auditory distraction impaired performance in both conditions and was not impacted by sex [66]. Overall, the accumulating data suggests that working memory impairments may actually be driven by degradation in alertness and vigilance, rather than the specific executive functions such as the ability to maintain and manipulate information, and these impairments are sex-specific.

Memorizing encoding, consolidation, and retrieval

While many studies have taken interest in sleep’s ability to strengthen memories, more recent investigations have focused on deficiencies in learning and information retention while sleep deprived. According to the American Psychology Association (2018), learning refers to the acquisition of new information following experience, observation, or practice [69]. This acquisition can be measured by changes to behavior, knowledge, or brain functioning [69]. Memory formation of new stimuli is typically divided into three phases: encoding, consolidation, and retrieval. The consolidation process is dependent on initial encoding, which cannot take place without hippocampal activation. During sleep, consolidation occurs with the transfer of information from the hippocampus (place of encoding) to the neocortex where it will then be “converted” into long-term memories and integrated with prior knowledge [70–72]. Alternatively, sleep

deprivation decreases hippocampal activation and its connectivity to other regions of the brain, thereby degrading the capacity to encode new information. Therefore, sleep loss can induce deficiencies in the consolidation process, suggesting that hippocampal-dependent information may not be properly or fully retained [73]. Following proper encoding and consolidation, retrieval of information occurs with the reinstatement of the necessary hippocampal and cortical activation that took place at the time of learning [74]. The combination of these three processes (encoding, consolidation, and retrieval) is important and necessary for proper cognitive functioning, as learning cannot take place without them. In summation, the effects of sleep loss on memory presents major concerns for chronically sleep restricted individuals.

Hippocampal activity is necessary for many critical memory functions, including the process of “information binding”, referring to one’s ability to “bind” (associate, or link) novel stimuli to the context in which it is experienced. This process is critical for tasks that require working memory and decision making. Failure to bind novel information can be harmful depending on the situation. For example, if an eyewitness to a car crash was unable to properly bind descriptive information, such as vehicle color or type, to the context of the accident (location, person driving, or circumstances of the collision), this could result in the spread of misinformation and lead to harmful outcomes such as wrongful accusations. In a recent study by Kurinec and colleagues (2021), sleep deprivation was found to inhibit the binding process, thus having downstream effects on decisive decision making [73]. While this inhibition appears to be clearly linked to the deactivation of the hippocampus, researchers suggest this could also involve a decline in functioning of the prefrontal cortex (PFC), which has been similarly implicated in various forms of cognitive functioning, such as working memory and goal-directed behaviors [75]. To test the effect of sleep deprivation on binding, Kurinec et al. (2021) utilized a source memory paradigm to assess contextual memory during and following total sleep deprivation [73]. Tasks that utilize “source memory” require participants to memorize a series of items and their originally presented context. This study revealed that both the encoding process of the individual items and the recognition of correctly remembered items’ association to their sources is impaired during sleep deprivation. The importance of this finding is the revelation that sleep deprivation can induce decrements to the binding process as a whole, effecting both source and item memory, rather than impairing one mechanism while the other remains intact [71–74].

Inhibitory control

Some actions may be adaptive under one set of circumstances, yet maladaptive in other circumstances. A key

aspect of executive functioning is the ability to inhibit inappropriate responses or behaviors in a particular context. For instance, lack of inhibitory control can lead to impulsive decisions that may have negative consequences. Inhibitory control is typically assessed using response inhibition tasks, including the stop signal task or go/no-go paradigms. These tasks are designed to measure the ability to withhold a prepotent (i.e., automatic) response [76]. In a typical go/no-go task, individuals learn to respond to a specific set of stimuli (*go* stimuli) and learn to withhold a response for a different set of stimuli (*no-go* stimuli). Performance is assessed based on correctly responding to *go* stimuli (simple attention and response time) and correctly withholding a response to *no-go* stimuli (inhibitory control).

Neuroimaging studies using the go/no-go paradigm suggest that the task recruits several PFC regions. Specifically, the ability to correctly withhold a response most consistently activates the right lateral PFC and bilateral insula. In contrast, failure to withhold a response engages the right anterior cingulate cortex (ACC), medial frontal gyrus and portions of the parietal lobe. All of which are regions often associated with error detection and behavioral monitoring [77]. These are some of the same regions that show reduced metabolic activity following sleep loss [51]. Thus, it would be expected that sleep loss impairs the ability to withhold inappropriate responses, which has been observed. In fact, sleep deprived individuals who are unable to efficiently inhibit responses on the go/no-go have difficulty recruiting the ventrolateral PFC. Conversely, resilient individuals show increased activation within this region [78].

Drummond et al. [79] used the go/no-go to assess the effects of 64 h of sleep deprivation on inhibitory control. As expected, the ability to inhibit inappropriate responses decreased as a function of time awake. Interestingly, hit rates (correct *go* responses) remained unaffected for most of the sleep deprivation period, but rapidly declined at 55 h of wakefulness [79]. Another sleep deprivation study found similar results [80]. In addition, these findings have been replicated under conditions of partial sleep restriction, where sleep was limited to 6 h per night for four nights. Study participants showed impaired inhibitory actions while maintaining correct responses [81]. Sleep loss causes a steady decline in response withholding with increasing time spent awake, while maintaining the ability to attend to incoming stimuli. These findings emphasize the fact that sleep deprivation does not result in a global degradation of cognitive performance due to impaired basic attention, thus cognitive impairment is task and domain-specific [32,54,82].

Cognitive control

A hallmark characteristic of executive function is the ability to modulate cognitive processes. In a broad

sense, cognitive control is the ability to regulate and coordinate thoughts and actions in-line with behavioral goals or changes in situational demands [83]. This allows us to balance cognitive *stability*—the ability to actively focus on and maintain task-relevant information—with cognitive *flexibility*—the ability to update information according to changes in situational demands, while also suppressing irrelevant information in order to appropriately adapt behavioral actions to meet new goals [83–85]. For example, you may be driving down a long, straight highway when a large deer jumps out in front of your vehicle. Your current goal of driving down a straight highway is disrupted by the unexpected object in the road. You must update your goal in order to appropriately adapt your response to the situation (i.e., avoid hitting the deer). Impairments in cognitive control can lead to perseverative, or over-focused, behaviors that can have serious consequences. These types of behaviors are often seen in psychiatric conditions such as obsessive compulsive disorder and schizophrenia [86].

Cognitive control encompasses the interaction of multiple cognitive processes, including working memory, attention, decision-making, response selection, response inhibition, and associated learning [86]. These processes underlie several behaviors such as multi-tasking/task-switching, changing behavior to fit a new rule, or suppressing distractions. Multi-tasking and task-switching are typically assessed using paradigms that require an individual to rapidly switch between response sets. The effect of *interference* (i.e., failure to suppress distractions) is often assessed using task paradigms that involve ignoring irrelevant information presented in order to stay focused on the task goal. Whereas *flexibility* (changing behavior to fit a new rule) is often measured using reversal learning tasks that require an individual to recognize changes in contingencies (changes in stimulus-response patterns) and update behavior accordingly.

In well-rested individuals, these task paradigms have been shown to reliably recruit areas of the PFC, specifically the orbitofrontal cortex (OFC) and dorsolateral PFC. There are also several reciprocal projections between the PFC and subcortical structures such as the ventral striatum, amygdala, and thalamus that are involved in maintaining cognitive control [86,87]. Additionally, both the cortical and subcortical regions are highly sensitive to disruptions in the neurochemical environment. Dopamine is a primary neuromodulator in the fronto-striatal pathway that is quite sensitive to perturbations such as sleep loss. Even small variations in dopamine levels can result in cognitive impairment [86,88]. Thus, alteration of functioning within the dopamine system may be one of the primary ways that sleep deprivation can affect cognition.

Multi-tasking and task-switching

In safety-critical operations, the ability to rapidly and efficiently switch between multiple tasks is paramount. Unfortunately, many of the occupations (e.g., airline pilots, truck drivers, medical personnel, military personnel, etc.) that require multi-tasking are also often subjected to chronic sleep loss. During a typical task-switching paradigm, individuals perform two types of tasks in succession in which numerical stimuli are presented. On one task type study participants are asked to identify which of the numbers is even or odd. On another task type study participants are asked to identify if the number presented is smaller or larger than a predetermined value. When two of the same task types are presented one after another, this is considered a repetition trial. When the trial switches from one task to the other this is considered a switch trial. Switch trials are used to calculate *switch cost*, or the change in reaction time and accuracy between the switch and repetition trials. Essentially, switch cost is a measure of the amount of time that is required to reconfigure the cognitive processes needed to perform the new task—a basic executive function.

A recent neuroimaging study found that while performing a task-switching paradigm following sleep deprivation, neural activation increased in the fronto-parietal network and cingulate gyrus as compared to the well-rested state. However, different brain regions were involved in the switch trials. Task-switching was associated specifically with increased activation in the superior temporal gyrus and thalamus. Based on the cerebral metabolic data described earlier, it would seem sensible to expect reduced activation in these key brain regions. However, the fact that sleep deprivation was associated with increased neural activation suggests that compensatory mechanisms may be initiated to maintain some level of information retrieval necessary for the task [89]. Nonetheless, from a behavioral perspective, sleep loss results in slowed RTs, especially during switch trials [89,90]. A single night of sleep loss also reduces performance accuracy and increases switch costs [90].

Total sleep deprivation studies are extreme cases of sleep loss and often do not translate to real-world scenarios. Haavisto et al. [91] investigated how multi-tasking performance is affected by sleep restriction over the course of what some would consider a typical workweek. Individuals in the restricted condition were only allowed to sleep for 4 h per night for five consecutive nights, compared to those in the well-rested condition who were allowed to sleep for 8 h per night. A multi-tasking paradigm was used in which study participants performed a series of subtasks to assess short-term memory, arithmetic skills, and visual and auditory monitoring. Sleep restriction impaired the ability to multi-task as a function of the

number of days of sleep restriction, with performance also degrading further as time-on-task increased. Additionally, it took two nights of recovery sleep (8 h) to return to baseline performance levels [91]. Because sleep loss degrades the ability to multi-task or rapidly switch between activities, the potential for errors and accidents significantly increases.

Cognitive interference

Another aspect of cognitive control is being able to suppress irrelevant or distracting information while maintaining focus on relevant task information. When the irrelevant aspects of the task cannot be ignored, this is known as *cognitive interference*. Typically, cognitive interference is measured using various forms of the Stroop paradigm. The goal of a Stroop task is to inhibit a common or “prepotent” response in favor of a less common response. For example, the brain naturally reads printed words it sees without any effort. This automatic tendency to read is known as a prepotent response. During a typical Stroop task, the participant is presented with a series of words depicting color names (e.g., “RED,” “GREEN,” “BLUE”). In some conditions the words are printed in either congruent (e.g., “RED” in red letters) or incongruent (e.g., “RED” in blue letters) ink colors, while in the neutral condition the words are printed in black ink. Individuals are to state the color of the ink in which the word appears, but not the word itself. The goal is to suppress the prepotent response (i.e., reading the word) in favor of the less common response (i.e., saying the color of the ink in which the word appears). This induces cognitive interference. Interestingly, several studies using the Stroop task have found that sleep deprivation does not affect cognitive interference, but rather only causes a general slowing of RTs [92–94]. A recent study found that resilience to slowed RTs and increased errors on the Stroop during a 30 h sleep deprivation period was related to a genetic polymorphism of the brain derived neurotrophic factor (BDNF) gene. Those individuals with the common Val allele had fewer errors compared to those with the Met allele [95], suggesting that some aspects of cognitive interference are predictable by genetic markers.

However, Gevers et al. [96] recognized the importance of assessing task performance in relevant components rather than assessing performance across the task as a whole. The Stroop task was administered once after a full night of sleep and again following a night of sleep deprivation. The task was decomposed into three components for analysis: size of the interference effect, bottom-up modulation (facilitated processing after repetitions), and top-down modulation (cognitive control adjustments for incongruent trials). They found that sleep deprivation impaired top-down control such that there was a reduced

ability to efficiently recognize and adapt to conflicts (i.e., incongruent trials) [96]. It is possible that earlier studies did not find an effect of cognitive interference because different aspects of the task, as demonstrated by Gevers et al. [96], are differentially impacted by sleep loss, further highlighting the importance of deconstructing a task into specific, well-defined cognitive components.

Flexible attentional control

As with multi-tasking, the ability to think flexibly and quickly adapt to changing environmental circumstances is important in safety-critical operations. Effective attentional control requires an individual to anticipate responses and outcomes based on a predetermined set of expectations. However, real-world situations place individuals in dynamic environments that often challenge set expectations. Thus, individuals must be able to effectively recognize a change in circumstances and appropriately update the behavioral response. Reversal learning paradigms are typically used to assess flexible attentional control. While there are a wide variety of reversal learning paradigms, in the simplest form these tasks involve learning specific stimulus-response mappings that are tied to a reward and those that are tied to an unfavorable outcome. At a point in the middle of the task, the stimulus-response contingencies are reversed, such that previously rewarding stimuli become unfavorable and vice versa. Those that are able to maintain flexible attentional control will quickly recognize a change has occurred and adapt their responses. In contrast, those that do not think flexibly tend to show perseverative behavior by responding to the old stimulus-response mappings.

Interestingly, impairments in cognitive flexibility mimic impairments seen in individuals suffering from damage to the OFC and the basal ganglia [86,97–99]. Neuroimaging studies in well-rested adults show that reversal learning recruits the ventrolateral PFC when a subject stops responding to the previously correct stimuli and starts responding to the new, relevant stimuli. When a subject makes a reversal error (i.e., responding to the incorrect stimulus following the stimulus-response reversal), there is neural activation within the ventral striatum [100]. Until recently, flexible attentional control had not been thoroughly explored under conditions of sleep deprivation. Whitney et al. [101,102] conducted a series of sleep deprivation studies to assess how sleep loss impacts the ability to maintain flexible attentional control. In the first study, research participants were exposed to a 62 h sleep deprivation period. These individuals performed a modified version of the basic go/no-go paradigm during well-rested baseline, after 55 h of extended wakefulness, and following recovery sleep. During this novel task,

participants were required to respond to a specific set of numeric stimuli (*go* stimuli) and withhold their response from a different set of numeric stimuli (*no-go* stimuli). However, they were required to learn which stimuli were *go* and which were *no-go* based on monetary reward feedback. Halfway throughout the task, the stimulus-response contingencies were reversed. Stimuli that were previously *go* stimuli became *no-go* stimuli and stimuli that were previously *no-go* stimuli became *go* stimuli. Participants were unaware of the reversal, and were again required to use monetary reward feedback to determine the correct stimulus-response mappings [101]. Sleep deprivation degraded pre-reversal performance, and even further degraded post-reversal performance (Fig. 29.10). Importantly, the profound impairment seen on the reversal learning task was distinct from vigilant attention impairment [101]. Further, it was found that the Val165Met genetic polymorphism of catechol-*O*-methyltransferase (i.e., the enzyme that degrades dopamine in the PFC) was associated with resilience to impairment on the go/no-go reversal learning task. Specifically, individuals carrying the Met allele were protected from the post-reversal performance impairment described above [84]. Additionally, past neuroimaging research has shown this same polymorphism of the COMT gene influences multiple processes of cognitive control [103–105]. This combined with Satterfield's (2017) [84] findings suggests that differing genetic modulations of dopamine availability within the PFC can have significant effects on individuals' vulnerability to sleep loss, especially working memory and attentional control.

In a follow-up study, Whitney et al. [102] used a novel adaptation of the continuous performance task (AX-CPT) in which previous cue-probe contingencies were switched halfway throughout the task. They again demonstrated that sleep deprivation diminishes flexible attentional control, and also found that top-down control does not efficiently prevent errors [102]. They also found that a polymorphism that affects the binding potential of the dopamine D₂ receptor (DRD2) is associated with protection from impairment. Specifically, individuals homozygous for the C allele were resilient to impaired flexible attentional control. Together, these findings demonstrate that sleep deprivation profoundly degrades the ability to maintain flexible attention control, which can lead to maladaptive behaviors, including perseveration. Further, resilience to cognitive control impairment seems to be mediated by functional dopaminergic polymorphisms involved in the fronto-striatal pathways.

Problem solving

The ability to solve problems is a core aspect of nearly any job. Depending on the operational environment, the kinds

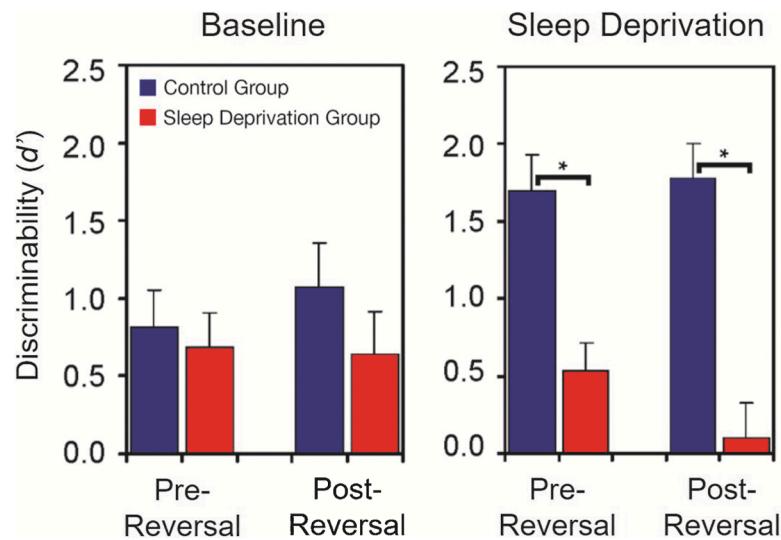


FIGURE 29.10 Discriminability scores (\pm SE) on the go/no-go reversal learning paradigm. At baseline (left), there were no significant differences in pre- or post-reversal performance between the well-rested control and the sleep deprived groups. However, performance was profoundly degraded in the sleep deprived group (right). Impairment was further impaired following the stimulus-response reversal. Asterisks (*) indicate statistically significant pairwise differences. Modified from Whitney P, Hinson JM, Jackson ML, Van Dongen HPA. Feedback blunting: Total sleep deprivation impairs decision making that requires updating based on feedback. *Sleep* 2015;38(5):745–54, with permission from Oxford University Press.

of problems that workers may encounter can range from simple mundane challenges to those that can be mission critical or even life threatening. Because many occupations require individuals to remain awake for extended periods or during times that are out of phase with their circadian rhythm, it is important to understand how various aspects of problem-solving ability can be impacted by lack of sleep.

Convergent thinking and logical deduction

Different kinds of problems require different kinds of solutions. One type of problem can be solved through the process of *convergent thinking*. This type of problem solving involves the step-by-step application of logical deductive reasoning and the use of established rules to reach a solution. These kinds of problems can be solved by beginning with an established set of information or major premise, adding a second minor premise, and finally arriving at a logical conclusion. For example, given the major premise that “every A is B” and the minor premise that “this C is A,” then it is logical to conclude that “therefore this C is B.” Concretely, we could apply this to a real-life example such as “all bulldogs are animals. Baxter is a bulldog. Therefore, Baxter is an animal.” While this process sounds complex, evidence suggests that this form of convergent thinking is not significantly degraded by sleep deprivation [50]. Most studies that have specifically tested outcome measures such as logical deduction, intellectual functioning, grammatical reasoning, reading comprehension, and nonverbal problem solving have found

negligible effects of sleep deprivation on these capacities [11,50].

Divergent and innovative thinking

In contrast to the convergent thought processes discussed above, the ability to think laterally, innovatively, and flexibly does appear to be particularly susceptible to sleep deprivation [50]. In one study, a single night without sleep was associated with fewer creative responses and greater difficulty letting go of unsuccessful strategies [106]. Similarly, sleep deprivation has also been shown to adversely affect the ability to generate lists of novel words and produces slower and less efficient performance on the Tower of London, a task that requires planning, forethought, and cognitive flexibility [50]. The ability to generate and vocalize a series of random numbers is also degraded by sleep deprivation, leading to increased redundancy and stereotypy of responses and frequent rule violations [107]. On the other hand, inconsistent effects of sleep deprivation have been reported for the Wisconsin Card Sorting Test (WCST), a clinically based test of concept formation, set shifting, and mental flexibility [108]. It is important to keep in mind, however, that the WCST is a clinical task that was designed to detect relatively severe brain injuries and may not be sensitive enough to detect the subtle effects produced by sleep loss.

One particularly interesting study attempted to mimic real life decision-making during sleep deprivation by using a complex marketing strategy game. The task required participants to engage in several high level executive

function tasks during a prolonged period of sleep loss. In particular, participants had to continuously monitor ongoing activities, revise their marketing strategies in light of periodically appearing new information, and apply available information to develop creative and innovative solutions under severe time constraints [109]. When normally rested, participants were able to think flexibly and innovatively, but once sleep deprived, they showed rigid thinking and perseverated on poor and ineffective strategies. As they reached the end of the game, these sleep deprived individuals had exhausted their financial resources and were in a significantly worse financial position than compared to playing the same game in a rested state [109]. While such tasks can be incredibly ecologically valid and applicable to real-world situations, these types of complex tasks also suffer from the previously described task impurity problem [54,55]. These types of tasks are not designed to deconstruct the component processes most affected by sleep loss, but do provide important understanding of how lack of sleep may actually be manifested in real-world situations.

Risk-taking, judgment, and decision-making

Can sleep deprivation increase the tendency to engage in high-risk activities or does it affect decisions that involve risk? While these questions seem simple, the answers appear to be complex and depend on a number of factors. We will address several issues, including how sleep loss affects self-reported risk-taking propensity, decision-making under conditions of uncertainty, the role of effort on risky behavior, implicit cognitive biases, aggressive behaviors, and moral decision-making.

Self-rated risk propensity

People can engage in high risk activities for a number of reasons. The construct of *risk-taking* is often confused with the closely related construct of *sensation seeking*, a preference for seeking out novel experiences and other thrilling activities that produce high levels of physiological arousal [110]. In contrast to sensation seeking, *Risk-Taking Propensity* represents the tendency to engage in activities that include a high level of risk, danger, or uncertainty of outcome [111,112]. Although risk taking can occur because an individual is sensation seeking, risky behavior can also occur for reasons other than the pursuit of thrills or excitement. Accordingly, these two constructs are only modestly correlated with one another [113].

Interestingly, sleep deprivation has been shown to affect scores on measures of both sensation seeking and risk-taking, but the associations are typically inverse. For instance, one night of total sleep deprivation has been

shown to significantly reduce scores on measures of self-reported sensation-seeking and self-reported risk-taking propensity [114,115]. Similar findings have also been reported following two nights without sleep [35,116]. Such findings are not surprising when considered in light of the fact that one of the most common symptoms of sleep loss is increased fatigue and reduced physical and mental energy [117]. It seems sensible that increased fatigue would lead to a reduction in activities requiring energy expenditure or exertion of mental or physical effort. Interestingly, longer periods of total sleep deprivation (i.e., 75 h awake) have been associated with a reversal of this trend, with participants showing greater interest in risky activities by the third night without sleep [35]. It is not entirely clear why this upsurge in risky preferences may occur, but it is conceivable that severe extended sleep deprivation may (1) substantially alter judgment, (2) lead to a burst of hypomanic disinhibition due to altered prefrontal functioning, or (3) be an attempt of participants to seek out stimulation as a means to behaviorally induce arousal. Notably, repeated doses of caffeine (200 mg every 2 h) appeared to be protective against this sudden surge in self-reported risk-seeking. Overall, these findings suggest that short term sleep deprivation (one or two nights) reduces interest in high-risk sensational activities, whereas that interest may show a rebound when sleep deprivation becomes extreme (≥ 3 nights).

Risky decision-making

While it is clear that sleep loss can lead to altered risk-related perceptions, it is also important to understand how sleep deprivation can affect actual risk-taking behavior. During studies of sleep deprivation, propensity of risky behaviors is often assessed through the administration of gambling or other similar game-like risk tasks that often require different applications of decision making and information binding [73]. In the following sections, we will discuss how sleep deprivation can lead to altered perception of risk, and therefore alter behavioral outcomes.

Cognitive framing

Sleep deprivation can affect how a person responds to the way in which a risk is presented to them, a phenomenon known as “framing.” In most circumstances, risks can be framed as a potential gain (e.g., would you rather have an 80% chance of winning \$4000, or a 100% chance of winning \$3000) or as a potential loss (e.g., would you prefer an 80% chance of losing \$4000 or a 100% chance of losing \$3000). In such cases, it is well established that most people are risk avoiding when considering possible gains (i.e., they would prefer the “sure thing”) and risk seeking when considering possible losses (i.e., they would prefer

the “long shot”) [118]. Interestingly, sleep deprivation appears to shift this basic cognitive bias. For example, in one study using a gambling game, when possible outcomes were described in terms of potential gains, sleep deprivation produced an increase in risk-taking above baseline. However, when possible outcomes were framed as potential losses, sleep deprivation caused participants to become more risk averse than when normally rested [119]. These findings suggest that sleep deprivation modifies the typical framing effect, increasing risk-taking when gains are emphasized and increasing risk-aversion when losses are emphasized, thus magnifying our typical tendencies.

Altered expectations of reward

Sleep deprivation appears to alter the cognitive assessment of risk by changing functioning within brain regions that assign value to objects or situations. For example, one study examined the effects of sleep deprivation on brain activation while participants completed a roulette-style gambling task [120]. During a neuroimaging session, participants completed a series of roulette gambles that ranged from certain wins to highly risky bets. One night of sleep deprivation led to increased activation within the nucleus accumbens during high-risk decisions. This brain structure is involved in the anticipation of rewards and the increased responsiveness of this area following sleep loss suggests that it may be increasing the expected value of the risky bets. Simultaneously, sleep deprivation also blunted activation within the insular cortex during losses. Together, these findings suggest that sleep deprivation alters brain activation in a way that could bias an individual toward risky-behavior (i.e., increasing expectation of rewards and minimizing responses to losses).

The same research team conducted a follow-up study to examine the effects of sleep deprivation on complex reward-based decision-making [121]. Research participants completed a series of trials, some of which focused on gains and others that focused on losses. For instance, during the gain-focused trials, participants could choose to increase the potential amount of money that could be won or increase the probability of winning a particular amount. On the other hand, loss-focused trials permitted the participant to either reduce the amount of money that could be lost or lower the probability of losing a specified amount. Rested individuals showed a bias toward minimizing losses, but this pattern shifted toward maximizing gain after sleep deprivation. These changes were associated with increased activation of reward processing regions, including the ventromedial PFC, and a decline in activation of the insular cortex, which is generally associated with aversion and negative affective experiences [121]. Together, these findings suggest that sleep deprivation alters functional activation in brain regions associated with

reward and punishment, which may increase the expectation that risky decisions will lead to reward.

Reward-based learning

Poor decision-making is often characterized by a preference for short-term gains that ultimately lead to long-term losses. Everyday life is full of choices that involve deciding whether to forgo immediate satisfaction in service of longer lasting benefits. One experimental paradigm that seems to get to the heart of these kinds of decisions is the Iowa Gambling Task (IGT), a computerized gambling game-like task that involves selecting cards from four decks with varied, but unstipulated, payout schedules. Two of the decks are high risk because of their widely variable payouts that lead to a net loss, and two of the decks are low risk because they have very consistent but small payouts that reliably lead to a net gain. When healthy normal individuals play this game, they rapidly learn to maximize long-term profits over short-term gains by sticking with the low risk decks. In contrast, patients with focal lesions to the ventromedial PFC, a region critical to learning from rewards and punishments, tend to become selectively attracted to the short-term gains associated with the high-risk decks, which eventually leads them to progressively lose money throughout the course of the game [122,123].

The IGT has been studied in several studies of sleep deprivation, which have consistently demonstrated that lack of sleep is associated with a pattern of performance that is qualitatively similar to that of patients with lesions in the ventromedial region of the PFC [124–126]. In short, sleep deprivation leads to a short-term focus on immediate gains to the detriment of longer-term outcomes, a pattern that appears to be more severe with greater durations of sleep deprivation. This effect is mediated, in part, by the DAT1 polymorphism, such that individuals with the 9-repeat allele have elevated responsivity to gain anticipations [127]. Interestingly, stimulant countermeasures such as caffeine, modafinil, and dextroamphetamine have not been effective at restoring performance on the IGT (Fig. 29.11), despite normalizing performance on psychomotor vigilance [124,125]. This lack of effect of stimulants suggests that the deficits on the IGT are probably not due to problems with attention and vigilance and are brought about by alteration in the process of integrating information about rewards and punishments with ongoing decision-making processes. In another study, we also showed that daytime sleepiness reduces the psychological weight that individuals give to more temporally distant versus more recent trials on the IGT in their decision-making strategy [128]. These data suggest that sleepiness may shorten the “time horizon” over which decision information is integrated into the decision-making process. Recently, Lim and colleagues reanalyzed data from one of

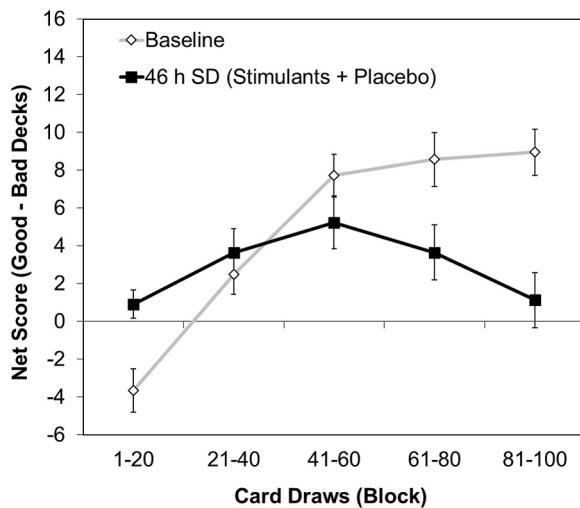


FIGURE 29.11 Net scores on the IGT for each block of the task. Study participants performed the task following 46 h of extended wakefulness. Stimulants (600 mg caffeine, 20 mg dextroamphetamine, 400 mg modafinil, or placebo) were administered at 44 h wakefulness. Stimulants did not affect IGT performance, and are thus grouped with the placebo group here. Stimulants (black squares) were not effective at restoring IGT performance back to baseline levels (white diamonds). Modified from Killgore WDS, Grugle NL, Balkin TJ. Gambling when sleep deprived: don't bet on stimulants. *Chronobiol Int* 2012; 29(1):43–54, with permission from Taylor & Francis Ltd. (<http://www.informaworld.com>).

these key IGT studies using advanced computational modelling [129]. This contemporary modelling approach supported the initial report that caffeine had no effect on IGT performance, but further revealed that some of the increase in risky decision making after two nights of sleep loss was due to increased random behavior rather than intentional risk-taking. The computational modelling also showed a previously unidentified tendency toward reduced sensitivity to rewards/punishments evident during the third night without sleep. Together, these findings suggest that sleep deprivation impairs decision-making through several mechanisms—including shortened integration horizons, increased random behavior, and reduced sensitivity to rewards and punishments—and that the relative influence of these processes changes as sleep loss becomes more prolonged.

Impulsive behavior

While risk taking often involves deciding between high and low risk options, another form of risk-taking involves “pressing one’s luck” beyond the point where the benefits of success are outweighed by the costs of failure. A task that assesses the tendency to push the limits and behave impulsively is known as the Balloon Analog Risk Task (BART). The BART is a computerized task that presents a series of 30 virtual balloons that must be inflated on the screen to win money. To inflate each balloon, the participant presses the spacebar on the keyboard. With each key press, or “pump,” the balloon increases in size slightly and gains an additional five cents in value. The larger the balloon becomes, the greater its potential monetary value.

The participant can “bank” the accumulated value of a balloon at any time, as long as it has not exploded. If the balloon is inflated too much, the balloon will explode and all accumulated value for that balloon will be lost. Each balloon has a different breaking point that is not known to the participant. In order to win the most money possible, the participant must make a judgment about how much to inflate each balloon and then attempt to cash in before reaching the unknown explosion point. A commonly used output variable from this task is mean number of key presses for the unexploded balloon trials (i.e., those trials that were “banked” without popping the balloon), which is commonly known as the Adjusted Average Number of Pumps. Some studies have also calculated a “Cost/Benefit Ratio,” which considers both the Cost (i.e., proportion of exploded balloons) versus the Benefit (i.e., the proportion of all potential money that was actually banked) [35,115,116]. Higher Cost/Benefit Ratio scores suggest greater risk-taking.

Several sleep deprivation studies have used the BART to examine the effects of sleep loss on risky behavior. The first published study to examine the BART during sleep deprivation showed that one night without sleep led to a decline in the Cost/Benefit Ratio, suggesting a tendency toward less behavioral risk-taking [115]. A second study published around the same time also found that a single night of sleep deprivation was associated with reduced risk-taking (i.e., lower Adjusted Average Number of Pumps) among women but not men [130]. Later work further confirmed that risk taking on the BART was reduced with two nights of sleep deprivation, but was

returned to baseline levels with a 20 mg dose of dextroamphetamine, but not by similarly alerting doses of 400 mg modafinil, or 600 mg of caffeine [116]. In contrast, Killgore et al. found that BART Cost/Benefit scores were generally unaffected by two nights of sleep deprivation, but this was followed by a surge in behavioral risk-taking after three nights without sleep [35]. The cause of this surge in risk-taking after extreme sleep deprivation is not clear, but it is possible that inhibitory capacity eventually fails after several nights awake, or that the increased risk taking is simply a way for participants to stimulate arousal [35].

The fact that the BART typically shows reduced risk-taking during sleep loss seems to stand in contradiction to the increased risk-taking that is consistently found on the IGT. One explanation for this discrepancy may involve the difference in effort required by these two tasks [115]. While both the IGT and BART involve risky decision-making, risky choices on the IGT require no more effort than the safe options (i.e., a single button press is required regardless of which option is selected), while greater risk taking on the BART requires the expenditure of additional physical and cognitive effort (i.e., more button presses are required to be risky, while fewer button presses are safer). This explanation was given further support by a study that showed that sleep deprivation leads to “effort discounting,” a willingness to accept less reward if it requires only minimal effort rather than expend greater effort to obtain higher value rewards [131]. Sleep deprived individuals appear to be less willing to expend effort to engage in risky activities.

Aggressive/punitive responses

Negative mood states are common during sleep deprivation and evidence suggests that individuals may become more easily frustrated by even minor hassles or interpersonal slights. For instance, sleep deprivation appears to increase the willingness to blame others for frustrating problems and makes people less willing to work with others to achieve mutually satisfying outcomes [132]. Without sleep, people often feel picked on or targeted for persecution [133]. Sometimes, this can even lead to aggressive behaviors [134]. In one study, participants played a series of “bargaining” and “trust” games that required them to interact with other players to earn various levels of money [135]. On these games, sleep deprivation increased the tendency to engage in aggressive exchanges with the other players. Moreover, sleep deprived individuals were less trusting of their partners and more often rejected monetary offers that were perceived as unfair, even when rejecting the offer would come at a financial cost to themselves. Sleep deprivation appears to have an adverse effect on trust and normal social discourse.

Moral judgment

Our stable moral precepts and beliefs dictate our responses to difficult situations where the appropriate decision is not obvious. A few studies have demonstrated moral judgment and moral decision-making can be affected by sleep deprivation. In the earliest published study to examine moral judgment following sleep loss, participants completed a series of moral and nonmoral dilemmas when fully rested and again following 53 h of sleep deprivation [136]. The findings showed that most decision-making processes were relatively unaffected by sleep deprivation, including nonmoral decisions and moral decisions that were generally low in emotional intensity. However, sleep deprivation appeared to significantly slow responses to difficult moral decisions that involved high levels of emotional conflict. Compared to the speed of decisions at baseline, the time to respond to emotionally challenging situations was much slower, suggesting that sleep deprivation does not affect all decisions equally—sleep deprivation specifically impairs the ability to make emotionally based decisions. Moreover, sleep deprivation also altered the qualitative direction of the judgments. Specifically, sleep deprived individuals were more likely to make utilitarian type judgments that violated their own moral beliefs compared to when they were well rested [136]. However, this effect was not significant in a second study of only a single night of sleep loss [137], suggesting that deficits in moral judgments may only emerge with prolonged periods without sleep. Other evidence also suggests that moral reasoning may be affected by partial sleep restriction as well. For instance, when sleep was restricted to approximately 2.5 h per night over 5 days, military personnel showed significant reductions in principle-oriented moral reasoning [138]. Among this sample of military cadets, their moral decisions became more rules-focused and self-oriented over the course of sleep restriction, and they showed progressively greater difficulty with higher-level principle-oriented reasoning. Overall, it appears clear that sleep deprivation affects the speed and quality of moral decisions and judgments.

Teamwork and cooperative behavior

As revealed by many of the studies discussed throughout this chapter, a majority of research in the field has focused on the effect of sleep deprivation on individual performance and experiences. Given modern society’s reliance on effective collaboration, it is critical to understand how sleep loss undermines team dynamics and cooperative behavior—potentially compromising performance, decision-making, and overall mission success. Further, there are many occupational settings that are often subjected to chronic sleep loss or circadian misalignment and

depend heavily on team-based behaviors, including occupations in medicine, emergency response, and the military. Therefore, it is important to understand the effects of fatigue on group performance and how this may change in real world occupational settings. While a plethora of negative impacts following sleep loss have been identified, a study by Benderoth et al., (2025) interestingly found that when applied in a controlled, laboratory study, cooperative teamwork can work as a countermeasure to performance impairments during sleep loss [139]. Specifically, when comparing teamwork among well-rested and sleep deprived subjects, individuals reported identifying more with their team members and having higher team cohesion, as well as higher acceptance of other's knowledge during sleep deprivation compared to controls. These factors also positively affected work mode, despite sleep deprived individuals reporting less motivation to perform the task compared to those who were well-rested [139]. While this finding is promising and somewhat surprising, real world implications make it difficult to draw inferences on how teamwork behavior interacts with sleep loss in dynamic occupational settings. When attempting to draw such inferences, it is critical to consider how individual vulnerability to fatigue may carry over into group performance. For example, an individual who is unable to update information and maintain attention while sleep deprived is less likely to prevent errors caused by counter information, [102] leading to poor adaptation during quickly evolving situations that can put themselves and others at risk [140]. Considering that a team can be made up of one or more vulnerable individuals, it is logical to infer that these scenarios can allow for reduced effectiveness of team operations, stemming from diminished available knowledge, skills, and abilities needed to complete the task at hand [140]. Further, there are three primary elements that are considered critical to team cohesion, including affective states (such as emotional processing and reactions), cognitive states, and behavioral processes [141,142]. Sleep loss can interact with each of these elements separately or combined, allowing for multiple avenues in which teamwork may be impaired [140].

Practical implications

Extreme cases of acute sleep deprivation often fail to be generalizable to real-word situations. However, a common occurrence in everyday life is that of chronic sleep restriction. It is common for individuals to repeatedly, and regularly, obtain insufficient amounts of sleep. Individuals that are chronically sleep-restricted often have difficulty with day-to-day tasks, and they may not even realize it until it is too late. For example, individuals that are leaving a night shift often drive drowsy. While drowsy driving may not always lead to a direct negative consequence, under the

right circumstances the results can be catastrophic due to the unpredictable nature of sleep loss induced impairments. For instance, if an individual experiences even a single lapse in attention at the same moment a stop light turns red, the result could be disastrous. Further, the inability to effectively inhibit responses and make rational decisions can significantly impact work performance and interpersonal relationships. As sleep loss impairs inhibitory control, individuals that are sleep-restricted may make decisions or act in ways that are out of character or inappropriate to the context due to a diminished capacity to inhibit responses. This could prove harmful to an individual's social or professional reputation or could damage close interpersonal relationships. Additionally, sleep loss alters reward expectation in such a way that individuals do not realize the consequences of their actions, as they expect to be rewarded by their choices, regardless of the quality of the decisions. This exaggerated expectation of reward may lead individuals to make risky decisions, which could affect economic choices such as gambling or selecting risky investments. Of course, these same unrealistic expectations of reward could potentially affect other behaviors as well, including social, interpersonal, and professional decisions. Overall, it is important for individuals to recognize the range of cognitive consequences of sleep loss and the downstream effects that insufficient sleep can have on basic day-to-day activities and interpersonal relationships.

Often times, the effects of sleep loss can be mitigated with effective countermeasure strategies, including caffeine and strategic napping [6], although there is some evidence that widely used stimulants, such as caffeine, may improve some executive functions [35,143,144] while having no discernible effects on others [124,125]. However, many of the negative consequences associated with sleep loss can be avoided all together with a proactive approach. Those who are often faced with chronic sleep loss should take the steps necessary to educate themselves on causes and consequences of fatigue. It is also important to become educated about and implement proper sleep hygiene techniques, including making sleep a priority, standardizing sleep schedules, creating a good sleep environment, and "unplugging" from technology and other forms of stimulation at least 30 min before bed [145]. In addition, individuals should attempt to align lifestyle choices with their work and social schedules to maximize sleep opportunities [6].

Conclusions

Sleep loss appears to have a multifaceted impact on both neural and behavioral measures. These impacts affect both global and domain-specific aspects of cognition. This, in part, is due to the differential responsiveness of the

interconnected brain regions underlying each specific cognitive task. Sleep loss consistently impairs vigilant attention performance, resulting in increased lapses of attention and slowed response times. However, the literature is mixed as to if, and how, insufficient sleep influences performance on higher-order executive function and decision-making tasks. For example, the executive and nonexecutive components of working memory are differentially impacted by sleep loss. Further, other complex executive functions, such as cognitive control, are negatively impacted by sleep loss, yet impaired vigilant attention does not seem to be the underlying cause. For some higher-level tasks that involve judgment and decision-making, the effects of sleep loss on emotional systems may be particularly important. While research into the underlying mechanisms of cognitive impairment due to sleep loss has increased in recent years, more work is needed in order to fully elucidate how sleep loss specifically impacts various aspects of cognition. Identification of task-specific impairments, and the mechanisms subserving these impairments, can aid in the development of appropriate countermeasures and fatigue risk management strategies for those most at risk for experiencing chronic and acute sleep loss.

References

- [1] Center for Disease Control and Prevention. Insufficient sleep is a public health epidemic. 2015. p. 2015.
- [2] Bayon V, Leger D, Gomez-Merino D, Vecchierini M-F, Chennaoui M. Sleep debt and obesity. *Ann Med* 2014;46(5):264–72. <https://doi.org/10.3109/07853890.2014.931103>.
- [3] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC, Adams Hillard PJ. National sleep foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 2015;1(1):40–3. <https://doi.org/10.1016/j.slehd.2014.12.010>.
- [4] Borbely AA. A two process model of sleep regulation. *Hum Neurobiol* 1982;1(3):195–204.
- [5] Daan S, Beersma DG, Borbely AA. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol Regul Integr Comp Physiol* 1984;246(2):R161. <https://doi.org/10.1152/ajpregu.1984.246.2.r161>.
- [6] Satterfield BC, Van Dongen HPA. Occupational fatigue, underlying sleep and circadian mechanisms, and approaches to fatigue risk management. *Fatigue Biomed Health Behav* 2013;1(3):118–36. <https://doi.org/10.1080/21641846.2013.798923>.
- [7] Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Methods Instrum Comput* 1985;17(6):652–5. <https://doi.org/10.3758/BF03200977>.
- [8] Lim J, Dinges DF. Sleep deprivation and vigilant attention. *Ann N Y Acad Sci* 2008;1129:305–22. <https://doi.org/10.1196/annals.1417.002>.
- [9] Dorrian J, Rogers NL, Dinges DF. Psychomotor vigilance performance: neurocognitive assay sensitive to sleep loss. Informa UK Limited, Informa UK Limited; 2004. p. 39–70. <https://doi.org/10.3109/9780203998007-4>.
- [10] Doran SM, Van Dongen HPA, Dinges DF. Sustained attention performance during sleep deprivation: evidence of state instability. *Arch Ital Biol* 2001;139(3):253–67.
- [11] Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol Bull* 2010;136(3):375–89. <https://doi.org/10.1037/a0018883>.
- [12] Drummond SPA, Bischoff-Grethe A, Dinges DF, Ayalon L, Mednick SC, Meloy MJ. The neural basis of the psychomotor vigilance task. *Sleep* 2005;28(9):1059–68.
- [13] Wesensten NJ, Killgore WDS, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. *J Sleep Res* 2005;14(3):255–66. <https://doi.org/10.1111/j.1365-2869.2005.00468.x>.
- [14] Cajochen C, Khalsa SBS, Wyatt JK, Czeisler CA, Dijk DJ. EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *Am J Physiol Regul Integr Comp Physiol* 1999;277(3):R640. <https://doi.org/10.1152/ajpregu.1999.277.3.r640>.
- [15] Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res* 2003;12(1):1–12. <https://doi.org/10.1046/j.1365-2869.2003.00337.x>.
- [16] Van Dongen HPA, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26(2):117–26. <https://doi.org/10.1093/sleep/26.2.117>.
- [17] Chee MWL, Tan JC. Lapsing when sleep deprived: neural activation characteristics of resistant and vulnerable individuals. *Neuroimage* 2010;51(2):835–43. <https://doi.org/10.1016/j.neuroimage.2010.02.031>.
- [18] van Dongen HPA, Belenky G, Krueger JM. A local, bottom-up perspective on sleep deprivation and neurobehavioral performance. *Curr Top Med Chem* 2011;11(19):2414–22. <https://doi.org/10.2174/156802611797470286>.
- [19] Bills AG. Blocking: a new principle of mental fatigue. *Am J Psychol* 1931;43(2):230. <https://doi.org/10.2307/1414771>.
- [20] Nancy Barone Kribbs, Dinges D. Vigilance decrement and sleepiness. American Psychological Association (APA); 1994. p. 113–25. <https://doi.org/10.1037/10166-007>.
- [21] Van Dongen HPA, Dinges DF. Investigating the interaction between the homeostatic and circadian processes of sleep-wake regulation for the prediction of waking neurobehavioural performance. *J Sleep Res* 2003;12(3):181–7. <https://doi.org/10.1046/j.1365-2869.2003.00357.x>.
- [22] Arthur G. Bills, fatigue in mental work. *Physiol Rev* 1937;17(3):436–53. <https://doi.org/10.1152/physrev.1937.17.3.436>.
- [23] Dongen B, Krueger JM. Cognitive fatigue: multidisciplinary perspectives on current research and future applications. American Psychological Association; 2011. p. 127–47.
- [24] Van Dongen HPA, Dinges DF. Sleep, circadian rhythms, and psychomotor vigilance. *Clin Sports Med* 2005;24(2):237–49. <https://doi.org/10.1016/j.csm.2004.12.007>.

- [25] Van Dongen HPA, Belenky G. Individual differences in vulnerability to sleep loss in the work environment. *Ind Health* 2009;47(5):518–26. <https://doi.org/10.2486/indhealth.47.518>.
- [26] Krueger JM, Rector DM, Roy S, Van Dongen HPA, Belenky G, Panksepp J. Sleep as a fundamental property of neuronal assemblies. *Nat Rev Neurosci* 2008;9(12):910–9. <https://doi.org/10.1038/nrn2521>.
- [27] Wilkinson RT. Interaction of lack of sleep with knowledge of results, repeated testing, and individual differences. *J Exp Psychol* 1961;62(3):263–71. <https://doi.org/10.1037/h0048787>.
- [28] Leproult EFC, Berardi AM, Stickgold R, Kosslyn SM, Van Cauter E. Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. *Am J Physiol Regul Integr Comp Physiol* 2003;284:280–90.
- [29] Tucker AM, Dinges DF, Van Dongen HPA. Trait interindividual differences in the sleep physiology of healthy young adults. *J Sleep Res* 2007;16(2):170–80. <https://doi.org/10.1111/j.1365-2869.2007.00594.x>.
- [30] Grant DA, Van Dongen HPA. Individual differences in sleep duration and responses to sleep loss the genetic basis of sleep and sleep disorders. United States: Cambridge University Press; 2006. p. 189–96. <https://doi.org/10.1017/CBO9781139649469.020>.
- [31] Rupp TL, Wesensten NJ, Balkin TJ. Trait-like vulnerability to total and partial sleep loss. *Sleep* 2012;35(8):1163–72. <https://doi.org/10.5665/sleep.2010>.
- [32] Van Dongen HPA, Baynard MD, Maislin G, Dinges DF. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep* 2004;27(3):423–33.
- [33] Dongen GM, Dinges DF. Dealing with inter-individual differences in the temporal dynamics of fatigue and performance: importance and techniques. *Aviat Space Environ Med* 2004;75:147–54.
- [34] Killgore WDS, Richards JM, Killgore DB, Kamimori GH, Balkin TJ. The trait of Introversion-extraversion predicts vulnerability to sleep deprivation. *J Sleep Res* 2007;16(4):354–63. <https://doi.org/10.1111/j.1365-2869.2007.00611.x>.
- [35] Killgore WDS, Kamimori GH, Balkin TJ. Caffeine protects against increased risk-taking propensity during severe sleep deprivation. *J Sleep Res* 2011;20(3):395–403. <https://doi.org/10.1111/j.1365-2869.2010.00893.x>.
- [36] Chee MWL, Van Dongen HPA. Functional imaging of interindividual differences in response to sleep deprivation neuroimaging of sleep and sleep disorders. Singapore: Cambridge University Press; 2010. p. 154–62. <https://doi.org/10.1017/CBO9781139088268>.
- [37] Goel N. Genetic markers of sleep and sleepiness. *Sleep Med Clin* 2017;12(3):289–99. <https://doi.org/10.1016/j.jsmc.2017.03.005>.
- [38] Mu Q, Mishory A, Johnson KA, Nahas Z, Kozel FA, Yamanaka K, Bohning DE, George MS. Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. *Sleep* 2005;28(4):433–46. <https://doi.org/10.1093/sleep/28.4.433>.
- [39] Mu Q, Nahas Z, Johnson KA, Yamanaka K, Mishory A, Koola J, Hill S, Horner MD, Bohning DE, George MS. Decreased cortical response to verbal working memory following sleep deprivation. *Sleep* 2005;28(1):55–67. <https://doi.org/10.1093/sleep/28.1.55>.
- [40] Lythe KE, Williams SCR, Anderson C, Libri V, Mehta MA. Frontal and parietal activity after sleep deprivation is dependent on task difficulty and can be predicted by the fMRI response after normal sleep. *Behav Brain Res* 2012;233(1):62–70. <https://doi.org/10.1016/j.bbr.2012.04.050>.
- [41] Yeo BTT, Tandi J, Chee MWL. Functional connectivity during rested wakefulness predicts vulnerability to sleep deprivation. Singapore NeuroImage: Academic Press Inc.; 2015. p. 147–58. <https://doi.org/10.1016/j.neuroimage.2015.02.018>.
- [42] Cui J, Tkachenko O, Gogel H, Kipman M, Preer LA, Weber M, Divatia SC, Demers LA, Olson EA, Buchholz JL, Bark JS, Rosso IM, Rauch SL, Killgore WDS. Microstructure of fronto-parietal connections predicts individual resistance to sleep deprivation. *NeuroImage* 2015;106:123–33. <https://doi.org/10.1016/j.neuroimage.2014.11.035>.
- [43] Goel N. Neurobehavioral effects and biomarkers of sleep loss in healthy adults. *Curr Neurol Neurosci Rep* 2017;17(11). <https://doi.org/10.1007/s11910-017-0799-x>.
- [44] Ulv Larsen SM, Landolt H-P, Berger W, Nedergaard M, Knudsen GM, Holst S. Haplotype of the astrocytic water channel AQP4 is associated with slow wave energy regulation in human NREM sleep. *PLoS Biol* 2020;18(5):e3000623. <https://doi.org/10.1371/journal.pbio.3000623>.
- [45] Bodenmann S, Hohoff C, Freitag C, Deckert J, Rétey JV, Bachmann V, Landolt H-P. Polymorphisms of ADORA2A modulate psychomotor vigilance and the effects of caffeine on neurobehavioural performance and sleep EEG after sleep deprivation. *Br J Pharmacol* 2012;165(6):1904–13. <https://doi.org/10.1111/j.1476-5381.2011.01689.x>.
- [46] Satterfield BC, Wisor JP, Schmidt MA, Van Dongen HPA. Time-on-Task effect during sleep deprivation in healthy young adults is modulated by dopamine transporter genotype. *Sleep* 2017;40(12). <https://doi.org/10.1093/sleep/zsx167>.
- [47] Holst SC, Müller T, Valomon A, Seebauer B, Berger W, Landolt HP. Functional polymorphisms in dopaminergic genes modulate neurobehavioral and neurophysiological consequences of sleep deprivation. *Sci Rep* 2017;7. <https://doi.org/10.1038/srep45982>.
- [48] Satterfield BC, Wisor JP, Field SA, Schmidt MA, Van Dongen HPA. TNF α G308A polymorphism is associated with resilience to sleep deprivation-induced psychomotor vigilance performance impairment in healthy young adults. *Brain Behav Immun* 2015;47:66–74. <https://doi.org/10.1016/j.bbi.2014.12.009>.
- [49] Miller EK, Wallis JD. Executive function and higher-order cognition: definition and neural substrates. Elsevier BV; 2009. p. 99–104. <https://doi.org/10.1016/b978-008045046-9.00418-6>.
- [50] Harrison Y, Horne JA. The impact of sleep deprivation on decision making: a review. *J Exp Psychol Appl* 2000;6(3):236–49. <https://doi.org/10.1037/1076-898X.6.3.236>.
- [51] Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, Wagner H, Thorne D, Popp K, Rowland L, Welsh A, Balwinski S, Redmond D. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res* 2000;9(4):335–52. <https://doi.org/10.1046/j.1365-2869.2000.00225.x>.
- [52] Wu JC, Gillin JC, Buchsbaum MS, Chen P, Keator DB, Khosla Wu N, Darnall LA, Fallon JH, Bunney WE. Frontal lobe metabolic decreases with sleep deprivation not totally reversed by recovery sleep. *Neuropsychopharmacology* 2006;31(12):2783–92. <https://doi.org/10.1038/sj.npp.1301166>.

- [53] Van Dongen HPA, Bender AM, Dinges DF. Systematic individual differences in sleep homeostatic and circadian rhythm contributions to neurobehavioral impairment during sleep deprivation. *Accid Anal Prev* 2012;45:11–6. <https://doi.org/10.1016/j.aap.2011.09.018>.
- [54] Jackson ML, Gunzelmann G, Whitney P, Hinson JM, Belenky G, Rabat A, Van Dongen HPA. Deconstructing and reconstructing cognitive performance in sleep deprivation. *Sleep Med Rev* 2013;17(3):215–25. <https://doi.org/10.1016/j.smrv.2012.06.007>.
- [55] Tucker AM, Whitney P, Belenky G, Hinson JM, Van Dongen HPA. Effects of sleep deprivation on dissociated components of executive functioning. *Sleep* 2010;33(1):47–57. <https://doi.org/10.1093/sleep/33.1.47>.
- [56] Reichert C, Maire M, Schmidt C, Cajochen C. Sleep-wake regulation and its impact on working memory performance: the role of adenosine. *Biology* 2016;5(1):11. <https://doi.org/10.3390/biology5010011>.
- [57] Frenda SJ, Fenn KM. Sleep less, think worse: the effect of sleep deprivation on working memory. *J Appl Res Mem Cogn* 2016;5(4):463–9. <https://doi.org/10.1016/j.jarmac.2016.10.001>.
- [58] Baddeley A. Working memory: theories, models, and controversies. *Annu Rev Psychol* 2012;63:1–29. <https://doi.org/10.1146/annurev-psych-120710-100422>.
- [59] Chee MWL, Choo WC. Functional imaging of working memory after 24 hr of total sleep deprivation. *J Neurosci* 2004;24(19):4560–7. <https://doi.org/10.1523/JNEUROSCI.0007-04.2004>.
- [60] Chee MWL, Chuah LYM, Venkatraman V, Chan WY, Philip P, Dinges DF. Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: correlations of fronto-parietal activation with performance. *Neuroimage* 2006;31(1):419–28. <https://doi.org/10.1016/j.neuroimage.2005.12.001>.
- [61] Choo WC, Lee WW, Venkatraman V, Sheu FS, Chee MWL. Dissociation of cortical regions modulated by both working memory load and sleep deprivation and by sleep deprivation alone. *Neuroimage* 2005;25(2):579–87. <https://doi.org/10.1016/j.neuroimage.2004.11.029>.
- [62] Bell-McGinty S, Habeck C, Hilton HJ, Rakitin B, Scarmeas N, Zarahn E, Flynn J, DeLaPaz R, Basner R, Stern Y. Identification and differential vulnerability of a neural network in sleep deprivation. *Cerebr Cortex* 2004;14(5):496–502. <https://doi.org/10.1093/cercor/bhh011>.
- [63] Drummond SPA, Meloy MJ, Yanagi MA, Orff HJ, Brown GG. Compensatory recruitment after sleep deprivation and the relationship with performance. *Psychiatr Res Neuroimaging* 2005;140(3):211–23. <https://doi.org/10.1016/j.pscychresns.2005.06.007>.
- [64] Groeger JA, Viola AU, Lo JCY, Von Schantz M, Archer SN, Dijk DJ. Early morning executive functioning during sleep deprivation is compromised by a PERIOD3 polymorphism. *Sleep* 2008;31(8):1159–67.
- [65] Drummond SPA, Anderson DE, Straus LD, Vogel EK, Perez VB. The effects of two types of sleep deprivation on visual working memory capacity and filtering efficiency. *PLoS One* 2012;7(4). <https://doi.org/10.1371/journal.pone.0035653>.
- [66] Rångtell FH, Karamchedu S, Andersson P, Liethof L, Olaya Búcaro M, Lampola L, Schiöth HB, Cedernaes J, Benedict C. A single night of sleep loss impairs objective but not subjective working memory performance in a sex-dependent manner. *J Sleep Res* 2019;28(1). <https://doi.org/10.1111/jsr.12651>.
- [67] Santhi N, Lazar AS, McCabe PJ, Lo JC, Groeger JA, Dijk DJ. Sex differences in the circadian regulation of sleep and waking cognition in humans. *Proc Natl Acad Sci USA* 2016;113(19):E2730. <https://doi.org/10.1073/pnas.1521637113>.
- [68] Chee MWL, Chuah YML. Functional neuroimaging and behavioral correlates of capacity decline in visual short-term memory after sleep deprivation. *Proc Natl Acad Sci USA* 2007;104(22):9487–92. <https://doi.org/10.1073/pnas.0610712104>.
- [69] APA Dictionary of Psychology. <https://dictionary.apa.org/learning>; 2018.
- [70] Takashima A, Nieuwenhuis IL, Jensen O, Talamini LT, Rijpkema M, Fernandez G. Shift from hippocampal to neocortical centered retrieval network with consolidation. *J Neurosci* 2009;29(32):10089–93. <https://doi.org/10.1523/JNEUROSCI.0799-09.2009>.
- [71] Born J, Wilhelm I. System consolidation of memory during sleep. *Psychol Rev* 2012;76(2):192–203. <https://doi.org/10.1007/s00426-011-0335-6>.
- [72] Rasch B, Born J. About sleep's role in memory. *Physiol Rev* 2013;9(2):681–766. <https://doi.org/10.1152/physrev.00032.2012>.
- [73] Kurinec CA, Whitney P, Hinson JM, Hansen DA, Van Dongen HPA. Sleep deprivation impairs binding of information with its context. *Sleep* 2021;44(8):zsab113. <https://doi.org/10.1093/sleep/zsab113>.
- [74] Whitney P, Kurinec CA, Hinson JM. Temporary amnesia from sleep loss: a framework for understanding consequences of sleep deprivation. *Front Neurosci* 2023;17:1134757. <https://doi.org/10.3389/fnins.2023.1134757>.
- [75] Miller JA, Constantinidis C. Inhibition and impulsivity: behavioral and neural basis of response control. *Nat Rev Neurosci* 2024;25(9):597–610. <https://doi.org/10.1038/s41583-024-00836-8>.
- [76] Bari A, Robbins TW. Inhibition and impulsivity: behavioral and neural basis of response control. *Prog Neurobiol* 2013;108:44–79. <https://doi.org/10.1016/j.pneurobio.2013.06.005>.
- [77] Taylor SF, Stern ER, Gehring WJ. Neural systems for error monitoring: recent findings and theoretical perspectives. *Neuroscientist* 2007;13(2):160–72. <https://doi.org/10.1177/107385406298184>.
- [78] Chuah YML, Venkatraman V, Dinges DF, Chee MWL. The neural basis of interindividual variability in inhibitory efficiency after sleep deprivation. *J Neurosci* 2006;26(27):7156–62. <https://doi.org/10.1523/JNEUROSCI.0906-06.2006>.
- [79] Drummond SPA, Paulus MP, Tapert SF. Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. *J Sleep Res* 2006;15(3):261–5. <https://doi.org/10.1111/j.1365-2869.2006.00535.x>.
- [80] Sagaspe P, Taillard J, Amiéva H, Beck A, Rascol O, Dartigues J-F, Capelli A, Philip P, Martinez LM. Influence of age, circadian and homeostatic processes on inhibitory motor control: a go/no-go task study. *PLoS One* 2012;7(6):e39410. <https://doi.org/10.1371/journal.pone.0039410>.
- [81] Demos KE, Hart CN, Sweet LH, Mailloux KA, Trautvetter J, Williams SE, Wing RR, McCaffery JM. Partial sleep deprivation impacts impulsive action but not impulsive decision-making. *Physiol Behav* 2016;164:214–9. <https://doi.org/10.1016/j.physbeh.2016.06.003>.

- [82] Killgore WDS. Effects of sleep deprivation on cognition. *Prog Brain Res* 2010;185:105–29. <https://doi.org/10.1016/B978-0-445-53702-7.00007-5>.
- [83] Braver TS. The variable nature of cognitive control: a dual mechanisms framework. *Trends Cognit Sci* 2012;16(2):106–13. <https://doi.org/10.1016/j.tics.2011.12.010>.
- [84] Satterfield BC, Hinson JM, Whitney P, Schmidt MA, Wisor JP, Van Dongen HPA. Catechol-O-methyltransferase (COMT) genotype affects cognitive control during total sleep deprivation. *Cortex* 2018;99:179–86. <https://doi.org/10.1016/j.cortex.2017.11.012>.
- [85] Cools R. The costs and benefits of brain dopamine for cognitive control. *Wiley Interdiscip Rev Cogn Sci* 2016;7(5):317–29. <https://doi.org/10.1002/wcs.1401>.
- [86] Klanker M, Feenstra M, Denys D. Dopaminergic control of cognitive flexibility in humans and animals. *Front Neurosci* 2013;7). <https://doi.org/10.3389/fnins.2013.00201Netherlands>.
- [87] Botvinick M, Braver T. Motivation and cognitive control: from behavior to neural mechanism. *Ann Rev Psychol* 2015;66:83–113. <https://doi.org/10.1146/annurev-psych-010814-015044>.
- [88] Cools R, Robbins TW. Chemistry of the adaptive mind. *Philos Trans R Soc A Math Phys Eng Sci* 2004;362(1825):2871–88. <https://doi.org/10.1098/rsta.2004.1468>.
- [89] Nakashima A, Bouak F, Lam Q, Smith I, Vartanian O. Task switching following 24 h of total sleep deprivation. *Neuroreport* 2018;29(2):123–7. <https://doi.org/10.1097/WNR.0000000000000934>.
- [90] Couyoumdjian A, Sdoia S, Tempesta D, Curcio G, Rastellini E, de Gennaro L, Ferrara M. The effects of sleep and sleep deprivation on task-switching performance. *J Sleep Res* 2010;19(1-Part I):64–70. <https://doi.org/10.1111/j.1365-2869.2009.00774.x>.
- [91] Haavisto ML, Porkka-Heiskanen T, Hublin C, Härmä M, Mutanen P, Müller K, Virkkala J, Sallinen M. Sleep restriction for the duration of a work week impairs multitasking performance: sleep restriction and multitasking. *J Sleep Res* 2010;19(3):444–54. <https://doi.org/10.1111/j.1365-2869.2010.00823.x>.
- [92] Sagaspe P, Sanchez-Ortuno M, Charles A, Taillard J, Valtat C, Bioulac B, Philip P. Effects of sleep deprivation on Color-Word, Emotional, and Specific Stroop interference and on self-reported anxiety. *Brain Cognit* 2006;60(1):76–87. <https://doi.org/10.1016/j.bandc.2005.10.001>.
- [93] Cain SW, Silva EJ, Chang AM, Ronda JM, Duffy JF. One night of sleep deprivation affects reaction time, but not interference or facilitation in a stroop task. *Brain Cognit* 2011;76(1):37–42. <https://doi.org/10.1016/j.bandc.2011.03.005>.
- [94] Bratzke D, Steinborn MB, Rolke B, Ulrich R. Effects of sleep loss and circadian rhythm on executive inhibitory control in the stroop and simon tasks. *Chronobiol Int* 2012;29(1):55–61. <https://doi.org/10.3109/07420528.2011.635235>.
- [95] Grant LK, Cain SW, Chang AM, Saxena R, Czeisler CA, Anderson C. Impaired cognitive flexibility during sleep deprivation among carriers of the Brain Derived Neurotrophic Factor (BDNF) Val66Met allele. *Behav Brain Res* 2018;338:51–5. <https://doi.org/10.1016/j.bbr.2017.09.025>.
- [96] Gevers W, Deliens G, Hoffmann S, Notebaert W, Peigneux P. Sleep deprivation selectively disrupts top-down adaptation to cognitive conflict in the stroop test. *J Sleep Res* 2015;24(6):666–72. <https://doi.org/10.1111/jsr.12320>.
- [97] Frank MJ, Claus ED. Anatomy of a decision: striato-orbitofrontal interactions in reinforcement learning, decision making, and reversal. *Psychol Rev* 2006;113(2):300–26. <https://doi.org/10.1037/0033-295X.113.2.300>.
- [98] Fellows LK. The role of orbitofrontal cortex in decision making: a component process account. *Ann N Y Acad Sci* 2007;1121(1):421–30. <https://doi.org/10.1196/annals.1401.023>.
- [99] Pauli WM, Hazy TE, O'Reilly RC. Expectancy, ambiguity, and behavioral flexibility: separable and complementary roles of the orbital frontal cortex and amygdala in processing reward expectancies. *J Cognit Neurosci* 2012;24(2):351–66. https://doi.org/10.1162/jocn_a_00155.
- [100] Cools R, Clark L, Owen AM, Robbins TW. Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci* 2002;22(11):4563–7. <https://doi.org/10.1523/jneurosci.22-11-04563.2002>.
- [101] Whitney P, Hinson JM, Jackson ML, Van Dongen HPA. Feedback blunting: total sleep deprivation impairs decision making that requires updating based on feedback. *Sleep* 2015;38(5):745–54. <https://doi.org/10.5665/sleep.4668>.
- [102] Whitney P, Hinson JM, Satterfield BC, Grant DA, Honn KA, Van Dongen HPA. Sleep deprivation diminishes attentional control effectiveness and impairs flexible adaptation to changing conditions. *Sci Rep* 2017;7(1). <https://doi.org/10.1038/s41598-017-16165-z>.
- [103] Jaspar M, Dideberg V, Bouras V, Maquet P, Collette F. Modulating effect of COMT Val(158)Met polymorphism on interference resolution during a working memory task. *Brain Cognit* 2015;95:7–18. <https://doi.org/10.1016/j.bandc.2015.01.013>.
- [104] Jaspar M, Genon S, Muto V, Meyer C, Manard M, Dideberg V, et al. Modulating effect of COMT genotype on the brain regions underlying proactive control process during inhibition. *Cortex* 2014;50:148–61. <https://doi.org/10.1016/j.cortex.2013.06.003>.
- [105] Jaspar M, Manard M, Dideberg V, Bouras V, Maquet P, Collette F. Influence of COMT genotype on antero-posterior cortical functional connectivity underlying interference resolution. *Cereb Cortex* 2016;26(2):498–509. <https://doi.org/10.1093/cercor/bhu188>.
- [106] Horne JA. Sleep loss and “divergent” thinking ability. *Sleep* 1988;11(6):528–36. <https://doi.org/10.1093/sleep/11.6.528>.
- [107] Cade BE, Gottlieb DJ, Lauderdale DS, Bennett DA, Buchman AS, Buxbaum SG, De Jager PL, Evans DS, Fülop T, Gharib SA, Johnson WC, Kim H, Larkin EK, Lee SK, Lim AS, Punjabi NM, Shin C, Stone KL, Tranah GJ, Weng J, Yaffe K, Zee PC, Patel SR, Zhu X, Redline S, Saxena R. Common variants in DRD2 are associated with sleep duration: the CARE consortium. *Hum Mol Genet* 2016;25(1):167–79. <https://doi.org/10.1093/hmg/ddv434>.
- [108] Jones K, Harrison Y. Frontal lobe function, sleep loss and fragmented sleep. *Sleep Med Rev* 2001;5(6):463–75. <https://doi.org/10.1053/smrv.2001.0203>.
- [109] Harrison Y, Horne JA. One night of sleep loss impairs innovative thinking and flexible decision making. *Organ Behav Hum Decis Process* 1999;78(2):128–45. <https://doi.org/10.1006/obhd.1999.2827>.
- [110] Hoyle RH, Stephenson MT, Palmgreen P, Lorch EP, Donohew RL. Reliability and validity of a brief measure of sensation seeking. *Pers Indiv Differ* 2002;32(3):401–14.
- [111] Killgore WDS, Vo A, Castro C, Hoge C. Assessing risk propensity in American soldiers: preliminary reliability and validity of the evaluation of risks (EVAR) scale—English version. *Mil Med* 2006;171(3):233–9.

- [112] Sicard B, Jouve E, Blin O. Risk propensity assessment in military special operations. *Mil Med* 2001;166(10):871–4.
- [113] Killgore WDS, Grugle NL, Killgore DB, Balkin TJ. Sex differences in self-reported risk-taking propensity on the evaluation of risks scale. *Psychol Rep* 2010;106(3):693–700.
- [114] Chaumet G, Taillard J, Sagaspe P, Pagani M, Dinges DF, Pavly-Le-Traon A, Bareille MP, Rascol O, Philip P. Confinement and sleep deprivation effects on propensity to take risks. *Aviat Space Environ Med* 2009;80(2):73–80.
- [115] Killgore WDS. Effects of sleep deprivation and morningness-eveningness traits on risk-taking. *Psychol Rep* 2007;100:613–26.
- [116] Killgore WDS, Grugle NL, Killgore DB, Leavitt BP, Watlington GI, McNair S, Balkin TJ. Restoration of risk-propensity during sleep deprivation: caffeine, dextroamphetamine, and modafinil. *Aviat Space Environ Med* 2008;79(9):867–74.
- [117] Dinges DF, Pack F, Williams K, Gillen K, Powell J, Ott G, Aptowicz C, Pack AI. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep* 1997;20(4):267–77.
- [118] Kahneman D. A perspective on judgment and choice: mapping bounded rationality. *Am Psychol* 2003;58(9):697–720.
- [119] McKenna BS, Dickinson DL, Orff HJ, Drummond SPA. The effects of one night of sleep deprivation on known-risk and ambiguous-risk decisions. *J Sleep Res* 2007;16(3):245–52.
- [120] Venkatraman V, Chuah LY, Huettel SA, Chee MW. Sleep deprivation elevates expectation of gains and attenuates response to losses following risky decisions. *Sleep* 2007;30(5):603–9.
- [121] Venkatraman V, Huettel SA, Chuah LYM, Payne JW, Chee MWL. Sleep deprivation biases the neural mechanisms underlying economic preferences. *J Neurosci* 2011;31(10):3712–8.
- [122] Bechara A, Damasio H, Tranel D, Damasio AR. Deciding advantageously before knowing the advantageous strategy. *Science* 1997;275(5304):1293–5.
- [123] Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;50(1–3):7–15.
- [124] Killgore WDS, Grugle NL, Balkin TJ. Gambling when sleep deprived: don't bet on stimulants. *Chronobiol Int* 2012;29(1):43–54.
- [125] Killgore WDS, Lipizzi EL, Kamimori GH, Balkin TJ. Caffeine effects on risky decision making after 75 hours of sleep deprivation. *Aviat Space Environ Med* 2007;78(10):957–62.
- [126] Killgore WDS, Balkin TJ, Wesensten NJ. Impaired decision making following 49 hours of sleep deprivation. *J Sleep Res* 2006;15(1):7–13.
- [127] Greer SM, Goldstein AN, Knutson B, Walker MP. A genetic polymorphism of the human dopamine transporter determines the impact of sleep deprivation on brain responses to rewards and punishments. *J Cognit Neurosci* 2016;28(6):803–10.
- [128] Olson EA, Weber M, Rauch SL, Killgore WDS. Daytime sleepiness is associated with reduced integration of temporally distant outcomes on the Iowa gambling task. *Behav Sleep Med* 2016;14(2):200–11.
- [129] Lim JYL, Killgore WDS, Bennett D, Drummond SPA. The impact of sleep loss on decision making: opening the cognitive black box. *Sleep Med Rev* 2025;82:102114. <https://doi.org/10.1016/j.smrv.2025.102114>.
- [130] Acheson A, Richards JB, de Wit H. Effects of sleep deprivation on impulsive behaviors in men and women. *Physiol Behav* 2007;91(5):579–87.
- [131] Libedinsky C, Massar SAA, Ling A, Chee W, Huettel SA, Chee MWL. Sleep deprivation alters effort discounting but not delay discounting of monetary rewards. *Sleep* 2013;36(6):899–904.
- [132] Kahn-Greene ET, Lipizzi EL, Conrad AK, Kamimori GH, Killgore WDS. Sleep deprivation adversely affects interpersonal responses to frustration. *Pers Indiv Differ* 2006;41(8):1433–43.
- [133] Kahn-Greene ET, Killgore DB, Kamimori GH, Balkin TJ, Killgore WDS. The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Med* 2007;8(3):215–21.
- [134] Kamphuis J, Meerlo P, Koolhaas JM, Lancel M. Poor sleep as a potential causal factor in aggression and violence. *Sleep Med* 2012;13(4):327–34.
- [135] Anderson C, Dickinson DL. Bargaining and trust: the effects of 36-h total sleep deprivation on socially interactive decisions. *J Sleep Res* 2010;19:54–63.
- [136] Killgore WDS, Killgore DB, Day LM, Li C, Kamimori GH, Balkin TJ. The effects of 53 hours of sleep deprivation on moral judgement. *Sleep* 2007;30(3):345–52.
- [137] Tempesta D, Couyoumdjian A, Moroni F, Marzano C, De Gennaro L, Ferrara M. The impact of one night of sleep deprivation on moral judgments. *Soc Neurosci* 2012;7(3):292–300.
- [138] Olsen OK, Pallesen S, Eid J. The impact of partial sleep deprivation on moral reasoning in military officers. *Sleep* 2010;33(8):1086–90.
- [139] Benderoth S, Mühl C, Bruder C, Kissing DS, Aeschbach D. Cooperative teamwork in a simulated control room as a countermeasure against performance impairment due to the combined effects of sleep loss and circadian misalignment. *Sleep* 2025;48(7):zsaf092. <https://doi.org/10.1093/sleep/zsaf092>.
- [140] Banks S, Landon LB, Dorrian J, Waggoner LB, Centofanti SA, Roma PG, et al. Effects of fatigue on teams and their role in 24/7 operations. *Sleep Med Rev* 2019;48:101216. <https://doi.org/10.1016/j.smrv.2019.101216>.
- [141] Mathieu J, Maynard MT, Rapp T, Gibson L. Team effectiveness 1997–2007: a review of recent advancements and a glimpse into the future. *J Manag* 2008;34(3):309–27. <https://doi.org/10.1177/0149206308316061>.
- [142] Kozlowski SW. Enhancing the effectiveness of work groups and team. *Perspect. Psychol. Sci.* 2018;13(2):205–12. <https://doi.org/10.1177/1745691617697078>.
- [143] Killgore WDS, Kamimori GH, Balkin TJ. Caffeine improves the efficiency of planning and sequencing abilities during sleep deprivation. *J Clin Psychopharmacol* 2014;34(5):660–2.
- [144] Killgore WDS, Kahn-Greene ET, Grugle NL, Killgore DB, Balkin TJ. Sustaining executive functions during sleep deprivation: a comparison of caffeine, dextroamphetamine, and modafinil. *Sleep* 2009;32(2):205–16.
- [145] National Sleep Foundation. Healthy sleep tips. 2018. <https://sleepfoundation.org/sleep-tools-tips/healthy-sleep-tips>.
- [146] Chauhan S, Norbury R, Fabender KC, Ettinger U, Kumari V. Beyond sleep: A multidimensional model of chronotype. *Neurosci Biobehav Rev* 2023;148:105114. <https://doi.org/10.1016/j.neubiorev.2023.105114>.

- [147] Arora S, Dharavath RN, Bansal Y, Bishnoi M, Kondepudi KK, Chopra K. Neurobehavioral alterations in a mouse model of chronic partial sleep deprivation. *Metabol Brain Dis* 2021;36(6):1315–30. <https://doi.org/10.1007/s11011-021-00693-9>.
- [148] Gaur A, Rivet L, Mah E, Bawa K, Gallagher D, Hermann N, et al. Novel fluid biomarkers for mild cognitive impairment: a systematic review and meta-analysis. *Age Res Rev* 2023;91:102046. <https://doi.org/10.1016/j.arr.2023.102046>.

This page intentionally left blank

Chapter 30

Sleep and healthy decision-making

Kelly Glazer Baron^{a, b} and Elizabeth Culnan^b

^aDivision of Public Health, Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, United States; ^bDepartment of Behavioral Sciences, Rush University Medical Center, Chicago, IL, United States

Abbreviations

CPAP Continuous positive airway pressure

ICSD3 International classification of sleep disorders, 3rd edition

OSA Obstructive sleep apnea

Introduction

Engaging in healthy behaviors is critical to the prevention of the most prevalent chronic illnesses including cardiovascular disease, diabetes, and cancer. For example, a study of adults in the United Kingdom demonstrated adults with poor health behaviors in all four categories studied (smoking, low physical activity, low fruit and vegetable intake, and high alcohol intake) had a 3.5-fold mortality rate over a 20-year follow-up compared with those who did not engage in these unhealthy behaviors [1]. The authors suggested that having poor health habits in all four behaviors was equivalent to increasing participants' chronological age by 12 years. Sleep loss and circadian disruption are linked to both poorer health behaviors and the development of chronic illnesses. Therefore, health behaviors are thought to be one of the pathways by which sleep and circadian rhythms influence chronic disease risk. The focus of this chapter is to defining how changes in sleep and circadian rhythms influence the decisions to engage in healthy behaviors (e.g., physical activity) or avoid unhealthy behaviors (e.g., smoking). We will first start with a discussion of how sleep behavior itself is a daily health decision with some controllable components (leisure and social time) and some uncontrollable (sleep disorders, commute times, work hours). Next, we will examine several key behavioral pathways linking sleep loss and circadian disruption to health behaviors. The chapter will focus on examples from four health behaviors: physical activity, diet, smoking, and alcohol use. In this chapter we will present what is known about how and why sleep loss and circadian disruption influence these important health

behaviors including (1) environmental exposures at night, (2) neurocognitive changes experienced after sleep loss and circadian disruption, (3) affective response to sleep loss and circadian disruption, and (4) how sleep loss and circadian disruption affect effort and motivation for health behaviors. Last, we will discuss what is known about whether improving sleep and circadian rhythms may influence the ability to make changes to other health behaviors.

Sleep as a health behavior

Influences on sleep and health behaviors

Health behaviors are defined as “overt behavioral patterns, actions, and habits that relate to health maintenance, health restoration or health improving” [2]. Sleep is considered a “pillar of health” along with diet and exercise. Sleep is also a unique health behavior in that it involves the physiological ability to sleep as well as volitional processes (opportunity to sleep). According to the two-process model of sleep regulation [3], sleep propensity, or the physiologic ability to sleep, is determined by the homeostatic pressure to sleep (process S) as well as circadian timing (process C). To sleep well, an individual must have a high drive to sleep and sleep is better quality if it occurs in alignment with the internal circadian rhythm. If either of these processes is impaired, sleep is more difficult to achieve (e.g., low homeostatic pressure due to napping or mistimed sleep opportunity, such as day sleep due to shift work).

There are some similarities between sleep and eating behavior, which is driven by both hunger (desire to eat) and appetite (desire for particular food categories). More specifically, eating behavior is controlled by an interaction of homeostatic and hedonic influences [4]. The homeostatic drive refers to an increased drive to eat as a response to depleted energy stores. However, individuals can override these messages regarding energy stores to consume

palatable foods when there is no caloric need, which is called hedonic eating (eating for pleasure) [5]. It is thought that hedonic eating is one of the main drivers of the obesity epidemic, due to the abundance of readily available palatable and high-caloric food. Like sleep, there are also circadian influences on eating. Studies have been conducted using a forced desynchrony protocol, a laboratory sleep schedule in which individuals are on a 22 or 28 h “day,” which progressively moves sleep around the clock and allows researchers to conduct assessments at multiple circadian phases while controlling for sleep duration. Research conducted by Scheer et al. [6] using this protocol demonstrated that hunger as well as appetite for sweet, salty, starchy foods, fruits, meat/poultry, and food overall and ability to eat demonstrated a robust circadian rhythm, with the lowest values around the biological morning (8:00 a.m.) and peak values around 8:00 p.m.

Short sleep duration is highly prevalent in the population

According to data from the National Health Interview Survey, 70.1 million US adults (29.2%) sleep <6 h per 24 h period [7]. Short sleep duration is highly prevalent and linked to negative mental and physical health consequences, including increased cardiovascular disease risk [8]. These statistics are a stark contrast to recommendations made by a recent consensus panel of sleep experts that concluded “at least 7 h” as the amount of sleep needed for health and performance among adults [9]. Therefore, a high number of US adults could benefit from extending sleep duration. The high prevalence of short sleep duration is leading researchers to consider how sleep behaviors can be influenced, through intervention, public health education, and occupational policies.

What predicts the decision to sleep or not to sleep?

In the epidemiologic literature, short sleep duration is more prevalent in males than females and more prevalent among blacks compared with whites [10–13]. Short sleep duration is also more common in urban areas compared with rural areas and in areas with lower safety and social cohesion [10,14]. However, short sleep duration is present across the SES spectrum. Basner et al. [15] conducted an analysis of the American Time Use Survey and pooled data from 3 years of telephone surveys that asked participants (all age >14) to report on their activities from the past 24 h. The data demonstrated the most common trade-offs for sleep were work and commute time. Shorter sleepers engaged in more social and leisure activities, whereas both shorter and longer sleepers watched more TV than the average sleeper. A later study found similar results and demonstrated for

every hour that work or educational activities started earlier, sleep duration was 20 min shorter [16]. Furthermore, individuals working more than one job had the highest risk for short sleep duration.

Several studies have examined the role of social cognitive factors (knowledge, beliefs, social norms, etc.) in sleep duration. These studies have demonstrated that attitudes toward the importance of sleep and social norms are associated with sleep duration. This suggests that individuals’ beliefs about sleep influence sleep behaviors, which is similar to what has been documented with other health behaviors [17]. In addition, perceived control over sleep and self-efficacy (the belief that one can control and overcome barriers to sleep) are strongly associated with sleep duration. Another potentially modifiable correlate of short sleep duration is “bedtime procrastination,” which is based in self-control theory, and refers to delaying bedtime due to not wanting to stop other activities (e.g., working and watching TV) [18]. Bedtime procrastination has been associated with lower overall self-control as well as poorer sleep habits and lower self-reported sleep duration [18]. These studies suggest that cognitive and behavioral techniques such as education, goal setting, and self-monitoring may be successful for extending sleep duration, as has been demonstrated in improving other domains of health behaviors, such as diet and physical activity.

Some individuals make time to sleep but cannot sleep

For individuals with sleep disorders, desire to sleep may be present but they are unable to achieve adequate sleep quality or quantity. Multiple studies demonstrating that psychosocial factors such as stress and perceived discrimination are associated with short sleep duration [19–21]. Insomnia is diagnosed if an individual has difficulty falling asleep, staying asleep or waking up too early despite adequate opportunity for sleep (ICSD3). It has been estimated that 9%–12% of the population has chronic insomnia. Often is the case in insomnia, the individual will engage in what would typically be a good health behavior (spending time in bed trying to sleep) but this can serve to exacerbate their insomnia because it provides greater opportunity for worry, rumination, and frustration. Data suggest that having both short sleep time and an insomnia diagnosis has the greatest impact on health [22]. This combination has been considered “most severe phenotype” of insomnia. It is unclear whether this subtype of sleeper (insomnia with short sleep duration) would respond to the same interventions as individuals with short sleep time but not insomnia. For example, it has been demonstrated that individuals with short sleep time and insomnia respond poorly to cognitive behavioral therapy for insomnia, the recommended behavioral insomnia treatment [23].

Proposed pathways linking sleep to other health behaviors

Data from many studies have demonstrated that sleep loss and/or circadian disruption are associated with poorer health behaviors, including poorer dietary patterns, lower physical activity, higher alcohol intake, and more smoking. However, only a few studies have examined the mechanisms driving these effects. We are going to discuss these proposed pathways in the next section including environmental exposure, neuropsychological, affective responses to sleep loss and circadian disruption, and the impact of sleep loss and circadian disruption to effort and motivational processes.

Exposure

The physical and social environment contributes to health behaviors. Additional exposure to certain social scenarios and environments late at night also likely interacts with the difficulty of making decisions later in the evening to ultimately impact engagement in healthy or unhealthy behaviors. For instance, Campbell et al. [24] found availability of junk food in the home environment to be associated with consumption of unhealthy foods and beverages among adolescents. Similarly, exposure to cues for smoking (e.g., seeing a picture of a cigarette and seeing a picture of a bar) also leads to increased cravings to smoke a cigarette when compared to scenarios not associated with smoking (e.g., seeing a picture of a gym) [25]. Exposure to environments that offer unhealthy choices may be higher in the evening. For instance, individuals may be more likely to go to bars or clubs and be exposed to alcohol and tobacco in the late evening hours.

One hypothesis is that the ability to self-regulate is a finite resource, and that repeated decision-making depletes the ability to self-regulate [26]. Thus, it may be that the longer one is awake, the more opportunities one has to make decisions regarding health behaviors and the more difficult it becomes to self-regulate. This may make it more likely that an individual engages in an unhealthy behavior (e.g., smoking a cigarette, eating more calories than planned, and consuming junk food). Research suggests that individuals who remain awake engage in more unhealthy behaviors when compared to those who do not remain awake late into the night. For instance, Onyper et al. [27] found that college students who stayed awake all night at least once during a 2 week time period were more likely to report engaging in binge drinking and using stimulants. Similarly, participants with experimentally restricted sleep demonstrated increased snacking after dinner [28].

Evening chronotypes, who likely delay bedtime due to their preference for engaging in evening activity, have also been noted to have worse health behaviors. This may be due to a variety of factors (e.g., impulsivity and emotional dysregulation) including having additional time awake in the evening [29,30]. For example, evening types have been found to use more nicotine and alcohol than their morning

type counterparts [31]. Furthermore, evening types have been noted to have higher scores on a measure of hazardous alcohol use [31], indicating that they are not only consuming more alcohol, but that the manner in which they consume alcohol may be more problematic than morning and neither types. Evening types have also been shown to consume fewer servings of fruits and vegetables [32] and more fast food [33].

In sum, environmental exposure likely influences decision-making processes. Staying up later in the evening likely influences not only the environments an individual is exposed to (e.g., a bar), but also the ability to self-regulate and make healthy choices. Further research is needed to fully understand the associations between decision-making processes, sleep and circadian factors, and environmental exposure.

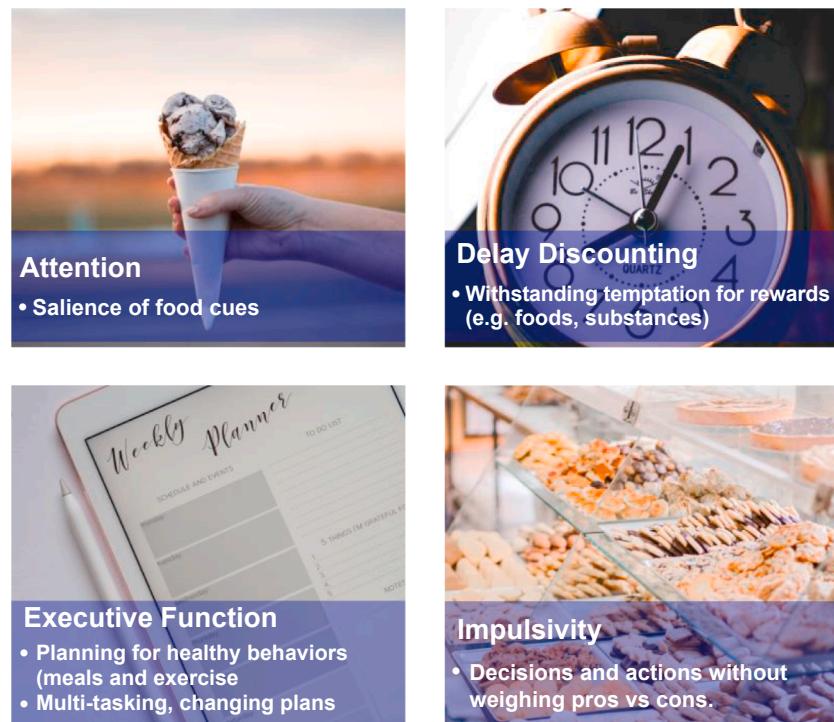
Neurocognitive factors

Sleep loss and/or circadian disruption has an impact on health behaviors, such as increases in dietary intake [34] and decreases in physical activity [35]. One pathway that may explain these behavior changes is the effects of sleep on neurocognitive functioning in that the way individuals process information in their environment, such as salience of health-related cues or their ability to think about short and long-term consequences before acting, is affected by sleep and circadian factors. In fact, sleep and circadian rhythms are critical to cognitive processes including attention, memory, and executive function, domains of cognition that support decision-making processes as they allow individuals to attend to information, remember that information, and subsequently plan or inhibit behaviors. There is a large literature examining the neurocognitive changes with sleep loss (see Refs. [36,37] for review). Short-term experiments have demonstrated that both partial (decreased sleep duration over days or weeks) and total (e.g., 24 h or more for a few days) sleep loss are associated with changes in vigilance, processing speed, executive function, decision-making, and impulsivity/risk taking (see Ref. [38], for review). These cognitive changes have clear indications for health behaviors but only a few studies have examined these changes in applied settings.

Fig. 30.1 demonstrates some of the possible neurocognitive processes that may link sleep loss and circadian disruption to health behaviors.

Attention: The ability to attend to information is crucial for cognitive functioning and subsequent decision-making. Sustained attention decreases with chronic sleep restriction, and is further worsened during the circadian night [39]. Given this, sleep loss may alter attention or attentional bias for health-related cues. Similarly, attempting to make decisions during the circadian night would be impaired due to the difficulty with attending at this time. There is much research on the attentional biases associated with food cues and it has been demonstrated that individuals are faster to detect food cues and have greater

FIGURE 30.1 Neurocognitive processes affected by sleep loss and circadian disruption.



difficulty disengaging from food cues [40]. It is currently unknown how sleep loss affects food-related or other health-related attentional biases.

Executive function: Executive function comprises a variety of cognitive skills including working memory, inhibition, and cognitive flexibility [41]. These cognitive skills have been linked to eating behaviors, exercise, and weight gain. It is thought that these cognitive processes are important to maintaining healthy behaviors, such as navigating the obesogenic food environment and planning to fit in a workout. Binks et al. [42] reported no difference in higher-order cortical functions such as sustained attention or cognitive flexibility after 34–36 h of wakefulness compared with nonsleep deprived controls. However, this study was conducted under controlled conditions. Killgore [43] suggests that the interaction of declines in attention and emotional control may have an effect on these higher-order processes as well.

Delay (temporal) discounting: Delay discounting refers to the relative preference for immediate versus delayed rewards. This measure has been associated with behaviors such as propensity for drug abuse [44–47]; as well as eating behaviors and weight gain over time [48]. Current data suggest that sleep loss itself is not associated with delay discounting [49]. Other studies have suggested that delay discounting may be trait-like and related to chronotype rather than sleep duration. One study demonstrated that evening types have a steeper discounting curve, which

indicates a greater preference for more immediate rewards and are thought to be more “present oriented” than “future oriented” [50]. It is unclear whether circadian rhythm disruption affects delay discounting.

Effort discounting: Effort discounting refers to the effort an individual will put forth to achieve a reward. Data have demonstrated that sleep loss is associated with decreased effort discounting (or less effort to earn a reward) [49]. This may suggest that sleep loss could influence health behaviors because individuals put less effort toward them (e.g., effort to prepare healthy meals).

Impulsivity: Can be conceptualized as impulsive action (responding quickly/carelessly) or impulsive decision-making, which involves weighing risks versus rewards [51]. Studies have demonstrated sleep loss affects impulsive behavior and possibly decision-making in cognitive tasks [52–54]. Given the number of health behavior decisions made each and every day, increased impulsivity could affect a multitude of choices in daily life. There are several studies demonstrating individuals with evening chronotype have greater impulsivity.

Linking sleep related changes in neurocognitive function to health behaviors

Despite the many studies linking these neurocognitive processes to sleep and circadian rhythms, few studies have applied these concepts to healthy behaviors. Cedernaes

et al. [55] demonstrated greater impulsivity in a go/no go task that asked participants to respond to food related cues after total sleep deprivation. Participants committed more errors of commission (i.e., responded to nonfood related cues) after total sleep deprivation when compared to a control condition. In addition, participants reported greater hunger after the sleep deprivation condition. This study did not have a condition in which individuals had to inhibit responses to food related cues, and therefore it is not clear whether these results were due to general impulsivity or specific to food related impulsivity. In another study, Chan [56] found that circadian disruption, as measured by inconsistent bedtimes, rather than sleep duration was associated with high BMI only in individuals with low delay discounting. This study demonstrates the potential that individual differences in trait-like cognitive factors rather than a simple cause-effect relationship.

Neuroimaging data

Several studies using neuroimaging have found that sleep loss is correlated with changes in brain regions implicated in healthy decision-making. Greer et al. [57] found that after one night of total sleep deprivation, individuals had increases in appetitive evaluation regions within the pre-frontal cortex and insular cortex during food desirability choices, combined with increased activity in the amygdala. Similarly, St-Onge et al. [58] found that after receiving just 4 h per night in bed, participants displayed greater activation in the thalamus and areas of the orbitofrontal cortex (part of the prefrontal cortex) in response to food-related images when compared to nonfood images. These relationships were attenuated in the group receiving a 9 h sleep opportunity. In addition, St-Onge et al. [59] conducted a partial sleep deprivation study and exposed individuals to 5 versus 9 h time in bed for five nights. After a period of restricted sleep, viewing unhealthy foods led to greater activation in the superior and middle temporal gyri, middle and superior frontal gyri, left inferior parietal lobule, orbitofrontal cortex, and right insula compared with healthy foods. These same stimuli presented after a period of habitual sleep did not produce marked activity patterns specific to unhealthy foods. Furthermore, food intake during restricted sleep increased in association with a relative decrease in brain oxygenation level-dependent (BOLD) activity observed in the right insula. In sum, the above studies demonstrate that sleep loss may impact cognitive processes in areas of the brain such as the pre-frontal cortex, which assists in planning, complex decision-making, and moderating behavior. These studies also demonstrate that longer sleep opportunities may protect an individual from experiencing these effects.

Most of the above studies were conducted in a highly controlled environment with scheduled meals. In contrast,

Fang et al. [60] conducted a total sleep deprivation study to examine the impact that sleep deprivation may have on the salience network, which is thought play a role in reward processing and homeostatic regulation [61]. Throughout the course of the study, participants were able to consume food ad libitum, with the exception of when receiving fMRI scans. Results indicated that after a night of total sleep deprivation, participants consumed a greater percentage of calories from fat and lower percentage of calories from carbohydrates than they had after a baseline night of sleep (9 h of time in bed). Furthermore, after total sleep deprivation, enhanced functional connectivity within regions of the salience network was noted, and these changes appeared to predict the increased fat and decreased carbohydrate intake. This study indicates that changes in neuronal activity and functional connectivity that affect reward processing associated with sleep loss may lead to changes in behavior. More specifically, the neurocognitive changes may have directly impacted decision-making surrounding food choices and may have led to the increased consumption of fat and carbohydrates.

There is less research on the changes in neuronal activity associated with circadian rhythm disruption. Much of this research has focused on chronotype, the self-reported preference for timing of sleep and activity. Hasler has explored the associations between eveningness and alcohol among late adolescents and young adults. Hasler and Clark [62] explored brain-related pathways (medial prefrontal cortex and ventral striatum) and alcohol intake in late adolescents (age 20). He reported evening types had an altered response to reward stimuli compared with morning types. Furthermore, this decreased activation in response to rewards was associated with more symptoms of alcohol dependence. He later reported in a longitudinal study that evening chronotype at age 20 predicted alcohol dependence at age 22 via these brain reward pathways [63].

In summary, there are many studies of the influence of sleep and circadian factors on neurocognitive function but only a handful of studies have examined these in reference to health behaviors. Data suggests that sleep loss affects many of the cognitive processes needed to navigate the multitude of healthy decisions needed in daily life.

Affective response to sleep loss

Sleep loss and circadian disruption may also affect health decision-making through their impact on emotional functioning. There are well-known effects of sleep loss on emotional functioning. In the short term, there is an anti-depressant effect of sleep deprivation but the antidepressant effects are reversed after sleep duration is restored [64]. In contrast, chronic sleep restriction can lead to depression and irritability [65]. The impact of sleep loss on psychopathology is not just limited to depression.

Kahn-Greene et al. [66] reported that after 56 h of wakefulness, Personality Assessment Inventory clinical scales of somatic complaints, anxiety, depression, and paranoia were higher when compared to assessments completed prior to sleep deprivation. Post hoc analyses revealed that the increase in somatic complaints was associated with an increase in the score on the health concerns subscale, the increase in anxiety was associated with an increase in the score on the physiological subscale, the increase in depression was associated with an increase in both the cognitive and affective subscales, and the increase in paranoia was associated with an increase in both the persecution and the resentment subscales [66]. Negative emotions may impact decision-making processes [67], thus, these mood changes may have an impact on health behaviors. There is evidence that the mood effects of sleep loss may interfere with healthy behaviors. One study demonstrated that when individuals were required to exercise during 30 h of sleep loss had greater negative mood than those who did not exercise [68].

The role of circadian factors in mood and mood disorders has been widely studied with far-reaching implications for mood disorders and health behaviors [69]. There is a well-known circadian rhythm of mood, with lowest mood in the morning hours and higher mood around 8:00 p.m. [70]. Disruption of the circadian rhythm via travel or shift work may affect health behaviors via mood. Silva et al. [71] demonstrated that among shift workers, anxiety ratings were increased the morning after night shift work when compared to the morning after a night of sleep. Furthermore, anxiety scores were negatively associated with hunger ratings, indicating that those with greater anxiety reported less hunger.

Effort and motivation

"I want to exercise but I am just too tired." This is a common statement that health care providers hear from their patients, who report poor sleep, fatigue, long work hours and exhaustion interfere with the ability to participate in regular exercise. Yet, on the contrary, data suggest that sleep loss itself does not affect aerobic capacity. It does impact their perception and emotional responses to physical activity, however. Even 24-h sleep loss has a relatively small effect on aerobic capacity, although this study did report there was significant variability in response to sleep loss [72]. For example, half of the participants demonstrated a very small change in aerobic capacity after sleep loss (5%), while the other half showed larger decrements in exercise tolerance (15%–40%). Notably, participants reported perceptions of greater effort following sleep loss, regardless of change in exercise tolerance, suggesting that exercise felt more difficult for everyone. Baron and colleagues also reported in analyses of an exercise intervention for older adults with insomnia, although the intervention overall improved aerobic

capacity, sleep quality, and daytime sleepiness over the 16-week intervention period, individuals who had higher self-reported sleepiness had lower exercise participation in the trial [73]. Therefore, an important message to patients is that losing sleep does make exercise feel harder but their physical performance is still relatively preserved in most cases.

In addition to sleep loss, circadian factors play a role in physical activity [74]. Studies have reported that evening chronotypes have lower physical activity, particularly in the morning [75,76]. Individuals with evening chronotype also report higher perceived effort and demonstrate a higher heart rate to exercise in the morning [77,78]. Therefore, time of day and chronotype both play a role in the perception of physical activity. There is little research about whether circadian rhythm disruption affects physical activity.

There is a dearth of research examining the relationships between sleep, circadian factors, and motivation, which can be defined as "Wanting. A condition of an organism that includes a subjective sense (not necessarily conscious) of desiring some change in self and/or environment" [79], p. 1. Motivation is influenced by cognitive processes and emotion [79], which as reviewed earlier, are factors that can be impacted by sleep loss and circadian dysfunction. Thus, it might be postulated that disruptions to cognitive processes and to emotional functioning may in turn lead to decreased motivation to engage in health behaviors, and may ultimately result in less healthy decision-making.

To our knowledge, there have been no studies directly examining the links between sleep loss, subjectively reported motivation, and health behaviors such as physical activity and diet. However, there have been studies examining the impact of sleep loss on motivation and studies that indirectly measure motivation (e.g., wanting), sleep loss, and health behaviors. Motivation to engage in cognitive tasks has been found to decrease across a night of total sleep deprivation [80]. It might be hypothesized that a similar relationship may exist between sleep deprivation and motivation to engage in healthy decision-making, where the more sleep deprived an individual becomes, the less motivated they feel to engage in health behaviors such as physical activity. Of note, evidence has shown that rewards can influence the ability to attend after sleep deprivation [81]. More specifically, when asked to complete a task of sustained attention after sleep deprivation, those who are offered low rewards for doing so have more attentional lapses and slowed reaction time when compared with those who are offered high rewards for doing so. These findings demonstrate that a reward may increase motivation to perform. Thus, rewards may help to protect against some of the effects of sleep loss on motivational processes.

Although not measured directly, sleep loss may result in increased motivation to obtain unhealthy foods. Participants have indicated wanting more high-fat than low-fat

foods after partial sleep restriction [82], which may translate into increased motivation to obtain these foods under conditions of sleep loss. Participants have also rated their desire to eat as higher after partial sleep restriction when compared to a control condition [82]. However, the literature has been mixed regarding the degree to which individuals may increase intake in association with increased hunger ratings [82–84]. Thus, it is unclear to what extent increased motivation to obtain highly palatable food results in a clinically significant change in behavior.

There is also some limited evidence that circadian disruption influences motivation. For instance, circadian disruption in the form of jetlag has been associated with temporary decreases in ratings of motivation to engage in physical activity [85]. Furthermore, motivation has been shown to be lower after eastward travel when compared to westward travel [85].

Given that an individual's level of motivation may ultimately impact engagement in health behaviors, it is crucial to consider these factors when examining the pathways through which sleep and circadian functioning may impact health. Further research directly examining the relationships between sleep, circadian rhythms, and motivation for different health behaviors is needed. In addition, research is needed to assess how these relationships ultimately impact decision-making regarding health behaviors. For instance, if sleep loss leads to reduced motivation, and the reduced motivation leads to difficulty selecting healthy foods, interventions to increase motivation among those not receiving enough sleep may help to improve cardiometabolic health.

Does changing sleep make it easier to make healthy decisions?

Despite the data linking sleep loss and circadian disruption to poorer health behaviors, there are few studies that evaluate whether extending sleep or aligning circadian rhythms leads to improved health behaviors. There have been several studies that have looked at whether treating obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) improves other health behaviors. OSA is a disorder characterized by repeated airway collapse that leads to intermittent hypoxia and sleep fragmentation. It was hypothesized that individuals with OSA, once treated, would have more energy to engage in better health behaviors. However, this has not been supported by the literature. In general, individuals with OSA who are treated with CPAP actually have an increase in BMI [86] rather than a decrease. It has also been shown that individuals in general do not change their diet or become more physically active after treatment [87]. On the contrary, multiple studies have evaluated intensive lifestyle interventions in patients with OSA and have demonstrated that these interventions can achieve weight loss in this population [88].

There has also been research conducted to examine the effects of insomnia treatment (cognitive behavioral therapy for insomnia or CBT-I) among individuals with alcohol dependence. It is well known that alcohol use and abuse are implicated in the development and maintenance of insomnia [89]. For example, individuals may consume alcohol to cope with sleep problems. Furthermore, if alcohol dependent, they also experience sleep problems in response to abstaining from alcohol. There are multiples studies that demonstrate that CBT-I is effective at improving sleep among individuals with alcohol dependence [90]. However, a recent clinical trial did not demonstrate an improvement in relapse.

A handful of studies have evaluated effects of extending sleep duration on eating and weight-related outcomes. One study by Cizza et al. [91] conducted sleep extension intervention; however, they found improvements in the intervention and control group in metabolic factors. It is thought that a Hawthorne effect occurred in the lengthy period between the screening and intervention period, in that the act of completing sleep logs and enrolling in a study lead to improvements in both groups. Two more recent studies have demonstrated changes in eating behaviors with sleep extension. A study of sleep extension in adolescents (bedtime advancement) demonstrated adolescents with earlier bedtimes increased low GI fruit and dairy at post-treatment [92]. Another study demonstrated 4 weeks of sleep extension in adults reduced appetite, desire for sweet and salty foods [93]. In this study, individuals extended their sleep by an enormous 1.6 h. It is not clear whether this amount of sleep extension is possible in most participants. Two other sleep extension studies were published that demonstrated more modest improvements in sleep duration (about 40 min) [94,95]. More studies are needed to evaluate whether changing sleep will improve other health behaviors. Therefore, these studies suggest that it is possible that extending sleep can have a broader-reaching effect on other health behaviors. The limitation is that existing studies are small, short term, and intensive interventions. More research is needed to test whether these interventions can lead to sustained sleep behavior change and sustained changes to health behaviors.

Summary

In summary, we have presented multiple environmental, social, neurocognitive, and behavioral pathways by which sleep and circadian rhythms can influence healthy decision-making. We have depicted these pathways in a conceptual diagram (Fig. 30.2). Environmental factors, changes to cognitive function, and emotional changes are all altered by sleep loss and can influence desire and self-control, motivation and energy to engage in health behaviors. Although a great deal of research has focused on how sleep loss affects these basic cognitive processes, only a few studies have evaluated how these changes affect

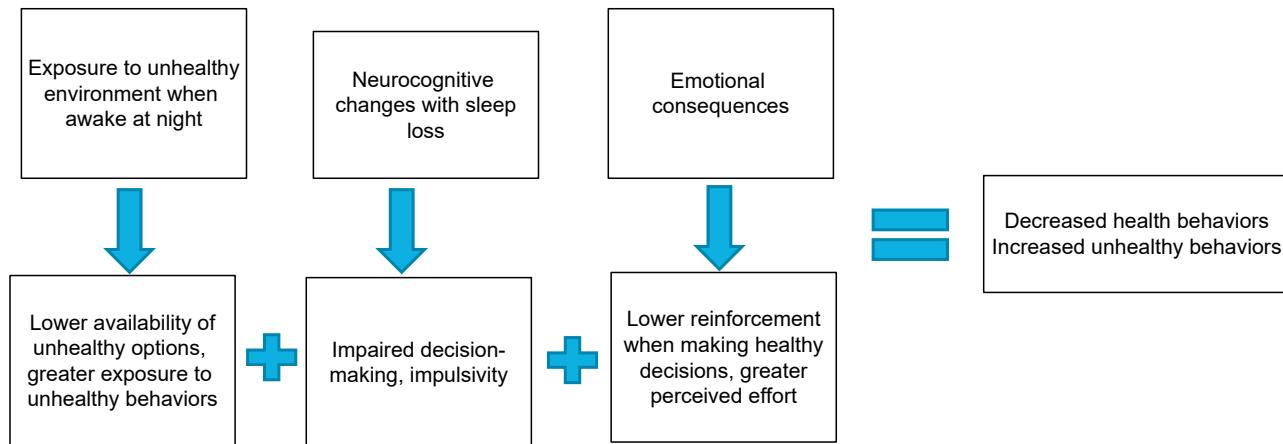


FIGURE 30.2 Conceptual diagram demonstrating the complex interaction of environment, neurocognitive function, and emotional changes associated with sleep loss and circadian disruption.

health behavior and decision-making. In addition, translational research is needed to understand how sleep affects behavioral decision-making in naturalistic settings. Finally, given that vulnerabilities exist, interventions are needed to (1) determine if improving sleep can help other health behaviors and (2) when changing sleep is not possible, if addressing the underlying vulnerability in those at risk for sleep loss (e.g., cognitive interventions).

Glossary

Bedtime procrastination A lack of self-regulation at bedtime that involves avoiding interrupting a more pleasurable activity to go to bed

Chronotype Self-reported preference for timing of sleep/wake schedule and activities

Circadian rhythm The approximately 24 h rhythm generated by the suprachiasmatic nucleus, in humans. Circadian rhythms are observed in sleep wake patterns, mood, cognitive performance and many hormones (cortisol) and physiological processes (heart rate, blood pressure)

Delay discounting The ability to delay immediate rewards for later rewards

Effort discounting The willingness to exert effort to obtain a reward.

Eveningness Self-reported preference for delayed timing of activity and sleep wake schedule

Executive function A collection of top down cognitive processes including inhibitory control, multi-tasking, planning, switching tasks

Forced desynchrony A laboratory protocol that examines the circadian rhythm while controlling for sleep duration. Individuals are put on a shorter (22 h) or longer (28 h) “day” and sleep is moved progressively around the clock to examine performance and physiology at different phases of the circadian rhythm

Hawthorne effect When participants change based on being observed, rather than the intervention

Hedonic eating Eating for pleasure

Homeostatic Refers to the system of balance, discussed in terms of both sleep propensity and hunger. The build-up of drive to eat or sleep is in part driven by the time since the last sleep or meal

Impulsivity Refers to impulsive action or decision making made without weighing the pros and cons

References

- [1] Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom Health and Lifestyle Survey. *Arch Intern Med* 2010;170(8):711–8. <https://doi.org/10.1001/archinternmed.2010.76Norway>.
- [2] Gochman DS. Handbook of health behavior research IV: relevance for professionals and issues for the future. Springer US; 1997. <https://doi.org/10.1007/978-1-4899-0484-3>.
- [3] Borbely AA. A two process model of sleep regulation. *Hum Neurobiol* 1982;1(3):195–204.
- [4] Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr* 2009;139(3):629–32. <https://doi.org/10.3945/jn.108.097618>.
- [5] Lowe MR, Butryn ML. Hedonic hunger: a new dimension of appetite? *Physiol Behav* 2007;91(4):432–9. <https://doi.org/10.1016/j.physbeh.2007.04.006>.
- [6] Scheer FAJL, Morris CJ, Shea SA. The internal circadian clock increases hunger and appetite in the evening independent of food intake and other behaviors. *Obesity* 2013;21(3):421–3. <https://doi.org/10.1002/oby.20351>.
- [7] Ford ES, Cunningham TJ, Croft JB. Trends in self-reported sleep duration among US adults from 1985 to 2012. *Sleep* 2015;38(5):829–32. <https://doi.org/10.5665/sleep.4684>.
- [8] Grandner MA, Chakravorty S, Perlis ML, Oliver L, Gurubhagavatula I. Habitual sleep duration associated with self-reported and objectively determined cardiometabolic risk factors. *Sleep Med* 2014;15(1):42–50. <https://doi.org/10.1016/j.sleep.2013.09.012>.
- [9] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M,

- Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL. Joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. *Sleep* 2015;38(8):1161–83. <https://doi.org/10.5665/sleep.4886>.
- [10] Grandner MA, Jackson NJ, Izci-Balserak B, Gallagher RA, Murray-Bachmann R, Williams NJ, Patel NP, Girardin J-L. Social and behavioral determinants of perceived insufficient sleep. *Front Neurol* 2015;6:1664–2295. <https://doi.org/10.3389/fneur.2015.00112>.
- [11] Hale L, Do DP. Racial differences in self-reports of sleep duration in a population-based study. *Sleep* 2007;30(9):1096–103. <https://doi.org/10.1093/sleep/30.9.1096>.
- [12] Whinnery J, Jackson N, Rattanaumpawan P, Grandner MA. Short and long sleep duration associated with race/ethnicity, sociodemographics, and Socioeconomic position. *Sleep* 2014;37(3):601–11. <https://doi.org/10.5665/sleep.3508>.
- [13] Williams NJ, Grandner MA, Wallace DM, Cuffee Y, Airhihenbuwa C, Okuyemi K, Ogedegbe G, Jean-Louis G. Social and behavioral predictors of insufficient sleep among African Americans and Caucasians. *Sleep Med* 2016;18:103–7. <https://doi.org/10.1016/j.sleep.2015.02.533>.
- [14] De Santis AS, Roux AVD, Moore K, Baron KG, Mujahid MS, Javier Nieto F. Associations of neighborhood characteristics with sleep timing and quality: the multi-ethnic study of atherosclerosis. *Sleep* 2013;36(10):1543–51. <https://doi.org/10.5665/sleep.3054India>.
- [15] Basner M, Fomberstein KM, Razavi FM, Banks S, William JH, Rosa RR, Dinges DF. American time use survey: sleep time and its relationship to waking activities. *Sleep* 2007;30(9):1085–95. <https://doi.org/10.1093/sleep/30.9.1085>.
- [16] Basner M, Spaeth AM, Dinges DF. Sociodemographic Characteristics and Waking Activities and their role in the timing and duration of sleep. *Sleep* 2014;37(12):1889–906. <https://doi.org/10.5665/sleep.4238>.
- [17] Knowlden AP, Sharma M. Health belief structural equation model predicting sleep behavior of employed college students. *Fam Community Health* 2014;37(4):271–8. <https://doi.org/10.1097/FCH.0000000000000043>.
- [18] Kroese FM, De Ridder DTD, Evers C, Adriaanse MA. Bedtime procrastination: introducing a new area of procrastination. *Front Psychol* 2014;5. <https://doi.org/10.3389/fpsyg.2014.00611>.
- [19] Hoggard LS, Hill L BK. Examining how racial discrimination impacts sleep quality in African Americans: is perseveration the answer? *Behav Sleep Med* 2018;16(5):471–81. <https://doi.org/10.1080/15402002.2016.1228648>.
- [20] Johnson DA, Lisabeth L, Lewis TT, Sims M, Hickson DMA, Samdarshi T, Taylor H, Diez Roux AV. The contribution of psychosocial stressors to sleep among African Americans in the Jackson heart study. *Sleep* 2016;39(7):1411–9. <https://doi.org/10.5665/sleep.5974>.
- [21] Sims M, Lipford KJ, Patel N, Ford CD, Min YI, Wyatt SB. Psychosocial factors and behaviors in African Americans: the Jackson heart study. *Am J Prev Med* 2017;52(1):S48. <https://doi.org/10.1016/j.amepre.2016.09.020>.
- [22] Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev* 2013;17(4):241–54. <https://doi.org/10.1016/j.smrv.2012.09.005>.
- [23] Bathgate CJ, Edinger JD, Krystal AD. Insomnia patients with objective short sleep duration have a blunted response to cognitive behavioral therapy for Insomnia. *Sleep* 2017;40(1). <https://doi.org/10.1093/sleep/zsw012>.
- [24] Campbell KJ, Crawford DA, Salmon J, Carver A, Garnett SP, Baur LA. Associations between the home food environment and obesity-promoting eating behaviors in adolescence. *Obesity* 2007;15(3):719–30. <https://doi.org/10.1038/oby.2007.553>.
- [25] Conklin CA, Robin N, Perkins KA, Salkeld RP, McClernon FJ. Proximal versus distal cues to smoke: the effects of environments on smokers' cue-reactivity. *Exp Clin Psychopharmacol* 2008;16(3):207–14. <https://doi.org/10.1037/1064-1297.16.3.207>.
- [26] Vohs KD, Baumeister RF, Schmeichel BJ, Twenge JM, Nelson NM, Tice DM. Making choices impairs subsequent self-control: a limited-resource account of decision making, self-regulation, and active initiative. *J Pers Soc Psychol* 2008;94(5):883–98. <https://doi.org/10.1037/0022-3514.94.5.883>.
- [27] Onyper SV, Thacher PV, Gilbert JW, Grader SG. Class start times, Sleep, and academic performance in college: a path analysis. *Chronobiol Int* 2012;29(3):318–35. <https://doi.org/10.3109/07420528.2012.655868>.
- [28] Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, Wright KP. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Natl Acad Sci USA* 2013;110(14):5695–700. <https://doi.org/10.1073/pnas.1216951110>.
- [29] Caci H, Robert P, Boyer P. Novelty seekers and impulsive subjects are low in morningness. *Eur Psychiatry* 2004;19(2):79–84.
- [30] Chelminski I, Ferraro FR, Petros TV, Plaud JJ. An analysis of the “eveningness-morningness” dimension in “depressive” college students. *J Affect Disord* 1999;52(1–3):19–29.
- [31] Prat G, Adam A. Influence of circadian typology on drug consumption, hazardous alcohol use, and hangover symptoms. *Chronobiol Int* 2011;28(3):248–57.
- [32] Patterson F, Malone SK, Lozano A, Grandner MA, Hanlon AL. Smoking, screen-based sedentary behavior, and diet associated with habitual sleep duration and chronotype: data from the UK Biobank. *Ann Behav Med* 2016;50(5):715–26.
- [33] Fleig D, Randler C. Association between chronotype and diet in adolescents based on food logs. *Eat Behav* 2009;10(2):115–8.
- [34] Brondel L, Romer MA, Nouges PM, Touyarou P, Davenne D. Acute partial sleep deprivation increases food intake in healthy men. *Am J Clin Nutr* 2010;91(6):1550–9.
- [35] Schmid SM, Hallschmid M, Jauch-Chara K, Wilms B, Benedict C, Lehnert H, et al. Short-term sleep loss decreases physical activity under free-living conditions but does not increase food intake under time-deprived laboratory conditions in healthy men. *Am J Clin Nutr* 2009;90(6):1476–82.
- [36] Durmer JS, Dinges DF, editors. *Neurocognitive consequences of sleep deprivation*. Seminars in neurology; 2005. New York, NY.
- [37] Kilgore W. Socio-emotional and neurocognitive effects of sleep loss. In: The handbook of operator fatigue. Boca Raton, FL: Taylor & Francis Group; 2012. p. 173–85.
- [38] Goel N, Rao H, Durmer JS, Dinges DF, editors. *Neurocognitive consequences of sleep deprivation*. Seminars in neurology; NIH; 2009.
- [39] McHill AW, Hull JT, Wang W, Czeisler CA, Klerman EB. Chronic sleep curtailment, even without extended (> 16-h) wakefulness, degrades human vigilance performance. *Proc Natl Acad Sci* 2018;115(23):6070–5.

- [40] Pool E, Brosch T, Delplanque S, Sander D. Where is the chocolate? Rapid spatial orienting toward stimuli associated with primary rewards. *Cognition* 2014;130(3):348–59.
- [41] Diamond A. Executive functions. *Annu Rev Psychol* 2013;64:135–68.
- [42] Binks PG, Waters WF, Hurry M. Short-term total sleep deprivation does not selectively impair higher cortical functioning. *Sleep* 1999;22(3):328–34.
- [43] Killgore WD. Effects of sleep deprivation on cognition. *Prog Brain Res* 2010;185:105–29.
- [44] Amlung M, MacKillop J. Delayed reward discounting and alcohol misuse: the roles of response consistency and reward magnitude. *J Exp Psychol* 2011;2(3).
- [45] Audrain-McGovern J, Rodriguez D, Epstein LH, Cuevas J, Rodgers K, Wileyto EP. Does delay discounting play an etiological role in smoking or is it a consequence of smoking? *Drug Alcohol Depend* 2009;103(3):99–106.
- [46] Bickel WK, Odum AL, Madden GJ. Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. *Psychopharmacology* 1999;146(4):447–54.
- [47] Fernie G, Peeters M, Gullo MJ, Christiansen P, Cole JC, Sumnall H, et al. Multiple behavioural impulsivity tasks predict prospective alcohol involvement in adolescents. *Addiction* 2013;108(11):1916–23.
- [48] Appelhans BM, Waring ME, Schneider KL, Pagoto SL, DeBiasse MA, Whited MC, et al. Delay discounting and intake of ready-to-eat and away-from-home foods in overweight and obese women. *Appetite* 2012;59(2):576–84.
- [49] Libedinsky C, Massar SA, Ling A, Chee W, Huettel SA, Chee MW. Sleep deprivation alters effort discounting but not delay discounting of monetary rewards. *Sleep* 2013;36(6):899–904.
- [50] Milfont TL, Schwarzenthal M. Explaining why larks are future-oriented and owls are present-oriented: self-control mediates the chronotype-time perspective relationships. *Chronobiol Int* 2014;31(4):581–8.
- [51] Krishnan-Sarin S, Reynolds B, Duhig AM, Smith A, Liss T, McFetridge A, et al. Behavioral impulsivity predicts treatment outcome in a smoking cessation program for adolescent smokers. *Drug Alcohol Depend* 2007;88(1):79–82.
- [52] Acheson A, Richards JB, de Wit H. Effects of sleep deprivation on impulsive behaviors in men and women. *Physiol Behav* 2007;91(5):579–87.
- [53] Demos K, Hart C, Sweet L, Mailloux K, Trautvetter J, Williams S, et al. Partial sleep deprivation impacts impulsive action but not impulsive decision-making. *Physiol Behav* 2016;164:214–9.
- [54] McKenna BS, Dickinson DL, Orff HJ, Drummond SP. The effects of one night of sleep deprivation on known-risk and ambiguous-risk decisions. *J Sleep Res* 2007;16(3):245–52.
- [55] Cedernaes J, Brandell J, Ros O, Broman JE, Hogenkamp PS, Schiöth HB, et al. Increased impulsivity in response to food cues after sleep loss in healthy young men. *Obesity* 2014;22(8):1786–91.
- [56] Chan WS. Delay discounting and response disinhibition moderate associations between actigraphically measured sleep parameters and body mass index. *J Sleep Res* 2017;26(1):21–9.
- [57] Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. *Nat Commun* 2013;4.
- [58] St-Onge M-P, McReynolds A, Trivedi ZB, Roberts AL, Sy M, Hirsch J. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. *Am J Clin Nutr* 2012;95(4):818–24.
- [59] St-Onge M, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. *Int J Obes* 2014;38(3):411.
- [60] Fang Z, Spaeth AM, Ma N, Zhu S, Hu S, Goel N, et al. Altered salience network connectivity predicts macronutrient intake after sleep deprivation. *Sci Rep* 2015;5:8215.
- [61] Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 2007;27(9):2349–56.
- [62] Hasler BP, Clark DB. Circadian misalignment, reward-related brain function, and adolescent alcohol involvement. *Alcohol Clin Exp Res* 2013;37(4):558–65.
- [63] Hasler BP, Casement MD, Sitnick SL, Shaw DS, Forbes EE. Eveningness among late adolescent males predicts neural reactivity to reward and alcohol dependence 2 years later. *Behav Brain Res* 2017;327:112–20.
- [64] Giedke H, Schwarzer F. Therapeutic use of sleep deprivation in depression. *Sleep Med Rev* 2002;6(5):361–77.
- [65] Zhai L, Zhang H, Zhang D. Sleep duration and depression among adults: a meta-analysis of prospective studies. *Depress Anxiety* 2015;32(9):664–70.
- [66] Kahn-Greene ET, Killgore DB, Kamimori GH, Balkin TJ, Killgore WD. The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Med* 2007;8(3):215–21.
- [67] Raghunathan R, Pham MT. All negative moods are not equal: motivational influences of anxiety and sadness on decision making. *Organ Behav Hum Decis Process* 1999;79(1):56–77.
- [68] Scott JP, McNaughton LR, Polman RC. Effects of sleep deprivation and exercise on cognitive, motor performance and mood. *Physiol Behav* 2006;87(2):396–408.
- [69] Li JZ. Circadian rhythms and mood: opportunities for multi-level analyses in genomics and neuroscience: circadian rhythm -dysregulation in mood disorders provides clues to the brain's organizing principles, and a touchstone for genomics and neuroscience. *Bioessays* 2014;36(3):305–15.
- [70] Monk T, Buysse D, Reynolds C, Berga S, Jarrett D, Begley A, et al. Circadian rhythms in human performance and mood under constant conditions. *J Sleep Res* 1997;6(1):9–18.
- [71] Silva AASC, TdVC L, Teixeira KR, Mendes JA, de Souza Borba ME, Mota MC, et al. The association between anxiety, hunger, the enjoyment of eating foods and the satiety after food intake in individuals working a night shift compared with after taking a nocturnal sleep: a prospective and observational study. *Appetite* 2017;108:255–62.
- [72] Martin BJ. Effect of sleep deprivation on tolerance of prolonged exercise. *Eur J Appl Physiol Occup Physiol* 1981;47(4):345–54.
- [73] Baron KG, Reid KJ, Zee PC. Exercise to improve sleep in insomnia: exploration of the bidirectional effects. *J Clin Sleep Med* 2013;9(08):819–24.
- [74] Vitale JA, Weydahl A. Chronotype, physical activity, and sport performance: a systematic review. *Sports Med* 2017;47(9):1859–68.
- [75] McNeil J, Doucet É, Brunet J-F, Hintze LJ, Chaumont I, Langlois É, et al. The effects of sleep restriction and altered sleep timing on energy intake and energy expenditure. *Physiol Behav* 2016;164:157–63.

- [76] Shechter A, St-Onge M-P. Delayed sleep timing is associated with low levels of free-living physical activity in normal sleeping adults. *Sleep Med* 2014;15(12):1586–9.
- [77] Rae DE, Stephenson KJ, Roden LC. Factors to consider when assessing diurnal variation in sports performance: the influence of chronotype and habitual training time-of-day. *Eur J Appl Physiol* 2015;115(6):1339–49.
- [78] Rossi A, Formenti D, Vitale JA, Calogiuri G, Weydahl A. The effect of chronotype on psychophysiological responses during aerobic self-paced exercises. *Percept Mot Skills* 2015;121(3):840–55.
- [79] Baumeister RF. Toward a general theory of motivation: problems, challenges, opportunities, and the big picture. *Motiv Emot* 2016;40(1):1–10.
- [80] Odle-Dusseau HN, Bradley JL, Pilcher JJ. Subjective perceptions of the effects of sustained performance under sleep-deprivation conditions. *Chronobiol Int* 2010;27(2):318–33.
- [81] Massar SA, Lim J, Sasmita K, Chee MW. Sleep deprivation increases the costs of attentional effort: performance, preference and pupil size. *Neuropsychologia* 2019;123:169–77.
- [82] McNeil J, Forest G, Hintze LJ, Brunet J-F, Finlayson G, Blundell JE, et al. The effects of partial sleep restriction and altered sleep timing on appetite and food reward. *Appetite* 2017;109:48–56.
- [83] Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. *Am J Clin Nutr* 2008;89(1):126–33.
- [84] St-Onge M-P, Roberts AL, Chen J, Kelleman M, O’Keeffe M, RoyChoudhury A, et al. Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. *Am J Clin Nutr* 2011;94(2):410–6.
- [85] Fowler PM, Knez W, Crowcroft S, Mendham AE, Miller J, Sargent C, et al. Greater effect of east vs. west travel on jet lag, sleep, and team-sport performance. *Med Sci Sports Exerc* 2017;49(12):2548–61.
- [86] Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Benseñor IM, Lotufo PA. Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax* 2015;70(3):258–64.
- [87] Batool-Anwar S, Goodwin JL, Drescher AA, Baldwin CM, Simon RD, Smith TW, et al. Impact of CPAP on activity patterns and diet in patients with obstructive sleep apnea (OSA). *J Clin Sleep Med* 2014;10(05):465–72.
- [88] Thomasouli M-A, Brady EM, Davies MJ, Hall AP, Khunti K, Morris DH, et al. The impact of diet and lifestyle management strategies for obstructive sleep apnoea in adults: a systematic review and meta-analysis of randomised controlled trials. *Sleep Breath* 2013;17(3):925–35.
- [89] Brower KJ. Insomnia, alcoholism and relapse. *Sleep Med Rev* 2003;7(6):523–39.
- [90] Brooks AT, Wallen GR. Sleep disturbances in individuals with -alcohol-related disorders: a review of cognitive-behavioral therapy for insomnia (CBT-I) and associated non-pharmacological therapies. *Subst Abuse* 2014;8:55–62.
- [91] Cizza G, Piaggi P, Rother KI, Csako G. Hawthorne effect with transient behavioral and biochemical changes in a randomized controlled sleep extension trial of chronically short-sleeping obese adults: implications for the design and interpretation of clinical studies. *PLoS One* 2014;9(8).
- [92] Asarnow LD, Greer SM, Walker MP, Harvey AG. The impact of sleep improvement on food choices in adolescents with late bedtimes. *J Adolesc Health* 2017;60(5):570–6.
- [93] Tasali E, Chapotot F, Wroblewski K, Schoeller D. The effects of extended bedtimes on sleep duration and food desire in overweight young adults: a home-based intervention. *Appetite* 2014;80:220–4.
- [94] Haack M, Serrador J, Cohen D, Simpson N, Meier-Ewert H, Mullington JM. Increasing sleep duration to lower beat-to-beat blood pressure: a pilot study. *J Sleep Res* 2013;22(3):295–304.
- [95] Leproult R, Deliens G, Gilson M, Peigneux P. Beneficial impact of sleep extension on fasting insulin sensitivity in adults with habitual sleep restriction. *Sleep* 2015;38(5):707–15.

This page intentionally left blank

Chapter 31

Sleep and mild traumatic brain injury

Jocelyn McCallum¹, Amanda Black², Charles H. Samuels³ and Jonathan Charest⁴

¹University of Calgary, Faculty of Kinesiology, Calgary, AB, Canada; ²Department of Kinesiology, Faculty of Applied Health Sciences, Brock University, St. Catharines, ON, Canada; ³Faculty of Medicine, Faculty of Kinesiology, University of Calgary, Calgary, AB, Canada; ⁴School of Psychology, Université Laval, Québec, QC, Canada

Introduction

In recent years, there has been a notable and rapidly increasing interest in furthering our comprehension of the role of sleep in mild traumatic brain injury (mTBI) and concussion. This surge in interest can be attributed to several factors, such as the heterogeneous nature of mTBI symptoms among individuals, the considerable variability in recovery patterns and durations, and the persistence of long-term symptoms. [1–3]. Sleep difficulties and symptomology prior [4] and following a concussion [5,6] have garnered increasing attention within diverse populations. This includes research conducted on adults and adolescents [7], athletes and student-athletes [8], and women [9]. Furthermore, there exists a close and reciprocal association between sleep [4,10] and mental health [11] in the context of concussion, which significantly impacts an individual's social, athletic, and academic capability [12,13]. Growing evidence has underscored the critical influence of sleep on both the expression and recovery of concussion symptoms. This recognition is particularly significant within populations such as athletes and student-athletes, who are disproportionately affected by concussions due to the intense physical demands and unique environmental stressors associated with their activities. The risk of concussions in these populations is amplified by multiple factors, including frequent travel across time zones, circadian rhythm disturbances inherent in rigorous training schedules, and the psychological pressures stemming from academic and athletic performance expectations [14,15]. These factors collectively contribute to suboptimal sleep patterns, which have been identified as a significant risk factor for both concussion occurrence and recovery. Although historically underexplored, recent empirical research has substantially expanded our understanding of how sleep, both pre- and

postconcussion, can influence recovery outcomes. As a result, there has been a significant increase in studies examining the relationship between sleep and concussion recovery, reflecting a growing recognition of its importance in broader health considerations.

Defining sport-related concussion

The sixth International Consensus on Concussion in Sport [15] defines sport-related concussion (SRC) “*sport-related concussion is a traumatic brain injury caused by a direct blow to the head, neck or body resulting in an impulsive force being transmitted to the brain that occurs in sports and exercise-related activities*.” This initiates a neurotransmitter and metabolic cascade, with possible axonal injury, blood flow change and inflammation affecting the brain. Symptoms and signs may present immediately, or evolve over minutes or hours, and commonly resolve within days, but may be prolonged. No abnormality is seen on standard structural neuroimaging studies (computed tomography or magnetic resonance imaging T1-and T2-weighted images), but in the research setting, abnormalities may be present on functional, blood flow or metabolic imaging studies. Sport-related concussion results in a range of clinical symptoms and signs that may or may not involve loss of consciousness. The clinical symptoms and signs of concussion cannot be explained solely by (but may occur concomitantly with) drug, alcohol, or medication use, other injuries (such as cervical injuries, peripheral vestibular dysfunction) or other comorbidities (such as psychological factors or coexisting medical conditions).” It should be noted that many studies use the terms concussion and mTBI interchangeably, with mTBI usually signifying an injury with a mild Glasgow Coma Scale score (between 13 and 15) [16]. The Department of Veteran Affairs and Department of Defense (VA/DoD) have suggested that using the term “concussion” when communicating with

patients may be preferable. This recommendation stems from the belief that the term “concussion” conveys a transient condition, whereas the term “mild traumatic brain injury” may inadvertently contribute to stigma due to its association with brain damage (Guide, P. 2016). Nevertheless, evidence of the variability in pathophysiology among sport-related concussions, characterized by differential symptoms and recovery trajectories, suggests the existence of distinct subtypes within SRC [17]. Emerging research has proposed the existence of five distinct subtypes within sport-related concussions, with each subtype exhibiting a specific combination of symptoms and impairments cluster [17]. The five symptoms cluster that have been proposed include a migraine cluster (headache, sensitivity to light, sensitivity to noise and nausea), cognitive-emotional cluster (difficulty concentrating, difficulty remembering, foginess, feeling more emotional, irritability, feeling slowed down, sadness and nervousness), sleep-emotional cluster (trouble falling asleep, sleeping less, feeling more emotional, irritability, sleeping more, sadness and nervousness) neurological cluster (blurred vision, vomiting, neck pain, pressure in head, visual problems and double vision), and undefined feelings cluster (do not feel right and confusion) [17]. It is worth noting that the literature has reported two main clusters, namely the migraine cluster (24%) and the sleep-emotional cluster (21%) [17]. Moreover, regardless of the prevalence of the reported cluster, they all have been associated with negative clinical outcomes alongside prolonged recovery. Adding to the complexity of defining sports-related concussion (SRC), it is essential to acknowledge that there is currently no universally accepted set of physiological thresholds to diagnose this condition [18].

Prevalence of concussion

Every year, it is estimated that approximately 42 million individuals globally experience an mTBI or concussion [19]. Among this population, approximately 100–300 per 100,000 individuals seek medical attention [19] resulting in more than half going undiagnosed and without any treatment. In Canada and the United States, 200,000 and three million concussion are reported each year respectively [18,20]. Sport-related concussions are recognized as a prominent etiological factor contributing to the occurrence of mTBI and concussions, alongside various other causes like motor vehicle accidents, falls, and self-harm [21,22]. Nonetheless, the existing literature provides limited data to sufficiently draw definitive conclusions regarding the prevalence of specific etiologies of concussions. In a comprehensive survey conducted in 2016 by the Monitoring the Future project, a total of 13,088 adolescents from grades 8, 10, and 12 participated, including 50.2% females, revealed that 19.5% of the participants reported at least one

concussion throughout their lifetime, while 5.5% reported multiple diagnosed concussions [23]. In a subsequent study conducted by the National Youth Risk Behavior project, the CDC revealed that around 2.5 million high school students had experienced at least one concussion. Additionally, within the past 12 months, 6% of these students reported having sustained two or more concussions [24]. According to the Centers for Disease Control and Prevention (CDC), an estimated 207,830 visits to emergency departments annually between 2001 and 2005 were specifically related to concussions and other TBIs resulting from recreational and sports activities (Centres for Disease Control and Prevention, 2011). Notably, 65% of these patients fell within the age range of 5–18 years old. The Canadian National Health Population Survey, conducted by Health Canada, involved a sample of 81,634 respondents who were queried regarding the nature of significant injuries that restricted their regular activities within the previous year [22]. The results from the Health Canada survey indicated an annual prevalence rate of 110 reported cases of concussion per 100,000 individuals, with concussion being identified as the most severe injury reported [22].

Cantu [25] estimated the prevalence of concussions to be approximately 5% among all sports injuries. However, there is a concerning issue regarding underdiagnosis of concussions in athletes, with up to 50% of cases going unrecognized [26–28]. This lack of recognition and diagnosis exposes athletes, including student-athletes, to a heightened risk of various health complications. Globally, the highest rate of concussion in athlete is observed within the prepubescent age group (Ropper and Gorson, 2007). Studies have indicated that between 8.3% and 19.5% of high school students in the United States have experienced at least one concussion in their lifetime (Gessel et al., 2007; [29,30]). Moreover, children aged 0–14 years, regardless of gender, were equally likely to report concussion as their most serious injury, whereas individuals aged 15 and older showed a male overrepresentation in reporting concussion as their most serious injury [22]. In recent systematic review, it has been established that sex continues to exert a notable influence on the concussion rate [31]. Only this time, females were found to have a higher likelihood of experiencing a concussion, with incidences of 3.76 compared to 3.65 per 100,000 exposures for males. Differences between games and practices were also uncovered. Concussions rates were significantly lower during practices (2.87 concussions per 10,000 athlete exposures) relatively to in games (4.89 concussions per 10,000 athlete exposures) [31]. Notably, from 2001 to 2018, the rate of concussions has shown a steady increase of 0.19 per 10,000 exposures. This persistent rise indicates that concussions continue to be a crucial safety and health concern for athletes of all ages [31]. Conversely to Van pelt (2021),

an Alberta-based study revealed males were more prone to experiencing concussions compared to females and individuals identifying their sex as “other,” with percentages of 28.6%, 22.1%, and 14.2%, respectively (McCallum et al., 2021). However, these estimations may be misrepresentations of the true burden of concussion due to the largely subjective nature of concussion diagnosis [32], the imbalanced collaboration of various healthcare professions regarding best and most recent practices in concussion assessment (Tiwari et al., 2022), as well as the tendency of physicians to inadequately document their examinations of suspected concussions (Cools et al., 2021).

Persistent symptoms and postconcussion

Concussions can have notable impacts on cognitive functioning and balance in the initial 24 h after the injury [33,34]. It has been estimated that a considerable percentage, ranging from 13.7% to 33%, of children and adolescents may experience persistent symptoms for up to 3 months following the injury [1,35]. Furthermore, approximately 28% of children may continue to manifest postconcussion symptoms for an extended period, spanning from 12 to 24 months [36]. It is crucial to acknowledge that the definitive time frame for concussion recovery is not yet scientifically established and is heavily influenced by various factors, such as age, sex, and previous history of concussions [37–39]. For instance, while the majority of patients with sport-related concussions may recover within 7–10 days, it is well recognized that children and adolescents generally require more time to recover compared to collegiate and professional athletes [40,41]. In non-sport-related concussion, recovery periods are harder to identify. In cases of non-sport-related concussions, determining recovery periods becomes more challenging. This difficulty primarily arises from the inconsistent tracking of individuals who experience concussions outside of athletic settings and the logistical complexities associated with such tracking compared to athletes [42]. As a result, many studies involving non-athletes with concussions resort to using predetermined time frames for appointment intervals, which can artificially prolong the perceived recovery period [43]. Almost 2 decades ago, two separate researchers introduced the concept that elite athletes recover faster from concussions compared to other athletes, primarily due to their superior fitness levels and access to better medical resources [44–46]. Therefore, considerable discrepancies exist in concussion recovery trajectory and the postconcussion syndrome (PCS) remains quite elusive given its complexity [42]. PCS is defined by the fifth edition of the Diagnostic and Statistics Manual as cognitive deficits in attention or memory, at least three or more of the following symptoms:

fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, apathy, or personality change [47]. These criteria are considered conservative as the broader definition of PCS produced by the World Health Organization’s International Classification of Disease (ICD-10) requires three or more of these clinical symptoms: headache, dizziness, fatigue, irritability, insomnia, concentration difficulty, or memory difficulty [48]. The fifth International Consensus Statement on Concussion in Sport employs the term “persistent symptoms” to describe clinical symptoms resulting from a sport-related concussion that extend beyond 10–14 days in adults and beyond 4 weeks in pediatric populations [49]. Empirical research indicates substantial variability in the estimated prevalence of postconcussion syndrome (PCS), contingent upon the diagnostic criteria applied [50]. Notably, PCS rates determined using the ICD-10 criteria are approximately six times higher than those based on the DSM-IV criteria, underscoring the influence of definitional frameworks on prevalence metrics [51]. The diagnostic criteria for postconcussion syndrome (PCS) vary significantly among physicians, leading to heterogeneity in clinical definitions. A survey revealed that 26.6% of clinicians diagnose PCS when symptoms persist for less than two weeks, 20.4% after two weeks to 1 month, 33% after one to 3 months, and 11.1% only after symptoms have exceeded 3 months [52]. These findings underscore the ongoing debate in the medical community regarding the temporal threshold for diagnosing PCS, reflecting inconsistencies in clinical practice and the need for standardized guidelines. In the absence of a standardized definition for postconcussion syndrome (PCS), and with a tendency for numerous studies to fail to clarify the specific diagnostic criteria employed, the interpretation of PCS outcomes remains highly variable. This lack of consensus may result in significant clinical repercussions, influencing both the accuracy of diagnoses and the trajectory of patient recovery [53]. Inconsistent application of diagnostic criteria can lead to misclassification, complicating treatment strategies and potentially prolonging recovery times.

Sleep

Sleep is an indispensable aspect of human existence, characterized by its nonnegotiable nature, akin to the significance attributed to water consumption, dietary intake, and the oxygen we breathe. It underpins a diverse array of fundamental biological systems crucial for sustaining life, encompassing immune functions, emotional modulation, cognitive processes, and various metabolic activities specific to each living organism. Sleep can also be described as an intricate fusion of physiological and behavioral mechanisms, constituting a naturally occurring and reversible state marked by reduced movement, diminished

engagement with one's surroundings, and an elevated threshold of consciousness. Importantly, sleep does not equal an absence of neural activity like coma or anesthesia would. Collaboration between voluntary behavior and biological activities is necessary to achieve proper and adequate sleep. For example, turning off the light, adjusting your bedroom temperature, and reducing light exposure in the evening will result in a biological increase of melatonin and several other patterns of the brain throughout the entire night. According to the National Sleep Foundation (NSF), it is recommended for adult aged between 18 and 64 to obtain 7–9 h of sleep per night [54]. In addition to recognizing the significance of sleep duration, it constitutes only one element within the broader view of sleep health. The comprehensive perspective of sleep health also includes the importance of sleep efficiency, continuity, timing, regularity, perceived satisfaction, and daytime alertness [55].

In humans, sleep is principally organized by a sequence of neurophysiological progressions within the brain. These progressions are categorized into distinct stages using predefined criteria and scoring methodologies. This categorization encompasses a spectrum of alertness transitioning from wakefulness to nonrapid eye movement (NREM) sleep, and subsequently to rapid eye movement (REM) sleep, thereby reflecting the cyclical dynamics of wakefulness and sleep that have persisted for numerous decades [56]. These stages are discernible by observing various physiological changes, encompassing alterations in brain activity, heart rate, respiratory rate, body temperature, and muscle tone, among other factors [56,57]. While the exact physiological role of sleep continues to be a subject of ongoing research, it is widely acknowledged that sleep substantially contributes to a range of critical functions. These functions encompass vital aspects including neural development and maturation, physiological recovery and repair, elimination of metabolic waste and brain toxins, as well as memory consolidation, among other essential processes [58]. Currently sleep is primarily quantified by sleep staging based on electroencephalogram, electromyogram, electrooculogram, and electrocardiogram signals. As previously mentioned, sleep is subdivided into two distinct phases, NREM and REM. In the most recent sleep staging guidelines, NREM sleep will be further divided into three stages namely N1, N2, and N3, the latter often being recognized or identified as slow-wave sleep (SWS) [59].

Stage N1 of sleep is a transitional state characterized by rapid EEG activity coupled with low voltage. Stage N1 is scored when more than 15 s ($\geq 50\%$) of the epoch consist of theta activity (4–7 Hz), sometimes mixed with low-amplitude beta activity replacing the alpha activity of the wake state. EEG activity amplitudes range from 50 to 75 μ V. Spindles of 4–7 Hz at amplitudes less than 75 μ V

may occur. Alpha activity in the EEG drops to less than 50%. Sharp waves at the vertex (vertex spikes) may occur toward the end of Stage N1, but sleep spindles and K-complexes (two sleep EEG graphoelements) never occur in Stage N1, nor do rapid eye movements. Stage N1 constitutes approximately 2%–5% of the total sleep night and corresponds to the initial falling asleep phase, transitioning into drowsiness. Stage N2 is a phase characterized by the absence of slow-rolling eye that typically follows the initial falling asleep period. During this stage, the sleeper is better protected against environmental disturbances compared to Stage N1; however, sensitivity to stimuli persists. In terms of EEG activity, theta waves increase and become dominant, and short electrical complexes appear referred to as phasic events. These phasic events include sleep spindles and K-complexes that are present in the EEG recording. K-complexes are recognized as very rapid sinusoidal waves ranging from 11 to 16 Hz, lasting only 1–2 s, and it is hypothesized that they play a role in protecting and stabilizing sleep. The density of sleep spindles is thought to reflect the quality and effectiveness of thalamic mechanisms in filtering out irrelevant environmental stimuli from the sleeper's surroundings. K-complexes are easily identifiable due to their distinct two-phase pattern: a distinct negative wave followed immediately by a positive component lasting ≥ 500 ms in the EEG trace (Bastien et al., 2002). Another hypothesis suggests that these phenomena support memory consolidation; however, their true functions remain unknown to this day. Eye movements and EMG activity also diminish during Stage N2, and this change is readily visible in the EEG trace. Stage N2 constitutes approximately 45%–55% of a healthy adult sleeper's night and is considered a link between stage N1 and stage N3. Stage N3 is also known as slow-wave sleep (SWS) or deep sleep. In fact, delta waves (0.5–4 Hz) characterize SWS (Hoehn and Marieb, 2010). There are no specific EOG and EMG criteria for SWS, but generally, muscle tone decreases more compared to Stage N2. Stage N3 sleep constitutes the deepest, most restorative, and refreshing type of sleep. Physiologically, a sleeper in Stage N3 has the highest threshold for arousal. This stage is often associated with diffuse dreams (20% of dreams) and numerous parasomnias (night terrors, sleepwalking). Eye movements can completely cease during this stage of sleep. Physiologically, Stage N3 sleep is often linked to a peak in growth hormone secretion. Stage N3 sleep accounts for approximately 18%–25% of a healthy sleeper's night.

Circadian rhythms

Circadian rhythms are described based on the following parameters: the period (i.e., the time required to complete a full cycle or oscillation, with a circadian cycle being approximately 24 h [60]) and the amplitude (i.e., the

maximum variability between the highest value, or peak, known as acrophase, and the lowest value, known as bathyphase, of the biological variable studied during the cycle). It was long believed that the endogenous circadian rhythm synchronized through meals, physical activity, and social rhythms (or nonphotic zeitgebers) [61,62]. This understanding was overturned following studies on samples of blind individuals and enucleated individuals (i.e., those whose eyes have been surgically removed). These studies demonstrated that, despite exposure to nonphotic zeitgebers, the endogenous rhythm of these individuals did not synchronize with the habitual day but remained in free-running mode [63]. Thus, it is now established that the most potent zeitgeber for the endogenous circadian rhythm (i.e., the SCN) is light, a photic zeitgeber, while meals, activity, and social behaviors, as nonphotic zeitgebers, would contribute to the fine-tuning of the central circadian clock but to a lesser extent [62,64,65]. The term “zeitgebers” (i.e., time giver or synchronizer in German) refers to signals that convey temporal information to the circadian system. The oscillators thus receive information from structures sensitive to environmental or endogenous changes that can provide temporal cues to the central circadian clock. Among the most studied zeitgebers are the light-dark cycle, social rhythms, physical exercise, and meal timing [66].

Concussion: Impact on the physiology

After a concussion, a disruption in cellular homeostasis occurs, initiating a cascade of biochemical events that can lead to hormonal fluctuations and neurotransmitter imbalances. These disturbances are linked to altered brain activity and contribute to the symptoms and recovery trajectory following an mTBI [67,68]. Cellular processes such as energy demand and neurotransmitter release are affected, which can lead to cognitive and mood impairments [69]. These disturbances are primarily attributed to the metabolic and ionic changes following neuronal injury [70]. Specifically, the axonal stretch and shear forces during a concussion lead to an imbalance in energy demands, which disrupts cellular integrity and metabolism. At the onset of a concussion, it is hypothesized that an ionic dysregulation occurs, marked by an efflux of intracellular potassium and an influx of calcium ions into the cell ([70]; Hughes et al., 2022). This ionic flux disrupts cellular homeostasis, initiating metabolic and excitotoxic processes that can impair neuronal function and contribute to the pathophysiology of mTBI [68]. Elevated intracellular calcium concentrations can precipitate increased metabolic demand [70], promote cellular damage or apoptosis through excitotoxic mechanisms [68], and disrupt the regulation of sleep architecture, impairing both REM and NREM sleep cycle [71,72]. Sleep disturbances

following concussion are hypothesized to arise from neurochemical disruptions affecting key regulatory systems of sleep and arousal [67]. Specifically, damage to orexinergic neurons, which modulate wakefulness and energy homeostasis, and GABAergic neurons, which inhibit excitatory activity to promote sleep, may impair the balance between sleep and wake states [73]. Similarly, disruptions in monoaminergic systems, responsible for stabilizing sleep-wake transitions, can lead to fragmented or dysregulated sleep patterns. Additionally, injury-induced alterations in pineal gland function may reduce melatonin secretion, further compromising circadian rhythm entrainment and sleep quality [74]. These mechanistic insights underscore the complex interplay between neurochemical damage and postconcussion sleep pathology. Sleep disturbances following concussion are hypothesized to arise from damage to specific neural substrates that regulate the sleep-wake cycle, including the hypothalamus, thalamus, and brainstem. These regions are critical for the coordination of neurochemical and circadian processes governing sleep architecture. Studies suggest that localized injury to these areas disrupts the balance of neurotransmitters such as orexin, GABA, and monoamines, as well as the secretion of melatonin, leading to unpredictable physiological changes and altered recovery trajectories (Mollayeva et al., 2016) [75]. Such disruptions underscore the complex interplay between injury localization and the manifestation of postconcussion sleep disturbances. The postconcussion alterations in glutamate activity remain an area of significant interest and complexity in neurobiology. Following a concussion, the activity of glutamate, an excitatory neurotransmitter, has been found to exhibit variable changes depending on the context and timing of the assessment [68]. Some studies have documented an increase in glutamate activity following concussion, potentially contributing to excitotoxicity, while others have reported a decrease in its levels [76,77]. Further, some investigations have indicated that there are no significant changes in glutamate concentrations in both the acute and sub-acute phases following a mTBI [78,79]. These divergent findings highlight the need for further exploration into the temporal dynamics of glutamate release, reuptake, and its subsequent effects on neuronal signaling and recovery processes after a concussion. Chronic alterations in glutamate dynamics have been identified as significant contributors to postconcussion outcomes, particularly within specific populations such as female athletes [80]. Studies have demonstrated that glutamate levels fluctuate in response to injury, with certain athletes exhibiting increased concentrations, which correlate with negative long-term outcomes [74]. These fluctuations appear to be region-dependent and time-dependent, with the severity and location of the injury playing a pivotal role in glutamate signaling [68]. As

glutamate is a key excitatory neurotransmitter primarily active during periods of wakefulness, its dysregulation may explain the fatigue and daytime drowsiness reported by individuals with concussion [76]. Notably, research comparing athletes from contact vs. noncontact sports has revealed that individuals involved in contact sports often exhibit lower levels of both glutamate and GABA, the major inhibitory neurotransmitter [81]. This dysregulation could explain the heightened cognitive dysfunction observed in athletes participating in contact sports, as these neurotransmitter imbalances may impair neuroplasticity and cognitive recovery after concussion [82]. These findings highlight the importance of considering both the type of sport and the neurobiological response to injury when assessing concussion outcomes. The glymphatic system, responsible for maintaining cerebral homeostasis, plays a critical role in clearing metabolic waste products and neurotoxic proteins from the brain. This process is facilitated by the exchange between cerebrospinal fluid and interstitial fluid, which also delivers essential molecules such as neurotransmitters and amino acids to the brain [83,84]. Glymphatic function is primarily active during sleep, particularly during non-REM phases, underscoring its dependence on proper sleep architecture for optimal performance [85,86]. Traumatic brain injuries, including mild [87,88], moderate, and severe concussions [67], have been shown to significantly disrupt glymphatic pathways, particularly within the thalamus, hypothalamus, hippocampus, and cerebellum—regions essential for sleep/wake regulation and cognitive processing. Glymphatic dysfunction in the thalamus and hypothalamus, in particular, impairs waste clearance and neurotransmitter balance, potentially explaining the onset of postconcussive sleep disturbances [87,88]. This disruption exacerbates the accumulation of metabolic byproducts, such as amyloid-beta and tau proteins, which are implicated in neurodegeneration and may contribute to the long-term cognitive and behavioral sequelae observed in some individuals following concussive injuries [89]. Furthermore, the chronic impairment of glymphatic exchange following TBI highlights a potential therapeutic target for addressing postconcussive symptoms. Interventions aimed at restoring glymphatic activity, such as improving sleep quality, managing circadian rhythm disruptions, or exploring pharmacological modulation, could provide avenues for enhancing recovery and mitigating long-term outcomes.

Sleep disturbances following a concussion

Sleep disturbances are among the most prevalent and persistent sequelae of mTBI, with an estimated 50% of affected individuals (range: 30%–92%) reporting disrupted sleep that can persist for months or even years following the

injury (Grima et al., 2017; [90]). Concussions induce acute neuropathological changes, which can escalate the risk of chronic neurodegenerative conditions, including Alzheimer's and Parkinson's diseases [91,92]. Suboptimal sleep, encompassing fragmented sleep architecture, insufficient or excessive sleep duration, misaligned circadian rhythms, and reduced sleep quality, has been implicated in delaying the physiological recovery process [93] and aggravating post-concussion symptomatology (Murdaugh et al., 2018). The deleterious impact of sleep disturbances extends beyond recovery delay, contributing to heightened neuropsychiatric morbidity such as depression and post-traumatic stress disorder (Mollayeva et al., 2016), alongside impairments in cognitive function (Kostyun et al., 2015), academic achievement (Hysing et al., 2016), and athletic performance (Walsh et al., 2021). These adverse outcomes underscore the critical need for timely, targeted sleep-focused interventions to enhance recovery trajectories (Kontos et al., 2018; Ludwig et al., 2020). However, identifying risk factors for preinjury suboptimal sleep remains challenging, limiting the development of preemptive strategies.

Research points to a constellation of risk factors, including pre-existing sleep habits [94], comorbid conditions [95], sex-based biological differences [94], and injury-specific variables such as cumulative concussion exposure (Bryan 2013) and initial symptom burden (Murdaugh et al., 2018).

As previously mentioned, sleep disturbances are a well-documented and pervasive consequence of mTBI [67,96], with individuals demonstrating significantly greater odds of sleep-related problems compared to uninjured controls (Walton et al., 2021). Young adults appear particularly susceptible, reporting a 3.09-fold increased risk of sleep difficulties among children and adolescents following concussion relative to noninjured peers (Theadom et al., 2016). This heightened risk underscores the need to address sleep disturbances as a critical component of post-mTBI care. At least one sleep-related symptom is reported by 39%–72% of individuals aged 5–60 years following mTBI, as documented in hospital-based and longitudinal studies [96,97]. Among adolescents specifically, 21.6% develop new sleep problems after concussion [98]. Variability in reported prevalence is likely attributable to differences in study methodologies and measurement tools. Clinically significant disturbances, as assessed using standardized instruments such as the Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS), are observed in 27.1%–84.2% of individuals postinjury (Brooks et al., 2019; [4,99]). The range of sleep-related symptoms is extensive. Difficulty initiating sleep is reported in 31.2%–85% of cases (Brooks et al., 2019; Howell et al., 2019; Tkachenko et al., 2016), while maintaining sleep continuity is problematic for 53%–65% (Brooks et al., 2019). Excessive daytime sleepiness is

noted in 50%–85% [67,90], with 49.5%–79% of individuals complaining of fatigue [100] and 31.2% experiencing persistent drowsiness (Tkachenko et al., 2016). Adolescents with a concussion frequently articulate the impact of these disruptions on their quality of life, with 72% expressing concern about their sleep disturbances and 88% reporting interference with daily activities (Brooks et al., 2019). A history of concussion is positively correlated with a higher incidence of reported sleep disturbances, particularly in adolescents and young adults (Brooks et al., 2019 [101]). Interestingly, those with mTBI often report more pronounced sleep disruptions compared to individuals who sustain more severe traumatic brain injuries [75]. This counterintuitive finding highlights the multifactorial nature of post-mTBI sleep disturbances, implicating preinjury sleep patterns, cumulative injury burden, and neurobiological factors tied to injury severity.

Sleep duration—concussion

Sleep disturbances following a concussion can manifest as either an increase or decrease in sleep duration, often accompanied by a decline in sleep quality (Chung et al., 2019; Kostyun et al., 2015). It was also reported that at 3 weeks postconcussion, 9.9% of individuals self-reported sleeping less than 7 h per night, while 27.7% indicated sleeping more than 9 h (Kostyun et al., 2015). By 11 weeks postinjury, these numbers decreased, with 8.4% reporting short sleep duration and 12% continuing to experience extended sleep duration (Kostyun et al., 2015). Shortened sleep duration relative to baseline is associated with heightened symptom severity, prolonged reaction times, decreased processing speed, impaired memory recall, and increased errors in balance testing [14]. Conversely, excessive sleep duration has been linked to poorer outcomes on the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) battery, suggesting that deviations in either direction from normal sleep patterns can negatively impact recovery and cognitive function (Kostyun et al., 2015).

Other factors that are known to influence sleep, such as pre-existing mental health conditions and medication usage, should be considered when examining sleep disturbances following a concussion. It is noteworthy that over 10% of athletes are prescribed sedative or hypnotic medications [102], while more than 5% report opioid use [103]. These medications, which can significantly influence sleep patterns and overall recovery, underscore the necessity of comprehensive preseason screening. Such screenings are essential for identifying athletes who may be at an increased risk for exacerbated sleep disturbances or compromised recovery following concussion [4]. Early identification of these factors can enable more tailored management strategies, promoting better outcomes in concussion care. Additionally, pre-existing sleep disorders,

despite emerging evidence indicating that insomnia-like symptoms (e.g., difficulties initiating or maintaining sleep) or obstructive sleep apnea (OSA)—which leads to intermittent nocturnal hypoxemia—are prevalent in athletes [104]. Notably, insomnia-like disturbances during the preseason have been associated with an increased susceptibility to sport-related concussions (SRC), and both insomnia and OSA are independently linked to elevated levels of amyloid- β and tau proteins (Liguori et al., 2017; Ooms et al., 2014). These proteins contribute to disruptions in deep sleep, potentially creating a detrimental feedback loop of disrupted sleep and protein accumulation [105]. Therefore, implementing screening for sleep disorders in athletes could help identify individuals at greater risk of mTBI and poor recovery outcomes.

Sleep and demographic differences

Sex differences in sleep disturbances following concussion have been documented [106], with several studies indicating that females report higher levels of sleep disruption compared to males (Davis-Hayes et al., 2017; Kostyun et al., 2015; [106]). However, some studies show conflicting results, with no significant differences observed in sleep symptomatology between sexes [107]. Notably, some research suggests that males may experience longer recovery times—up to three times longer—when sleep disturbances are present, while females take about twice as long to recover under similar conditions [10]. It is important to consider that females tend to experience more concussions than males, particularly in high school and college athletics (Davis-Hayes et al., 2017; Kerr et al., 2019; [30]). Additionally, females generally report a higher frequency of symptoms related to vision, concentration, headaches, emotional disturbances, and sleep difficulties compared to males, even in baseline assessments (Brown et al., 2015). Age also appears to play a role in sleep disturbances following concussion, with older individuals experiencing higher rates of sleep disruptions [17,108]. Studies have shown that younger children tend to report fewer sleep-related problems than adolescents, though some studies suggest that the youngest and oldest children may report fewer sleep disturbances compared to those in the middle age group [109]. Finally, athletes, despite experiencing fewer sleep-related symptoms following concussion compared to nonathletes, tend to have worse baseline sleep habits, with 27%–37% of healthy athletes reporting insomnia-like symptoms [104].

Measuring sleep—concussion

Polysomnography is regarded as the gold standard for assessing sleep disturbances, providing objective data on sleep architecture. Studies utilizing PSG have demonstrated

that individuals with mTBI exhibit significant alterations in sleep patterns, including increased sleep fragmentation, delayed sleep onset, a higher frequency of awakenings [67], reduced sleep efficiency [67,75], and prolonged nocturnal wakefulness [75]. These disruptions are consistently associated with an exacerbation of mTBI symptoms, highlighting the clinical significance of sleep disturbances in concussion recovery [67]. However, discrepancies persist in the literature regarding the specific effects of concussion on various sleep stages. While most studies agree that individuals with mTBI spend less time in rapid eye movement (REM) sleep, there is inconsistency regarding the impact on phase 2 nonrapid eye movement (NREM) sleep (Mollayeva et al., 2017). Some studies report a reduction in phase 2 NREM, while others suggest an increase in its duration following concussion [71]. Furthermore, research has shown that adolescents with a concussion exhibit decreased total sleep time, increased number of awakenings, and poorer sleep efficiency compared to healthy controls, as assessed using Actigraphy [95]. Subjective sleep reports also play a crucial role in postconcussion symptomatology (Brooks et al., 2019; Raikes et al., 2019; Sullivan et al., 2016). Many individuals with concussion report sleep disturbances, even though these subjective complaints are not always corroborated by objective sleep assessments like PSG or Actigraphy (Barlow et al., 2020; Gosselin et al., 2009). Factors such as injury severity, type of sleep monitoring tool used, and the presence of comorbid symptoms may influence these discrepancies. As advancements in sleep tracking technologies performance continue (De Zambotti et al., 2024), the integration of both subjective and objective sleep assessments is becoming increasingly critical for obtaining a comprehensive understanding of postconcussion sleep disturbances and their impact on recovery. The combination of subjective reports, such as patient-reported outcomes, and objective measures, including polysomnography and actigraphy, would provide a more robust assessment of sleep quality and patterns following concussion. This dual approach allows for a more nuanced understanding of the complex relationship between sleep disturbances and recovery outcomes, facilitating better-targeted interventions. Furthermore, advancements in wearable sleep trackers and their growing accuracy in detecting sleep-related variables such as sleep-onset latency, fragmentation, and efficiency have the potential to enhance the monitoring of sleep during concussion recovery.

Conclusion

In conclusion, the expanding body of literature on the role of sleep in mTBI and concussion underscores the critical importance of understanding sleep disturbances as a central factor in both concussion occurrence and recovery. As research across diverse populations, including athletes,

adolescents, and women, reveals, sleep disturbances are a common and significant consequence of concussion, with profound implications for recovery and long-term symptomatology. The bidirectional relationship between sleep and mental health further amplifies the impact of sleep disruptions, influencing cognitive, emotional, and social outcomes postconcussion. Polysomnography has provided objective data confirming that individuals with mTBI exhibit significant alterations in sleep architecture, including fragmented sleep, delayed sleep onset, frequent awakenings, and reduced sleep efficiency. These disruptions are consistently linked to exacerbated mTBI symptoms, emphasizing the clinical relevance of sleep disturbances in concussion recovery. However, discrepancies in the literature regarding the effects of concussion on specific sleep stages, such as phase 2 nonrapid eye movement (NREM) sleep, suggest that further research is needed to better understand the full spectrum of sleep changes following concussion. Subjective sleep reports, while informative, may not always align with objective measurements such as PSG or actigraphy, highlighting the need for a more integrated approach to sleep assessment. Factors such as injury severity, the type of sleep monitoring tool, and the presence of comorbid symptoms can influence the accuracy of these measures, underscoring the complexity of sleep disturbances in postconcussion recovery. As advancements in sleep tracking technologies continue, the integration of both subjective and objective assessments will be essential for a comprehensive understanding of postconcussion sleep disturbances and their impact on recovery outcomes. This dual approach, incorporating patient-reported outcomes alongside objective measures, will provide a more nuanced understanding of sleep quality, facilitate better-targeted interventions, and improve concussion management strategies. Ultimately, recognizing and addressing sleep disturbances in concussion care will be crucial for optimizing recovery and minimizing long-term sequelae.

References

- [1] Barlow KM. Postconcussion syndrome: a review. *J Child Neurol* 2016;31(1):57–67. <https://doi.org/10.1177/0883073814543305>.
- [2] Barnhart M, Bay RC, Valovich McLeod TC. The influence of timing of reporting and clinic presentation on concussion recovery outcomes: a systematic review and meta-analysis. *Sports Med* 2021;51(7):1491–508. <https://doi.org/10.1007/s40279-021-01444-7>.
- [3] Zemek R, Barrowman N, Freedman SB, et al. Clinical risk score for persistent postconcussion symptoms among children with acute concussion in the ED. *JAMA* 2016;315(10):1014. <https://doi.org/10.1001/jama.2016.1203>.
- [4] Raikes AC, Athey A, Alfonso-Miller P, Killgore WDS, Grandner MA. Insomnia and daytime sleepiness: risk factors for sports-related concussion. *Sleep Med* 2019;58:66–74. <https://doi.org/10.1016/j.sleep.2019.03.008>.

- [5] Raikes AC, Satterfield BC, Killgore WDS. Evidence of actigraphic and subjective sleep disruption following mild traumatic brain injury. *Sleep Med* 2019;54:62–9. <https://doi.org/10.1016/j.sleep.2018.09.018>.
- [6] Raikes AC, Schaefer SY. Sleep quantity and quality during acute concussion: a pilot study. *Sleep* 2016;39(12):2141–7. <https://doi.org/10.5665/sleep.6314>.
- [7] Schneider KJ, Critchley ML, Anderson V, et al. Targeted interventions and their effect on recovery in children, adolescents and adults who have sustained a sport-related concussion: a systematic review. *Br J Sports Med* 2023;57(12):771–9. <https://doi.org/10.1136/bjsports-2022-106685>.
- [8] Pierpoint LA, Collins C. Epidemiology of sport-related concussion. *Clin Sports Med* 2021;40(1):1–18. <https://doi.org/10.1016/j.csm.2020.08.013>.
- [9] Valera EM, Joseph ALC, Snedaker K, et al. Understanding traumatic brain injury in females: a state-of-the-art summary and future directions. *J Head Trauma Rehabil* 2021;36(1):E1–17. <https://doi.org/10.1097/HTR.0000000000000652>.
- [10] Bramley H, Henson A, Lewis MM, Kong L, Stetter C, Silvis M. Sleep disturbance following concussion is a risk factor for a prolonged recovery. *Clin Pediatr* 2017;56(14):1280–5. <https://doi.org/10.1177/0009922816681603>.
- [11] Rice SM, Parker AG, Rosenbaum S, Bailey A, Mawren D, Purcell R. Sport-related concussion and mental health outcomes in elite athletes: a systematic review. *Sports Med* 2018;48(2):447–65. <https://doi.org/10.1007/s40279-017-0810-3>.
- [12] Iverson GL, Williams MW, Gardner AJ, Terry DP. Systematic review of preinjury mental health problems as a vulnerability factor for worse outcome after sport-related concussion. *Orthop J Sports Med* 2020;8(10). <https://doi.org/10.1177/2325967120950682>.
- [13] Turner IIRW, Kalpana V, Hall C, et al. Sleep problems are associated with academic performance in a national sample of collegiate athletes. *J Am Coll Health* 2019;69(1):74–81. <https://doi.org/10.1080/07448481.2019.1655027>.
- [14] Hoffman NL, O'Connor PJ, Schmidt MD, Lynall RC, Schmidt JD. Relationships between post-concussion sleep and symptom recovery: a preliminary study. *J Neurotrauma* 2020;37(8):1029–36. <https://doi.org/10.1089/neu.2019.6761>.
- [15] Patricios JS, Schneider KJ, Dvorak J, et al. Consensus statement on concussion in sport: the 6th international conference on concussion in sport—amsterdam, october 2022. *Br J Sports Med* 2023;57(11):695–711. <https://doi.org/10.1136/bjsports-2023-106898>.
- [16] Sussman ES, Pendharkar AV, Ho AL, Ghajar J. Mild traumatic brain injury and concussion: terminology and classification. *Handb Clin Neurol* 2018;158:21–4. <https://doi.org/10.1016/B978-0-444-63954-7.00003-3>.
- [17] Langdon S, Königs M, Adang EAMC, Goedhart E, Oosterlaan J. Subtypes of sport-related concussion: a systematic review and meta-cluster analysis. *Sports Med* 2020;50(10):1829–42. <https://doi.org/10.1007/s40279-020-01321-9>.
- [18] Mucha A, Trbovich A. Considerations for diagnosis and management of concussion. *J Orthop Sports Phys Ther* 2019;49(11):787–98. <https://doi.org/10.2519/jospt.2019.8855>.
- [19] Cassidy JD, Carroll L, Peloso P, et al. Incidence, risk factors and prevention of mild traumatic brain injury: results of the who collaborating centre task force on mild traumatic brain injury. *J Rehabil Med* 2004;36(0):28–60. <https://doi.org/10.1080/16501960410023732>.
- [20] Rausa VC, Shapiro J, Seal ML, et al. Neuroimaging in paediatric mild traumatic brain injury: a systematic review. *Neurosci Biobehav Rev* 2020;118:643–53. <https://doi.org/10.1016/j.neubiorev.2020.08.017>.
- [21] Gardner AJ, Quarrie KL, Iverson GL. The epidemiology of sport-related concussion: what the rehabilitation clinician needs to know. *J Orthop Sports Phys Ther* 2019;49(11):768–78. <https://doi.org/10.2519/jospt.2019.9105>.
- [22] Gordon KE, Dooley JM, Wood EP. Descriptive epidemiology of concussion. *Pediatr Neurol* 2006;34(5):376–8. <https://doi.org/10.1016/j.pediatrneurol.2005.09.007>.
- [23] Veliz P, McCabe SE, Eckner JT, Schulenberg JE. Prevalence of concussion among US adolescents and correlated factors. *JAMA* 2017;318(12):1180. <https://doi.org/10.1001/jama.2017.9087>.
- [24] DePadilla L, Miller GF, Jones SE, Peterson AB, Breiding MJ. Self-reported concussions from playing a sport or being physically active among high school students — United States, 2017. *MMWR Morb Mortal Wkly Rep* 2018;67(24):682–5. <https://doi.org/10.15585/mmwr.mm6724a3>.
- [25] Cantu RC. Concussion (mild traumatic brain injury) and the team physician: a consensus statement—2011 update. *Year Bk Sports Med* 2012;2012:35–6. <https://doi.org/10.1016/j.yspm.2011.12.004>.
- [26] Chrisman SP, Schiff MA, Chung SK, Herring SA, Rivara FP. Implementation of concussion legislation and extent of concussion education for athletes, parents, and coaches in Washington state. *Am J Sports Med* 2014;42(5):1190–6. <https://doi.org/10.1177/0363546513519073>.
- [27] Echlin PS, Skopelja EN, Worsley R, et al. A prospective study of physician-observed concussion during a varsity university ice hockey season: incidence and neuropsychological changes. Part 2 of 4. *FOC* 2012;33(6):E2. <https://doi.org/10.3171/2012.10.FOCUS12286>.
- [28] Meehan WP, Mannix RC, O'Brien MJ, Collins MW. The prevalence of undiagnosed concussions in athletes. *Clin J Sport Med* 2013;23(5):339–42. <https://doi.org/10.1097/JSM.0b013e318291d3b3>.
- [29] Kerr ZY, Chandran A, Nedimyer AK, Arakkal A, Pierpoint LA, Zuckerman SL. Concussion incidence and trends in 20 high school sports. *Pediatrics* 2019;144(5).
- [30] Marar M, McIlvain NM, Fields SK, Comstock RD. Epidemiology of concussions among United States high school athletes in 20 sports. *Am J Sports Med* 2012;40(4):747–55. <https://doi.org/10.1177/0363546511435626>.
- [31] Van Pelt KL, Puetz T, Swallow J, Lapointe AP, Broglio SP. Data-driven risk classification of concussion rates: a systematic review and meta-analysis. *Sports Med* 2021;51(6):1227–44. <https://doi.org/10.1007/s40279-021-01428-7>.
- [32] King D, Brughelli M, Hume P, Gissane C. Assessment, management and knowledge of sport-related concussion: systematic review. *Sports Med* 2014;44(4):449–71. <https://doi.org/10.1007/s40279-013-0134-x>.
- [33] Broglio SP, Puetz TW. The effect of sport concussion on neurocognitive function, self-report symptoms and postural control: a meta-analysis. *Sports Med* 2008;38(1):53–67. <https://doi.org/10.2165/00007256-200838010-00005>.
- [34] Dougan BK, Horswill MS, Geffen GM. Athletes' age, sex, and years of education moderate the acute neuropsychological impact of sports-related concussion: a meta-analysis. *J Int Neuropsychol Soc* 2014;20(1):64–80. <https://doi.org/10.1017/S1355617712001464>.

- [35] Leddy JJ, Sandhu H, Sodhi V, Baker JG, Willer B. Rehabilitation of concussion and post-concussion syndrome. *Sports Health* 2012;4(2):147–54. <https://doi.org/10.1177/1941738111433673>.
- [36] Starkey NJ, Jones K, Case R, Theadom A, Barker-Collo S, Feigin V. Post-concussive symptoms after a mild traumatic brain injury during childhood and adolescence. *Brain Inj* 2018;32(5):617–26. <https://doi.org/10.1080/02699052.2018.1439533>.
- [37] Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA concussion study. *JAMA* 2003;290(19):2549. <https://doi.org/10.1001/jama.290.19.2549>.
- [38] Iverson GL, Gaetz M, Lovell MR, Collins MW. Cumulative effects of concussion in amateur athletes. *Brain Inj* 2004;18(5):433–43. <https://doi.org/10.1080/02699050310001617352>.
- [39] McCauley SR, Boake C, Levin HS, Contant CF, Song JX. Post-concussion disorder following mild to moderate traumatic brain injury: anxiety, depression, and social support as risk factors and comorbidities. *J Clin Exp Neuropsychol* 2001;23(6):792–808. <https://doi.org/10.1076/jcen.23.6.792.1016>.
- [40] Belanger HG, Vanderploeg RD. The neuropsychological impact of sports-related concussion: a meta-analysis. *J Int Neuropsychol Soc* 2005;11(4):345–57. <https://doi.org/10.1017/S1355617705050411>.
- [41] McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA concussion study. *JAMA* 2003;290(19):2556. <https://doi.org/10.1001/jama.290.19.2556>.
- [42] D’Lauro C, Johnson BR, McGinty G, Allred CD, Campbell DE, Jackson JC. Reconsidering return-to-play times: a broader perspective on concussion recovery. *Orthop J Sports Med* 2018;6(3):232596711876085. <https://doi.org/10.1177/2325967118760854>.
- [43] Covassin T, Elbin RJ, Harris W, Parker T, Kontos A. The role of age and sex in symptoms, neurocognitive performance, and postural stability in athletes after concussion. *Am J Sports Med* 2012;40(6):1303–12. <https://doi.org/10.1177/0363546512444554>.
- [44] Pellman EJ, Viano DC, Casson IR, Arfken C, Feuer H. Concussion in professional football: players returning to the same game—Part 7. *Neurosurgery* 2005;56(1):79–92. <https://doi.org/10.1227/01.NEU.0000150180.16552.8D>.
- [45] Pellman EJ, Lovell MR, Viano DC, Casson IR. Concussion in professional football: recovery of NFL and high school athletes assessed by computerized neuropsychological testing—Part 12. *Neurosurgery* 2006;58(2):263–74. <https://doi.org/10.1227/01.NEU.0000200272.56192.62>.
- [46] Putukian M, Aubry M, McCrory P. Return to play after sports concussion in elite and non-elite athletes? *Br J Sports Med* 2009;43(Suppl. 1_1):i28–31. <https://doi.org/10.1136/bjsm.2009.058230>.
- [47] American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. American Psychiatric Association; 2013.
- [48] International statistical classification of diseases and related health problems. 10th revision. 5th ed. World Health Organization; 2016.
- [49] McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med* 2017;51(11):838–47. <https://doi.org/10.1136/bjsports-2017-097699>.
- [50] Langer LK, Alavinia SM, Lawrence DW, et al. Prediction of risk of prolonged post-concussion symptoms: derivation and validation of the TRICORDRR (toronto rehabilitation institute concussion outcome determination and rehab recommendations) scoreMenon D, editor. *PLoS Med* 2021;18(7):e1003652. <https://doi.org/10.1371/journal.pmed.1003652>.
- [51] Polinder S, Cnossen MC, Real RGL, et al. A multidimensional approach to post-concussion symptoms in mild traumatic brain injury. *Front Neurol* 2018;9:1113. <https://doi.org/10.3389/fneur.2018.01113>.
- [52] Rose SC, Fischer AN, Heyer GL. How long is too long? The lack of consensus regarding the post-concussion syndrome diagnosis. *Brain Inj* 2015;29(7–8):798–803. <https://doi.org/10.3109/02699052.2015.1004756>.
- [53] Taylor AA, McCauley SR, Strutt AM. Postconcussion syndrome. *Neurol Clin* 2023;41(1):161–76. <https://doi.org/10.1016/j.ncl.2022.08.003>.
- [54] Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation’s updated sleep duration recommendations: final report. *Sleep Health* 2015;1(4):233–43. <https://doi.org/10.1016/j.slehd.2015.10.004>.
- [55] Buysse DJ. Sleep health: can we define it? Does it matter? *Sleep* 2014;37(1):9–17. <https://doi.org/10.5665/sleep.3298>.
- [56] Hirshkowitz M. Normal human sleep: an overview. *Med Clin North Am* 2004;88(3):551–65. <https://doi.org/10.1016/j.mcna.2004.01.001>.
- [57] Rb B. AASM scoring manual version 2.2. 2015.
- [58] Heller HC. The functions of sleep. In: Encyclopedia of sleep and circadian rhythms. Elsevier; 2023. p. 478–86. <https://doi.org/10.1016/B978-0-12-822963-7.00111-0>.
- [59] Moser D, Anderer P, Gruber G, et al. Sleep classification according to AASM and rechtschaffen & kales: effects on sleep scoring parameters. *Sleep* 2009;32(2).
- [60] Czeisler CA, Duffy JF, Shanahan TL, et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 1999;284(5423):2177–81. <https://doi.org/10.1126/science.284.5423.2177>.
- [61] Buxton OM, Lee CW, L’Hermite-Balériaux M, Turek FW, Van Cauter E. Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. *Am J Physiol Regul Integr Comp Physiol* 2003;284(3):R714–24. <https://doi.org/10.1152/ajpregu.00355.2002>.
- [62] Mistlberger RE, Skene DJ. Nonphotic entrainment in humans? *J Biol Rhythms* 2005;20(4):339–52. <https://doi.org/10.1177/0748730405277982>.
- [63] Lockley SW, Skene DJ, Arendt J, Tabandeh H, Bird AC, DeFrance R. Relationship between melatonin rhythms and visual loss in the blind. *J Clin Endocrinol Metab* 1997;82(11).
- [64] Roenneberg T, Kumar CJ, Merrow M. The human circadian clock entrains to sun time. *Curr Biol* 2007;17(2):R44–5. <https://doi.org/10.1016/j.cub.2006.12.011>.
- [65] Schibler U, Ripperger J, Brown SA. Peripheral circadian oscillators in mammals: time and food. *J Biol Rhythms* 2003;18(3):250–60. <https://doi.org/10.1177/0748730403018003007>.
- [66] Honma A, Yamada Y, Nakamaru Y, Fukuda S, Honma K ichi, Honma S. Glucocorticoids reset the nasal circadian clock in mice. *Endocrinology* 2015;156(11):4302–11. <https://doi.org/10.1210/en.2015-1490>.
- [67] Piantino J, Lim MM, Newgard CD, Iliff J. Linking traumatic brain injury, sleep disruption and post-traumatic headache: a potential role for glymphatic pathway dysfunction. *Curr Pain Headache Rep* 2019;23(9):62. <https://doi.org/10.1007/s11916-019-0799-4>.

- [68] Romeu-Mejia R, Giza CC, Goldman JT. Concussion pathophysiology and injury biomechanics. *Curr Rev Musculoskelet Med* 2019;12(2):105–16. <https://doi.org/10.1007/s12178-019-09536-8>.
- [69] Teleanu RI, Niculescu AG, Roza E, Vladâcenco O, Grumezescu AM, Teleanu DM. Neurotransmitters—key factors in neurological and neurodegenerative disorders of the central nervous system. *IJMS* 2022;23(11):5954. <https://doi.org/10.3390/ijms23115954>.
- [70] Giza CC, Hovda DA. The neurometabolic cascade of concussion.
- [71] Schreiber S, Barkai G, Gur-Hartman T, et al. Long-lasting sleep patterns of adult patients with minor traumatic brain injury (mTBI) and non-mTBI subjects. *Sleep Med* 2008;9(5):481–7. <https://doi.org/10.1016/j.sleep.2007.04.014>.
- [72] Tatsuki F, Sunagawa GA, Shi S, et al. Involvement of Ca²⁺-dependent hyperpolarization in sleep duration in mammals. *Neuron* 2016;90(1):70–85. <https://doi.org/10.1016/j.neuron.2016.02.032>.
- [73] Kilduff TS, Peyron C. The hypocretin/orexin ligand–receptor system: implications for sleep and sleep disorders. *Trends Neurosci* 2000;23(8):359–65.
- [74] Kierans AS, Kirov II, Gonen O, et al. Myoinositol and glutamate complex neurometabolite abnormality after mild traumatic brain injury. *Neurology* 2014;82(6):521–8. <https://doi.org/10.1212/WNL.0000000000000105>.
- [75] Viola-Saltzman M, Watson NF. Traumatic brain injury and sleep disorders. *Neurol Clin* 2012;30(4):1299–312. <https://doi.org/10.1016/j.ncl.2012.08.008>.
- [76] Henry LC, Tremblay S, Boulanger Y, Ellemborg D, Lassonde M. Neurometabolic changes in the acute phase after sports concussions correlate with symptom severity. *J Neurotrauma* 2010;27(1):65–76. <https://doi.org/10.1089/neu.2009.0962>.
- [77] Tremblay S, Beaulé V, Proulx S, et al. Multimodal assessment of primary motor cortex integrity following sport concussion in asymptomatic athletes. *Clin Neurophysiol* 2014;125(7):1371–9. <https://doi.org/10.1016/j.clinph.2013.11.040>.
- [78] Yasen AL, Smith J, Christie AD. Glutamate and GABA concentrations following mild traumatic brain injury: a pilot study. *J Neurophysiol* 2018;120(3):1318–22. <https://doi.org/10.1152/jn.00896.2017>.
- [79] Yasen AL, Lim MM, Weymann KB, Christie AD. Excitability, inhibition, and neurotransmitter levels in the motor cortex of symptomatic and asymptomatic individuals following mild traumatic brain injury. *Front Neurol* 2020;11:683. <https://doi.org/10.3389/fneur.2020.00683>.
- [80] Chamard E, Henry L, Boulanger Y, Lassonde M, Théoret H. A follow-up study of neurometabolic alterations in female concussed athletes. *J Neurotrauma* 2014;31(4):339–45. <https://doi.org/10.1089/neu.2013.3083>.
- [81] Lefebvre G, Chamard E, Proulx S, et al. Increased myo-inositol in primary motor cortex of contact sports athletes without a history of concussion. *J Neurotrauma* 2018;35(7):953–62. <https://doi.org/10.1089/neu.2017.5254>.
- [82] Hume PA, Treadom A, Lewis GN, et al. A comparison of cognitive function in former rugby union players compared with former non-contact-sport players and the impact of concussion history. *Sports Med* 2017;47(6):1209–20. <https://doi.org/10.1007/s40279-016-0608-8>.
- [83] Benveniste H, Lee H, Volkow ND. The glymphatic pathway: waste removal from the CNS via cerebrospinal fluid transport. *Neuroscientist* 2017;23(5):454–65. <https://doi.org/10.1177/1073858417691030>.
- [84] Cheng Y, Haorah J. How does the brain remove its waste metabolites from within?
- [85] Anzai Y, Minoshima S. Why we need to sleep: glymphatic pathway and neurodegenerative disease. *Radiology* 2021;300(3):669–70. <https://doi.org/10.1148/radiol.2021211140>.
- [86] Chong PLH, Garic D, Shen MD, Lundgaard I, Schwichtenberg AJ. Sleep, cerebrospinal fluid, and the glymphatic system: a systematic review. *Sleep Med Rev* 2022;61:101572. <https://doi.org/10.1016/j.smrv.2021.101572>.
- [87] Ferrara M, Bertozzi G, Volonnino G, et al. Glymphatic system a window on TBI pathophysiology: a systematic review. *IJMS* 2022;23(16):9138. <https://doi.org/10.3390/ijms23169138>.
- [88] Li L, Chopp M, Ding G, et al. MRI detection of impairment of glymphatic function in rat after mild traumatic brain injury. *Brain Res* 2020;1747:147062. <https://doi.org/10.1016/j.brainres.2020.147062>.
- [89] Marino MA, Petrova S, Swiss R, Duong J, Miulli DE. A review of glymphatics and the impact of osteopathic manipulative treatment in Alzheimer's disease, concussions, and beyond. *Cureus* 2022. <https://doi.org/10.7759/cureus.23620>.
- [90] Raikes AC, Bajaj S, Dailey NS, et al. Diffusion tensor imaging (DTI) correlates of self-reported sleep quality and depression following mild traumatic brain injury. *Front Neurol* 2018;9:468. <https://doi.org/10.3389/fneur.2018.00468>.
- [91] Brett BL, Gardner RC, Godbout J, Dams-O'Connor K, Keene CD. Traumatic brain injury and risk of neurodegenerative disorder. *Biol Psychiatry* 2022;91(5):498–507. <https://doi.org/10.1016/j.biopsych.2021.05.025>.
- [92] Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. *Mol Cell Neurosci* 2015;66:75–80. <https://doi.org/10.1016/j.mcn.2015.03.001>.
- [93] Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science* 2013;342(6156):373–7. <https://doi.org/10.1126/science.1241224>.
- [94] Tham SW, Palermo TM, Vavilala MS, et al. The longitudinal course, risk factors, and impact of sleep disturbances in children with traumatic brain injury. *J Neurotrauma* 2012;29(1):154–61. <https://doi.org/10.1089/neu.2011.2126>.
- [95] Tham SW, Fales J, Palermo TM. Subjective and objective assessment of sleep in adolescents with mild traumatic brain injury. *J Neurotrauma* 2015;32(11):847–52. <https://doi.org/10.1089/neu.2014.3559>.
- [96] Master CL, Curry AE, Pfeiffer MR, et al. Characteristics of concussion in elementary school-aged children: implications for clinical management. *J Pediatr* 2020;223:128–35. <https://doi.org/10.1016/j.jpeds.2020.04.001>.
- [97] Montgomery MC, Baylan S, Gardani M. Prevalence of insomnia and insomnia symptoms following mild-traumatic brain injury: a systematic review and meta-analysis. *Sleep Med Rev* 2022;61:101563. <https://doi.org/10.1016/j.smrv.2021.101563>.
- [98] Eisenberg MA, Meehan WP, Mannix R. Duration and course of post-concussive symptoms. *Pediatrics* 2014;133(6):999–1006. <https://doi.org/10.1542/peds.2014-0158>.

- [99] Ma HP, Chen PS, Wong CS, et al. Psychometric evaluation of anxiety, depression, and sleep quality after a mild traumatic brain injury: a longitudinal study. *Behav Neurol* 2019;2019:1–9. <https://doi.org/10.1155/2019/4364592>.
- [100] Barlow KM, Crawford S, Stevenson A, Sandhu SS, Belanger F, Dewey D. Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. *Pediatrics* 2010;126(2):e374–81. <https://doi.org/10.1542/peds.2009-0925>.
- [101] Oyegbile TO, Dougherty A, Tanveer S, Zecavati N, Delasobera BE. High sleep disturbance and longer concussion duration in repeat concussions. *Behav Sleep Med* 2020;18(2):241–8. <https://doi.org/10.1080/15402002.2019.1578223>.
- [102] Juliff LE, Halson SL, Peiffer JJ. Understanding sleep disturbance in athletes prior to important competitions. *J Sci Med Sport* 2015;18(1):13–8. <https://doi.org/10.1016/j.jsams.2014.02.007>.
- [103] Ekhtiari S, Yusuf I, AlMakadma Y, MacDonald A, Leroux T, Khan M. Opioid use in athletes: a systematic review. *Sports Health* 2020;12(6):534–9. <https://doi.org/10.1177/1941738120933542>.
- [104] Charest J, Grandner MA. Sleep and athletic performance. *Sleep Med Clin* 2020;15(1):41–57. <https://doi.org/10.1016/j.jsmc.2019.11.005>.
- [105] Mander BA, Marks SM, Vogel JW, et al. β -amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci* 2015;18(7):1051–7. <https://doi.org/10.1038/nn.4035>.
- [106] Oyegbile TO, Delasobera BE, Zecavati N. Gender differences in sleep symptoms after repeat concussions. *Sleep Med* 2017;40:110–5. <https://doi.org/10.1016/j.sleep.2017.09.026>.
- [107] Bock S, Grim R, Barron TF, et al. Factors associated with delayed recovery in athletes with concussion treated at a pediatric neurology concussion clinic. *Childs Nerv Syst* 2015;31(11):2111–6. <https://doi.org/10.1007/s00381-015-2846-8>.
- [108] Schmidt AT, Li X, Hanten GR, McCauley SR, Faber J, Levin HS. A longitudinal investigation of sleep quality in adolescents and young adults after mild traumatic brain injury. *Cognit Behav Neurol* 2015;28(2):53–62. <https://doi.org/10.1097/WNN.000000000000056>.
- [109] Gerald B, Ortiz JB, Green TRF, et al. Traumatic brain injury characteristics predictive of subsequent sleep-wake disturbances in pediatric patients. *Biology* 2022;11(4):600. <https://doi.org/10.3390/biology11040600>.

Chapter 32

Sleep health and dementia risk

Christopher N. Kaufmann^a, Chien-Yu Tseng^b, Brendan P. Lucey^c, Atul Malhotra^d and Adam P. Spira^{e, f, g}

^aDepartment of Health Outcomes and Biomedical Informatics, University of Florida College of Medicine, Gainesville, FL, United States;

^bDepartment of Pharmaceutical Outcomes and Policy, University of Florida College of Pharmacy, Gainesville, FL, United States; ^cDepartment of Neurology, Washington University School of Medicine in St. Louis, St. Louis, MO, United States; ^dDivision of Pulmonary, Critical Care, Sleep Medicine, and Physiology, Department of Medicine, University of California San Diego, San Diego, CA, United States; ^eDepartment of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; ^fDepartment of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, United States; ^gJohns Hopkins Center on Aging and Health, Baltimore, MD, United States

Introduction

Dementia is a global public health crisis, and with the aging of the population, the number of dementia cases will likely rise. In 2022, there were 58 million U.S. adults aged ≥ 65 years, and this figure is expected to reach 82 million in 2050 [1]. Alzheimer's disease (AD) is the most common cause of dementia, and there are currently no treatments available that meaningfully improve clinical trajectories for persons with AD. Consequently, efforts to prevent AD and related dementias are critical to maintaining brain health in the aging population [2].

Disturbed sleep has long been recognized as common among people with dementia and is a pronounced stressor for those who live with and care for them [3]. In the past 20 years, however, the sleep field has gradually shifted its conception of the nature of the association between sleep and dementia. Specifically, in addition to being recognized as a prominent manifestation of dementing diseases, sleep disturbances—including alterations in sleep duration, fragmentation, and sleep architecture, as well as sleep-disordered breathing and circadian rhythm abnormalities—are now recognized as predicting and likely contributing to dementia onset and course. Therefore, it is highly important that the sleep field understands the nature of these associations, the factors contributing to sleep's impact on dementia risk, and how sleep treatments may affect AD risk.

In this chapter, we provide an overview of the current understanding of sleep-dementia associations. First, we introduce how sleep changes with age broadly. We then shift our focus to dementia and characterize the key concepts of this condition to lay the foundation for our discussion of associations with sleep. Next, we specifically

identify the ways in which sleep may be related to dementia risk. We then examine the links of sleep interventions (including behavioral therapies, hypnotic medications, and sleep-disordered breathing therapies) with cognition and brain health. Finally, we identify gaps in the literature for future investigation in the field of sleep and dementia. The overarching theme is that the relationship between sleep and dementia is complex and bidirectional—requiring more research to understand the diverse effects on dementia risk and treatment, especially within specific subgroups that may be at greatest risk for dementia.

Sleep and aging

A seminal meta-analysis of sleep parameters across the life course by Ohayon et al. showed that compared with the sleep of younger adults, older adults' sleep is shorter, more fragmented, and less efficient with less time spent in rapid eye movement (REM) sleep and non-REM (NREM) slow-wave sleep and more time spent in lighter sleep [4]. These changes typically occur by age 60 years, and if older adults remain relatively healthy, sleep efficiency may be the only sleep parameter that deteriorates with subsequent aging [4]. In the general population of older adults, however, sleep-related symptoms are highly prevalent. Almost 60% of older adults report at least one sleep-related symptom (e.g., difficulty falling asleep, nighttime waking, early waking, and daytime sleepiness requiring a nap) "most of the time" [5]. This is likely due to numerous factors that may accompany aging, including medical or psychiatric conditions and medications [6] and psychosocial changes (e.g., retirement, bereavement, and caregiving roles) that can adversely affect sleep [7], and circadian rhythm

alterations (i.e., phase advance and reductions in rhythm amplitude) [8]. The increasing prevalence of sleep disorders with age, including insomnia, obstructive sleep apnea (OSA), and restless legs syndrome, also contribute to reports of sleep-related symptoms [9].

Overview of dementia

One important factor in the aging process that can track age-related changes in sleep architecture is the cognitive aspect of health and, by extension, the clinical signs of dementia. Historically, dementia has been defined in various ways, but the term typically refers to a significant decline in cognitive function, beyond what would be expected for an individual of a particular age and educational attainment, that impairs social and occupational functioning. Previous iterations of diagnostic criteria for dementia required a decline in memory plus one other domain (e.g., language, visuospatial ability, and executive function) [10], but criteria have evolved to include non-amnestic presentations, characterized by decline in cognitive domains other than memory, and by the emergence of neuropsychiatric symptoms (e.g., apathy, agitation, and depressive and anxiety symptoms) [11].

AD, defined histopathologically by extraneuronal plaques consisting of aggregated β -amyloid (A β) protein and intraneuronal neurofibrillary tangles formed by hyperphosphorylated tau protein, is the most common cause of dementia. Until recently, AD could only be definitively identified through postmortem examination of brain tissue, and AD dementia was thus a clinical diagnosis made by ruling out other contributing disease processes (e.g., cerebrovascular disease). This situation changed with the advent and proliferation of neuroimaging biomarkers of AD, including [^{11}C] Pittsburgh Compound B (PiB) and [^{18}F] florbetapir positron emission tomography (PET) ligands that bind to A β and [^{18}F] flortaucipir PET ligand that binds to tau, and cerebrospinal fluid (CSF) markers of A β and tau, as well as nonspecific markers of neurodegeneration from magnetic resonance imaging (brain atrophy) and CSF (e.g., neurofilament light). Resulting studies have transformed understanding of the pathological course of AD and AD-related dementias (e.g., vascular contributions to cognitive impairment and dementia, Lewy body dementia) [12,13]. For example, we now know that, in AD, A β begins to aggregate up to decades before any measurable cognitive impairment, and that cognitive impairment and decline are driven by pathological tau-facilitated neurodegeneration [13]. In 2011, the diagnostic criteria for AD dementia were updated by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) to integrate AD/ADR-D biomarkers [11].

A substantial proportion of older adults exhibit mild cognitive impairment (MCI) that does not significantly

affect functioning but is characterized by a measurable decline from prior cognitive status beyond what would be expected based on age and education [14]. Like dementia, MCI is an etiologically heterogeneous category. It can be caused by numerous dementing diseases, including AD, and diagnostic criteria that include AD biomarkers, analogous to the NIA-AA criteria for AD dementia, were developed in 2011 [15].

Sleep and dementia risk

Sleep disturbances are common in individuals with dementia; however, growing evidence suggests that sleep disturbances also can predate and may be a modifiable risk factor for dementia in healthier populations. For instance, short sleep duration in cognitively unimpaired middle-aged adults is associated with a greater risk of cognitive impairment decades later [16], and cognitively unimpaired older adults who reported insomnia were more likely to develop cognitive impairment approximately 8 years later [17]. Furthermore, older women with moderate/severe OSA had a greater risk of MCI or dementia an average of 5 years later [18]. Fig. 32.1 presents a model that characterizes potential pathways linking sleep health and dementia outcomes.

Studies employing AD biomarkers also indicate that disturbed sleep occurs during the asymptomatic or “pre-clinical” stages of AD. Cognitively unimpaired older adults with amyloid plaques have been reported to have lower sleep efficiency and longer daytime napping [20] and shorter sleep duration [21]. Excessive daytime sleepiness was associated with almost 3 times the odds of positive amyloid PET scans an average of ~16 years later [22]. Furthermore, measures of poor sleep quality, such as low NREM slow wave activity, are associated with both amyloid and tau pathology even in cognitively unimpaired or mildly impaired older adults [21,23]. These findings strongly support a complicated, bidirectional relationship between sleep and dementia, such as that due to AD. Contemporary models suggest that sleep disturbance plays a causal role in the initiation of the AD pathological cascade, and that as AD pathology develops in regions that affect sleep regulation, there is a positive-feedback loop: increasing pathology leads to worsening sleep, which leads to greater pathology, and so on [24,25]. Further research is needed to determine when and how disturbed sleep is related to the onset and progression of dementia.

In the case of OSA, there is extensive evidence showing the condition is linked with dementia pathology. Past studies have shown that those with OSA are more likely to have the APOE $\epsilon 4$ gene than those without, suggesting some shared genetic susceptibility [26]. Furthermore, the repeated apnea/hypopnea events inherent in the condition lead to depletion of oxygen saturation,

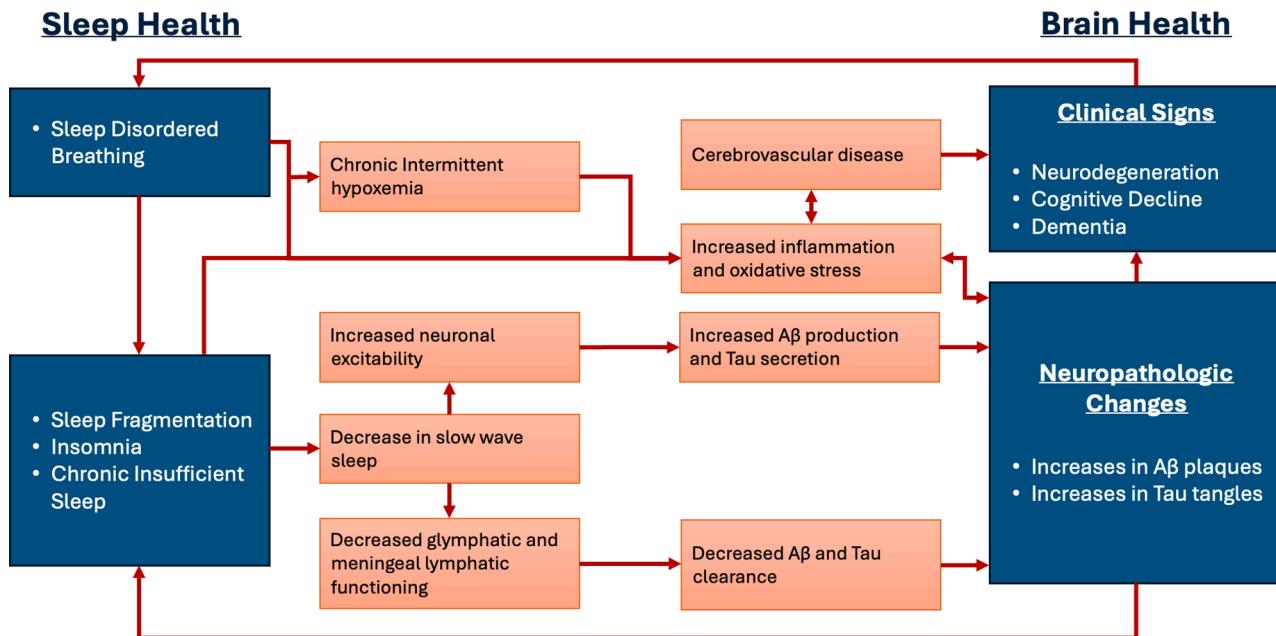


FIGURE 32.1 Mechanisms linking sleep health and brain health. Adapted from Gottesman RF, Lutsey PL, Benveniste H, et al. Impact of sleep disorders and disturbed sleep on brain health: a Scientific Statement from the American Heart Association. *Stroke* 2024;55(3):e61–e76. <https://doi.org/10.1161/STR.0000000000000453>.

which is rapidly replenished once normal breathing resumes, leading to oxidative stress [27–29], thought to be a major contributor to the development of AD [30–33]. Furthermore, the sleep fragmentation inherent in OSA may also contribute to AD pathology, as decreased time in SWS is associated with the development of dementia [34]. As discussed above, more work is needed to determine the nature of this association and further elucidate its mechanisms.

Dementias have long asymptomatic periods during which pathologic changes occur in the brain. Sleep disturbances detected during this asymptomatic period may be amenable to intervention to prevent or delay the onset of dementia. A key question is the mechanism underlying the relationship between sleep disturbance and dementia. Investigations in both mice and humans found that soluble concentrations of amyloid-beta fluctuate in the fluid around the brain (interstitial fluid [ISF] and CSF) with sleep-wake activity [35,36]. In transgenic mice that develop amyloid plaques, prolonged sleep deprivation increases both the soluble concentrations of A β in ISF and the accumulation of A β plaques, while treatment with a dual orexin receptor antagonist (ORA) to increase sleep decreased amyloid plaques [35]. Similar findings have emerged from studies of transgenic tau mice that develop tau pathology [37]. In humans, disruption of SWS and behavioral sleep deprivation increase the soluble levels of A β , tau, and tau phosphorylation in CSF [38–40].

As there is ample evidence demonstrating a relationship between sleep disturbance and AD pathology, there is a

need to understand better whether this relationship is causal or at least partially in the causal pathway, as this may have implications for the potential for sleep interventions to minimize risk for dementia. Two mechanisms have been proposed to describe mediators of causal links between sleep disturbances and AD: excess neuronal activity and disrupted “glymphatic” clearance. Neuronal activity decreases during sleep, with the greatest reduction occurring during SWS [41]. Research in animal models found that neuronal activity increases A β and tau release, and that brain regions associated with the default mode network, in which neuronal activity is greatest over the lifespan, are the regions most susceptible to A β deposition [42–45]. These findings strongly support that changes in neuronal activity with sleep-wake activity increase or decrease the production or release of A β and tau. A β clearance has also been found to be affected by sleep-wake activity, however. Increases in sleep, especially SWS, increase ISF-CSF exchange in the brain (i.e., glymphatic flow) and therefore clearance of proteins like amyloid-beta from the brain parenchyma [46]. Other clearance mechanisms, such as meningeal lymphatics, have also been associated with time of day suggesting either a sleep- or circadian-related mechanism [47].

It is important to note that multiple factors affect sleep, including age, sex, medical comorbidities, psychiatric conditions, social determinants of health, and others. Because these factors are also associated with increased AD risk, how they interact with sleep (and each other), or mediate, associations of sleep with biomarker and

cognitive trajectories in AD is unknown and likely complex. Both sleep and AD risk differ as a function of sex and social determinants of health [48–52] but it is unknown if or how these factors affect sleep to alter AD risk. An example of a major unanswered question would be how sleep and AD risk differs in men and women (who have different aging-related changes in sleep) by exposure to factors such as social determinants of health that also affect sleep. Research is clearly needed to clarify these relationships.

Impact of sleep interventions on dementia risk

The links of disturbed sleep with cognition and brain health beg the question of whether interventions to improve poor sleep might prevent or delay the onset of dementia. This is an important question as there are a number of efficacious treatments available for sleep disturbances and related disorders, including medications (benzodiazepines [BZDs], non-BZD hypnotics [z-drugs], and newer ORAs), behavioral treatments such as cognitive behavioral therapy for insomnia (CBT-I) [53] and psychoeducation targeting sleep hygiene [54], and finally for OSA, continuous positive airway pressure (CPAP) [55] and mandibular advancement devices. Thus far, only limited research has examined the effects of these treatments on cognitive and brain health outcomes.

The links between the use of certain medications, BZDs and z-drugs, and the risk for cognitive decline and dementia have been the subject of much debate. While these medications do improve sleep maintenance and/or onset (depending on the mechanism of action), there are concerns about the long-term side effects. Of note, the Beers Criteria, published by the American Geriatrics Society, lists BZDs and z-drugs as potentially inappropriate for use in older adults in part due to evidence of associations with adverse health outcomes, including cognitive problems [56]. Moreover, a sizable epidemiologic literature supports the possibility that sedative-hypnotic medications—particularly BZDs [57,58] but also z-drugs [59,60]—exert adverse effects on brain health, but controversy exists about their long-term cognitive effects or if individuals treated with these drugs had sleep disturbances due to Alzheimer pathology during the long “preclinical” asymptomatic period when amyloid plaques accumulate without cognitive impairment. Large claims-based studies have shown associations between BZD use and dementia diagnosis, but some show these associations to be limited to use at higher doses [61] or use of medications with a greater half-life [62]. For example, Billioti de Gage et al. examined the association between BZD use and incident dementia, and found links with dementia, specifically a dose-response relationship with generally higher doses increasing the risk [63].

Later research countered this finding—Gray et al. did not observe a dose-response trend, suggesting that a causal relationship between the two may not exist [64]. Long-term cognitive effects of z-drugs are thought to be comparably lower than BZDs [65]. The more recent ORAs have emerged as alternatives to GABA-targeting drugs and to date show fewer cognitive effects [66–68]. Indeed, even in people with mild/moderate AD and sleep disturbances, ORAs do not appear to negatively affect cognitive functioning [69]. Further research is needed to characterize their long-term cognitive effects, especially given their recent entry into the market.

Despite the proven effectiveness of CBT-I for treating insomnia, the impact of the therapy on cognitive function is not well studied. Some studies have examined the effect of CBT-I on subjective measures of cognitive functioning [70–72], but only a few have studied objective cognitive outcomes [73–75]. Indeed, one systematic review in 2018 found only 18 studies examining CBT-I on cognitive functioning, but the vast majority reported cognition as a secondary outcome [76]. A small uncontrolled study found evidence that receipt of CBT-I was associated with improved performance on several tasks in a small sample ($N = 10$) [77]. Furthermore, an RCT conducted among older adults with MCI and comorbid insomnia found that CBT-I was effective in improving not only sleep quality but several cognitive facilities, including executive functioning among others [78]. Additional rigorous trials are clearly needed to determine the specific effect of behavioral sleep interventions and CBT-I on cognition.

Finally, although CPAP and mandibular advancement devices are highly efficacious for improving OSA, relatively little is known about their effects on cognitive outcomes. To our knowledge, no studies have investigated effects of mandibular advancement devices; the majority of work has focused on CPAP. While one RCT by Dalmases et al. found that CPAP use improved episodic/short-term memory and executive functioning [79], other studies have garnered mixed findings. For example, in an RCT of CPAP (vs. placebo) in older adults with AD and comorbid OSA, Ancoli-Israel et al. reported no group differences in cognitive performance, although there appeared to be an effect on global cognition pre–post among those who received the CPAP intervention [80]. The Apnea Positive Pressure Long-term Efficacy Study trial, one of the largest multicentered RCTs investigating CPAP’s effect on cognition, showed no appreciable improvements in cognition 6 months later [81–83]. It should be noted that adherence to the use of CPAP is often low [84], and while it appears CPAP may be efficacious for treating OSA symptoms, the effectiveness of the therapy on changing cognitive outcomes outside the rigor of a clinical trial remains to be known. This suggests a need for more studies using real-world data (RWD), including Medicare claims,

electronic health records, and other data sources routinely collected in standard clinical care. One study using RWD by Dunietz et al., in Medicare claims, found that beneficiaries who had claims for CPAP use yielded a 22% lower odds of developing dementia and that greater adherence enhanced this effect; however, outcomes were studied over only 3 years, and studies using these type of data with longer follow-up times are needed to make definitive conclusions [85].

Conclusions and future directions

In this chapter, we reviewed the literature on sleep health and the risk of dementia. While much has been discovered over the past 2 decades, more research is needed to understand the mechanisms, directionality of the association, and subgroups at greatest risk. We also reviewed what is known about the effects of various sleep interventions on brain health. Despite the growth of our understanding of links between sleep and dementia, there are several gaps in knowledge that must be addressed to promote both sleep health and brain health.

First, our review highlighted the nature of the role that sleep plays in cognitive health, including biological mechanisms such as excess neuronal activity and disrupted glymphatic clearance. However, more research is needed to evaluate the heterogeneity of these effects across specific subgroups. For example, women, adults of more advanced age, and minoritized groups, particularly Black individuals, have a greater risk for dementia [86], but little is known about the relative effects of sleep on dementia risk in these groups specifically. This *heterogeneity* of relationships between sleep and brain health across groups needs further investigation and has the potential to inform efforts to address insomnia in those at greatest risk for dementia.

Second, more work is needed to differentiate between potential cognitive side effects of sleep treatment and cognitive consequences of poor sleep itself. As discussed above, a variety of treatments are available for sleep disorders, but there is little consensus on whether they in fact lower the risk for dementia and related pathology. This issue is particularly important when considering the cognitive effects of sleep medications. Studies investigating this issue are often limited by confounding by indication, which raises the possibility of whether the medication itself leads to dementia or the poor sleep for which it is indicated. These considerations, not only for medications but also for other treatments, are crucial and have important implications for developing interventions to improve poor sleep.

Third, new treatments are being developed, requiring investigation into their effects on dementia risk. For example, sleep drugs used to treat insomnia are being tested for potential repurposing to prevent/delay the onset

of AD. Similar to findings in mice, treatment with an ORA (suvorexant) acutely decreased soluble concentrations of A β and phosphorylated tau over hours in adults without AD [87]. Ongoing trials are testing the effects of ORAs on AD biomarkers over months. New modalities of CBT-I, a nonpharmacologic treatment of insomnia, have been developed that deliver it over the internet or via smartphone apps [72,88,89]. These “digital therapeutics” show great promise in improving insomnia symptoms [89]. However, more research is needed to determine their effectiveness in improving cognition both short- and long-term. In the case of OSA, an exciting recent development is the efficacy of glucagon-like peptide-1 (GLP-1) receptor agonists as a treatment for OSA, particularly in obese patients [90]. A recent study found that tirzepatide was effective in lowering the apnea-hypopnea index of obese patients randomized to tirzepatide and these improvements were sustained at long-term follow-up [90]. With the likely emergence of an era of GLP-1 receptor agonists for the treatment of OSA [91], further research will be necessary to study the effects of this therapy on brain health specifically. This notion includes examining the impacts of the medication itself as well as any potential benefits from improved OSA symptoms.

Finally, more research is necessary to comprehend circadian influences on cognitive health. Although outside the scope of this review, epidemiologic studies suggest circadian rhythms affect cognitive health in later life [92]; however, more research is necessary to determine how changes in these patterns throughout the life course may affect long-term brain health. For example, it is not yet known whether significant life events, such as starting college or retiring, could lead to changes in circadian patterns and have adverse effects on cognitive function. It is also uncertain whether individuals with unusual changes in circadian patterns due to these events may experience poorer cognitive outcomes.

In summary, our chapter provided an overview of current knowledge on the link between sleep and dementia and identified potential areas for future research. While significant progress has been made, more work is needed to translate findings to inform treatment decisions for poor sleep with the goal of dementia prevention. As research on dementia, sleep, and their respective treatments develops, it will become increasingly important for the field to delve into the underlying mechanisms that drive these relationships. Ultimately, this work could lead to therapeutic strategies that not only improve sleep but also offer new hope in the fight against dementia.

Funding

This study was supported in part by the National Institute on Aging (R01AG079391, K01AG061239, P30AG028740)

and the Sleep Research Society Foundation (23-FRA-001). Dr. Malhotra is funded by NIH. Dr. Lucey is funded by NIH and Good Ventures.

Conflicts of interest

Dr. Malhotra reports income from Livanova, Eli Lilly, Zoll, and Powell Mansfield. ResMed gave a philanthropic donation to UCSD. Dr. Lucey reports income from Eli Lilly, Eisai, and Beacon Biosignals. Dr. Spira received payment for serving as a consultant for Merck, received honoraria from Springer Nature Switzerland AG for guest editing special issues of *Current Sleep Medicine Reports*, and is a paid consultant to Sequoia Neurovitality, BellSant, Inc., and Amissa, Inc.

References

- [1] 2024 Alzheimer's disease facts and figures. *Alzheimers Dement* 2024;20(5):3708–821. <https://doi.org/10.1002/alz.13809>.
- [2] Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* August 8, 2020;396(10248):413–46. [https://doi.org/10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6).
- [3] Blilwise DL. Sleep disorders in Alzheimer's disease and other dementias. *Clin Cornerstone* 2004;6(Suppl. 1A):S16–28.
- [4] Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep* November 1, 2004;27(7):1255–73. <https://doi.org/10.1093/sleep/27.7.1255>.
- [5] Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep* July 1995;18(6):425–32. <https://doi.org/10.1093/sleep/18.6.425>.
- [6] Li J, Vitiello MV, Gooneratne NS. Sleep in normal aging. *Sleep Med Clin* March 2018;13(1):1–11. <https://doi.org/10.1016/j.jsmc.2017.09.001>.
- [7] Ancoli-Israel S, Cook J. Prevalence and comorbidity of insomnia and effect on functioning in elderly populations. *J Am Geriatr Soc* 2005;53:S264–71.
- [8] Czeisler CA, Dumont M, Duffy JF, et al. Association of sleep-wake habits in older people with changes in output of circadian pacemaker. *Lancet* October 17, 1992;340(8825):933–6. [https://doi.org/10.1016/0140-6736\(92\)92817-y](https://doi.org/10.1016/0140-6736(92)92817-y).
- [9] Vitiello M. Sleep in normal aging. *Sleep Med Clin* 2006;1(2):171–6. <https://doi.org/10.1016/j.jsmc.2006.04.007>.
- [10] American Psychiatric Association. American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed. American Psychiatric Association; 1994. p. 886.
- [11] McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* May 2011;7(3):263–9. <https://doi.org/10.1016/j.jalz.2011.03.005>.
- [12] Jack Jr CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* January 2010;9(1):119–28. [https://doi.org/10.1016/S1474-4422\(09\)70299-6](https://doi.org/10.1016/S1474-4422(09)70299-6).
- [13] Jack Jr CR, Bennett DA, Blennow K, et al. NIA-AA Research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's Dement* April 2018;14(4):535–62. <https://doi.org/10.1016/j.jalz.2018.02.018>.
- [14] Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* September 2004;256(3):183–94.
- [15] Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement* May 2011;7(3):270–9. <https://doi.org/10.1016/j.jalz.2011.03.008>.
- [16] Sabia S, Fayosse A, Dumurgier J, et al. Association of sleep duration in middle and old age with incidence of dementia. *Nat Commun* April 20, 2021;12(1):2289. <https://doi.org/10.1038/s41467-021-22354-2>.
- [17] Osorio RS, Pirraglia E, Aguera-Ortiz LF, et al. Greater risk of Alzheimer's disease in older adults with insomnia. *J Am Geriatr Soc* March 2011;59(3):559–62. <https://doi.org/10.1111/j.1532-5415.2010.03288.x>.
- [18] Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* August 10, 2011;306(6):613–9. <https://doi.org/10.1001/jama.2011.1115>.
- [19] Gottesman RF, Lutsey PL, Benveniste H, et al. Impact of sleep disorders and disturbed sleep on brain health: a scientific statement from the American Heart Association. *Stroke* March 2024;55(3):e61–76. <https://doi.org/10.1161/STR.0000000000000453>.
- [20] Spira AP, An Y, Wu MN, et al. Excessive daytime sleepiness and napping in cognitively normal adults: associations with subsequent amyloid deposition measured by PiB PET. *Sleep* December 1, 2018;41(12). <https://doi.org/10.1093/sleep/zsy184>.
- [21] Mander BA, Marks SM, Vogel JW, et al. β -amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci* July 2015;18(7):1051–7. <https://doi.org/10.1038/nn.4035>.
- [22] Spira AP, An Y, Wu MN, et al. Excessive daytime sleepiness and napping in cognitively normal adults: associations with subsequent amyloid deposition measured by PiB PET. *Sleep* September 5, 2018. <https://doi.org/10.1093/sleep/zsy152>.
- [23] Lucey BP, McCullough A, Landsness EC, et al. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med* 2019;11(474).
- [24] Ju YE, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nat Rev Neurol* February 2014;10(2):115–9. <https://doi.org/10.1038/nrneurol.2013.269>.
- [25] Ferini-Strambi L, Liguori C, Lucey BP, et al. Role of sleep in neurodegeneration: the consensus report of the 5th think tank world sleep forum. *Neurology Sci* December 13, 2024;45(2):749–67. <https://doi.org/10.1007/s10072-023-07232-7>.
- [26] Gottlieb DJ, Destefano AL, Foley DJ, et al. APOE ϵ 4 is associated with obstructive sleep apnea/hypopnea. *Neurology* 2004;63:664–8.
- [27] Lavie L. Obstructive sleep apnoea syndrome—an oxidative stress disorder. *Sleep Med Rev* February 2003;7(1):35–51. <https://doi.org/10.1053/smrv.2002.0261>.
- [28] Suzuki YJ, Jain V, Park AM, Day RM. Oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular

- diseases. *Free Radic Biol Med* May 15, 2006;40(10):1683–92. <https://doi.org/10.1016/j.freeradbiomed.2006.01.008>.
- [29] Yamauchi M, Nakano H, Maekawa J, et al. Oxidative stress in obstructive sleep apnea. *Chest* May 2005;127(5):1674–9. <https://doi.org/10.1378/chest.127.5.1674>.
- [30] Pohanka M. Alzheimer's disease and oxidative stress: a review. *Curr Med Chem* 2014;21(3):356–64. <https://doi.org/10.2174/09298673113206660258>.
- [31] Padurariu M, Ciobica A, Hritcu L, Stoica B, Bild W, Stefanescu C. Changes of some oxidative stress markers in the serum of patients with mild cognitive impairment and Alzheimer's disease. *Neurosci Lett* January 18, 2010;469(1):6–10. <https://doi.org/10.1016/j.neulet.2009.11.033>.
- [32] Pratico D, Clark CM, Liun F, Rokach J, Lee VY, Trojanowski JQ. Increase of brain oxidative stress in mild cognitive impairment: a possible predictor of Alzheimer disease. *Arch Neurol* June 2002;59(6):972–6. <https://doi.org/10.1001/archneur.59.6.972>.
- [33] Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat Rev Neurosci* March 2019;20(3):148–60. <https://doi.org/10.1038/s41583-019-0132-6>.
- [34] Himali JJ, Baril AA, Cavuoto MG, et al. Association between slow-wave sleep loss and incident dementia. *JAMA Neurol* October 30, 2023. <https://doi.org/10.1001/jamaneurol.2023.3889>.
- [35] Kang J-E, Lim MM, Bateman RJ, et al. Amyloid- β dynamics are regulated by orexin and the sleep-wake cycle. *Science* 2009;326(5955):1005–7.
- [36] Huang Y, Potter R, Sigurdson W, et al. Effects of age and amyloid deposition on A β dynamics in the human central nervous system. *Arch Neurol* 2012;69(1):51–8.
- [37] Holth JK, Fritschi SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* February 22, 2019;363(6429):880–4. <https://doi.org/10.1126/science.aav2546>.
- [38] Ju YS, Ooms SJ, Sutphen C, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-beta levels. *Brain* August 1, 2017;140(8):2104–11. <https://doi.org/10.1093/brain/awx148>.
- [39] Lucey BP, Hicks TJ, McLeland JS, et al. Effect of sleep on overnight cerebrospinal fluid amyloid beta kinetics. *Ann Neurol* January 2018;83(1):197–204. <https://doi.org/10.1002/ana.25117>.
- [40] Barthelemy NR, Liu H, Lu W, Kotzbauer PT, Bateman RJ, Lucey BP. Sleep deprivation affects tau phosphorylation in human cerebrospinal fluid. *Ann Neurol* May 2020;87(5):700–9. <https://doi.org/10.1002/ana.25702>.
- [41] Dang-Vu TT, Schabus M, Desseilles M, Sterpenich V, Bonjean M, Maquet P. Functional neuroimaging insights into the physiology of human sleep. *Sleep* December 2010;33(12):1589–603. <https://doi.org/10.1093/sleep/33.12.1589>.
- [42] Cirrito JR, Yamada KA, Finn MB, et al. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. *Neuron* December 22, 2005;48(6):913–22. <https://doi.org/10.1016/j.neuron.2005.10.028>.
- [43] Yamada K, Holth JK, Liao F, et al. Neuronal activity regulates extracellular tau in vivo. *J Exp Med* March 10, 2014;211(3):387–93. <https://doi.org/10.1084/jem.20131685>.
- [44] Bero AW, Yan P, Roh JH, et al. Neuronal activity regulates the regional vulnerability to amyloid-beta deposition. *Nat Neurosci* June 2011;14(6):750–6. <https://doi.org/10.1038/nn.2801>.
- [45] Buckner RL, Snyder AZ, Shannon BJ, et al. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J Neurosci* August 24, 2005;25(34):7709–17. <https://doi.org/10.1523/JNEUROSCI.2177-05.2005>.
- [46] Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science* October 18, 2013;342(6156):373–7. <https://doi.org/10.1126/science.1241224>.
- [47] Hablitz LM, Plá V, Giannetto M, et al. Circadian control of brain glymphatic and lymphatic fluid flow. *Nat Commun* September 2, 2020;11(1):4411. <https://doi.org/10.1038/s41467-020-18115-2>.
- [48] Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med* February 23, 2004;164(4):406–18. <https://doi.org/10.1001/archinte.164.4.406>.
- [49] Wang YT, Therriault J, Servaes S, et al. Sex-specific modulation of amyloid-beta on tau phosphorylation underlies faster tangle accumulation in females. *Brain* April 4, 2024;147(4):1497–510. <https://doi.org/10.1093/brain/awad397>.
- [50] Vila-Castelar C, Chen Y, Langella S, et al. Sex differences in blood biomarkers and cognitive performance in individuals with autosomal dominant Alzheimer's disease. *Alzheimer's Dement* September 2023;19(9):4127–38. <https://doi.org/10.1002/alz.13314>.
- [51] Libre-Guerra JJ, Jiang M, Acosta I, et al. Social determinants of health but not global genetic ancestry predict dementia prevalence in Latin America. *Alzheimer's Dement* July 2024;20(7):4828–40. <https://doi.org/10.1002/alz.14041>.
- [52] Jackson CL, Walker JR, Brown MK, Das R, Jones NL. A workshop report on the causes and consequences of sleep health disparities. *Sleep* August 12, 2020;43(8). <https://doi.org/10.1093/sleep/zsaa037>.
- [53] Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. *Ann Intern Med* August 4, 2015;163(3):191–204. <https://doi.org/10.7326/M14-2841>.
- [54] Morin CM, Beaulieu-Bonneau S, LeBlanc M, Savard J. Self-help treatment for insomnia: a randomized controlled trial. *Sleep* October 2005;28(10):1319–27. <https://doi.org/10.1093/sleep/28.10.1319>.
- [55] Lindberg E, Berne C, Elmasry A, Hedner J, Janson C. CPAP treatment of a population-based sample—what are the benefits and the treatment compliance? *Sleep Med* October 2006;7(7):553–60. <https://doi.org/10.1016/j.sleep.2005.12.010>.
- [56] By the American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers criteria(R) for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* July 2023;71(7):2052–81. <https://doi.org/10.1111/jgs.18372>.
- [57] Bang YR, Jeon HJ, Yoon IY. Effect of long-term benzodiazepines for chronic insomnia on cognitive function and waking electroencephalography: a case-control study. *Psychiatry Investig* April 2022;19(4):259–67. <https://doi.org/10.30773/pi.2021.0316>.
- [58] Zetser SPG, Schellekens AFA, Paling EP, Kan CC, Kessels RPC. Cognitive functioning in long-term benzodiazepine users. *Eur Addict Res* September 2022;28(5):377–81. <https://doi.org/10.1159/000525988>.
- [59] Neylan TC, Richards A, Metzler TJ, et al. Acute cognitive effects of the hypocretin receptor antagonist almorexant relative to zolpidem and placebo: a randomized clinical trial. *Sleep* October 2020;43(10). <https://doi.org/10.1093/sleep/zsaa080>.

- [60] Dinges DF, Basner M, Ecker AJ, Baskin P, Johnston SL. Effects of zolpidem and zaleplon on cognitive performance after emergent morning awakenings at Tmax: a randomized placebo-controlled trial. *Sleep* March 2019;42(3). <https://doi.org/10.1093/sleep/zsy258>.
- [61] Zhong GC, Wang Y, Zhang Y, Zhao Y. Association between benzodiazepine use and dementia: a meta-analysis. *PLoS One* May 27, 2015;10(5). <https://doi.org/10.1371/journal.pone.0127836>.
- [62] Torres-Bondia F, Dakterzada F, Galván L, et al. Benzodiazepine and Z-drug use and the risk of developing dementia. *Int J Neuropsychopharmacol* April 19, 2022;25(4):261–8. <https://doi.org/10.1093/ijnp/pyab073>.
- [63] Billioti de Gage S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ* September 9, 2014;349:g5205. <https://doi.org/10.1136/bmj.g5205>.
- [64] Gray SL, Dublin S, Yu O, et al. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. *BMJ* February 2, 2016;352. <https://doi.org/10.1136/bmj.i90>.
- [65] Kaufmann CN, Moore AA, Bondi MW, Murphy JD, Malhotra A, Hart LA. Association between the use of non-benzodiazepine hypnotics and cognitive outcomes: a systematic review. *Curr Sleep Med Rep* March 2020;6(1):11–20. <https://doi.org/10.1007/s40675-020-00163-1>.
- [66] Hori H. Successful treatment of switching from benzodiazepine to orexin receptor antagonists improves cognitive function in psychiatric disorders: four case reports. *Int Clin Psychopharmacol* May 2023;38(3):192–4. <https://doi.org/10.1097/Yic.0000000000000450>.
- [67] Zhou ML, Xie Z. The effects of different dosages of dual orexin receptor antagonists and zolpidem on sleep and cognitive function: a meta-analysis and systematic review. *Sleep Epidemiol* 2023;3:100068. <https://doi.org/10.1016/j.sleepe.2023.100068>.
- [68] Landry I, Hall N, Alur J, et al. Acute cognitive effects of the dual orexin receptor antagonist lemborexant compared with suvorexant and zolpidem in recreational sedative users. *J Clin Psychopharmacol* 2022;42(4).
- [69] Hayashi T, Yamanashi T, Iwata M. Comparative efficacy and safety of suvorexant and lemborexant for insomnia treatment. *Psychiatry Clin Neurosci Rep* 2023;2(1). <https://doi.org/10.1002/pcn.5.85>.
- [70] Jansson M, Linton SJ. Cognitive-behavioral group therapy as an early intervention for insomnia: a randomized controlled trial. *J Occup Rehabil* June 2005;15(2):177–90. <https://doi.org/10.1007/s10926-005-1217-9>.
- [71] Casault L, Savard J, Ivers H, Savard MH. A randomized-controlled trial of an early minimal cognitive-behavioural therapy for insomnia comorbid with cancer. *Behav Res Ther* April 2015;67:45–54. <https://doi.org/10.1016/j.brat.2015.02.003>.
- [72] Ritterband LM, Bailey ET, Thorndike FP, Lord HR, Farrell-Carnahan L, Baum LD. Initial evaluation of an internet intervention to improve the sleep of cancer survivors with insomnia. *Psychooncology* July 2012;21(7):695–705. <https://doi.org/10.1002/pon.1969>.
- [73] Miro E, Lupianez J, Martinez MP, et al. Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: a pilot, randomized controlled trial. *J Health Psychol* July 2011;16(5):770–82. <https://doi.org/10.1177/1359105310390544>.
- [74] Omvik S, Sivertsen B, Pallesen S, Bjorvatn B, Havik OE, Nordhus IH. Daytime functioning in older patients suffering from chronic insomnia: treatment outcome in a randomized controlled trial comparing CBT with zopiclone. *Behav Res Ther* May 2008;46(5):623–41. <https://doi.org/10.1016/j.brat.2008.02.013>.
- [75] Wilckens KA, Hall MH, Nebes RD, Monk TH, Buysse DJ. Changes in cognitive performance are associated with changes in sleep in older adults with insomnia. *Behav Sleep Med* 2016;14(3):295–310. <https://doi.org/10.1080/15402002.2014.1002034>.
- [76] Herbert V, Kyle SD, Pratt D. Does cognitive behavioural therapy for insomnia improve cognitive performance? A systematic review and narrative synthesis. *Sleep Med Rev* June 2018;39:37–51. <https://doi.org/10.1016/j.smrv.2017.07.001>.
- [77] Roniger DDG, Lechuga YA, Leon EE, et al. Cognitive behavioral therapy for insomnia helps to reverse cognitive impairment in insomnia patients. *Sleep Sci* Apr-Jun;15(Spec 2):355–60. <https://doi.org/10.5935/1984-0063.20210026>.
- [78] Cassidy-Eagle E, Siebern A, Unti L, Glassman J, O'Hara R. Neuro-psychological functioning in older adults with mild cognitive impairment and insomnia randomized to CBT-I or control group. *Clin Gerontol* 2018;41(2):136–44. <https://doi.org/10.1080/07317115.2017.1384777>.
- [79] Dalmases M, Sole-Padulle C, Torres M, et al. Effect of CPAP on cognition, brain function, and structure among elderly patients with OSA: a randomized pilot study. *Chest* November 2015;148(5):1214–23. <https://doi.org/10.1378/chest.15-0171>.
- [80] Ancoli-Israel S, Palmer BW, Cooke JR, et al. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. *J Am Geriatr Soc* November 2008;56(11):2076–81. <https://doi.org/10.1111/j.1532-5415.2008.01934.x>.
- [81] Berlowitz DJ, Shafazand S. CPAP and cognition in OSA (APPLES). *J Clin Sleep Med* May 15, 2013;9(5):515–6. <https://doi.org/10.5664/jcsm.2682>.
- [82] Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* December 1, 2012;35(12):1593–602. <https://doi.org/10.5665/sleep.2226>.
- [83] Bliwise DL, Greenaway MC. Will APPLES hit a ceiling? *Sleep* March 1, 2011;34(3):249–50. <https://doi.org/10.1093/sleep/34.3.249>.
- [84] Qiao M, Xie Y, Wolff A, Kwon J. Long term adherence to continuous positive airway pressure in mild obstructive sleep apnea. *BMC Pulm Med* September 1, 2023;23(1):320. <https://doi.org/10.1186/s12890-023-02612-3>.
- [85] Dunietz GL, Chervin RD, Burke JF, Conceicao AS, Braley TJ. Obstructive sleep apnea treatment and dementia risk in older adults. *Sleep* September 13, 2021;44(9). <https://doi.org/10.1093/sleep/zsab076>.
- [86] Aranda MP, Kremer IN, Hinton L, et al. Impact of dementia: health disparities, population trends, care interventions, and economic costs. *J Am Geriatr Soc* July 2021;69(7):1774–83. <https://doi.org/10.1111/jgs.17345>.
- [87] Lucey BP, Liu H, Toedebusch CD, et al. Suvorexant acutely decreases tau phosphorylation and A β in the human CNS. *Ann Neurol* July 2023;94(1):27–40. <https://doi.org/10.1002/ana.26641>.
- [88] Zhou ES, Revette A, Ritterband LM, et al. Developing a culturally tailored digital health intervention for insomnia in Black women. *Transl Behav Med* September 16, 2023. <https://doi.org/10.1093/tbm/ibad056>.
- [89] Ritterband LM, Thorndike FP, Ingersoll KS, et al. Effect of a web-based cognitive behavior therapy for insomnia intervention with 1-year

- follow-up: a randomized clinical trial. *JAMA Psychiatry* January 1, 2017;74(1):68–75. <https://doi.org/10.1001/jamapsychiatry.2016.3249>.
- [90] Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N Engl J Med* 2024.
- [91] Patel SR. Entering a new era in sleep-apnea treatment. *N Engl J Med* June 21, 2024. <https://doi.org/10.1056/NEJMMe2407117>.
- [92] Blackwell TL, Figueiro MG, Tranah GJ, et al. Associations of 24-hour light exposure and activity patterns and risk of cognitive impairment and decline in older men: the MrOS sleep study. *J Gerontol A Biol Sci Med Sci* September 26, 2022. <https://doi.org/10.1093/gerona/glac187>.

This page intentionally left blank

Part VII

Public health implications of sleep disorders

This page intentionally left blank

Chapter 33

Insomnia and psychiatric disorders

Ivan Vargas^{a,b,e}, Sheila N. Garland^{c,d}, Jacqueline D. Kloss^a and Michael L. Perlis^a

^aBehavioral Sleep Medicine Program, University of Pennsylvania, Philadelphia, PA, United States; ^bCenter for Sleep and Circadian Neurobiology, University of Pennsylvania, Philadelphia, PA, United States; ^cDepartment of Psychology and Discipline of Oncology, Memorial University, St. John's, NL, Canada; ^dDivision of Oncology, Faculty of Medicine, Memorial University, St. John's, NL, Canada; ^eDepartment of Psychology, University of Notre Dame, Notre Dame, IN, United States

Abbreviations

ACP	American College of Physicians
ADHD	Attention-deficit/hyperactivity disorder
APA	American Psychiatric Association
ASD	Autism spectrum disorder
AUD	Alcohol use disorder
CBT-I	Cognitive Behavioral Therapy for Insomnia
DLMO	Dim light melatonin onset
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
GABA	Gamma-aminobutyric acid
GERD	Gastroesophageal reflux disease
MDD	Major depressive disorder
MDE	Major depressive episode
NHANES	National Health and Nutrition Examination Survey
PSG	Polysomnography
PTSD	Post-traumatic stress disorder
REM	Rapid eye movement

Introduction

Sleep continuity disturbance (i.e., insomnia) is ubiquitous among psychiatric conditions and is a diagnostic feature and/or correlate of most, if not all, “Axis 1” disorders [1]. Approximately, 40% of patients with insomnia report at least one other comorbid psychiatric disorder [2]. Of those reporting insomnia complaints, only 16% met criteria for primary insomnia (i.e., no other comorbidities), whereas 36% met criteria for another Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnoses (e.g., major depression, bipolar, etc.) [3]. Therefore, the study and treatment of insomnia must take into consideration the relative impact of psychiatric comorbidities, and vice versa. In the present chapter we aim to: (1) review the definition, incidence, prevalence, and theoretical perspectives on the etiology of insomnia; (2) summarize the

literature on the relationship between insomnia and various psychiatric conditions, particularly with respect to comorbidity rates, insomnia as a risk factor, and the potential mechanisms that may explain the association; (3) briefly introduce the theoretical components of Cognitive Behavioral Therapy for Insomnia (CBT-I); and (4) examine the evidence for the efficacy of CBT-I among patients with comorbid psychiatric conditions.

Definition, incidence, and prevalence

Definition

Insomnia, broadly defined, refers to difficulty initiating and maintaining sleep. Insomnia is often conceptualized in terms of frequency, chronicity, type, and subtype. Frequency refers to how often an individual experiences insomnia symptoms (typically days per week). Chronicity refers to whether the insomnia is acute or chronic. Type refers to the forms of insomnia that have been historically identified as distinct entities previously included in the International Classification of Sleep Disorders [4] nosology including idiopathic insomnia, psychophysiological insomnia, paradoxical insomnia, insomnia due to inadequate sleep hygiene, and insomnia comorbid with medical or psychiatric illness; however, these types are no longer included in the most current version [5]. Subtype refers to the insomnia phenotype (initial, middle, late, or mixed insomnia). The formal definition or diagnostic criteria for insomnia disorder (DSM-5, 6) is outlined below, but what is relevant for this chapter is that these distinctions with regard to chronicity, type, and subtype exist and should be taken into account. Notably, while frequency and chronicity are defined in the diagnostic criteria, severity is not. It is, however, common in research criteria to use 30 min as a severity threshold (e.g., a sleep

latency greater than or equal to 30 min is considered clinically significant). Why it is not adopted into the clinical nosology is still unclear. This may be related to the relative difference in how one interprets the severity criteria (i.e., for one individual, 30 min may be functionally impairing or distressing, but for someone else it may not be). Taylor and colleagues reported, however, that greater than 30 min was reliably endorsed as a “problem” [6].

Historically, insomnia was considered “just a symptom” of a medical or psychiatric disease, and it was believed that the treatment of the underlying disorder was sufficient and would consequently ameliorate the insomnia as well. Long-term management of insomnia, therefore, was thought to be unnecessary. This perspective has since changed, to where chronic insomnia is now conceptualized as an independent disorder [7]. Adopted by the American Psychiatric Association’s (APA) diagnostic nomenclature (i.e., DSM-5), “insomnia disorder” is used to distinguish insomnia, what is considered to be a distinct diagnostic entity (see diagnostic criteria below), from the sleep continuity disturbance that is a symptom of an underlying medical and/or psychiatric condition, eliminating the need for the “primary” or “secondary” distinctions. Of note, sleep continuity refers to a class, or set, of variables, that we use to talk about “sleep performance” in the context of insomnia. Polysomnography (PSG) recorded sleep has the class term “sleep architecture” which refers to a group of variables that we use to discuss differences in PSG-recorded sleep (e.g., sleep stages, REM onset latency, REM density, K-complexes). Our field, however, has yet to “doctrinize” a class term that refers to all the sleep variables relevant to assessing insomnia (e.g., sleep latency, wake after sleep onset, total sleep time, sleep efficiency). When one or more of these variables are pathological, we refer to this as *sleep continuity disturbance*.

The specific DSM-5 criteria for insomnia disorder are [8]:

- A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one or more of the following symptoms:
 - > Difficulty initiating sleep;
 - > Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings; or
 - > Early-morning awakening with inability to return to sleep.
 - The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
 - The sleep difficulty occurs at least three nights per week.
 - The sleep difficulty is present for at least 3 months.
- The sleep difficulty occurs despite adequate opportunity for sleep.
 - The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder), the physiological effects of a substance (e.g., a drug of abuse, a medication), or coexisting mental disorders and medical conditions.

Incidence and prevalence

Approximately 30%–50% of the U.S. population experience acute sleep continuity disturbance per annum [9], and approximately 6%–10% of the population report chronic levels of insomnia [10]. Data from our group showed that the incident rate of acute insomnia was approximately 25%. Of those 357 individuals who developed new-onset acute insomnia, 72% recovered (i.e., resumed good sleep) and 7% developed insomnia disorder. Interestingly, the other 21% of subjects experienced a form of persistent poor sleep that was not consistent with good sleep but also did not meet diagnostic criteria for insomnia disorder [11]. With respect to insomnia subtypes (i.e., initial, middle, and late insomnia), data from the 2007–08 National Health and Nutrition Examination Survey (NHANES), which included a nationally representative sample of US adults, found that self-reported difficulty falling asleep (initial insomnia) was reported by about 19% of the US population [12]. Other insomnia subtypes, such as difficulty resuming sleep during the night (middle insomnia) and early morning awakenings (late insomnia), were endorsed at similar rates. These high prevalence and incidence estimates have important public health implications because insomnia is associated with significant daytime impairment, including mood dysregulation, cognitive deficits, and fatigue [13]. Just as or more importantly, insomnia is a risk factor for multiple psychiatric and medical disorders, including depression [14–18], hypertension [19–21], diabetes [22,23], and cardiovascular disease [24]. Taken together, efforts to identify the factors and/or mechanisms that explain the transition from acute to chronic insomnia and/or increase risk for chronic insomnia (in general) are an important research and public health priority.

Theoretical perspectives on the etiology of insomnia

No matter how important sleep may be, it was adaptively deferred when the mountain lion entered the cave.

Spielman and Glovinsky [24].

In keeping with this statement is the expression: “we live with insomnia today because at some point in our evolutionary history, insomnia allowed us to live” (Dean Handley, Sepracor, c.2005). Both of these quotes suggest that acute insomnia is adaptive. Most would argue that stress reactivity is adaptive. Physiological, cognitive, and behavioral responses to environmental challenges are not only necessary for survival; they directly bear on the individual’s health and wellbeing [25,26]. This said, altered stress responses are also risk factors for chronic disease, such as insomnia and depression [27–29]. Given this point of view, an essential question is “how does something that is inherently adaptive become maladaptive?” That is, how does acute sleeplessness in the face of a threat become pathological over time? While many things may precipitate acute sleeplessness, chronic insomnia is thought to be an independent disorder with a unique etiology (i.e., insomnia disorder). While the exact pathogenesis of insomnia disorder is likely to be multifactorial, five models are presented below. In addition to putting forward a transdiagnostic model, there is also one transtheoretical model summarized as well (see also Fig. 33.1). It is important to review these models and provide some context, as it may help explain the high comorbidity and shared pathophysiology between insomnia and psychiatric conditions. That is, understanding the factors that are

related to the transition from sleep continuity disturbance that is acute (and likely adaptive) to chronic and dysfunctional may shed some light on how insomnia subsequently increases the risk for psychiatric problems.

Stimulus control model

As originally described by Bootzin in 1972 [30], stimulus control is based on the behavioral principle that one stimulus may elicit a variety of responses, depending on the conditioning history. In the instance where one stimulus is always paired with a single behavior, there is a high probability that the stimulus will yield only one response. In good sleepers, the stimuli typically associated with sleep (e.g., bed, bedroom, etc.) are paired with (and subsequently elicit the response of) sleep. In the instance where there is a complex conditioning history, as typically occurs in patients with insomnia, this is often not the case. When a stimulus is paired with a variety of behaviors, there is a low probability that the stimulus will elicit only one response. In patients with insomnia, stimuli typically associated with sleep are often paired with activities other than sleep, such as reading and watching television in bed. The Stimulus Control Model of Insomnia suggests that engaging in these other behaviors sets the stage for a complex conditioning relationship, or stimulus dyscontrol, that is, reduced

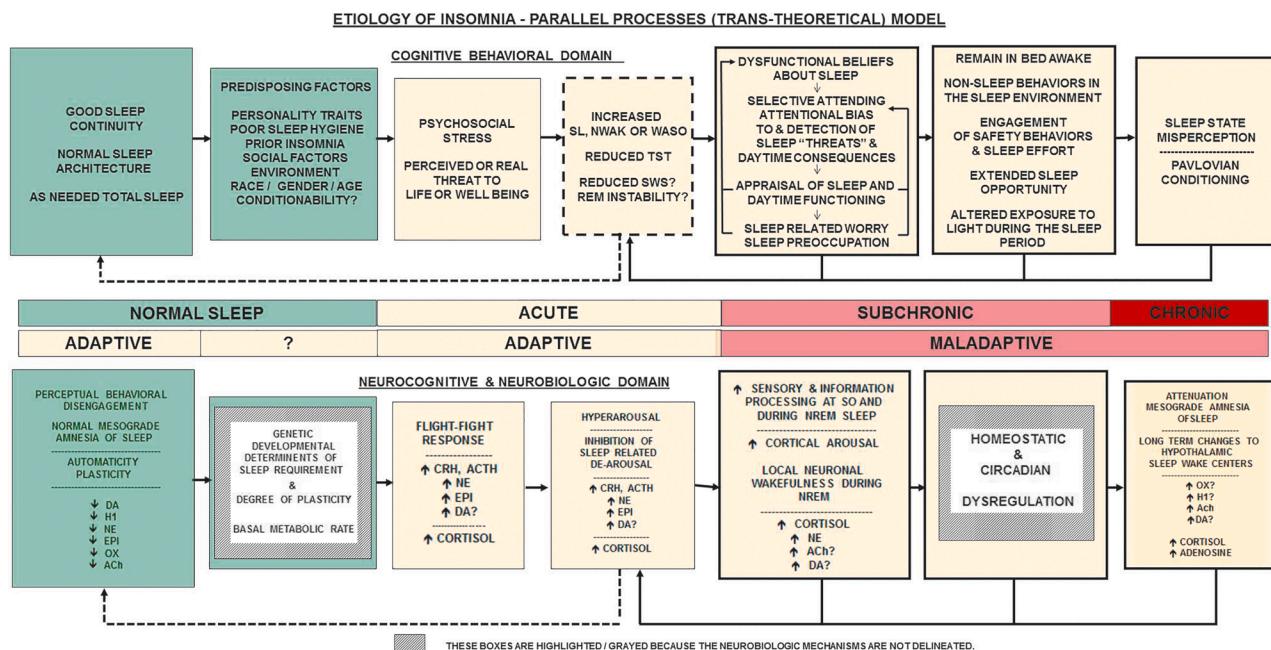


FIGURE 33.1 Parallel process (trans-theoretical) model. The parallel process model is provided to illustrate how the cognitive and behavioral domains may be viewed as parallel processes to the neurocognitive and neurobiologic domains. *ACH*, acetylcholine; *ACTH*, adrenocorticotrophic hormone; *CRH*, corticotrophin-releasing hormone; *DA*, dopamine; *EPI*, epinephrine; *H1*, histamine-1 receptor antagonist; *NE*, norepinephrine; *NWAK*, number of awakenings; *OX*, orexin; *SL*, sleep latency; *SO*, sleep onset; *TST*, total sleep time; *WASO*, wake after sleep onset. Adapted with permission from Perlis ML, Ellis JG, Kloss JD, Riemann D. Etiology and pathophysiology of insomnia. In: Principles and practice of sleep medicine; 2016. p. 769–84.

probability that sleep-related stimuli will elicit the desired response of sleepiness and sleep. Put differently, lying awake in bed (whether one is engaging in sleep effort or not) only further reduces the probability that lying in bed (stimulus) will result in sleep (response). More recently, this model has been expanded to suggest that part of stimulus dyscontrol is that while individuals are lying in bed, they are *microsleeping*. During these microsleeps, the sleep may not be perceptible to the individual but also the sleep is not of sufficient quality to be satiating. Microsleeps are, however, enough sleep to make it difficult to fall asleep later on (i.e., they reduce the homeostatic sleep drive).

Behavioral model (Spielman's 3P model)

In contrast to the stimulus control model, Spielman's 3P model proposes there are certain factors associated with both the onset of acute insomnia and the transition from acute to chronic insomnia. The first two sets of factors (predisposing and precipitating factors) represent a stress-diathesis conceptualization of how insomnia comes to be expressed, whereas the third set of factors (perpetuating factors) explain the mechanisms by which insomnia can become chronic. Predisposing factors increase the underlying vulnerability to develop insomnia and comprise biological features such as sex or a genetic predisposition to develop insomnia and psychological traits such as the tendency to worry and/or ruminate [31,32]. A predisposition to sleep disturbance, however, requires a sufficiently stressful *precipitant*, or combination of precipitants, before it may be expressed [4]. Perpetuating factors refer to the behaviors that an individual engages in while attempting to manage sleep continuity disturbance, which in turn actually contribute to the persistence of insomnia. Examples include: going to bed earlier, napping during the day, and delaying time out of bed. Collectively, these behaviors are referred to as "sleep extension." While typically used as an attempt to recover lost sleep, sleep extension instead results in a mismatch between sleep opportunity (i.e., how much time the person spends in bed) and sleep ability (i.e., how much time the person actually sleeps), thereby, increasing the likelihood of stimulus dyscontrol. Sleep extension also perpetuates insomnia by attenuating the homeostatic drive (i.e., pressure) to sleep, thus making it harder to fall and/or stay asleep. Taken together, addressing these two problems (i.e., stimulus dyscontrol and a reduced homeostatic sleep drive) are the primary therapeutic targets of cognitive behavioral therapy for insomnia (CBT-I; see "What is CBT-I" for more information).

Neurocognitive model

The neurocognitive model extends the behavioral models of insomnia by suggesting that the repeated pairing of

sleep-related stimuli with insomnia-related wakefulness leads to conditioned cortical hyperarousal. While hyperarousal is widely considered the underlying factor that gives rise to insomnia [33], a strength of the Neurocognitive Model is that it proposes a pluralistic perspective of hyperarousal, such that there are several forms of hyperarousal (e.g., cortical, cognitive, and somatic arousal). While the model suggests that hyperarousal may be construed in at least three dimensions, it is cortical hyperarousal (which may be indexed by increases in high frequency EEG activity [beta/gamma activity between 16 and 45 Hz]), that is central to the etiology and pathophysiology of insomnia [8]. Heightened cortical arousal is hypothesized to (1) allow for increased levels of sensory and information processing at and around sleep onset and during NREM sleep or (2) for the attenuation of the normal mesograde amnesia (middle of the night) that occurs in association with sleep. These two phenomena are hypothesized to increase the probability of difficulties falling and staying asleep and to contribute to sleep state misperception [34].

Cognitive model

Harvey's cognitive model of insomnia posits that, in chronic insomnia, increased negative cognitive biases (e.g., sleep-related worry, selective attention and monitoring, and the detection of sleep-related threats) perpetuate a level of physiologic arousal that interferes with sleep initiation or sleep maintenance [35]. In turn, this increased physiological arousal both during the day and at night initiates an attentional bias and a monitoring of perceived internal (e.g., body sensations for signs of fatigue) and external (e.g., the alarm clock) sleep-related threats that might indicate to a person that they did (or will) not receive enough sleep. Taken together, these processes lead to an exaggerated perception of sleep continuity disturbance and its potentially negative impact on daytime performance. Adding to the daytime dysfunction is the tendency to hold incorrect beliefs about the impact of sleep disruption and the utility of worrying and/or engaging in safety behaviors (e.g., canceling appointments or taking a nap during the day). The cognitive model highlights the importance of targeting specific factors that maintain the disorder (i.e., attentional bias) and eliminating the use of safety behaviors in the successful treatment of insomnia.

Psychobiological inhibition model

The psychobiological inhibition model suggests that difficulty with sleep initiation and maintenance is caused by the failure to inhibit wakefulness [36], as opposed to the conditioned hyperarousal [37]. Under normal circumstances, sleep occurs passively (without attention,

intention, or effort). In acute insomnia, acute stress precipitates both physiologic and psychological arousal, which can result in the inhibition of sleep-related dearousal and the occurrence of selective attending to the life stressors, and ultimately, interfere with the normal homeostatic and circadian regulation of sleep. Acute insomnia may, in turn, resolve or be perpetuated based on whether the stressor resolves or if the individual instead attends to the insomnia symptoms that occur with the acute insomnia. In chronic insomnia, failure to inhibit wakefulness is thought to occur from an activation of the cognitive attention-intention-effort pathway. When an individual experiences sleeplessness, their attention shifts toward the process of sleep, something that is typically an automatic and passive event. This shift in attention prevents the normal disengagement from wakefulness and makes the acquisition of sleep an intentional activity, where the person begins to demonstrate active effort to sleep and further weakens the processes related to the inhibition of wakefulness.

Parallel process (transtheoretical) model

Each of the models presented above provides a unique perspective, and for the most part, none are mutually exclusive. In recognition of this, we provide in Fig. 33.1 an integrative perspective, parallel process model [38]. This model is intended to illustrate how [1] all of the identified factors may be contributory and [2] the cognitive and behavioral domains may be viewed as parallel processes to the neurocognitive and neurobiologic domains. That is, the perspective that the cognitive-behavioral and the neurocognitive-neurobiologic domains represent two sides of the same phenomena.

Insomnia and psychiatric morbidity

Insomnia (both the symptom and the disorder) is a substantial risk factor for psychiatric morbidity [39] (Fig. 33.2). While sleep continuity disturbance is associated with a number of psychiatric conditions, it is a diagnostic feature for multiple disorders, such as depression, generalized anxiety disorder, and post-traumatic stress disorder (PTSD) [8]. Insomnia may be common in multiple psychiatric disorders because they share (1) a similar trigger (e.g., stress) and/or underlying pathophysiology (e.g., serotonin deficiency) [40–42] and (2) similar functional consequences (e.g., dysfunctional beliefs) [43]. With respect to similar trigger, most research suggests that an increase in stress is the most common precipitating event observed in insomnia but also in depression, anxiety, and by nature of the disorder, PTSD. More recent literature has also suggested that a potential underlying pathophysiology common among these disorders may be a decrease in serotonergic

neurotransmission [42]. With respect to similar functional consequences, insomnia and some of these other psychiatric conditions share many of the same symptoms or clinical presentation, such as depressed mood, worry, fatigue, and difficulty concentrating. For example, a core feature of insomnia is somatic and cognitive hyperarousal [44], which may increase severity of symptoms for both mood and anxiety disorders. Hyperarousal is also a core feature of PTSD and is known to interact with the hyperarousal present in insomnia [45]. Another consequence of insomnia is emotional dysregulation. Studies show that negative emotional experiences (i.e., mood and affect) are more common in insomnia, especially at night [46,47]. Insomnia has also been implicated in functional deficits across a wide range of domains [48] as well as reduced quality of life [49]. Taken together, an important question for the field is whether insomnia and these other disorders represent distinct clinical phenomena that are interrelated, such that they increase risk for one another or whether they represent a common disorder/disease with an array of possible clinical sequelae. To this end, the sections below review the relationships between insomnia and a number of psychiatric disorders, particularly with respect to prevalence, directionality of the association, and shared risk factors. Please note that while attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) may be better considered neurodevelopmental disorders, they were included given that they are a part of the psychiatric nosology (i.e., DSM-5) and are highly comorbid with insomnia.

Depressive disorders

Major depressive disorder (MDD) is a common and heterogeneous disorder that is primarily characterized by episodes (of at least 2 weeks) of depressed mood and/or anhedonia (a loss of interest or pleasure in daily activities) [8]. A major depressive episode (MDE) may also consist of significant changes in weight, sleep, psychomotor activity, fatigue, feelings of worthlessness/guilt, concentration, and/or suicidality. Unlike normal fluctuations in mood, MDD causes significant distress and/or functional impairment. Among all psychiatric disorders, the comorbidity between insomnia and depression is highest. Up to 90% of individuals with MDD experience insomnia [17]. The challenge in understanding the association between insomnia and depression is that insomnia can represent both a risk factor (or prodrome) and a consequence of depression (i.e., the relationship is bidirectional). For example, residual insomnia after treatment for depression [49] is the largest predictor of a subsequent MDE [50]. A meta-analysis of 21 longitudinal studies also identified insomnia as a significant predictor of the onset of an MDE, such that those with insomnia, compared to those without, were twice as likely

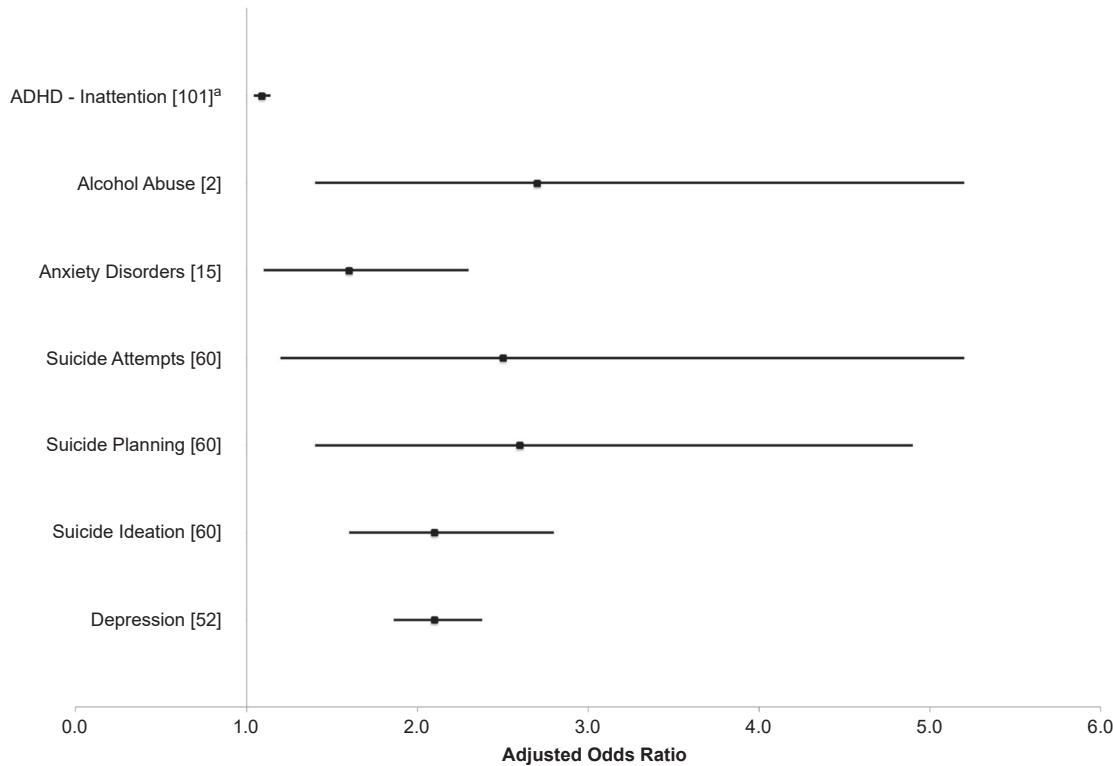


FIGURE 33.2 Insomnia as a risk factor for multiple psychiatric conditions. The forest plot below provides the adjusted odds ratio estimates for insomnia by psychiatric condition or phenomena. ^aRepresents adjusted odds ratio for ADHD-Inattention with Insomnia as predictor.

to develop depression [51]. A more recent meta-analysis of 34 cohort studies showed similar results (relative risk of developing depression was 2.3 among those with insomnia; [52]). These rates have been shown to be four times greater in adolescent samples [53]. Similarly, persistent poor sleep is a known risk factor for relapse after pharmacological [54] and nonpharmacological [55] treatment for MDD.

Despite research suggesting that insomnia is more than just a symptom of depression, and indeed, a risk factor, the mechanisms that explain the association between insomnia and depression are still unclear [17]. Staner [43] proposed that insomnia may directly and/or indirectly cause a depressive episode. For example, insomnia and/or insomnia-related daytime consequences may directly increase depressed mood and other depressive symptoms (e.g., increases in anhedonia, fatigue, and concentration problems). The severity and persistence of these symptoms may ultimately reach a point that is consistent with diagnostic criteria for an MDE. Alternatively, insomnia may cause and/or be caused by a common factor that also contributes to the development of MDD (i.e., indirect causality). The most obvious example of this is stress. Acute stressful life events can simultaneously lead to the development of both insomnia and depressive symptoms (albeit the insomnia symptoms may manifest first) but also insomnia or insomnia-related daytime consequences may

produce additional stress, which may culminate in the development of depression. A number of biological factors have also been identified as potential mechanisms that explain how insomnia may be a risk factor for MDD or at the very least explain why these two disorders are highly comorbid. These biological mechanisms include: monoaminergic neurotransmission, abnormalities in circadian genes, overactivity of the hypothalamic-pituitary-adrenal axis, and impaired functioning of plasticity-related gene cascades [42,56]. The nature and/or role that these biological mechanisms have on the association between insomnia and depression are unknown, but what is clear is that these are potential targets for future research.

Suicide

Insomnia has also been implicated in suicide. A meta-analysis indicated that the presence of insomnia is associated with an approximately threefold likelihood of suicide ideation, attempts, and death by suicide [57]. This research has been supported by population-level studies that show that suicidal ideation, even in the general population is predicted by insomnia symptoms [58,59]. While research consistently supports the association between insomnia and suicidal ideation, the specific mechanisms by which insomnia confers risk for suicidal ideation are unknown. A

number of psychological and physiological mechanisms have been proposed [60,61]. Potential psychological mechanisms include: insomnia-related psychosocial impairments (that may or may not be related to loneliness and lack of belonging); activation of hopelessness and/or helplessness schema; and/or diminished executive function. Potential physiological mechanisms, which may occur as a result of insomnia or a common neurobiologic substrate, include serotonin deficiency; hypercortisolemia; and/or elevated basal metabolic rate. There has also been additional evidence that suicides are disproportionately likely to occur at night [62] suggesting that nocturnal wakefulness itself may represent a risk factor for suicide [63]. That is, being awake at night, and the associated hypofrontality that occurs during the night and/or with sleep loss (i.e., decreased frontal lobe function), may be another mechanism by which insomnia increases risk for suicidal ideation [63]. Insomnia increases the likelihood of being awake at night, the time of day in which one's ability to reason, think rationally, and to engage in impulse control may be at its lowest [64,65]. Being awake at night, especially during times of increased stress or mood disturbance, may therefore increase risk for suicidal ideation.

Bipolar disorder

In contrast to depression, bipolar disorder is characterized by episodes of both mania (and/or hypomania) and depression. With respect to the depressive episodes in bipolar disorder, it is not surprising that similar challenges arise when teasing apart whether insomnia is a risk factor or a consequence (or symptom) of the depression. With respect to the manic episodes, sleeplessness is also a symptom of mania but qualitatively differs from insomnia in that patients experiencing manic episodes think and feel as though they do not *need* sleep [66]. Of note, the diagnostic criteria for insomnia states that the patient must experience difficulty initiating and/or maintaining sleep despite "adequate opportunity for sleep" [8], a condition that is often not met in patients experiencing manic episodes. Despite these nuances in diagnostic criteria, sleep continuity disturbance is highly prevalent among patients with bipolar disorder [67,68] and the most common prodromal symptom of a manic episode [69]. Sleep continuity disturbance is greater among patients with bipolar disorder, relative to controls, and nearly as severe as in patients with insomnia (without bipolar disorder). For example, lower sleep efficiency, night-to-night variability, and longer sleep latency have also been shown to be significantly associated with a history of depression in patients with bipolar disorder [70]. Talbot et al. [71] also reported that, in subjects with bipolar disorder, morning negative mood varied as a function of total sleep time during the preceding night [71]. Similarly, sleep loss is highly correlated with daily manic

symptoms among patients with bipolar [69]. These findings support the notion that there is a reciprocal relationship between sleep continuity disturbance and daily changes in mood [71]. As with all of the other psychiatric disorders discussed in this chapter, the nature of the association between insomnia and bipolar disorder is elusive. There has been some evidence for a possible genetic linkage between sleep/circadian dysregulation and bipolar disorder. A number of "clock" genes (e.g., per3 and gsk3) are associated with sleep and mood regulation and may have implications for the development and/or treatment of both insomnia and bipolar [68,72,73].

Anxiety disorders

Like depressive disorders, anxiety disorders are heterogeneous in their phenotypic presentation. So much so that the literature on the association between insomnia and each individual type of anxiety disorder is limited and therefore beyond the scope of the present chapter. Here, we discuss the relationship between insomnia and anxiety disorders, broadly defined, and go into more detail regarding the link between insomnia and PTSD in the next section. Common among anxiety disorders are feelings of intense fear or worry, avoidance-related behaviors, and that these feelings and behaviors are triggered by stress [74]. Not surprisingly, these are also core features of insomnia and may possibly explain the high comorbidity between the two phenomena [53,75]. According to one study, the prevalence rate of clinically significant anxiety among subjects with insomnia is nearly 20%, as compared to 3% in subjects without comorbid insomnia [6]. A large prospective study (approximately 25,000 Norwegian adults) also showed that subjects with insomnia were significantly more likely to endorse an anxiety disorder at follow-up. Similarly, those that endorsed insomnia were more than three times as likely to also report a concurrent anxiety disorder [15]. The evidence for anxiety as a potential risk factor for insomnia is even more compelling. An epidemiological study among Swedish adults supported that clinically significant anxiety increased the risk for developing clinically significant insomnia more than fourfold [76]. Another study that surveyed nearly 15,000 Europeans found that in new-onset cases of anxiety disorders (that were also comorbid with insomnia), insomnia preceded the anxiety disorder 18% of the time, the two disorders appeared simultaneously approximately 39% of the time, and the anxiety disorder came first approximately 44% of the time [49]. A separate study found that, in contrast to depression where insomnia occurred first in 69% of comorbid cases, anxiety disorders preceded insomnia 73% of the time [53]. Anxiety disorders and insomnia have often been thought of as disorders sharing certain vulnerabilities and characteristics and are often treated with similar pharmacological and behavioral interventions [77]. Because

of the high comorbidity and the bidirectional relationship between insomnia and anxiety, Uhde et al. [78] have proposed two potential explanatory models [78]. In the first model, anxiety and insomnia represent different dimensions of a common underlying disorder, whereby different clinical symptoms may emerge as a result of repeated stress. In the second model, anxiety and insomnia represent different neurobiological disorders, whereby each separately causes remarkably similar symptoms or that they are both produced by another widely prevalent third factor. How these disorders are conceptualized has important treatment implications; namely, will the treatment of one diminish symptoms of the other or should they be treated simultaneously?

Posttraumatic stress disorder

PTSD refers to a disorder characterized by a complex set of symptoms that arise following a life-threatening or traumatic event and typically include [1]: reexperiencing the traumatic event [2]; avoidance of stimuli that resemble or remind one of the event [3]; negative thoughts or feelings; and/or [4] increased arousal and/or reactivity (including difficulty sleeping). Studies suggest that there is a 60%–90% chance of experiencing insomnia following a traumatic event [79,80]. Sleep disturbance, in general, and insomnia and nightmares, in specific, have been referred to as the cardinal symptom of PTSD [81,82]. Moreover, insomnia symptoms following a traumatic event may increase the likelihood of developing PTSD and/or PTSD severity [83–85]. Other studies have also shown that treating insomnia among patients with PTSD may indirectly reduce the severity of PTSD symptoms [86–88]. Insomnia may therefore represent a risk factor and/or prodromal symptom of PTSD. In fact, insomnia is the most frequently reported symptom among individuals with PTSD and does not remit with otherwise successful first-line interventions [89,90]. With respect to sleep continuity disturbance, difficulty initiating and maintaining sleep at least “sometimes” were reported in 44% and 91% (respectively) of a sample comprised of Vietnam veterans with PTSD [79]. Similarly, Pigeon et al. [91] found that clinical levels of insomnia were significantly associated with greater baseline PTSD severity but also predicted increases in PTSD 6-month later, such that approximately 38% of subjects with insomnia endorsed PTSD at follow-up (as compared to 5% of subjects without insomnia) [91]. Consistent with other psychiatric disorders, the association between insomnia and PTSD also appears to be bidirectional, in that insomnia is a probable consequence of PTSD, yet insomnia may also further perpetuate the PTSD symptoms. The mechanisms that explain this bidirectional relationship are unknown, but relevant targets have been identified, such as hyperarousal related to increased

noradrenergic activity [92,93], sleep-related anxiety [94], comorbid depression [95,96].

Attention-deficit/hyperactivity disorder

ADHD is a neurodevelopmental disorder that emerges in youth (before age 12) and typically runs a lifelong course [97]. ADHD is characterized by a “persistent pattern of inattention and/or hyperactivity that interferes with functioning and/or development” (DSM-5). While ADHD is more commonly studied in youth, ADHD in adulthood is also common (an estimated prevalence of 14 million adults in the United States; [98]). Common among patients with ADHD is comorbid insomnia. According to results from a recent study, 67% of adult patients with ADHD also met DSM-based criteria for insomnia. This is compared to 28% of adults in the sample who did not have a diagnosis of ADHD [99]. The most common type of sleep continuity disturbance reported in ADHD patients is difficulty initiating sleep (also referred to as chronic sleep-onset insomnia or initial insomnia) [100–102]. While a prolonged sleep latency has often been thought to be a side effect of stimulant medication [103–105], other studies have hypothesized that initial insomnia may be instead related to abnormalities in circadian functioning among patients with ADHD. Specifically, Van Veen et al. assessed dim-light melatonin onset (DLMO) and rest-activity patterns in ADHD patients with initial insomnia, as compared to ADHD patients without initial insomnia and healthy controls [106]. Their data supported that ADHD patients with initial insomnia had a delayed DLMO and a reduced 24-h amplitude in their rest-activity cycle. Insomnia, in patients with ADHD, may therefore instead be a natural consequence of the mismatch between a patient’s (delayed) circadian rhythm and their attempt to adhere to a “normal” sleep schedule (due to obligations at home, school, or work). For example, as the research noted above suggests, patients with ADHD may be more likely to have a delayed circadian rhythm (i.e., natural tendency to want to go to sleep later) and consequently, experience insomnia when they attempt to go to sleep early. A delayed circadian rhythm in ADHD may be related to age (patients with ADHD are typically younger) or may be a byproduct of the disorder. This said, future work evaluating the association between insomnia and ADHD should consider the effect of age and how age-related differences in chronobiology may account for the presence and/or absence of insomnia. With regard to treatment, subjects with ADHD who are currently being treated with stimulant medication report less severe insomnia [99]. This suggests that the pharmacological treatment of ADHD does not exacerbate sleep continuity disturbance, and that sleep continuity disturbance may be a consequence of ADHD given that it subsides with the effective treatment of ADHD symptoms.

Alcohol use disorder

In contrast to prior versions of DSM criteria that divided alcohol use problems into abuse and dependence, DSM-5's Alcohol Use Disorder (AUD) makes no such distinction. AUD refers to, among others, problems related to how or how long one drinks, difficulty stopping or cutting back one's drinking, and functional/emotional impairment as a result of drinking [8]. Alcohol use problems and insomnia, not surprisingly, are highly comorbid [107,108]. While specific prevalence rates vary by how insomnia and/or alcohol use disorders are defined, Brower et al. [109] showed that 18% of subjects who met criteria for an alcohol use disorder also endorsed significant levels of insomnia (this is compared to 10% of subjects without alcohol problems). In a study of subjects being treated for alcohol dependence, 61% of subjects endorsed insomnia symptoms during the pretreatment phase. Sleep continuity disturbance has also been shown to persist through the early stages of alcohol recovery (up to 5 weeks following the abstinence of alcohol) [109]. In addition, subjects who endorsed insomnia symptoms were more likely to report using alcohol to self-medicate for their sleep problems, had more severe alcohol dependence, and were more likely to relapse to alcohol use (60% of subjects), as compared to subjects without insomnia (30% of subjects) [109]. Alternatively, in subjects with insomnia, 7%–19% of subjects also reported significant alcohol use problems (this is compared to 4%–9% of subjects without insomnia) [2,110]. The economic burden of alcohol-related insomnia is also considerable given that insomnia accounts for approximately 10% of all alcohol-related costs. That is the equivalent of about 28 billion dollars each year in the United States alone (please note the cost was converted to account for inflation) [111,112]. It is no surprise that alcohol is one of the most common self-medicating substances used among patients with insomnia [113,114], given its sedating effects [107]. This said, alcoholism is a significant predictor (i.e., risk factor) of insomnia [109,110]. The prevalence and economic/societal burden of comorbid insomnia and alcohol use disorders are relatively well defined; however, the neurobiological and psychosocial factors that explain this association are less clear. As indicated above, alcohol is considered a sedative and therefore has the potential to promote the initiation of sleep. The sleep-promoting effects of alcohol, however, are dose-dependent and do not persist with continued alcohol use (i.e., after 3 days of continued use), and more importantly, alcohol can significantly disrupt both sleep continuity and sleep architecture (i.e., increased likelihood of REM sleep inhibition, nocturnal arousals, and rebound insomnia during the second part of the night). Taken together, for individuals with insomnia, especially initial insomnia, alcohol might be appealing as a convenient, low-

cost hypnotic, yet the overall effects are detrimental and can ultimately lead to greater sleep continuity disturbance (particularly the perpetuation of middle and late insomnia) and more severe alcohol dependence (increased amounts of alcohol are required to achieve the same sedating effect). In conclusion, comorbid insomnia and alcohol use disorders are prevalent, costly to society, and associated with worse overall outcomes.

Autism spectrum disorder

The association between insomnia and ASD has recently become a topic of interest, given the increasing literature on sleep problems in children with ASD and the subsequent negative effects those sleep problems have on their overall functioning and quality of life [115]. Prevalence rates for sleep problems range from 50% to 80% of children with ASD [116,117]. While children with ASD experience a multitude of sleep problems, the most commonly reported sleep problem among parents of children with ASD is insomnia and more specifically, an extended sleep latency (i.e., initial insomnia) [118–120]. The link between ASD and insomnia is multifactorial. ASD is associated with abnormalities in several neurotransmitters that are also implicated in insomnia (e.g., GABA, serotonin, and melatonin) [121–124], and therefore, the two disorders may share a common neurobiological core. Alternatively, insomnia in individuals with ASD may be related to medical (e.g., epilepsy and GERD) and psychiatric comorbidities (depression and ADHD), the medications used to treat these comorbidities or the behavioral/emotional consequence of ASD (e.g., difficulties with transitions and emotion regulation) [115,125]. While it is unknown whether insomnia is a risk factor for a more severe course of ASD, there is some evidence to support that sleep continuity disturbance may exacerbate ASD symptoms and/or the functional consequences of ASD (e.g., increases in emotion dysregulation, inattention, and family stress) [115,126,127].

Schizophrenia

The association between schizophrenia and insomnia has also been documented [128]. Similar to most other psychiatric disorders, their co-occurrence is prevalent and their relationship bidirectional. Significant sleep disturbances are present in roughly 35%–50% of individuals with schizophrenia and other psychotic disorders [129–131] and are associated with exacerbated positive symptoms [132] and a reduced quality of life [129,133–136]. Past research supports that sleep continuity disturbance is a risk factor for relapse and may even be a prodromal sign of a psychotic relapse [137]. Moreover, insomnia symptoms increase over time following antipsychotic medication

withdrawal, which supports the notion that insomnia is also a consequence of schizophrenia that can be resolved with the successful treatment of the positive symptoms of schizophrenia [138]. While insomnia as a natural consequence of schizophrenia makes sense (i.e., patients with schizophrenia often have irregular schedules, increased depression and anxiety, extensive medication regimens), how insomnia increases risk for psychotic symptoms is much less clear. There are, however, some studies indicating that low melatonin levels at night may be a common neurobiological feature of both insomnia and schizophrenia, and exogenous melatonin administration may improve the overall quality and quantity of sleep in patients with schizophrenia [139]. Like ADHD, age and age-related differences in chronobiology may also explain part of the association between insomnia and schizophrenia and thus, should be the focus of future work.

Behavioral treatment of insomnia

What is CBT-I?

Cognitive behavioral therapy for insomnia (CBT-I) combines principles from stimulus control and sleep restriction therapy with formal cognitive restructuring in order to target hyperarousal, dysfunctional behaviors and maladaptive thoughts, beliefs, and attitudes about sleep [140]. Stimulus control targets a person's tendency to engage in behaviors other than sleep in the bedroom (e.g., reading or watching television in bed), thereby weakening the association between the sleep environment and the physiologic state of sleep. Stimulus control instructions, in general, are simple. Patients are to avoid using the bed for activities other than sleep or intimacy and get out of bed if unable to sleep within 15–20 min and return to bed only when sleepy [141]. The primary goal of sleep restriction is to address the mismatch between sleep opportunity (time in bed) and sleep ability (time asleep) by limiting the amount of time a patient spends in bed to the amount of time that they are actually sleeping. Sleep restriction has the following important objectives (1) it increases the homeostatic sleep drive (i.e., sleep "pressure") and reduces the heightened arousal caused by an individuals' effort to force sleep, and (2) it reduces time spent awake during the night by consolidating sleep into longer, more restorative periods. As mentioned above, cognitive restructuring is also commonly used in conjunction with the more behavioral interventions. The primary goal of cognitive restructuring is to identify problematic thoughts that may contribute to the development of, or reinforce, behaviors that produce presleep worry, examine these thoughts for accuracy, and if necessary, modify them to be more rational and/or realistic.

CBT-I was recently endorsed by the American College of Physicians [142]. Specifically, the official position of the

ACP is that not only is CBT-I recommended as the first-line therapy of choice, but that pharmacotherapy is only recommended in cases where its use is short-term, and/or in combination with behavioral treatment, and/or after discussion with patients regarding the limitations of this approach [142]. More specific information regarding the delivery of CBT-I can be found elsewhere [141].

CBT-I in the context of psychiatric disorders

A recent meta-analysis of 37 randomized controlled trials evaluated the impact of CBT-I not only on insomnia severity and sleep continuity disturbance but also on the symptoms of the comorbid disorder in a sample of 2189 participants [143]. Ten of the studies included in this meta-analysis were conducted in patients with comorbid psychiatric conditions (i.e., substance use disorders, depressive disorders, and PTSD), 26 with medical comorbidities, and 1 with a mixed sample. While patients with comorbid medical conditions, as compared to those with comorbid psychiatric conditions, improved equally on symptoms of insomnia, a larger effect of CBT-I was found for reducing symptoms of the comorbid psychiatric conditions ($g = 0.76$) than symptoms of medical comorbidities ($g = 0.20$). These data suggest that psychiatric symptoms may be more responsive to CBT-I than those associated with a medical condition. Consistent with other studies, the improvement in sleep continuity was maintained for 3–12 months after completing CBT-I. A number of recent trials of CBT-I have been conducted in patients with comorbid insomnia and depression [144,145]. These RCTs provide strong evidence that treatment of insomnia (alone or in combination with pharmacotherapy) in patients with depression can produce comparable effects for both depression and insomnia symptoms. This opens treatment options for patients who have not adequately responded to antidepressant medication or who would prefer a non-pharmacological option. Similarly, A meta-analytic review of the effect of CBT for anxiety on comorbid sleep continuity disturbance concluded that CBT for anxiety could be expected to have a moderate effect on sleep outcomes (effect size = 0.52), but that residual sleep problems should be expected [146].

There is a growing interest in the application of CBT-I with patients who have other potentially more serious psychiatric conditions such as PTSD, bipolar mood disorders, and psychotic disorders, but these areas are relatively underdeveloped compared to depressive and anxiety disorders. For example, there is growing evidence that CBT-I, alone or in combination with PTSD-specific treatment components, can significantly improve both subjective and objective sleep outcomes in patients with PTSD [87,147]. While treatment for insomnia comorbid with psychotic disorders is still largely pharmacological [148], some early

work has tested the ability of CBT-I to improve sleep and reduce delusions and hallucinations [149]. Similarly, a modified version of cognitive behavioral therapy for insomnia for patients with bipolar disorder (CBTI-BP) has demonstrated efficacy for both reducing sleep continuity problems but also reducing mood symptoms. Importantly, CBTI-BP takes a more conservative approach to sleep restriction (time in bed is restricted to no less than 6.5 h), given that it has the potential to increase the risk for a hypomanic/manic episode [150]. This said, subjects that underwent CBTI-BP were at a reduced risk for a mood episode relapse as compared to a psychoeducation control group (27% reduction in probability for manic/hypomanic episodes and 28.5% reduction for depressive episodes) [151].

Conclusion

Sleep has clear importance for the maintenance of physical and psychological health, making insomnia a serious public health concern. Insomnia increases the risk for, and severity of, a number of psychiatric conditions. When left unaddressed, insomnia negatively impacts the ability of the individual to completely recover from their disorder. Evidence-based treatment for insomnia, CBT-I, exists and is effective when delivered in individuals with comorbid psychiatric conditions, but it is currently underutilized. Increased attention and awareness of the importance of treating insomnia are needed. There is a clear and profound association between poor sleep and poor mental health. Apart from this association, there is the possibility that good sleep continuity may not only ward off new onset disease, but that it may also promote good mental health.

References

- [1] Harvey AG. Insomnia, psychiatric disorders, and the trans-diagnostic perspective. *Curr Dir Psychol Sci* 2008;17(5):299–303. <https://doi.org/10.1111/j.1467-8721.2008.00594.x>.
- [2] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? *JAMA, J Am Med Assoc* 1989;262(11):1479–84. <https://doi.org/10.1001/jama.1989.03430110069030>.
- [3] Diagnostic and statistical manual of mental disorders (DSM). APA; 1994. p. 866.
- [4] The International classification of sleep disorders. American Academy of Sleep Medicine; 2005.
- [5] International classification of sleep disorders. American Academy of Sleep Medicine; 2014.
- [6] Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. *Sleep* 2005;28(11):1457–64. <https://doi.org/10.1093/sleep/28.11.1457>.
- [7] Lichstein KL. Secondary insomnia: a myth dismissed. *Sleep Med Rev* 2006;10(1):3–5. <https://doi.org/10.1016/j.smrv.2005.10.001>.
- [8] Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Association—Google Books; 2018. p. 2018.
- [9] Ellis JG, Perlis ML, Neale LF, Espie CA, Bastien CH. The natural history of insomnia: focus on prevalence and incidence of acute insomnia. *J Psychiatr Res* 2012;46(10):1278–85. <https://doi.org/10.1016/j.jpsychires.2012.07.001>.
- [10] NIH. State-of-the- science conference statement on manifestations and management of chronic insomnia in adults. NIH; 2005. p. 2005.
- [11] Gencarelli WK, Morales K. A one year study of 1,069 good sleepers: the incidence of acute and chronic insomnia. *Sleep* 2018;41:2018.
- [12] Grandner MA, Ruiter Petrov ME, Rattanaumpawan P, Jackson N, Platt A, Patel NP. Sleep symptoms, race/ethnicity, and socioeconomic position. *J Clin Sleep Med* 2013;9(09):897–905. <https://doi.org/10.5664/jcsm.2990>.
- [13] Riedel BW, Lichstein KL. Insomnia and daytime functioning. *Sleep Med Rev* 2000;4(3):277–98. <https://doi.org/10.1053/smrv.1999.0074>.
- [14] Benca RM, Peterson MJ. Insomnia and depression. *Sleep Med* 2008;9(1):S3. [https://doi.org/10.1016/S1389-9457\(08\)70010-8](https://doi.org/10.1016/S1389-9457(08)70010-8).
- [15] Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. *Sleep* 2007;30(7):873–80. <https://doi.org/10.1093/sleep/30.7.873>.
- [16] Perlis ML, Smith LJ, Lyness JM, Matteson SR, Pigeon WR, Jungquist CR, et al. Insomnia as a risk factor for onset of depression in the elderly. *Behav Sleep Med* 2010;4(2):85–103. https://doi.org/10.1207/s15402010bsm0402_3.
- [17] Riemann D, Voderholzer U. Primary insomnia: a risk factor to develop depression? *J Affect Disord* 2003;76(1–3):255–9. [https://doi.org/10.1016/S0165-0327\(02\)00072-1](https://doi.org/10.1016/S0165-0327(02)00072-1).
- [18] Roane BM, Taylor DJ. Adolescent insomnia as a risk factor for early adult depression and substance abuse. *Sleep* 2008;31(10):1351–6.
- [19] Bathgate CJ, Edinger JD, Wyatt JK, Krystal AD. Objective but not subjective short sleep duration associated with increased risk for hypertension in individuals with insomnia. *Sleep* 2016;39(5):1037–45. <https://doi.org/10.5665/sleep.5748>.
- [20] Suka M, Yoshida K, Sugimori H. Persistent insomnia is a predictor of hypertension in Japanese male workers. *J Occup Health* 2003;45(6):344–50. <https://doi.org/10.1539/joh.45.344>.
- [21] Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep* 2009;32(4):491–7. <https://doi.org/10.1093/sleep/32.4.491>.
- [22] Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care* 2005;28(11):2762–7. <https://doi.org/10.2337/diacare.28.11.2762>.
- [23] Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diabetes Care* 2009;32(11):1980–5. <https://doi.org/10.2337/dc09-0284>.
- [24] Arthur JS, Glovinsky PB. Introduction. Springer Science and Business Media LLC; 1991. p. 1–15. https://doi.org/10.1007/978-1-4757-9586-8_1.
- [25] Cannon W. Bodily changes in pain, hunger, fear and rage. 2017.

- [26] Jansen ASP, Van Nguyen X, Karpitskiy V, Mettenleiter TC, Loewy AD. Central command neurons of the sympathetic nervous system: basis of the fight-or-flight response. *Science* 1995;270(5236):644–6. <https://doi.org/10.1126/science.270.5236.644>.
- [27] Harvey CJ, Gehrman P, Espie CA. Who is predisposed to insomnia: a review of familial aggregation, stress-reactivity, personality and coping style. *Sleep Med Rev* 2014;18(3):237–47. <https://doi.org/10.1016/j.smrv.2013.11.004>.
- [28] Drake CL, Pillai V, Roth T. Stress and sleep reactivity: a prospective investigation of the stress-diathesis model of insomnia. *Sleep* 2014;37(8):1295–304. <https://doi.org/10.5665/sleep.3916>.
- [29] Burke HM, Davis MC, Otte C, Mohr DC. Depression and cortisol responses to psychological stress: a meta-analysis. *Psychoneuroendocrinology* 2005;30(9):846–56. <https://doi.org/10.1016/j.psyneuen.2005.02.010>.
- [30] Bootzin RR. Stimulus control treatment for insomnia. *Proc Am Psychol Assoc* 1972;7:1972.
- [31] Singareddy R, Vgontzas AN, Fernandez-Mendoza J, Liao D, Calhoun S, Shaffer ML, Bixler EO. Risk factors for incident chronic insomnia: a general population prospective study. *Sleep Med* 2012;13(4):346–53. <https://doi.org/10.1016/j.sleep.2011.10.033>.
- [32] Laar Mvan de, Verbeek I, Pevernagie D, Aldenkamp A, Overeem S. The role of personality traits in insomnia. *Sleep Med Rev* 2010;14(1):61–8. <https://doi.org/10.1016/j.smrv.2009.07.007>.
- [33] Riemann D, Spiegelhalder K, Feige B, Ulrich V, Berger M, Perlis M, Nissen C. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 2010;14(1):19–31. <https://doi.org/10.1016/j.smrv.2009.04.002>.
- [34] Bastien CH, Ceklic T, St-Hilaire P, Desmarais F, Pérusse AD, Lefrançois J, Pedneault-Drolet M. Insomnia and sleep misperception. *Pathol Biol* 2014;62(5):241–51. <https://doi.org/10.1016/j.patbio.2014.07.003>.
- [35] Harvey AG. A cognitive model of insomnia. *Behav Res Ther* 2002;40(8):869–93. [https://doi.org/10.1016/s0005-7967\(01\)00061-4](https://doi.org/10.1016/s0005-7967(01)00061-4).
- [36] Espie CA, Broomfield NM, MacMahon KMA, Macphee LM, Taylor LM. The attention-intention-effort pathway in the development of psychophysiological insomnia: a theoretical review. *Sleep Med Rev* 2006;10(4):215–45. <https://doi.org/10.1016/j.smrv.2006.03.002>.
- [37] Perlis ML, Giles DE, Mendelson WB, Bootzin RR, Wyatt JK. Psychophysiological insomnia: the behavioural model and a neuropsychological perspective. *J Sleep Res* 1997;6(3):179–88. <https://doi.org/10.1046/j.1365-2869.1997.00045.x>.
- [38] Perlis JGE, Kloss JD, Riemann, etiology. In: Principles and practice of sleep medicine. Elsevier Health Sciences, Elsevier Health Sciences; 2016. p. 769–84.
- [39] Spiegelhalder K, Regen W, Nanovska S, Baglioni C, Riemann D. Comorbid sleep disorders in neuropsychiatric disorders across the life cycle. *Curr Psychiatry Rep* 2013;15(6). <https://doi.org/10.1007/s11920-013-0364-5>.
- [40] Morin CM, Rodrigue S, Ivers H. Role of stress, arousal, and coping skills in primary insomnia. *Psychosom Med* 2003;65(2):259–67. <https://doi.org/10.1097/01.psy.0000030391.09558.a3>.
- [41] Monroe SM, Harkness KL. Life stress, the “kindling” hypothesis, and the recurrence of depression: considerations from a life stress perspective. *Psychol Rev* 2005;112(2):417–45. <https://doi.org/10.1037/0033-295X.112.2.417>.
- [42] Adrien J. Neurobiological bases for the relation between sleep and depression. *Sleep Med Rev* 2002;6(5):341–51. [https://doi.org/10.1016/s1087-0792\(01\)90200-x](https://doi.org/10.1016/s1087-0792(01)90200-x).
- [43] Staner L. Comorbidity of insomnia and depression. *Sleep Med Rev* 2010;14(1):35–46. <https://doi.org/10.1016/j.smrv.2009.09.003>.
- [44] Bonnet MH, Arand DL. Hyperarousal and insomnia. *Sleep Med Rev* 1997;1(2):97–108. [https://doi.org/10.1016/s1087-0792\(97\)90012-5](https://doi.org/10.1016/s1087-0792(97)90012-5).
- [45] Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? *Sleep Med Rev* 2008;12(3):169–84. <https://doi.org/10.1016/j.smrv.2007.08.008>.
- [46] Buysse DJ, Thompson W, Scott J, Franzen PL, Germain A, Hall M, Moul DE, Nofzinger EA, Kupfer DJ. Daytime symptoms in primary insomnia: a prospective analysis using ecological momentary assessment. *Sleep Med* 2007;8(3):198–208. <https://doi.org/10.1016/j.sleep.2006.10.006>.
- [47] McCrae CS, McNamara JPH, Rowe MA, Dzierzewski JM, Dirk J, Marsiske M, Criggs JG. Sleep and affect in older adults: using multilevel modeling to examine daily associations. *J Sleep Res* 2008;17(1):42–53. <https://doi.org/10.1111/j.1365-2869.2008.00621.x>.
- [48] Fortier-Brochu É, Beaulieu-Bonneau S, Ivers H, Morin CM. Insomnia and daytime cognitive performance: a meta-analysis. *Sleep Med Rev* 2012;16(1):83–94. <https://doi.org/10.1016/j.smrv.2011.03.008>.
- [49] Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. *J Psychiatr Res* 2003;37(1):9–15. [https://doi.org/10.1016/S0022-3956\(02\)00052-3](https://doi.org/10.1016/S0022-3956(02)00052-3).
- [50] Perlis ML, Giles DE, Buysse DJ, Tu X, Kupfer DJ. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. *J Affect Disord* 1997;42(2–3):209–12. [https://doi.org/10.1016/s0165-0327\(96\)01411-5](https://doi.org/10.1016/s0165-0327(96)01411-5).
- [51] Baglioni C, Battagliere G, Feige B, Spiegelhalder K, Nissen C, Ulrich V, Lombardo C, Riemann D. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord* 2011;135(1–3):10–9. <https://doi.org/10.1016/j.jad.2011.01.011>.
- [52] Li L, Wu C, Gan Y, Qu X, Lu Z. Insomnia and the risk of depression: a meta-analysis of prospective cohort studies. *BMC Psychiatry* 2016;16(1). <https://doi.org/10.1186/s12888-016-1075-3>.
- [53] Johnson EO, Roth T, Breslau N. The association of insomnia with anxiety disorders and depression: exploration of the direction of risk. *J Psychiatr Res* 2006;40(8):700–8. <https://doi.org/10.1016/j.jpsychires.2006.07.008>.
- [54] Gulec M, Selvi Y, Boysan M, Aydin A, Besiroglu L, Yucel Agargun M. Ongoing or re-emerging subjective insomnia symptoms after full/partial remission or recovery of major depressive disorder mainly with the selective serotonin reuptake inhibitors and risk of relapse or recurrence: a 52-week follow-up study. *J Affect Disord* 2011;134(1–3):257–65. <https://doi.org/10.1016/j.jad.2011.05.056>.
- [55] Dombrovski AY, Cyranowski JM, Mulsant BH, Houck PR, Buysse DJ, Andreescu C, Thase ME, Mallinger AG, Frank E. Which symptoms predict recurrence of depression in women treated with maintenance interpersonal psychotherapy? *Depress Anxiety* 2008;25(12):1060–6. <https://doi.org/10.1002/da.20467>.

- [56] Pigeon WR, Perlis ML. Insomnia and depression: birds of a feather. *Int J Sleep Disord* 2007;1(3):82–91.
- [57] Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatr* 2012;73(9):e1160. <https://doi.org/10.4088/JCP.11r07586>.
- [58] Chakravorty S, Katy Siu HY, Lalley-Chareczko L, Brown GK, Findley JC, Perlis ML, Grandner MA. Sleep duration and insomnia symptoms as risk factors for suicidal ideation in a nationally representative sample. *Prim Care Companion J Clin Psychiatry* 2015;17(6):402–22. <https://doi.org/10.4088/PCC.13m01551>.
- [59] Wojnar M, Ilgen MA, Wojnar J, McCammon RJ, Valenstein M, Brower KJ. Sleep problems and suicidality in the national comorbidity survey replication. *J Psychiatr Res* 2009;43(5):526–31. <https://doi.org/10.1016/j.jpsychires.2008.07.006>.
- [60] McCall WV, Black CG. The link between suicide and insomnia: theoretical mechanisms. *Curr Psychiatry Rep* 2013;15(9). <https://doi.org/10.1007/s11920-013-0389-9>.
- [61] Woosley JA, Lichstein KL, Taylor DJ, Riedel BW, Bush AJ. Hopelessness mediates the relation between insomnia and suicidal ideation. *J Clin Sleep Med* 2014;10(11):1223–30. <https://doi.org/10.5664/jcsm.4208>.
- [62] Perlis ML, Grandner MA, Brown GK, Basner M, Chakravorty S, Morales KH, Gehrman PR, Chaudhary NS, Thase ME, Dinges DF. Nocturnal wakefulness as a previously unrecognized risk factor for suicide. *J Clin Psychiatr* 2016;77(6):e726. <https://doi.org/10.4088/JCP.15m10131>.
- [63] Perlis ML, Grandner MA, Chakravorty S, Bernert RA, Brown GK, Thase ME. Suicide and sleep: is it a bad thing to be awake when reason sleeps? *Sleep Med Rev* 2016;29:101–7. <https://doi.org/10.1016/j.smrv.2015.10.003>.
- [64] Blatter K, Cajochen C. Circadian rhythms in cognitive performance: methodological constraints, protocols, theoretical underpinnings. *Physiol Behav* 2007;90(2–3):196–208. <https://doi.org/10.1016/j.physbeh.2006.09.009>.
- [65] Schmidt C, Collette F, Cajochen C, Peigneux P. A time to think: circadian rhythms in human cognition. *Cogn Neuropsychol* 2007;24(7):755–89. <https://doi.org/10.1080/02643290701754158>.
- [66] Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatr* 1995;34(4):454–63. <https://doi.org/10.1097/00004583-199504000-00012>.
- [67] Hudson JI, Lipinski JF, Keck PE, Aizley HG, Lukas SE, Rothschild AJ, Waternaux CM, Kupfer DJ. Polysomnographic characteristics of young manic patients: comparison with unipolar depressed patients and normal control subjects. *Arch Gen Psychiatry* 1992;49(5):378–83. <https://doi.org/10.1001/archpsyc.1992.01820050042006>.
- [68] Peterson MJ, Rumble ME, Benca RM. Insomnia and psychiatric disorders. *Psychiatr Ann* 2008;38(9):597–605. <https://doi.org/10.3928/00485713-20080901-07>.
- [69] Harvey AG, Mullin BC, Hinshaw SP. Sleep and circadian rhythms in children and adolescents with bipolar disorder. *Dev Psychopathol* 2006;18(4):1147–68. <https://doi.org/10.1017/S095457940606055X>.
- [70] Eidelman P, Talbot LS, Gruber J, Harvey AG. Sleep, illness course, and concurrent symptoms in inter-episode bipolar disorder. *J Behav Ther Exp Psychiatr* 2010;41(2):145–9. <https://doi.org/10.1016/j.jbtexp.2009.11.007>.
- [71] Talbot LS, Stone S, Gruber J, Hairston IS, Eidelman P, Harvey AG. A test of the bidirectional association between sleep and mood in bipolar disorder and insomnia. *J Abnorm Psychol* 2012;121(1):39–50. <https://doi.org/10.1037/a0024946>.
- [72] Artioli P, Lorenzi C, Pirovano A, Serretti A, Benedetti F, Catalano M, Smeraldi E. How do genes exert their role? Period 3 gene variants and possible influences on mood disorder phenotypes. *Eur Neuropsychopharmacol* 2007;17(9):587–94. <https://doi.org/10.1016/j.euroneuro.2007.03.004>.
- [73] Benedetti F, Dallaspezia S, Cigala Fulgosi M, Lorenzi C, Serretti A, Barbini B, Colombo C, Smeraldi E. Actimetric evidence that CLOCK 3111 T/C SNP influences sleep and activity patterns in patients affected by bipolar depression. *Am J Med Genet B Neuropsychiatric Genetics* 2007;144B(5):631–5. <https://doi.org/10.1002/ajmg.b.30475>.
- [74] Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. *Am Psychol* 2000;55(11):1247–63. <https://doi.org/10.1037/0003-066X.55.11.1247>.
- [75] Mellman TA. Sleep and anxiety disorders. *Sleep Med Clin* 2008;3(2):261–8. <https://doi.org/10.1016/j.jsmc.2008.01.010>.
- [76] Jansson-Fröjmark M, Lindblom K. A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. *J Psychosom Res* 2008;64(4):443–9. <https://doi.org/10.1016/j.jpsychores.2007.10.016>.
- [77] Glidewell RN, McPherson Botts E, Orr WC. Insomnia and anxiety: diagnostic and management implications of complex interactions. *Sleep Med Clin* 2015;10(1):93–9. <https://doi.org/10.1016/j.jsmc.2014.11.008>.
- [78] Uhde TW, Cortese BM, Vedeniapin A. Anxiety and sleep problems: emerging concepts and theoretical treatment implications. *Curr Psychiatr Rep* 2009;11(4):269–76. <https://doi.org/10.1007/s11920-009-0039-4>.
- [79] Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DF, Delucchi KL, Wu RM, Schoenfeld FB. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam Veterans. *Am J Psychiatr* 1998;155(7):929–33. <https://doi.org/10.1176/ajp.155.7.929>.
- [80] Ohayon MM, Shapiro CM. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Compr Psychiatr* 2000;41(6):469–78. <https://doi.org/10.1053/comp.2000.16568>.
- [81] Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the Hallmark of posttraumatic stress disorder. *Am J Psychiatr* 1989;146(6):697–707. <https://doi.org/10.1176/ajp.146.6.697>.
- [82] Lamarche LJ, De Koninck J. Sleep disturbance in adults with posttraumatic stress disorder: a review. *J Clin Psychiatr* 2007;68(8):1257–70. <https://doi.org/10.4088/jcp.v68n0813>.
- [83] McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in U.S. service members returning from military deployments. *Mil Med* 2010;175(10):759–62. <https://doi.org/10.7205/MILMED-D-10-00193>.
- [84] Lavie P. Sleep disturbances in the wake of traumatic events. *N Engl J Med* 2001;345(25):1825–32. <https://doi.org/10.1056/nejmra012893>.
- [85] Koren D, Arnon I, Lavie P, Klein E. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. *Am J*

- Psychiatr 2002;159(5):855–7. <https://doi.org/10.1176/appi.ajp.159.5.855>.
- [86] Krakow B, Melendrez D, Pedersen B, Johnston L, Hollifield M, Germain A, Koss M, Warner TD, Schrader R. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. Biol Psychiatry 2001;49 (11):948–53. [https://doi.org/10.1016/s0006-3223\(00\)01087-8](https://doi.org/10.1016/s0006-3223(00)01087-8).
- [87] Margolies SO, Rybarczyk B, Vrana SR, Leszczyszyn DJ, Lynch J. Efficacy of a cognitive-behavioral treatment for insomnia and nightmares in Afghanistan and Iraq veterans with PTSD. J Clin Psychol 2013;69(10):1026–42. <https://doi.org/10.1002/jclp.21970>.
- [88] Ulmer CS, Edinger JD, Calhoun PS. A multi-component cognitive-behavioral intervention for sleep disturbance in Veterans with PTSD: a pilot study. J Clin Sleep Med 2011;7(1):57–68. <https://doi.org/10.5664/jcsm.28042>.
- [89] Green MM, McFarlane AC, Hunter CE, Griggs WM. Undiagnosed post-traumatic stress disorder following motor vehicle accidents. Med J Aust 1993;159(8):529–34. <https://doi.org/10.5694/j.1326-5377.1993.tb138006.x>.
- [90] Cox RC, Alex McIntyre W, Olatunji BO. Interactive effects of insomnia symptoms and trauma exposure on PTSD: Examination of symptom specificity. Psychol Trauma 2018;10(5):508–14. <https://doi.org/10.1037/tra0000336>.
- [91] Pigeon WR, Campbell CE, Possemato K, Ouimette P. Longitudinal relationships of insomnia, nightmares, and PTSD severity in recent combat veterans. J Psychosom Res 2013;75(6):546–50. <https://doi.org/10.1016/j.jpsychores.2013.09.004>.
- [92] Mellman TA, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. Biol Psychiatry 1995;38(3):174–9. [https://doi.org/10.1016/0006-3223\(94\)00238-x](https://doi.org/10.1016/0006-3223(94)00238-x).
- [93] Hendrickson RC, Raskind MA. Noradrenergic dysregulation in the pathophysiology of PTSD. Exp Neurol 2016;284:181–95. <https://doi.org/10.1016/j.expneuro.2016.05.014>.
- [94] Inman DJ, Silver SM, Doghramji K. Sleep disturbance in post-traumatic stress disorder: a comparison with non-PTSD insomnia. J Trauma Stress 1990;3(3):429–37. <https://doi.org/10.1002/jts.2490030311>.
- [95] Dow BM, Kelsoe JR, Gillin JC. Sleep and dreams in Vietnam PTSD and depression. Biol Psychiatr 1996;39(1):42–50. [https://doi.org/10.1016/0006-3223\(95\)00103-4](https://doi.org/10.1016/0006-3223(95)00103-4).
- [96] Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D. Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. J Clin Psychol 2011;67 (12):1240–58. <https://doi.org/10.1002/jclp.20845>.
- [97] Brod M, Schmitt E, Goodwin M, Hodgkins P, Niebler G. ADHD burden of illness in older adults: a life course perspective. Qual Life Res 2012;21(5):795–9. <https://doi.org/10.1007/s11136-011-9981-9>.
- [98] Kessler RC, Adler L, Berkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Seznik K, Spencer T, Ustun TB, Walters EE, Zaslavsky AM. The prevalence and correlates of adult ADHD in the United States: results from the national comorbidity Survey replication. Am J Psychiatr 2006;163 (4):716–23. <https://doi.org/10.1176/ajp.2006.163.4.716>.
- [99] Brevik EJ, Lundervold AJ, Halmøy A, Posserud M-B, Instanes JT, Bjorvatn B, Haavik J. Prevalence and clinical correlates of insomnia in adults with attention-deficit hyperactivity disorder. Acta Psychiatr Scand 2017;136(2):220–7. <https://doi.org/10.1111/acps.12756>.
- [100] Corkum P, Harvey M, Hogg-Johnson S, Humphries T, Tannock R. Sleep problems in children with attention-deficit/hyperactivity disorder: impact of subtype, comorbidity, and stimulant medication. J Am Acad Child Adolesc Psychiatr 1999;38(10):1285–93. <https://doi.org/10.1097/00004583-199910000-00018>.
- [101] Kooij JJS, Aeckerlin LP, Buitelaar JK. Functioning, comorbidity and treatment of 141 adults with attention deficit hyperactivity disorder (ADHD) at a Psychiatric Outpatients' Department. Ned Tijdschr Geneeskd 2001;145(31):1498–501.
- [102] Boonstra AM, Kooij JJS, Oosterlaan J, Sergeant JA, Buitelaar JK, Van Someren EJW. Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. Sleep 2007;30(4):433–42. <https://doi.org/10.1093/sleep/30.4.433>.
- [103] Barrett JR, Tracy DK, Giaroli G. To sleep or not to sleep: a systematic review of the literature of pharmacological treatments of insomnia in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2013;23 (10):640–7. <https://doi.org/10.1089/cap.2013.0059>.
- [104] Giblin JM, Strobel AL. Effect of lisdexamfetamine dimesylate on sleep in children with ADHD. J Atten Disord 2011;15(6):491–8. <https://doi.org/10.1177/1087054710371195>.
- [105] Huang Y-S, Tsai M-H. Long-term outcomes with medications for attention-deficit hyperactivity disorder. CNS Drugs 2011;25 (7):539–54. <https://doi.org/10.2165/11589380-000000000-00000>.
- [106] Van Veen MM, Kooij JJS, Boonstra AM, Gordijn MCM, Van Someren EJW. Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. Biol Psychiatry 2010;67(11):1091–6. <https://doi.org/10.1016/j.biopsych.2009.12.032>.
- [107] Stein MD, Friedmann PD. Disturbed sleep and its relationship to alcohol use. Subst Abuse 2005;26(1):1–13. https://doi.org/10.1300/J465v26n01_01.
- [108] Brower KJ. Insomnia, alcoholism and relapse. Sleep Med Rev 2003;7(6):523–39. [https://doi.org/10.1016/S1087-0792\(03\)90005-0](https://doi.org/10.1016/S1087-0792(03)90005-0).
- [109] Brower KJ, Aldrich MS, Robinson EAR, Zucker RA, Greden JF. Insomnia, self-medication, and relapse to alcoholism. Am J Psychiatr 2001;158(3):399–404. <https://doi.org/10.1176/appi.ajp.158.3.399>.
- [110] Janson C, Lindberg E, Gislason T, Ahmed E, Boman G. Insomnia in men—a 10-year prospective population based study. Sleep 2001;24(4):425–30. <https://doi.org/10.1093/sleep/24.4.425>.
- [111] Brower KJ. Alcohol's effects on sleep in alcoholics. Alcohol Res Health 2001;25(2):110–25.
- [112] Kaleta Stoller M. Economic effects of insomnia. Clin Ther 1994;16(5):873–97.
- [113] Israel A-, Roth T. Characteristics of insomnia in the United States: results of the 1991. National sleep foundation Survey. I. Sleep 1991;22:347–53.
- [114] Johnson EO, Roehrs T, Roth T, Breslau N. Epidemiology of medication as aids to alertness in early adulthood. Sleep 1999;22 (4):485–8. <https://doi.org/10.1093/sleep/22.4.485>.
- [115] Reynolds AM, Malow BA. Sleep and autism spectrum disorders. Pediatr Clin 2011;58(3):685–98. <https://doi.org/10.1016/j.pcl.2011.03.009>.

- [116] Richdale AL, Baker E, Short M, Gradisar M. The role of insomnia, pre-sleep arousal and psychopathology symptoms in daytime impairment in adolescents with high-functioning autism spectrum disorder. *Sleep Med* 2014;15(9):1082–8. <https://doi.org/10.1016/j.sleep.2014.05.005>.
- [117] Souders MC, Mason TBA, Valladares O, Bucan M, Levy SE, Mandell DS, Weaver TE, Pinto-Martin J. Sleep behaviors and sleep quality in children with autism spectrum disorders. *Sleep* 2009;32(12):1566–78. <https://doi.org/10.1093/sleep/32.12.1566>.
- [118] Krakowiak P, Goodlin-Jones B, Hertz-Pannier I, Croen LA, Hansen RL. Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: a population-based study. *J Sleep Res* 2008;17(2):197–206. <https://doi.org/10.1111/j.1365-2869.2008.00650.x>.
- [119] Richdale AL. Sleep problems in autism: prevalence, cause, and intervention. *Dev Med Child Neurol* 1999;41(1):60–6. <https://doi.org/10.1017/S0012162299000122>.
- [120] Patzold L, Richdale AL, Tonge B. An investigation into sleep characteristics of children with autism and Asperger's Disorder. *J Paediatr Child Health* 2002;34(6):528–33. <https://doi.org/10.1046/j.1440-1754.1998.00291.x>.
- [121] Levitt P, Eagleson KL, Powell EM. Regulation of neocortical interneuron development and the implications for neurodevelopmental disorders. *Trends Neurosci* 2004;27(7):400–6. <https://doi.org/10.1016/j.tins.2004.05.008>.
- [122] McCauley JL, Olson LM, Delahanty R, Amin T, Nurmi EL, Organ EL, Jacobs MM, Folstein SE, Haines JL, Sutcliffe JS. A linkage disequilibrium map of the 1-Mb 15q12 GABA A receptor subunit cluster and association to autism. *Am J Med Genet* 2004;131B(1):51–9. <https://doi.org/10.1002/ajmg.b.30038>.
- [123] Lin-Dyken DC, Eric Dyken M. Use of melatonin in young children for sleep disorders. *Infants Young Child* 2002;15(2):20–37. <https://doi.org/10.1097/00001163-200210000-00005>.
- [124] Rapin I, Katzman R. Neurobiology of autism. *Ann Neurol* 1998;43(1):7–14. <https://doi.org/10.1002/ana.410430106>.
- [125] Kotagal S, Broomall E. Sleep in children with autism spectrum disorder. *Pediatr Neurol* 2012;47(4):242–51. <https://doi.org/10.1016/j.pediatrneurol.2012.05.007>.
- [126] Honomichl RD, Goodlin-Jones BL, Burnham M, Gaylor E, Anders TF. Sleep patterns of children with pervasive developmental disorders. *J Autism Dev Disord* 2002;32(6):553–61. <https://doi.org/10.1023/A:1021254914276>.
- [127] Schreck KA, Mulick JA, Smith AF. Sleep problems as possible predictors of intensified symptoms of autism. *Res Dev Disabil* 2004;25(1):57–66. <https://doi.org/10.1016/j.ridd.2003.04.007>.
- [128] Monti JM, Monti D. Sleep disturbance in schizophrenia. *Int Rev Psychiatr* 2005;17(4):247–53. <https://doi.org/10.1080/095426050104516>.
- [129] Palmese LB, DeGeorge PC, Ratliff JC, Srihari VH, Wexler BE, Krystal AD, Tek C. Insomnia is frequent in schizophrenia and associated with night eating and obesity. *Schizophr Res* 2011;133(1–3):238–43. <https://doi.org/10.1016/j.schres.2011.07.030>.
- [130] Xiang YT, Weng YZ, Leung CM, Tang WK, Lai KYC, Ungvari GS. Prevalence and correlates of insomnia and its impact on quality of life in Chinese schizophrenia patients. *Sleep* 2009;32(1):105–9.
- [131] Freeman D, Pugh K, Vorontsova N, Southgate L. Insomnia and paranoia. *Schizophr Res* 2009;108(1–3):280–4. <https://doi.org/10.1016/j.schres.2008.12.001>.
- [132] Afonso P, Brissos S, Luísa Figueira M, Paiva T. Schizophrenia patients with predominantly positive symptoms have more disturbed sleep-wake cycles measured by actigraphy. *Psychiatry Res* 2011;189(1):62–6. <https://doi.org/10.1016/j.psychres.2010.12.031>.
- [133] Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. *Arch Gen Psychiatry* 1992;49(8):651–68. <https://doi.org/10.1001/archpsyc.1992.01820080059010>.
- [134] Haffmans PM, Hoencamp E, Knegtering HJ, van Heycop ten Ham BF. Sleep disturbance in schizophrenia. *Br J Psychiatr Mental Sci* 1994;165(5):697–8. <https://doi.org/10.1192/bj.p.165.5.697b>.
- [135] Chouinard S, Poulin J, Stip E, Godbout R. Sleep in untreated patients with schizophrenia: a meta-analysis. *Schizophr Bull* 2004;30(4):957–67. <https://doi.org/10.1093/oxfordjournals.schbul.a007145>.
- [136] Ritsner M, Kurs R, Ponizovsky A, Hadjez J. Perceived quality of life in schizophrenia: relationships to sleep quality. *Qual Life Res* 2004;13(4):783–91. <https://doi.org/10.1023/B:QURE.0000021687.18783.d6>.
- [137] Herz MI, Melville C. Relapse in schizophrenia. *Am J Psychiatr* 1980;137(7):801–5. <https://doi.org/10.1176/ajp.137.7.801>.
- [138] Chemerinski E, Ho BC, Flaum M, Arndt S, Fleming F, Andreasen NC. Insomnia as a predictor for symptom worsening following antipsychotic withdrawal in schizophrenia. *Compr Psychiatry* 2002;43(5):393–6. <https://doi.org/10.1053/comp.2002.34627>.
- [139] Kumar PNS, Andrade C, Bhakta SG, Singh NM. Melatonin in schizophrenic outpatients with insomnia: a double-blind, placebo-controlled study. *J Clin Psychiatr* 2007;68(2):237–41. <https://doi.org/10.4088/JCP.v68n0208>.
- [140] Morin CM. Cognitive-behavioral approaches to the treatment of insomnia. *J Clin Psychiatr* 2004;65(16):33–40.
- [141] Perlis ML, Jungquist CB, Smith MT, Posner DA. Cognitive behavioral treatment of insomnia. Springer Science+Business Media, Inc; 2005. p. 1–182.
- [142] Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Barry MJ, Boyd C, Chow RD, Fitterman N, Harris RP, Humphrey LL, Manaker S, McLean R, Mir TP, Schünemann HJ, Vijan S, Wilt T. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American college of physicians. *Ann Intern Med* 2016;165(2):125–33. <https://doi.org/10.7326/M15-2175>.
- [143] Wu JQ, Appleman ER, Salazar RD, Ong JC. Cognitive behavioral therapy for insomnia comorbid with psychiatric and medical conditions a meta-analysis. *JAMA Intern Med* 2015;175(9):1461–72. <https://doi.org/10.1001/jamainternmed.2015.3006>.
- [144] Manber R, Buysse DJ, Edinger J, Krystal A, Luther JF, Wisniewski SR, Trockel M, Kraemer HC, Thase ME. Efficacy of cognitive-behavioral therapy for insomnia combined with antidepressant pharmacotherapy in patients with comorbid depression and insomnia: a randomized controlled trial. *J Clin Psychiatr* 2016;77(10):e1316–23. <https://doi.org/10.4088/JCP.15m10244>.
- [145] Carney CE, Edinger JD, Kuchibhatla M, Lachowski AM, Bogouslavsky O, Krystal AD, Shapiro CM. Cognitive behavioral insomnia therapy for those with insomnia and depression: a randomized controlled clinical trial. *Sleep* 2017;40(4). <https://doi.org/10.1093/sleep/zsx019>.

- [146] Belleville G, Cousineau H, Levrier K, St-Pierre-Delorme M-È. Meta-analytic review of the impact of cognitive-behavior therapy for insomnia on concomitant anxiety. *Clin Psychol Rev* 2011;31(4):638–52. <https://doi.org/10.1016/j.cpr.2011.02.004>.
- [147] Talbot LS, Maguen S, Metzler TJ, Schmitz M, McCaslin SE, Richards A, Perlis ML, Posner DA, Weiss B, Ruoff L, Varbel J, Neylan TC. Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: a randomized controlled trial. *Sleep* 2014;37(2):327–41. <https://doi.org/10.5665/sleep.3408>.
- [148] Joober R, Cole K, Tabbane K, Boivin DB. An algorithmic approach to the management of insomnia in patients with schizophrenia. *Ann Clin Psychiatr* 2017;29(2):133–44.
- [149] Freeman D, Dunn G, Startup H, Pugh K, Cordwell J, Mander H, Černis E, Wingham G, Shirvell K, Kingdon D. Effects of cognitive behaviour therapy for worry on persecutory delusions in patients with psychosis (WIT): a parallel, single-blind, randomised controlled trial with a mediation analysis. *Lancet Psychiatr* 2015;2(4):305–13. [https://doi.org/10.1016/s2215-0366\(15\)00039-5](https://doi.org/10.1016/s2215-0366(15)00039-5).
- [150] Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatr Res* 1999;86(3):267–70. [https://doi.org/10.1016/s0165-1781\(99\)00036-0](https://doi.org/10.1016/s0165-1781(99)00036-0).
- [151] Harvey AG, Soehner AM, Kaplan KA, Hein K, Lee J, Kanady J, Li D, Rabe-Hesketh S, Ketter TA, Neylan TC, Buysse DJ. Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. *J Consult Clin Psychol* 2015;83(3):564–77. <https://doi.org/10.1037/a0038655>.

Chapter 34

Insomnia and cardiometabolic disease risk

Julio Fernandez-Mendoza^{a, b, c} and Casandra C. Nyhuis^b

^aPenn State Health Sleep Research & Treatment Center, Behavioral Sleep Medicine Program, Hershey, PA, United States; ^bPenn State College of Medicine, Hershey, PA, United States; ^cDepartment of Psychiatry and Behavioral Health, Penn State College of Medicine, Hershey, PA, United States

Abbreviations

BMI	Body mass index
BP	Blood pressure
CBVD	Cerebrovascular disease
CHD	Coronary heart disease
CMR	Cardiometabolic risk factors
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
HRV	Heart rate variability
HTN	Hypertension
IL-6	Interleukin 6
MetS	Metabolic syndrome
MI	Myocardial infarction
MSLT	Multiple sleep latency test
PSG	Polysomnography
SAM	Sympatho-adrenal-medullary
SBP	Systolic blood pressure
SDB	Sleep-disordered breathing
T2D	Type 2 diabetes
TNF- α	Tumor necrosis factor alpha

Introduction

Insomnia has been traditionally viewed either as a symptom of underlying medical or psychiatric disorders or as a symptom of “otherwise healthy but worried” individuals. However, accumulating evidence indicates that insomnia, particularly when chronic and coupled with objective short sleep duration, is associated with cardiometabolic risk factors (CMR) such as hypertension (HTN) and type 2 diabetes (T2D) and increased risk of cardiovascular disease (CVD) and cerebrovascular disease (CBVD) morbidity and mortality. We will review

herein the evidence linking insomnia with these cardiometabolic disease outcomes as well as with the pathophysiological mechanisms (e.g., stress system activation, cardiac autonomic dysregulation, and chronic low-grade inflammation) and poor health behaviors (e.g., smoking and physical inactivity) that potentially mediate such increased risk. Finally, we will discuss the public health and clinical implications of these associations, including the need for efficacy and population-level interventions testing whether insomnia therapies improve clinical and subclinical biomarkers of cardiometabolic disease risk.

Insomnia: A symptom and a chronic disorder

Insomnia, the most common sleep disorder, exceeds sleep-disordered breathing (SDB) in terms of prevalence and poses a major public health problem. Approximately 20%–40% of people from the general population report insomnia symptoms and another 8%–15% fulfill criteria for a chronic insomnia disorder. Insomnia symptoms consist of self-reported difficulties initiating sleep, difficulties maintaining sleep or difficulties waking up too early and being unable to resume sleep (i.e., early morning awakening) without any chronicity or daytime impairment criteria [1,2]. A self-report of nonrestorative sleep has traditionally been included in experimental and epidemiological studies as a core insomnia symptom [1,2]; however, it was dropped in diagnostic nomenclature in 2014 [3]. Diagnostic criteria for chronic insomnia disorder include the self-report of at least one insomnia symptom, occurring at least three nights per week despite adequate circumstances and opportunity for sleep, for at least 3 months, and that is associated with significant daytime functioning impairment [3]. Both insomnia symptoms and

chronic insomnia disorder are associated with impaired quality of life and are well-established correlates and risk factors of mental health problems, such as depression, anxiety, and other psychiatric disorders (see Chapter 40). Natural history studies have shown that insomnia disorder is indeed a highly chronic condition with a remission rate as low as 25%, whereas the course of insomnia symptoms is characterized by a waxing-and-waning pattern with high remission rates (about 50%) [4–8]. These longitudinal, epidemiological data have supported that chronic insomnia is a disorder in its own right, whereas insomnia symptoms may occur in relation to the course of an underlying physical or mental health disorder, including depression, pain, or SDB [4–6,8]. As reviewed below, not many of the existing large, population-based studies have been able to examine these two mutually exclusive categories of insomnia symptoms and chronic

insomnia disorder separately. This distinction, however, is critical in population science and clinical practice (Table 34.1).

Another important issue unique to insomnia diagnosis is the absence of objective and/or quantitative criteria. Insomnia symptoms are, by definition, subjective complaints and, thus, chronic insomnia disorder is a diagnosis reached solely based on self-reports. While there are guiding thresholds to help define what is a clinically significant difficulty initiating or resuming sleep (>30 min), these quantitative criteria (Table 34.1) are not used alone to identify chronic insomnia disorder if there are no subjective complaints [3]. Furthermore, neither polysomnography (PSG) or actigraphy (ACT) are required for the diagnosis of chronic insomnia [3] despite PSG or ACT measured objective sleep of people with chronic insomnia

TABLE 34.1 Most frequent definitions used in insomnia studies.

Domain	Criteria	Method of measurement
Self-reported		
Sleep difficulties	Difficulty initiating sleep Difficulty maintaining sleep Early morning awakening Nonrestorative sleep	Retrospective questionnaire
Insomnia symptoms	At least one sleep difficulty Usually based on severity (moderate-to-severe) and/or frequency (≥ 3 nights per week)	Retrospective questionnaire
Chronic insomnia	Duration (≥ 3 months)	Retrospective questionnaire
Chronic insomnia disorder	ICD/DSM/ICSD (frequency, duration, daytime impairment and adequate sleep opportunities)	Retrospective questionnaire, clinical interview
Nighttime sleep continuity	Sleep onset latency (≥ 30 min) Wake after sleep onset (≥ 30 min) Total sleep time (< 7 or 6 h) Sleep efficiency ($< 85\%$)	Retrospective questionnaire, clinical interview or prospective sleep diary
Objective		
Nighttime sleep continuity	Sleep onset latency (≥ 30 min) Wake after sleep onset (≥ 30 min) Total sleep time (< 7 or 6 h) Sleep efficiency ($< 85\%$)	In-laboratory PSG, at-home PSG or at-home ACT
Daytime sleep propensity	Daytime sleep latency (> 14 min)	In-laboratory MSLT
Combined/phenotype		
Self-reported + self-reported	Insomnia symptoms + total sleep time Insomnia disorder + total sleep time	Retrospective questionnaires Retrospective questionnaire + sleep diary
Self-reported + objective	Insomnia symptoms + total sleep time Chronic insomnia + total sleep time Insomnia disorder + total sleep time Insomnia disorder + sleep efficiency Insomnia disorder + total sleep time Insomnia disorder + daytime sleep latency	Retrospective questionnaire + PSG Retrospective questionnaire + PSG Clinical interview + PSG Clinical interview + PSG Clinical interview + ACT Clinical interview + MSLT

ACT, actigraphy; *DSM*, diagnostic and statistical manual of mental disorders; *ICD*, international classification of disease; *ICSD*, international classification of sleep disorders; *MSLT*, multiple sleep latency test; *PSG*, polysomnography.

being significantly impaired compared with good sleepers [3], and that measurements of objective short sleep duration are a good predictor of the persistent course of insomnia disorder [8] and of who among those with insomnia symptoms are at risk of developing a chronic insomnia disorder [6]. This is in sharp contrast with the current use of PSG data for the evaluation of patients at risk of SDB (e.g., obese snorers), to establish the severity of SDB (e.g., apnea/hypopnea index [AHI], hypoxemia), and to predict its associated risk of CVD and CBVD [3]. More importantly, the association of insomnia, as measured by self-reports or objectively, with specific CMR, CVD, or CBVD (Table 34.2) remained largely ignored during several decades [9].

Hypertension and blood pressure

Since the 1970s, clinical studies had observed a high comorbidity of insomnia with clinical HTN, based on patient's clinical history [10]. However, the association of insomnia with clinical and subclinical measures of elevated blood pressure (BP) or BP dysregulation remained largely unexplored in favor of mental health comorbidities (see Chapter 40). In the past two decades, there has been a renewed interest and multiple studies, including several reviews [9,11–14] and two meta-analyses [15,16], have been published on the association of insomnia with HTN. Population-based studies using self-reported data have shown a significant relationship between insomnia, either defined as a symptom or as a disorder, and HTN [16–32]. As shown in Table 34.3, the most recent meta-analysis was performed by Li et al. [15] on findings from 14 large longitudinal studies comprising a total of 395,641 subjects, estimating that the risk of incident HTN associated with insomnia ranges between 14% and 27%. Prior to this meta-analysis, most studies that have examined the association of insomnia with HTN have primarily relied on self-reported insomnia symptoms [21–25,29], a couple on insomnia symptoms associated with impaired daytime functioning [26,27], and only three using insomnia disorder criteria [28,30,31]. In addition, these studies used either self-reported data on HTN as a current medical problem or antihypertensive medication use as well as prehypertensive (SBP \geq 130 mmHg or DDP \geq 85 mmHg) or hypertensive BP levels (SBP \geq 140 mmHg or DBP \geq 90 mmHg) and most of these studies did not include a PSG study and were, thus, unable to control for the presence of SDB. This is a significant caveat in these studies as SDB has long been associated with HTN (see Chapter 45). To add to this, one cross-sectional study from Norway (HUNT-3; N = 50,806) has shown that insomnia symptoms were associated with lower SBP or DBP levels [25]. Taken together, the degree of association found in previous reviews [9,11–14] and meta-analyses [15,16] have been regarded as preliminary.

Many of the caveats mentioned above were addressed by the work with the Penn State Adult Cohort (PSAC) conducted almost 10 years ago. These studies showed a synergistic effect between insomnia and PSG-measured short sleep duration (i.e., <6 h of sleep) on the risk of HTN, while adjusting for the potential effect of multiple demographic, lifestyle, and clinical factors, including SDB, T2D, smoking, alcohol or depression [17,18]. In the first study, Vgontzas et al. [17] showed that individuals with chronic insomnia who slept objectively between 5 and 6 h and those with chronic insomnia who slept <5 h were 3.5-fold and 5.1-fold times more likely to have HTN (defined as SBP \geq 140 mmHg or DBP \geq 90 mmHg and/or antihypertensive medication use), respectively, as compared to good sleepers. A similar but smaller association with prevalent HTN was found in individuals with insomnia symptoms who also slept objectively <6 h (OR = 1.5 if sleeping 5–6 h and OR = 2.4 if sleeping <5 h) [17]. In contrast, individuals with insomnia symptoms or chronic insomnia who slept objectively >6 h were not significantly associated with increased odds of prevalent HTN (OR = 0.8 and OR = 1.3, respectively) [17]. In a follow-up study of the PSAC, Fernandez-Mendoza et al. showed that, compared with good sleepers, individuals with chronic insomnia who slept <6 h were 3.8 times more likely to develop HTN after 7.5 years of follow-up (defined as a report of being treated for HTN adjusted for prehypertensive and hypertensive BP levels at baseline) [18]. Similarly to the cross-sectional study above [17], individuals with insomnia symptoms or chronic insomnia who slept objectively >6 h were not significantly associated with increased odds of incident HTN (OR = 0.50 and OR = 0.85, respectively) [18]. The findings of these seminal studies are included in Table 34.4.

Following these studies, several other studies have cemented the significance of short sleep duration in the association of insomnia with HTN, while the smaller effect sizes in some of these more recent studies can be explained by the use of subjective instead of objective sleep measures [19,29–31,65,67,69,70,73–76]. The findings of other studies using objective sleep measures are summarized in Table 34.4. Specifically, in a well-characterized sample of adults with chronic insomnia disorder (N = 255), Bathgate et al. [31] used average total sleep time across two consecutive nights of PSG to classify individuals with chronic insomnia disorder into those who slept objectively <6 h and >6 h. After controlling for numerous potential confounders, including SDB, T2D, hypercholesterolemia, or depression, adults with chronic insomnia disorder who slept objectively <6 h were 3.6 times more likely to have HTN (defined as a report of HTN as a current problem) than those with chronic insomnia disorder who slept >6 h. Interestingly, Bathgate et al. [31] did not observe a significant association with prevalent HTN using short sleep duration (<6 h) derived from self-reported 2-week sleep diaries (OR = 1.13).

TABLE 34.2 Most frequent cardiometabolic disease risk outcomes used in insomnia studies.

Domain	Criteria	Method of measurement
Self-reported		
Hypertension	Use of antihypertensive medication Treatment for high blood pressure Medical history of hypertension	Retrospective questionnaire or clinical interview
Type 2 diabetes	Use of insulin medication Treatment for type 2 diabetes Medical history of type 2 diabetes	Retrospective questionnaire or clinical interview
Cardiovascular disease	Treatment for heart disease Medical history of heart disease (myocardial infarction, coronary heart disease, heart failure)	Retrospective questionnaire or clinical interview
Cerebrovascular disease	Treatment for stroke Medical history of stroke	Retrospective questionnaire or clinical interview
Objective		
High blood pressure	Systolic (≥ 130 or 140 mmHg) Diastolic (≥ 80 , 85 or 90 mmHg) Mean arterial pressure	In-laboratory or at-home automatic blood pressure monitoring
Blood pressure regulation	Blood pressure dipping (day-to-night) Nighttime blood pressure (sleep stage-related) Blood pressure reactivity (stress test)	In-laboratory automatic blood pressure monitoring
Metabolic regulation	Fasting glucose levels (≥ 100 or 110 mg/dL) Fasting insulin levels Homeostatic model assessment Oral glucose tolerance test Hyperinsulinemic-euglycemic clamp	In-laboratory blood draw In-laboratory tests
Dyslipidemia	Fasting total cholesterol levels Fasting LDL cholesterol levels Fasting HDL cholesterol levels Fasting total triglycerides levels	In-laboratory blood draw
Metabolic syndrome	High blood pressure, insulin resistance, dyslipidemia and/or central obesity	In-laboratory blood draw and physical examination (waist circumference)
Type 2 diabetes	Fasting glucose levels (≥ 126 mg/dL)	In-laboratory blood draw
Cardiac autonomic modulation	Heart rate Heart rate variability (frequency, time) Preejection period Rate pressure product	In-laboratory nighttime EKG (polysomnography) In-laboratory or at-home 24-h EKG
Neuroendocrine regulation	Adrenocorticotrophic hormone levels Cortisol levels Overnight catecholamine secretion	In-laboratory blood draw In-laboratory or at-home salivary sampling
Inflammation	C-reactive protein levels Interleukin-6 levels Tumor necrosis factor alpha levels	In-laboratory blood draw
Mortality	Physician-confirmed death Physician-diagnosed cause of death	Death records (social security, national death index in the United States)

Similar findings were also reported in a recent study from Dai et al. [70], where data from the Sleep Heart Health Study (SHHS) were used to examine incident HTN in 1413 participants who did not have HTN or SDB at baseline. After a median follow-up time of 5.1 years, individuals

with insomnia symptoms and PSG-measured short sleep duration (<6 h) had significantly higher odds of developing HTN compared with individuals with insomnia and normal sleep duration (≥ 6 h; OR = 2.79) but found that individuals with insomnia who reported sleeping <6 h did

TABLE 34.3 Findings of available meta-analyses on the association between insomnia and cardiometabolic disease risk.

First author, year (design, vital status)	N (# of studies)	Insomnia definitions	Outcome	Findings
Cappuccio, 2010 [33] (longitudinal)	24,812 (6)	Difficulty initiating sleep Difficulty maintaining sleep	T2D	RR = 1.57 ^a RR = 1.84 ^a
Meng, 2013 [16] (longitudinal)	42,636 (7)	Difficulty initiating sleep Difficulty maintaining sleep Early morning awakening Insomnia symptoms	HTN	RR = 1.17 RR = 1.20 ^a RR = 1.14 ^a RR = 1.05 ^a
Li, 2014 [34] (longitudinal, mortality)	311,260 (17)	Insomnia symptoms	MI CHD CBVD Mortality	RR = 1.41 ^a RR = 1.28 ^a RR = 1.55 ^a RR = 1.33 ^a
Sofi, 2014 [35] (longitudinal, mortality)	122,501 (10)	Insomnia symptoms	CVD/CBVD	RR = 1.45 ^a
Li, 2014 [36] (longitudinal, mortality)	110,530 (10)	Difficulty initiating sleep Difficulty maintaining sleep Early morning awakening Nonrestorative sleep	CVD/CBVD Mortality	RR = 1.45 ^a RR = 1.02 RR = 1.00 RR = 1.30 ^a
Anothaisintawee, 2016 [37] (longitudinal)	289,588 (11)	Difficulty initiating sleep Difficulty maintaining sleep Insomnia symptoms	T2D	RR = 1.55 ^a RR = 1.74 ^a RR = 1.40 ^a
Irwin, 2016 [38] (cross-sectional and longitudinal)	34,943 (31)	Sleep disturbance	CRP IL-6 TNF- α	ES = 0.12 ^a ES = 0.20 ^a ES = 0.07
He, 2017 [39] (longitudinal)	160,867 (15)	Difficulty initiating sleep Difficulty maintaining sleep Early morning awakening Nonrestorative sleep	CBVD	RR = 1.27 ^a RR = 1.11 ^a RR = 1.02 RR = 1.18 ^a
Ge, 2019 [40] (longitudinal)	1,598,628 (29)	Difficulty initiating sleep Difficulty maintaining sleep Early morning awakening Nonrestorative sleep Insomnia symptoms	CVD mortality	HR = 1.20 ^a HR = 1.03 HR = 0.93 HR = 1.48 ^a HR = 1.66
Hu, 2021 [41] (longitudinal)	619,593 (7)	Difficulty initiating sleep Difficulty maintaining sleep Early morning awakening Nonrestorative sleep Insomnia symptoms	CVD	HR = 1.22 ^a HR = 1.14 ^a HR = 1.06 HR = 1.16 ^a HR = 1.13 ^a
Li, 2021 [15] (longitudinal)	395,641 (14)	Difficulty initiating sleep Difficulty maintaining sleep Early morning awakening Insomnia symptoms	HTN	RR = 1.14 RR = 1.27 ^a RR = 1.14 ^a RR = 1.21 ^a
Zhang, 2021 [42] (cross-sectional, case-control, and longitudinal)	151,299 (12)	Insomnia symptoms	HTN Hyperglycemia Hyperlipidemia Obesity	OR = 1.41 ^a OR = 1.29 ^a OR = 2.12 OR = 1.31 ^a
Dean, 2023 [43] (cross-sectional, case-control, longitudinal)	1,184,256 (9)	DIMS Nonrestorative and daytime dysfunction Insomnia symptoms	MI	RR = 1.69 ^a RR = 1.13 ^a RR = 1.06 ^a
Ali, 2023 [44] (longitudinal)	2,583,117 (12)	Insomnia symptoms	CVD mortality MI CVD risk	RR = 1.53 ^a RR = 1.48 ^a RR = 1.31 ^a

Note that some studies included death from CVD or CBVD as part of the outcome definition and this is noted as vital status. *CVD*, incident or death from cardiovascular disease, including myocardial infarction (MI), coronary heart disease (CHD) and/or heart failure (HF); *CBVD*, incident or death from cerebrovascular disease, including ischemic stroke; *ES*, effect size; *DIMS*, difficulty initiating and maintaining sleep; *HTN*, incident hypertension; *HR* hazard ratio; *NS*, not statistically significant; *OR* odds ratio; *RR*, relative risk; *T2D*, incident type 2 diabetes.

^aStatistically significant.

TABLE 34.4 Cardiometabolic disease risk associated with insomnia based on objective sleep measures.

First author, year (design, sample)	N (men, age)	Insomnia phenotype	Outcome	Findings
Stepanski, 1994 [45] (cross-sectional, research)	49 (100%, 21–50)	Chronic insomnia + 1-night PSG SE < 85%	Nighttime HR Stress-task HR	↑ HR ↑ HR reactivity
Bonnet, 1995 [46] (cross-sectional, research)	20 (NA, 18–50)	Chronic insomnia + 2-nights PSG SOL >30 min or SE < 85%	24-h VO ₂	↑ VO ₂
Bonnet, 1998 [47] (cross-sectional, research)	37 (NA, 18–50)	Chronic insomnia + 2-nights PSG SOL >30 min or SE < 85%	Nighttime HR Nighttime HRV	↑ HR ↓ SDNN ↑ LF ↓ HF
Vgontzas, 2001 [48] (cross-sectional, research)	24 (63%, 31.4 ± 6.7)	Chronic insomnia + 1-night PSG <80%	24-h HPA axis	↑ Cortisol ↑ ACTH 21:30–0:30
Shaver, 2002 [49] (cross-sectional, research)	53 (0%, 46.2 ± 3.3)	Chronic insomnia + 5-nights PSG <85%	HPA axis HR MAP NE	↑ Cortisol NS NS NS
Vgontzas, 2002 [50] (cross-sectional, research)	22 (64%, 31.6 ± 6.7)	Chronic insomnia + 1-night PSG <80%	IL-6 TNF- α	↑ IL-6 14:00–21:00
Vgontzas, 2009 [17] (cross-sectional, population-based)	1741 (48%, 20–88)	Insomnia symptoms + 1-night PSG 5–6 h Insomnia symptoms + 1-night PSG ≤5 h Chronic insomnia + 1-night PSG 5–6 h Chronic insomnia + 1-night PSG ≤5 h	HTN	OR = 1.48 OR = 2.43 ^a OR = 3.53 ^a OR = 5.12 ^a
Vgontzas, 2009 [51] (cross-sectional, population-based)	1741 (48%, 20–88)	Insomnia symptoms + 1-night PSG 5–6 h Insomnia symptoms + 1-night PSG ≤5 h Chronic insomnia + 1-night PSG 5–6 h Chronic insomnia + 1-night PSG ≤5 h	T2D	OR = 1.55 OR = 1.06 OR = 2.07 OR = 2.95 ^a
Vgontzas, 2010 [52] (longitudinal, population-based)	1741 (48%, 20–88)	Chronic insomnia + 1-night PSG <6 h Chronic insomnia + 1-night PSG <6 h	Mortality, men Mortality, women	OR = 4.00 ^a OR = 0.36
Knutson, 2011 [53] (cross-sectional, population-based)	571 (37%, 37–52)	Insomnia symptoms + 6-days ACT <80%	Glucose Insulin HOMA	↑ Glucose ↑ Insulin ↑ HOMA, if T2D
Spiegelhalder, 2011 [54] (cross-sectional, research)	104 (39%, 39.5 ± 11.8)	Insomnia disorder + 2nd-night PSG <85%	Nighttime HR Nighttime HRV	↓ SDNN ↓ RMSSD ↓ pNN50 ↓ HF
Fernandez-Mendoza, 2012 [18] (longitudinal, population-based)	786 (49%, 20–84)	Insomnia symptoms + 1-night PSG <6 h Chronic insomnia + 1-night PSG <6 h	HTN	OR = 1.34 OR = 3.75*
Nakazaki, 2012 [55] (cross-sectional, research)	86 (29%, 73.6 ± 4.9)	Insomnia or ACT <5 h Insomnia + ACT <5 h	CIMT CRP	↑ CIMT ↑ CIMT, ↑ CRP

Continued

TABLE 34.4 Cardiometabolic disease risk associated with insomnia based on objective sleep measures.—cont'd

First author, year (design, sample)	N (men, age)	Insomnia phenotype	Outcome	Findings
Vasisht, 2013 [56] (cross-sectional, research)	28 (39%, 30–64)	Insomnia disorder + 1-night PSG ≤ 6 h	Glucose 2-h Glucose HA1C Insulin HOMA-B HOMA-IR 2-h Insulin 2nd-phase ins. Resp. IS	NS NS NS \downarrow Insulin \downarrow HOMA-B \downarrow HOMA-IR \downarrow 2-h insulin \downarrow 2nd-phase ins. Resp. IS
Fernandez-Mendoza, 2014 [57] (cross-sectional, population-based)	327 (46%, 5–12)	Insomnia symptoms + 1-night PSG < 7.7 h	HPA axis	\uparrow Cortisol 19:00 & 7:00
D'Aurea, 2015 [58] (cross-sectional, research)	30 (17%, 30–55)	Insomnia disorder + 2-nights PSG ≤ 5 h	Glucose Cortisol Insulin HOMA ACTH GH	\uparrow Glucose \uparrow Cortisol NS NS NS NS
Li, 2015 [59] (cross-sectional, clinical)	315 (33%, 40.0 \pm 10.2)	Insomnia disorder + MSLT > 14 min Insomnia disorder + MSLT > 17 min	HTN	OR = 3.27 ^a OR = 4.33 ^a
Bathgate, 2016 [31] (cross-sectional, clinical)	255 (35%, 46.2 \pm 13.7)	Insomnia disorder + 2-nights PSG < 6 h	HTN	OR = 3.59 ^a
Castro-Diehl, 2016 [60] (cross-sectional, population-based)	527 (46%, 45–84)	Insomnia symptoms + 7-days ACT < 7 h	HR HF-HRV Reactivity	\uparrow HR \uparrow HF-HRV Reactivity
Fernandez-Mendoza, 2017 [61] (cross-sectional, population-based)	378 (54%, 12–23)	Insomnia symptoms + 1-night PSG ≤ 7 h	CRP IL-6 TNF- α	\uparrow CRP NS NS
Johann, 2017 [32] (cross-sectional, clinical)	328 (38%, 44.3 \pm 12.2)	Insomnia disorder + 1st-night PSG < 6 h Insomnia disorder + 2nd-night PSG < 6 h	HTN	OR = 0.79 OR = 1.21
Bertisch, 2018 [62] (longitudinal, population-based)	4994 (47%, 64.0 \pm 11.1)	Insomnia symptoms + 1-night PSG < 6 h	CVD/ CBVD Mortality	HR = 1.29 ^a HR = 1.07
Fernandez-Mendoza, 2018 [63] (cross-sectional, population-based)	1741 (48%, 20–88)	Chronic insomnia or symptoms + 1-night PSG < 6 h	CVD/ CBVD	OR = 2.00 ^a
Hein, 2018 [64] (cross-sectional, clinical)	1311 (53%, 45.1 \pm 12.4)	Insomnia symptoms + 1-night PSG 6.5–8 h Insomnia symptoms + 1-night PSG < 6.5 h	T2D	OR = 1.11 OR = 1.81
Huang, 2018 [65] (cross-sectional, clinical)	1047 (39%, 32–54)	Insomnia symptoms + 1-night PSG < 5.5 h	HTN	\uparrow HR
Jarrin, 2018 [66] (cross-sectional, research)	180 (37%, 49.9 \pm 11.3)	Insomnia disorder + 2-nights PSG < 6 h	Nighttime HR & HRV	\uparrow HR \downarrow HF \uparrow LF/HF
Hein, 2019 [67] (cross-sectional, clinical)	1272 (53%, 44.9 \pm 12.3)	Insomnia symptoms + PSG 5–7 h Insomnia symptoms + PSG < 5 h	HTN	OR = 0.89 OR = 1.91 ^a

Continued

TABLE 34.4 Cardiometabolic disease risk associated with insomnia based on objective sleep measures.—cont'd

First author, year (design, sample)	N (men, age)	Insomnia phenotype	Outcome	Findings
Hein, 2019 [68] (cross-sectional, clinical)	703 (45.5%, 44.9 ± 12.3)	Comorbid insomnia disorder + 1-night PSG SE ≥ 70% & < 85% Comorbid insomnia disorder + 1-night PSG < 70%	HTN	OR = 1.51 ^a OR = 3.54 ^a
Dai, 2023 [69] (cross-sectional, research)	498 (32.9%, 37.2 ± 11.2)	Normal sleepers + 1-night PSG < 7 h Chronic insomnia + 1-night PSG ≥ 7 h Chronic insomnia + 1-night PSG < 7 h	HTN	OR = 1.07 OR = 1.52 OR = 2.81 ^a
Dai, 2023 [70] (longitudinal, population-based sample)	1413 (40.6%, 58.8 ± 10.3)	Insomnia symptoms + 1-night PSG < 6 h	HTN	OR = 2.00 ^a
Miner, 2023 [71] (cross-sectional, population-based sample)	1324 men (76.3 ± 5.5)	Insomnia symptoms + ACT < 6 h in men	Obesity	OR = 2.00
Miner, 2023 [71] (cross-sectional, population-based sample)	1297 women (83.4 ± 3.7)	Insomnia symptoms + ACT < 6 h in women	Obesity	OR = 2.23 ^a
Sigurdardottir, 2023 [72] (cross-sectional, population-based sample)	2188 (53.6%, 68.8 ± 9.2)	Insomnia symptoms + > 6 h Insomnia symptoms + < 6 h	cTnT	NS ↑ cTnT

Note that when the age range was not available, the mean and standard deviation for the insomnia group is reported. *ACT*, actigraphy; *CRP*, C-reactive protein; *CVD*, prevalent or incident cardiovascular diseases in cross-sectional and longitudinal studies, respectively, including myocardial infarction (MI), coronary heart disease (CHD) and/or heart failure (HF); *CBVD*, prevalent or incident cerebrovascular diseases in cross-sectional and longitudinal studies, respectively, including ischemic stroke; *CMIT* carotid intima-medial thickness; *CRP* carotid plaque score; *cTnT* cardiac troponin T; *HTN*, prevalent or incident hypertension in cross-sectional and longitudinal studies, respectively; *HR*, hazard ratio or heart rate, depending on the study; *HRV*, heart rate variability; *IL-6*, interleukin 6; *IS*, insulin sensitivity; *MSLT*, multiple sleep latency test; *NA*, not available; *NE*, norepinephrine; *NS*, not statistically significant; *OR*, odds ratio; *PSG*, polysomnography; *T2D*, prevalent or incident type 2 diabetes in cross-sectional and longitudinal studies, respectively; *TNF-α*, tumor necrosis factor alpha.

^aStatistically significant.

not have a significantly higher odds of developing HTN at follow-up. In a large, community study ($N = 3911$), Kalmbach et al. found that individuals with insomnia disorder who reported sleeping < 6 h were 2.13 times more likely to have HTN (defined as a report of being treated with antihypertensive medication) than good sleepers, even after controlling for sex, age, and obesity, after excluding individuals at high risk for SDB or defining insomnia disorder as current or remitted [30]. Furthermore, African Americans were more likely to report insomnia disorder and sleeping < 6 h compared with their non-Hispanic White counterparts [30]. In a large prospective study from Taiwan ($N = 162,121$), Deng et al. stratified their analyses by the presence of self-reported insomnia symptoms and found that the risk of HTN was significantly elevated for individuals reporting insomnia symptoms and sleeping < 6 h (HR = 1.06), an effect size smaller than studies relying on objective sleep measures or on a chronic insomnia definition [29]. However, this study adds to the literature in other geographically, racially, and ethnically diverse populations [29,30]. Lastly, a recent meta-analysis from Johnson et al. [77] used data from seven studies

reported here [31,32,52,62,66,67,78], finding individuals with insomnia and objective short sleep duration have a 54% higher risk of HTN compared with individuals with insomnia and objective normal sleep duration.

In contrast to these recent studies, a study conducted in a sample of clinically referred patients with chronic insomnia disorder in Germany ($N = 328$) did not find a significant association between patients with chronic insomnia disorder who slept objectively < 6 h with prevalent HTN (defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and/or antihypertensive medication use) [32]. There are methodological differences with previous studies that need to be considered when interpreting these results. Although participants underwent two consecutive nights of PSG, each night was treated as an independent phenomenon and the two nights were not averaged to account for inter-individual and intra-individual variability across nights [31]. In addition, the method by which BP was ascertained changed across time, which may have influenced the precision of BP measurement and introduced variability across subjects. Importantly, this study relied on an opportunistic clinical sample of patients referred to a specialty sleep clinic housed within

psychiatry, rather than randomly selected from the general population or from more diverse outpatient clinics. In fact, population-based studies in Germany have suggested a downward trend in BP over the past decade among middle age and older adults [79], which is at odds with the increasing trajectory in the US population [80]. The authors were able to exclude, based on clinical interview and PSG, individuals with occult sleep disorders such as SDB, however, they also excluded those with psychiatric disorders or “serious medical conditions.” Thus, the sample included otherwise physically healthy individuals with “primary insomnia,” a diagnostic category that has been abandoned in current nosologies given the high comorbidity of insomnia with other medical and psychiatric disorders at any time point during its natural course. Nevertheless, the authors did replicate the finding that individuals with chronic insomnia disorder who slept objectively <6 h have a longer chronic course (specifically 3.7 years longer in this study) than those with chronic insomnia and normal sleep duration [6,8].

Other studies have also examined whether the association of insomnia with HTN is stronger on specific insomnia phenotypes using other sleep/wake-related measures. The multiple sleep latency (MSLT) is an in-laboratory measure of a person’s sleep propensity and, thus, daytime alertness. Interestingly, individuals with chronic insomnia show longer sleep latencies on the MSLT as compared to good sleepers. In fact, this increased alertness (MSLT >14 min) is primarily found in individuals with chronic insomnia and objective short sleep duration [12,81–84]. Based on this observation, Li et al. [59] showed in an in-laboratory study of 315 patients that chronic insomnia combined with an MSLT >14 min, was associated with 3.3-fold increased prevalence of HTN (defined as SBP ≥140 mmHg or DBP ≥90 mmHg and/or antihypertensive medication use), whereas chronic insomnia with MSLT <14 min was not (OR = 1.17). This association with HTN was 4.3-fold for chronic insomnia combined with an MSLT >17 min [59]. This study also showed that chronic insomnia was associated with increasing SBP and DBP levels in a dose-response manner as a function of increasing MSLT levels [59]. Taken together, there appears to be methodologically stronger evidence that supports the hypothesis that the association between chronic insomnia and HTN is primarily found in those with short sleep duration (<6 h) or other markers of physiologic hyperarousal (MSLT >14 min). Nevertheless, more studies are needed to examine the synergistic effect of having both insomnia disorder and objective short sleep duration on BP regulation and different levels of HTN using longitudinal design. Furthermore, previous studies using objective sleep or alertness measures could not examine other subclinical markers of BP regulation such as nighttime BP or nondipping BP levels.

The association of insomnia with subclinical markers of BP regulation has been examined primarily in laboratory-based studies. An elevated nighttime SBP and a lower day-to-night SBP dipping have been found in a study of otherwise normotensive patients with chronic insomnia disorder [85]. Interestingly, beta (15–35 Hz) activity in the electroencephalogram during the PSG study was positively correlated with concomitant nighttime SBP [85]. Also, BP dysregulation has been observed in individuals with chronic insomnia disorder in response to a psychosocial stress challenge test [86]. Another study has shown that morning-to-evening and day-to-day ambulatory BP variability was significantly higher in patients with chronic insomnia compared with good sleeping control, an association that was greatest in chronic insomnia combined with short sleep duration [87]. In a recent systematic review of 26 observational studies comprising 1484 subjects, Nano et al. [88] have reported that 80% of these studies found significant differences in cardiovascular activity, including impaired heart rate variability (HRV) or BP dysregulation, and that the insomnia with objective short sleep duration phenotype [12] presented most consistent findings across markers of impaired cardiovascular regulation [88]. The findings of several of these studies using objective sleep measures are summarized in Table 34.4.

In summary, epidemiologic and experimental studies support an association of insomnia with clinical HTN and subclinical BP dysregulation. However, most epidemiologic evidence pertains to insomnia symptoms, rather than chronic insomnia disorder, was not able to control for SDB, and reported modest effect sizes. The interest in understanding the dynamics of the association of chronic insomnia with HTN in those with objective short sleep duration is growing, as seen by the spurt of literature examining these associations in recent years.

Type 2 diabetes and insulin resistance

The relationship between insomnia and metabolic dysfunction has been examined using either subclinical markers such as insulin resistance, increased fasting glucose, dyslipidemia, or the clustering of these markers into the metabolic syndrome (MetS) as well as using clinically identified T2D. Multiple cross-sectional and longitudinal studies have reported significant associations between the presence of insomnia symptoms and insulin resistance, increased fasting glucose levels and prevalent or incident T2D [30,33,37,51,58,89]. As shown in Table 34.3, a meta-analysis performed by Cappuccio et al. [33] on findings from 10 large longitudinal studies comprising a total of 107,756 subjects, estimated that the risk of incident T2D associated with the insomnia symptoms of difficulty initiating sleep and difficulty maintaining sleep was about

57% and 84%, respectively. In a recent meta-analysis, Zhang et al. [42] examined data from 12 cross-sectional, case-control, and longitudinal studies comprising a total of 151,299 subjects and found that subjects with insomnia had a higher risk of several components of MetS compared with those without insomnia, such as a 41% increased risk of HTN, a 29% increased risk of hyperglycemia, and a 31% increased risk of obesity. vast majority of the epidemiologic studies relied on broad self-reported definitions of sleep disturbance/sleep quality and, in some studies, of insomnia symptoms. However, two experimental studies did not find an association between chronic insomnia disorder and impaired glucose metabolism in the oral glucose tolerance test [90] or hyperinsulinemic-euglycemic clamp [91] under laboratory conditions. The relationship between insomnia and MetS—the clustering of central obesity, dyslipidemia, insulin resistance or glucose dysregulation, and/or elevated BP—has revealed to be much more complex, if not limited and inconsistent [92–99]. The only longitudinal study to date found that while insomnia symptoms were associated with incident MetS over a 3-year follow-up, chronic insomnia disorder was not [97]. In contrast to these inconsistent findings, it is well-established that SDB is associated with the MetS (see Chapter 45). A potential explanation for the stronger association of SDB with MetS as compared to chronic insomnia disorder, may be related to differing underlying mechanisms. A core feature of MetS is central obesity, which is a strong risk factor for the development of SDB (see Chapter 45) but not chronic insomnia [5,6,8]. Individuals with chronic insomnia disorder are typically nonobese, not significantly heavier than healthy controls, and not likely to develop obesity despite sleeping objectively shorter than controls [100–102], findings consistent with the presence of increased whole-body metabolic rate [46]. Importantly, PSG sleep duration does not significantly correlate with body mass index in individuals with chronic insomnia disorder [101]. These data indicate that chronic insomnia may be linked to impaired glucose levels and T2D through underlying mechanisms other than central obesity.

As with HTN above, the risk of T2D has also been examined from the perspective of an interplay between insomnia and short sleep duration that can explain the heterogeneity and small effect sizes of previous findings (see Table 34.4). In another study of the PSAC, Vgontzas et al. showed that individuals with chronic insomnia who slept objectively between 5 and 6 h and those with chronic insomnia who slept <5 h were 2.1 and 3.0 times more likely to have T2D (defined as fasting plasma glucose ≥ 126 and/or use of T2D medication), respectively, as compared to good sleepers [51]. In contrast, individuals with chronic insomnia who slept objectively >6 h were not significantly associated with increased odds of prevalent

T2D (OR = 1.10) [51]. The few other epidemiologic studies that have examined the combined effect of insomnia symptoms and short sleep duration on T2D risk have reported similar findings. For example, a large study showed that individuals who reported poor sleep quality and sleeping <6 h had 6.4-fold odds of impaired glucose tolerance [103]. In addition, individuals with insomnia symptoms who objectively slept <6.5 h (as measured by PSG) had significantly higher odds of having T2D (OR = 1.81), compared with those who slept >8 h [64]. In another small study, individuals with chronic insomnia disorder who slept objectively <6 h (as measured by PSG) responded to an oral glucose tolerance test with lower insulin secretion in conjunction with greater insulin sensitivity, and no difference in glycemic control, compared with those with chronic insomnia disorder who slept objectively >6 h [56]. These findings were consistent with an epidemiologic study that found that individuals with insomnia symptoms who slept objectively short (ACT sleep efficiency $<80\%$) were associated with lower insulin levels and greater insulin sensitivity if they did not have T2D, while individuals with insomnia symptoms who slept objectively short were associated with worse insulin sensitivity if they also had T2D [53]. In a large, community study ($N = 3911$), Kalmbach et al. found that individuals with insomnia disorder who reported sleeping <6 h were 1.83 times more likely to report a history of T2D than good sleepers, even after adjusting for sex, age, and obesity [30]. In addition, in a recent study of 30 adults, D'Aurea et al. showed that individuals with chronic insomnia who slept objectively <5 h (as measured by PSG) had significantly higher fasting glucose levels than individuals with insomnia who slept objectively longer than 5 h [58]. The findings of these and other studies using objective sleep measures and metabolic function indices are summarized in Table 34.4. Furthermore, in the same meta-analysis from Johnson et al. discussed in the HTN section [77], they also found that individuals with insomnia and objective short sleep duration had a 63% higher risk of T2D compared with individuals with insomnia and objective normal sleep duration. There are no studies that have examined the synergistic effect of insomnia and objective short sleep duration on prevalent or incident MetS.

In summary, most research suggests a significant association between insomnia symptoms and metabolic dysfunction, including increased risk of T2D. The available evidence suggests that this risk is stronger in chronic insomnia disorder when coupled with objective short sleep duration. The association of chronic insomnia with MetS is not clear and deserves further investigation in well-defined samples by assessing the severity and chronicity of insomnia, including objective measures of relevant confounders such as SDB as well as of nighttime sleep (e.g., PSG or ACT) or daytime alertness (e.g., MSLT).

Heart disease and stroke

As mentioned above, clinical observation indicated early on a high comorbidity between insomnia and CVD and CBVD. Clinical patients with chronic insomnia were observed to have a history of heart disease or stroke to a greater rate than expected for the general population or similar outpatients [10,11,104]. However, whether insomnia itself conferred a significant increased risk of developing CVD or CBVD remained largely unstudied until the past decade, in which an abundance of data has flourished. Epidemiologic studies have examined whether insomnia is a risk factor for coronary heart disease (CHD), myocardial infarction (MI), heart failure, or, to a lesser extent, ischemic stroke [34–36,43,44]. As shown in Table 34.3, several systematic reviews and meta-analyses have been published in the past few years on the association of insomnia and the risk of CVD and CBVD [34,35,43,44]. The available longitudinal studies have estimated that individuals with insomnia symptoms have a 45% higher risk of incident CVD [35], a 48% risk of incident MI [44], and 55% of incident CHD or CBVD [34]. Once again, the available evidence on increased CVD/CBVD risk pertains primarily to insomnia symptoms, rather than chronic insomnia disorder, and most studies did not include PSG and could not control for SDB (see Chapter 45).

Following the seminal findings in the PSAC of a synergistic effect between insomnia and objective short sleep duration on the risk for HTN and T2D [17,18,51], other independent investigators have examined whether this insomnia phenotype is also more strongly associated with CVD/CBVD than insomnia with normal sleep duration. This hypothesis has been examined in several epidemiologic studies with the limitation that most of them relied on self-reported sleep duration, which may account for some of the inconsistent findings [30,62,63,73,74,76,105]. Specifically, Kalmbach et al. found in a large community study ($N = 3911$) that individuals with insomnia disorder who reported sleeping <6 h were 3.2 and 3.8 times more likely than good sleepers to report a history of MI and stroke, respectively, even after adjusting for sex, age, and obesity [30]. Recent work from the PSAC has also shown a cross-sectional association between insomnia with objective short sleep duration and prevalent CVD/CBVD [63]. This study showed that compared with normal sleepers who slept objectively >6 h (as measured by PSG), individuals with insomnia who slept objectively <6 h were 2.0 times more likely to have a history of CVD/CBVD, while individuals with insomnia who slept >6 h of sleep were not significantly associated with prevalent CVD/CBVD (OR = 1.3) [63]. Importantly, Bertisch et al. [62] examined whether insomnia symptoms with PSG-measured short sleep duration were associated with increased risk of incident CVD/CBVD in 4437 subjects from SHHS.

Individuals with insomnia symptoms who slept objectively <6 h showed a 29% higher risk of developing CVD/CBVD after a median of 11.4 years of follow-up, while individuals with insomnia symptoms who slept objectively >6 h were not at significantly increased risk of incident CVD/CBVD (HR = 0.99) [62]. In a smaller study of 86 subjects, Nakazaki et al. [55] examined atherosclerosis risk in older adults with insomnia and short sleep duration (<5 h, as measured by ACT), finding these individuals had higher carotid intima-medial thickness, a measure of atherosclerosis, and carotid plaque scores, a strong predictor of future ischemic stroke, compared with good sleepers. Thus, the available epidemiologic studies support an association of insomnia with CVD/CBVD and that this association is found when insomnia is defined based on objectively measured short sleep duration. The findings of studies using objective sleep measures are summarized in Table 34.4.

Finally, several large epidemiologic studies have examined the association of insomnia with all-cause and CVD/CBVD mortality. Early studies reported either a lack of mortality risk associated with insomnia or even a protective effect [9], however, two recent meta-analyses including 13 and 17 studies and 122,501 and 311,260 subjects, respectively, estimated that individuals with insomnia symptoms had a 33%–45% increased risk of CVD/CBVD mortality [34,35] as compared to good sleepers (see Table 34.3). Following the approach of a synergistic effect between insomnia and objective short sleep duration on the risk of HTN and T2D [17,18,51], Vgontzas et al. [52] found that men from the PSAC with chronic insomnia who slept objectively <6 h (as measured by PSG) were associated with a fourfold increased odds of all-cause mortality after 10 years of follow-up, a risk that was elevated to sevenfold among men with this insomnia phenotype and comorbid HTN or T2D at baseline. In contrast, no significant association was found in men who slept objectively >6 h or in women [52]. However, this study was limited by the small number of deceased men (21%) and women (5%), which precluded estimating the risk of CVD/CBVD mortality in either gender. Only three studies have further examined whether insomnia is associated with increased mortality in men, but not women, or when combined with short sleep duration. In a cohort study of 6236 adults (40–45 years old) followed up after 13–15 years, Sivertsen et al. [106] found that the risk of all-cause mortality associated with insomnia symptoms was 4.7-fold in men, a gender difference that has been replicated in another large study [107]. Furthermore, the authors found that individuals with insomnia symptoms who reported sleeping <6.5 h had a 2.8-fold risk of all-cause mortality, whereas individuals with insomnia symptoms who reported sleeping >6.5 h were not associated with a significant mortality risk (HR = 1.8) [106]. In

contrast, the recent study by Bertisch et al. [62] could not replicate these findings and found neither gender differences in mortality risk nor increased all-cause or CVD/CBVD mortality in individuals with insomnia symptoms who slept objectively <6 h ($HR = 1.07$) in the SHHS. Thus, the association between insomnia and mortality is rather modest and inconsistent, particularly when chronicity criteria are not used. Recent studies that have focused on chronic insomnia or used PSG measures have suggested an increased mortality risk, particularly in men and in those with short sleep duration. However, these findings have not been consistently replicated (see Table 34.4). It is likely that the association of insomnia with mortality is rather complex and multiple methodological (i.e., definitions used, cohort effects, and critical length of survival time) and developmental factors (i.e., aging in normal sleepers) are at play. Future studies are needed with larger cohorts, uniform criteria for insomnia disorder, and objective sleep data to identify the population with the greatest mortality risk.

Stress, immunity, and health behaviors

Regardless of the theoretical model adopted to explain the pathophysiology of insomnia (e.g., neurobiological and behavioral), the etiology of insomnia has been conceptualized from a diathesis-stress perspective since the 1980s. It is posited that the joint effects of stressful life events [108] and cognitive-emotional factors are central to the etiopathogenesis of insomnia [109]. In other words, certain individuals with predisposing traits, when faced with common, unexpected, or traumatic precipitating events, experience stress-related insomnia symptoms. To cope with this transient insomnia, individuals use maladaptive cognitive and behavioral resources that ultimately lead to developing a chronic insomnia disorder [109]. From a neurobiological perspective, however, it is hypothesized that physiologic changes in the stress and immune system are also responsible for the perpetuation of chronic insomnia [12,110,111].

Early studies focused on the neuroendocrine stress response and were driven by the seminal study on psychophysiologic hyperarousal in insomnia by Monroe [112]. The majority of in-laboratory studies, with three exceptions, have reported increased hypothalamic-pituitary-adrenal (HPA) axis activation in individuals with chronic insomnia, including increased cortisol secretion and alterations in the diurnal cortisol profile [12,110,111]. Other neuroendocrine studies found that overnight norepinephrine and catecholamine metabolite levels were increased in individuals with chronic insomnia or were correlated with PSG indices of sleep disturbance in insomnia patients [12,111]. Also, other studies, with a few exceptions, have found that insomnia is associated with increased nocturnal

HR, impaired HRV, altered sympathovagal balance, as measured by impedance cardiography, increased whole-body metabolic rate, increased pupil size (indicative of sympathetic activation), increased or altered systemic inflammation, and increased central nervous system activation during wake and sleep [12,38,88,110,111,113].

Physiologic changes in cardiac autonomic modulation and inflammation are of particular relevance to the increased cardiometabolic disease risk observed in individuals with insomnia (see Chapter 34). Only in the past few years, two systematic reviews and meta-analyses have been published on the association of insomnia with HR, HRV, and other indices of cardiac autonomic modulation [18,113]. The multiple studies to date suggest a shift toward a predominance of sympathetic modulation during both wake and nighttime periods in individuals with chronic insomnia disorder, given the observed decreased parasympathetic activity (as measured by high-frequency HRV) during NREM sleep and increased sympathetic nervous system activity, as measured by impedance cardiography and the low- to high-frequency (LF/HF) ratio in HRV [88]. Importantly, studies in which a positive association was reported, individuals with chronic insomnia were carefully screened and showed objective sleep disturbances (as measured by PSG or ACT), while studies that did not find an association between chronic insomnia and HRV parameters defined the disorder solely based on subjective reports [12,88]. For example, Spiegelhalder et al. [54] found that when objective measures were not used, chronic insomnia patients did not differ significantly from their good sleeper counterparts in either resting HR or nighttime HRV [54]. On the contrary, chronic insomnia subjects with objective short sleep duration (PSG sleep efficiency <85%) had reduced parasympathetic activity compared with good sleepers, while chronic insomnia subjects with normal sleep duration (PSG sleep efficiency >85%) had similar measures of HR and HRV as good sleeping controls [54]. The findings of the studies that used objective sleep measures in insomnia subjects are presented in Table 34.4.

Studies focusing on immune system activity in individuals with insomnia have been more limited and have reported modest associations [38]. Epidemiologic studies in adults reported no significant association between insomnia symptoms and C-reactive protein (CRP) levels, an acute-phase inflammatory protein of hepatic origin that increases following interleukin-6 (IL-6) secretion [114]. However, in-laboratory controlled studies found increased inflammation in individuals with chronic insomnia compared with good sleepers, as measured by the secretion [115] and diurnal profiles of IL-6 [50]. In these latter studies, individuals with chronic insomnia were carefully screened and showed objective sleep disturbances (as measured by PSG). Indeed, evidence accumulates that biomarkers of stress and immune system hyperarousal are

primarily present in individuals with insomnia and short sleep duration [12,58,60,78,116–118] (see Table 34.4). For example, in a controlled, in-laboratory study Floam et al. [117] showed that young adults with insomnia disorder slept objectively shorter (as measured by ACT) and had elevated HPA-axis and proinflammatory activity than good sleeping controls and that ACT-measured wake after sleep onset was positively associated with HPA-axis activity among insomnia participants. In another in-laboratory study, D'Aurea et al. [58] showed that middle-aged adults with chronic insomnia who slept objectively <5 h (as measured by PSG) had significantly higher cortisol levels than individuals with chronic insomnia who slept objectively >5 h and that cortisol and adrenocorticotropic hormone levels were inversely correlated with PSG-measured sleep duration among individuals with chronic insomnia. Castro-Diehl et al. [60] found in a population-based study of 527 adults from the MultiEthnic Study of Atherosclerosis that individuals with insomnia symptoms who slept objectively <7 h (as measured by ACT) had greater HR orthostatic reactivity and high-frequency HRV mental reactivity compared with good sleepers. The authors concluded that insomnia with objective short sleep duration was associated with lower levels of cardiac parasympathetic tone and/or higher levels of sympathetic activity [60], a finding consistent with de Zambotti et al. [118] data supporting dysfunctional sympathetic activity but normal parasympathetic modulation before and during sleep in young adults with chronic insomnia who sleep objectively shorter compared with controls. Finally, in a recent study of 378 adolescents from the Penn State Child Cohort, Fernandez-Mendoza et al. [61] found that adolescents with insomnia symptoms who slept objectively <7 h (as measured by PSG) had significantly higher CRP levels as compared to good sleepers. In contrast, adolescents with insomnia symptoms who slept objectively >7 h were not associated with significantly increased CRP levels [61].

In summary, peripheral and central markers of increased HPA axis activity and impaired cardiac autonomic modulation are primarily found in individuals with chronic insomnia and objective short sleep duration, a phenotype in which 24-h hyperarousal is the main pathophysiological mechanism [12,119]. Thus, neuroendocrine dysregulation, cardiac autonomic imbalance, and chronic low-grade inflammation are believed to underlie the increased cardiometabolic disease risk associated with chronic insomnia with objective short sleep duration. A diagrammatic representation of this conceptual model is presented in Fig. 34.1.

Another potential pathway by which insomnia is linked to greater cardiometabolic disease risk that deserves separate consideration is the presence of inadequate health-related behaviors (see Chapters 29–33). Individuals with insomnia are indeed more likely to report smoking,

excessive alcohol, or caffeine use and lack of physical activity [120], which are all well-established lifestyle CMR. Individuals with insomnia have also been found to have lower cardiorespiratory fitness, which is an independent risk factor for CVD/CBVD [121]. Another health-related behavior recently examined as a potential link between insomnia and cardiometabolic disease risk has been poor diet [122–124]. A recent large, general population study, for example, found that individuals who reported insomnia symptoms were associated with an inadequate intake of alpha-carotene, calcium, selenium, salt, carbohydrates, vitamin D, lycopene, or dodecanoic, hexadecanoic, butanoic, or hexanoic acids [123]. Another study found that individuals with insomnia who objectively slept <6 h were more likely to have a metabolically unhealthy diet compared with individuals with insomnia who slept >6 h [122]. It is likely that the relationship between insomnia and many of these health-related behaviors is bidirectional [5,6,8,120]. Interestingly, however, sleep hygiene therapy alone, which targets most of these inadequate health behaviors, is not an effective treatment for chronic insomnia disorder [125]. Importantly, most studies reviewed above on the association of insomnia with CMR or CVD/CBVD adjusted for the potential confounding effect of alcohol and smoking but not diet or physical activity. More work is needed to establish the relative contribution and potential causal role of inadequate health behaviors to the increased cardiometabolic disease risk associated with insomnia, above and beyond the other putative stress-, autonomic-, and immune-related mechanisms (see Fig. 34.1).

Public health and clinical implications

If insomnia symptoms and chronic insomnia account for about 40% of the population and are significantly associated with increased cardiometabolic disease risk, there is no doubt then that they should become a target of public health policies [126]. Better screening of insomnia in the general population is needed, including in family medicine, occupational and school settings. There are existing brief, reliable, valid, and easy-to-use self-reported tools that can help identify individuals from the general population with subthreshold insomnia symptoms and with clinically significant insomnia, such as the insomnia severity index, as well as objective measures of sleep duration such as ACT or home-based PSG. This improved detection of insomnia should lead to early phenotyping of those at greatest risk and early targeted treatment and may help prevent downstream adverse health outcomes, including cardiometabolic risk [119]. Such preventive interventions should also be conducted outside the clinical office at the community level, mimicking those that are applied for cardiometabolic disease risk reduction.

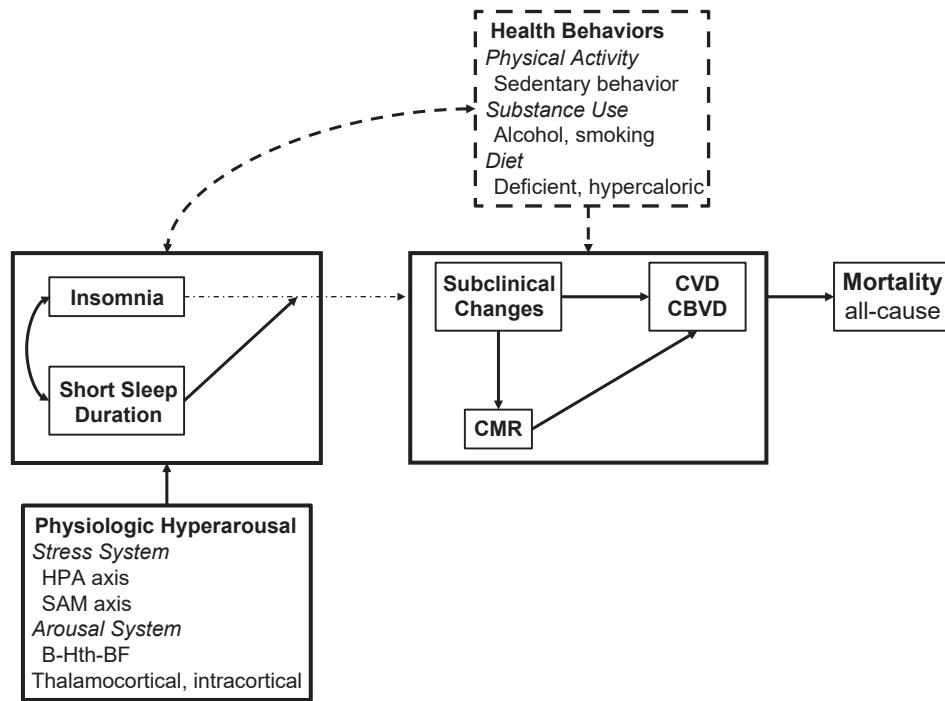


FIGURE 34.1 Insomnia with short sleep duration and cardiometabolic disease risk. The *dotted arrow* represents the synergistic effect between insomnia and objective short sleep duration on cardiometabolic disease risk. This diagram depicts how objective short sleep duration in individuals with insomnia is the result of physiologic hyperarousal and identifies those with increased risk of cardiometabolic disease morbidity and mortality. The arousal system includes ascending projections from the brainstem and hypothalamus to the diencephalon, limbic system, basal forebrain, and neocortex (B-Hth-BF) as well as descending projections regulating the autonomic nervous system. These ascending and descending projections interact with the acute or chronic activation of the stress system. This diagram includes potential subclinical changes such as chronic low-grade inflammation, impaired cardiac autonomic modulation, endothelial dysfunction, carotid intima media thickness or coronary artery calcification. It also depicts the potential relative role (discontinuous boxes) of inadequate health behaviors in increasing cardiometabolic disease risk. *CBVD*, cerebrovascular disease; *CMR*, cardiometabolic risk factors; *CVD*, cardiovascular disease; *HPA*, hypothalamic-pituitary-adrenal; *SAM*, sympatho-adrenal-medullary.

Chronic insomnia disorder has become the focus of many professional health organizations. The American College of Physicians has recently released a clinical guideline recommending that “all adult patients receive cognitive-behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder” and that “clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of (sleep) medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom CBT-I alone was unsuccessful” [125]. This clinical guideline represents a shift in the current treatment of insomnia and disseminates CBT-I as a well-established, first-line, effective treatment. However, the introduction of pharmacological therapy, which is the current norm, is left up to a failure to respond to CBT-I alone, which indicates that the field still has difficulties matching insomnia treatments to specific phenotypes. This issue pertains to the relationship between insomnia and cardiometabolic disease risk, as it is unknown whether insomnia therapies are associated with concomitant improvements in physiology (e.g., improved inflammation,

cortisol, and HRV) or health behaviors (e.g., increased physical activity and improved diet). It is also unclear whether any improvements in physiology and health behaviors would attenuate the long-term cardiometabolic disease risk associated with chronic insomnia disorder.

There are no randomized clinical trials (RCT) that have systematically assessed whether widely used pharmacological therapies (e.g., zolpidem and trazodone) improve CMR. A recent clinical trial found that the addition of the intermediate-acting benzodiazepine estazolam to usual antihypertensive treatment in individuals with insomnia produced significant mean decreases in BP levels of –8 to –11 mmHg as compared to placebo with antihypertensive treatment as usual, which produced mean decreased in BP levels of about –3 mmHg [127]. In contrast, a recent clinical trial that examined the effect of CBT-I, administered via a web platform (SLEEPPIO) for 8 weeks, on ambulatory BP levels showed no statistically significant or clinically meaningful changes as compared to the standard of care of education on vascular risk factors (–0.9 vs. 0.8 mmHg, respectively) [128]. Interestingly, Bathgate et al. [129] have recently reported that individuals with

chronic insomnia who slept objectively <6 h (as measured by ACT) had a blunted response to CBT-I, while individuals with chronic insomnia who slept objectively >6 h showed high response and remission rates after undergoing CBT-I.

Thus, future RCTs should be designed to test the effectiveness of pharmacological and cognitive-behavioral therapies for insomnia in improving subclinical and prognostic markers of cardiometabolic disease risk, particularly in individuals with chronic insomnia and objective short sleep duration. It is likely that combined CBT-I plus pharmacological treatment in the most severe insomnia phenotype would show the most significant and clinically relevant effects on cardiometabolic outcomes; however, this hypothesis needs to be tested.

Conclusion

Insomnia is a premorbid risk factor for CVD/CBVD, including mortality. Accumulating evidence suggests that the association of insomnia with CMR is more pronounced when insomnia is defined as a chronic disorder and is associated with objective short sleep duration (i.e., <6 h) or other measures of physiologic hyperarousal (e.g., such as longer latencies in the MSLT). Evidence suggests that measures of insomnia, and especially objective sleep measures, should be included in the estimation of cardiometabolic disease risk in the clinical and general population. Future studies should make use of sophisticated in-laboratory and ambulatory study designs to better understand the cardiovascular and metabolic profiles of individuals with chronic insomnia in an ecologically valid manner. Also, longitudinal studies with a lifespan perspective are needed to better understand in which critical developmental stages insomnia starts to have an impact on cardiometabolic disease risk. As mentioned above, well-designed RCTs are needed, as they will not only provide therapeutic evidence but also proof-of-concept that improving insomnia and sleep duration improves cardiometabolic biomarkers. Based on the current evidence, personalized medicine approaches using treatment matching to specific insomnia phenotypes in large RCTs are essential.

Glossary

Actigraphy An ambulatory method to estimate an individual's sleep and wake using an accelerometer attached to the nondominant wrist

Cardiometabolic risk factors Specific clinical and subclinical factors that put individuals at risk of cardiovascular or CBVD. Traditionally, elevated blood pressure, including HTN, insulin resistance, including T2D, dyslipidemia, and obesity are included. Lifestyle risk factors such as smoking, alcohol abuse,

physical inactivity, and inadequate diet are also included within this category

Cardiovascular disease A broad category that includes all disorders of the circulatory system, including CHD such as MI, peripheral artery disease, cardiomyopathy, heart failure, or cardiac arrhythmias

Cerebrovascular disease A broad category that includes all disorders of the cerebral circulatory system and blood vessels in the brain, including ischemic stroke, transient ischemic attack, and subarachnoid or intracerebral hemorrhage

Difficulty initiating sleep The report of inability to fall asleep at the desired bedtime.

Difficulty maintaining sleep The report of inability to resume sleep in the middle of the night or sleep period

Early morning awakening The report of waking up too early before desired and having difficulty resuming sleep.

Insomnia disorder The report of difficulties initiating sleep, difficulties maintaining sleep or early morning awakening that occur at least three nights per week for at least 3 months and are associated with significant daytime functioning impairment such as daytime fatigue, poor concentration, mood problems, or worry about insomnia itself, among others

Insomnia symptoms The report of difficulties initiating sleep, difficulties maintaining sleep, early morning awakening or, in some studies, nonrestorative sleep without any duration (chronicity) or impairment (daytime) criteria. Also referred to as "poor sleep" or "sleep difficulties" in some studies

Metabolic syndrome The clustering of three or more of the CMRs central obesity, elevated blood pressure, insulin resistance, hypercholesterolemia, and/or hypertriglyceridemia

Multiple sleep latency test The simultaneous recording of multiple physiologic measures (i.e., electroencephalography, electrooculography, electromyography, and electrocardiography, at minimum) during five daytime nap opportunities to ascertain a person's daytime alertness or sleep propensity. It can only be performed in the sleep laboratory attended by registered PSG technicians

Nonrestorative sleep The report of unrefreshing sleep upon awakening regardless of the amount of sleep obtained. An insomnia symptom included in most epidemiological studies and previous diagnostic nosologies

Polysomnography The simultaneous recording of multiple physiologic measures (i.e., electroencephalography, electrooculography, electromyography, and electrocardiography, at minimum) during the nighttime period to ascertain whether a person is asleep or awake and/or suffers from a sleep disorder. It can be performed in the sleep laboratory attended by registered PSG technicians or at home unattended using ambulatory monitoring

Sleep-disordered breathing A cluster of sleep disorders in which respiratory function during sleep is compromised and presence in the form of loud upper-airway related sounds (snoring), breathing pauses, and/or hypoventilation. It ranges from simple snoring to obstructive sleep apnea and central sleep apnea

Sleep fragmentation The report of multiple, brief (e.g., lasting <30 min) awakenings in the middle of the night or sleep period. A symptom typical of SDB, movement-related disorders, and other sleep disorders

References

- [1] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6(2):97–111. <https://doi.org/10.1053/smrv.2002.0186>.
- [2] Bixler EO, Vgontzas AN, Lin H-M, Vela-Bueno A, Kales A. Insomnia in central Pennsylvania. *J Psychosom Res* 2002;53(1):589–92. [https://doi.org/10.1016/s0022-3999\(02\)00450-6](https://doi.org/10.1016/s0022-3999(02)00450-6).
- [3] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darren, IL: American Academy of Sleep Medicine; 2014.
- [4] LeBlanc M, Mérette C, Savard J, Ivers H, Baillargeon L, Morin CM. Incidence and risk factors of insomnia in a population-based sample. *Sleep* 2009;32(8):1027–37. <https://doi.org/10.1093/sleep/32.8.1027>.
- [5] Singareddy R, Vgontzas AN, Fernandez-Mendoza J, Liao D, Calhoun S, Shaffer ML, Bixler EO. Risk factors for incident chronic insomnia: a general population prospective study. *Sleep* 2012;13(4):346–53. <https://doi.org/10.1016/j.sleep.2011.10.033>.
- [6] Fernandez-Mendoza J, Vgontzas AN, Bixler EO, Singareddy R, Shaffer ML, Calhoun SL, Karataraki M, Vela-Bueno A, Liao D. Clinical and polysomnographic predictors of the natural history of poor sleep in the general population. *Sleep* 2012;35(5):689–97. <https://doi.org/10.5665/sleep.1832>.
- [7] Morin CM, Bélanger L, Blanc ML, Ivers H, Savard J, Espie CA, Mérette C, Baillargeon L, Grégoire JP. The natural history of insomnia a population-based 3-year longitudinal study. *Arch Intern Med* 2009;169(5):447–53. [https://doi.org/10.1001/archinternmed.2008.610Canada](https://doi.org/10.1001/archinternmed.2008.610).
- [8] Vgontzas AN, Fernandez-Mendoza J, Bixler EO, Singareddy R, Shaffer ML, Calhoun SL, Liao D, Basta M, Chrousos GP. Persistent insomnia: the role of objective short sleep duration and mental health. *Sleep* 2012;35(1):61–8. <https://doi.org/10.5665/sleep.1586>.
- [9] Hall m, Fernandez-Mendoza J, Kline C, Vgontzas A. Principles and practice of sleep medicine. Elsevier; 2016. p. 794–803.
- [10] Kales A, Kales J. Evaluation and treatment of insomnia. Oxford University Press; 1984. p. 1984.
- [11] Bonnet MH, Arand DL. Cardiovascular implications of poor sleep. *Sleep Med Clin* 2007;2(4):529–38. <https://doi.org/10.1016/j.jsmc.2007.07.007>.
- [12] Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev* 2013;17(4):241–54. <https://doi.org/10.1016/j.smrv.2012.09.005>.
- [13] Spiegelhalder K, Scholtes C, Riemann D. The association between insomnia and cardiovascular diseases. *Nat Sci Sleep* 2010;2:71–8. <https://doi.org/10.2147/nss.s7471>.
- [14] Thomas SJ, Calhoun D. Sleep, insomnia, and hypertension: current findings and future directions. *J Am Soc Hypertens* 2017;11(2):122–9. <https://doi.org/10.1016/j.jash.2016.11.008>.
- [15] Li L, Gan Y, Zhou X, Jiang H, Zhao Y, Tian Q, He Y, Liu Q, Mei Q, Wu C, Lu Z. Insomnia and the risk of hypertension: a meta-analysis of prospective cohort studies. *Sleep Med Rev* 2021;56. <https://doi.org/10.1016/j.smrv.2020.101403>.
- [16] Lin M, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertens Res* 2013;36(11):985–95. <https://doi.org/10.1038/hr.2013.70>.
- [17] Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep* 2009;32(4):491–7. <https://doi.org/10.1093/sleep/32.4.491>.
- [18] Fernandez-Mendoza J, Vgontzas AN, Liao D, Shaffer ML, Vela-Bueno A, Basta M, Bixler EO. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension* 2012;60(4):929–35. <https://doi.org/10.1161/HYPERTENSIONAHA.112.193268>.
- [19] Vozoris NT. The relationship between insomnia symptoms and hypertension using United States population-level data. *J Hypertens* 2013;31(4):663–71. <https://doi.org/10.1097/JHH.0b013e32835ed5d0>.
- [20] Vozoris NT. Insomnia symptom frequency and hypertension risk: a population-based study. *J Clin Psychiatr* 2014;75(6):616–23. <https://doi.org/10.4088/JCP.13m08818>.
- [21] Shivashankar R, Kondal D, Ali MK, Gupta R, Pradeepa R, Mohan V, Kadir MM, Narayan KMV, Tandon N, Prabhakaran D, Peasey A. Associations of sleep duration and disturbances with hypertension in metropolitan cities of Delhi, Chennai, and Karachi in South Asia: cross-sectional analysis of the CARRS study. *Sleep* 2017;40(9). <https://doi.org/10.1093/sleep/zsx119>.
- [22] Wang YM, Song M, Wang R, Shi L, He J, Fan TT, Chen WH, Wang L, Yu LL, Gao YY, Zhao XC, Li N, Han Y, Liu MY, Lu L, Wang XY. Insomnia and multimorbidity in the community elderly in China. *China J Clin Sleep Med* 2017;13(4):591–7. <https://doi.org/10.5664/jcsm.6550>.
- [23] Clark AJ, Salo P, Lange T, Jennum P, Virtanen M, Pentti J, Kivimäki M, Rod NH, Vahtera J. Onset of impaired sleep and cardiovascular disease risk factors: a longitudinal study. *Sleep* 2016;39(9):1709–18. <https://doi.org/10.5665/sleep.6098>.
- [24] Leigh L, Hudson IL, Byles JE. Sleep difficulty and disease in a cohort of very old women. *J Aging Health* 2016;28(6):1090–104. <https://doi.org/10.1177/0898264315624907>.
- [25] Hauan M, Strand LB, Laugsand LE. Associations of insomnia symptoms with blood pressure and resting heart rate: the HUNT study in Norway. *Behav Sleep Med* 2016;16(5):504–22. <https://doi.org/10.1080/15402002.2016.1228651>.
- [26] Wang Y, Jiang T, Wang X, Zhao J, Kang J, Chen M, Wang H, Niu L, Wang Y, Zhou Y, Wu J, Fu H, Cai Z, Li Z, Chen J. Association between insomnia and metabolic syndrome in a Chinese han population: a cross-sectional study. *Sci Rep* 2017;7(1). <https://doi.org/10.1038/s41598-017-11431-6>.
- [27] Ramos AR, Weng J, Wallace DM, Petrov MR, Wohlgemuth WK, Sotres-Alvarez D, Loredo JS, Reid KJ, Zee PC, Mossavar-Rahmani Y, Patel SR. Sleep patterns and hypertension using actigraphy in the hispanic community health study/study of latinos. *Chest* 2018;153(1):87–93. <https://doi.org/10.1016/j.chest.2017.09.028>.
- [28] Lin C-L, Liu T-C, Lin F-H, Chung C-H, Chien W-C. Association between sleep disorders and hypertension in Taiwan: a nationwide population-based retrospective cohort study. *J Hum Hypertens* 2017;31(3):220–4. <https://doi.org/10.1038/jhh.2016.55>.
- [29] Deng Han-B, Tam T, Chung-Ying Zee B, Chung RY-N, Su X, Jin L, Chan T-C, Chang L-Y, Yeoh E-K, Xiang QL. Short sleep duration increases metabolic impact in healthy adults: a population-based cohort study. *Sleep* 2017;40(10). <https://doi.org/10.1093/sleep/zsx130>.

- [30] Kalmbach DA, Pillai V, Arnedt JT, Drake CL. DSM-5 insomnia and short sleep: comorbidity landscape and racial disparities. *Sleep* 2016;39(12):2101–11. <https://doi.org/10.5665/sleep.6306>.
- [31] Bathgate CJ, Edinger JD, Wyatt JK, Krystal AD. Objective but not subjective short sleep duration associated with increased risk for hypertension in individuals with insomnia. *Sleep* 2016;39(5):1037–45. <https://doi.org/10.5665/sleep.5748>.
- [32] Johann AF, Hertenstein E, Kyle SD, Baglioni C, Feige B, Nissen C, McGinnis AJ, Riemann D, Spiegelhalder K. Insomnia with objective short sleep duration is associated with longer duration of insomnia in the Freiburg Insomnia Cohort compared to insomnia with normal sleep duration, but not with hypertension. *PLoS One* 2017;12(7). <https://doi.org/10.1371/journal.pone.0180339>.
- [33] Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33(2):414–20. <https://doi.org/10.2337/dc09-1124>.
- [34] Li M, Zhang XW, Hou WS, Tang ZY. Insomnia and risk of cardiovascular disease: a meta-analysis of cohort studies. *Int J Cardiol* 2014;176(3):1044–7. <https://doi.org/10.1016/j.ijcard.2014.07.284>.
- [35] Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur J Prev Cardiol* 2014;21(1):57–64. <https://doi.org/10.1177/2047487312460020>.
- [36] Li Y, Zhang X, Winkelman JW, Redline S, Hu FB, Stampfer M, Ma J, Gao X. Association between insomnia symptoms and mortality a prospective study of us men. *Circulation* 2014;129(7):737–46. <https://doi.org/10.1161/CIRCULATIONAHA.113.004500>.
- [37] Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. *Sleep Med Rev* 2016;30:11–24. <https://doi.org/10.1016/j.smrv.2015.10.002>.
- [38] Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry* 2016;80(1):40–52. <https://doi.org/10.1016/j.biopsych.2015.05.014>.
- [39] He Q, Zhang P, Li G, Dai H, Shi J. The association between insomnia symptoms and risk of cardio-cerebral vascular events: a meta-analysis of prospective cohort studies. *Eur J Prev Cardiol* 2017;24(10):1071–82. <https://doi.org/10.1177/2047487317702043>.
- [40] Ge L, Guyatt G, Tian J, Pan B, Chang Y, Chen Y, Li H, Zhang J, Li Y, Ling J, Yang K. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: systematic review and meta-analysis of prospective cohort studies. *Sleep Med Rev* 2019;48. <https://doi.org/10.1016/j.smrv.2019.101215>.
- [41] Hu S, Lan T, Wang Y, Ren L. Individual insomnia symptom and increased hazard risk of cardiocerebral vascular diseases: a meta-analysis. *Front Psychiatr* 2021;12. <https://doi.org/10.3389/fpsyg.2021.654719>.
- [42] Zhang Y, Jiang X, Liu J, Lang Y, Liu Y. The association between insomnia and the risk of metabolic syndrome: a systematic review and meta-analysis. *J Clin Neurosci* 2021;89:430–6. <https://doi.org/10.1016/j.jocn.2021.05.039>.
- [43] Dean YE, Shebl MA, Rouzan SS, Bamousa BAA, Talat NE, Ansari SA, Tanas Y, Aslam M, Gebril S, Sbitli T, Eweis R, Shahid R, Salem A, Ahmed Abdelaziz H, Shah J, Hasan W, Hakim D, Aiash H. Association between insomnia and the incidence of myocardial infarction: a systematic review and meta-analysis. *Clin Cardiol* 2023;46(4):376–85. <https://doi.org/10.1002/cld.23984>.
- [44] Ali E, Shaikh A, Yasmin F, Sugra F, Sheikh A, Owais R, Raheel H, Hassan Virk HUI, Mustapha JA. Incidence of adverse cardiovascular events in patients with insomnia: a systematic review and meta-analysis of real-world data. *PLoS One* 2023;18(9). <https://doi.org/10.1371/journal.pone.0291859>.
- [45] Stepanski E, Glinn M, Zorick F, Roehrs T, Roth T. Heart rate changes in chronic insomnia. *Stress Med* 1994;10(4):261–6. <https://doi.org/10.1002/smj.2460100409>.
- [46] Bonnet MH, Arand DL. 24-Hour metabolic rate in insomniacs and matched normal sleepers. *Sleep* 1995;18(7):581–8. <https://doi.org/10.1093/sleep/18.7.581>.
- [47] Bonnet MH, Arand DL. Heart rate variability in insomniacs and matched normal sleepers. *Psychosom Med* 1998;60(5):610–5. <https://doi.org/10.1097/00006842-199809000-00017>.
- [48] Vgontzas AN, Bixler EO, Lin HM, Polo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab* 2001;86(8):3787–94. <https://doi.org/10.1210/jcem.86.8.7778>.
- [49] Shaver JLF, Johnston SK, Lentz MJ, Landis CA. Stress exposure, psychological distress, and physiological stress activation in midlife women with insomnia. *Psychosom Med* 2002;64(5):793–802. <https://doi.org/10.1097/01.PSY.0000024235.11538.9A>.
- [50] Vgontzas AN, Zoumakis M, Papanicolaou DA, Bixler EO, Polo P, Lin H-M, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. *Metabolism* 2002;51(7):887–92. <https://doi.org/10.1053/meta.2002.33357>.
- [51] Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diabetes Care* 2009;32(11):1980–5. <https://doi.org/10.2337/dc09-0284>.
- [52] Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Basta M, Fernández-Mendoza J, Bixler EO. Insomnia with short sleep duration and mortality: the Penn State cohort. *Sleep* 2010;33(9):1159–64. <https://doi.org/10.1093/sleep/33.9.1159>.
- [53] Knutson KL, Van Cauter E, Zee P, Liu K, Lauderdale DS. Cross-sectional associations between measures of sleep and markers of glucose metabolism among subjects with and without diabetes: the coronary artery risk development in young adults (CARDIA) sleep study. *Diabetes Care* 2011;34(5):1171–6. <https://doi.org/10.2337/dc10-1962>.
- [54] Spiegelhalder K, Fuchs L, Ladwig J, Kyle SD, Nissen C, Voderholzer U, Feige B, Riemann D. Heart rate and heart rate variability in subjectively reported insomnia. *J Sleep Res* 2011;20(1):137–45. <https://doi.org/10.1111/j.1365-2869.2010.00863.x>.
- [55] Nakazaki C, Noda A, Koike Y, Yamada S, Murohara T, Ozaki N. Association of insomnia and short sleep duration with atherosclerosis risk in the elderly. *Am J Hypertens* 2012;25(11):1149–55. <https://doi.org/10.1038/ajh.2012.107>.
- [56] Vasishth KP, Kessler LE, Booth JN, Imperial JG, Penev PD. Differences in insulin secretion and sensitivity in short-sleep insomnia. *Sleep* 2013;36(6):955–7. <https://doi.org/10.5665/sleep.2734>.
- [57] Fernandez-Mendoza J, Vgontzas AN, Calhoun SL, Vgontzas A, Tsiaousoglou M, Gaines J, Liao D, Chrousos GP, Bixler EO. Insomnia symptoms, objective sleep duration and hypothalamic-pituitary-adrenal activity in children. *Eur J Clin Invest* 2014;44(5):493–500. <https://doi.org/10.1111/eci.12263>.

- [58] Carolina D'Aurea, Poyares D, Piovezan RD, Passos GS, Tufik S, Tullio de Mello M. Objective short sleep duration is associated with the activity of the hypothalamic-pituitary-adrenal axis in insomnia. *Arq Neuropsiquiatr* 2015;73(6):516–9. <https://doi.org/10.1590/0004-282X20150053>.
- [59] Li Y, Vgontzas AN, Fernandez-Mendoza J, Bixler EO, Sun Y, Zhou J, Ren R, Li T, Tang X. Insomnia with physiological hyperarousal is associated with hypertension. *Hypertension* 2015;65(3):644–50. <https://doi.org/10.1161/HYPERTENSIONAHA.114.04604>.
- [60] Castro-Diehl C, Diez Roux AV, Redline S, Seeman T, McKinley P, Sloan R, Shea S. Sleep duration and quality in relation to autonomic nervous system measures: the multi-ethnic study of atherosclerosis (MESA). *Sleep* 2016;39(11):1927–40. <https://doi.org/10.5665/sleep.6218>.
- [61] Fernandez-Mendoza J, Baker JH, Vgontzas AN, Gaines J, Liao D, Bixler EO. Insomnia symptoms with objective short sleep duration are associated with systemic inflammation in adolescents. *Brain Behav Immun* 2017;61:110–6. <https://doi.org/10.1016/j.bbi.2016.12.026>.
- [62] Bertisch SM, Pollock BD, Mittleman MA, Buysse DJ, Bazzano LA, Gottlieb DJ, Redline S. Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: sleep Heart Health Study. *Sleep* 2018;41(6). <https://doi.org/10.1093/sleep/zsy047>.
- [63] Fernandez-Mendoza J, He L, Vgontzas B. Insomnia with objective short sleep duration is associated with increased risk of cardiovascular disease. Associated Professional Sleep Societies; 2018.
- [64] Hein M, Pol Lanquart J, Loas G, Hubain P, Linkowski P. Prevalence and risk factors of type 2 diabetes in insomnia sufferers: a study on 1311 individuals referred for sleep examinations. *Sleep Med* 2018;46:37–45. <https://doi.org/10.1016/j.sleep.2018.02.006>.
- [65] Huang Z, Goparaju B, Chen H, Matt T, Bianchi, Heart rate phenotypes and clinical correlates in a large cohort of adults without sleep apnea. *Nat Sci Sleep* 2018;111–25. <https://doi.org/10.2147/NSS.S155733>.
- [66] Jarrin DC, Ivers H, Lamy, Chen IY, Harvey AG, Morin CM. Cardiovascular autonomic dysfunction in insomnia patients with objective short sleep duration. *J Sleep Res* 2018;27.
- [67] Hein M, Pol Lanquart J, Loas G, Hubain P, Linkowski P. Objective sleep alterations and long-term use of short or intermediate half-life benzodiazepine receptor agonists are risk factors for high blood pressure in individuals with insomnia: a study in 1272 individuals referred for sleep examinations. *Sleep Med* 2019;53:115–23. <https://doi.org/10.1016/j.sleep.2018.08.030>.
- [68] Hein M, Lanquart J-P, Loas G, Hubain P, Linkowski P. Risk of high blood pressure associated with objective insomnia and self-reported insomnia complaints in major depression: a study on 703 individuals. *Clin Exp Hypertens* 2019;41(6):538–47. <https://doi.org/10.1080/10641963.2018.1516775>.
- [69] Dai Y, Chen B, Chen L, Vgontzas AN, Fernandez-Mendoza J, Karataraki M, Tang X, Li Y. Insomnia with objective short sleep duration is associated with hypertension. *J Sleep Res* 2023;32(4). <https://doi.org/10.1111/jsr.13833>.
- [70] Dai Y, Chen B, Chen L, Vgontzas AN, Fernandez-Mendoza J, Karataraki M, Tang X, Li Y. Insomnia with objective, but not subjective, short sleep duration is associated with increased risk of incident hypertension: the Sleep Heart Health Study. *J Clin Sleep Med* 2023;19(8). <https://doi.org/10.5664/jcsm.10570>.
- [71] Miner B, Doyle M, Knauert M, Yaggi HK, Stone KL, Ancoli-Israel S, Cauley JA, Redline S, Blackwell T, Gill TM. Osteoporotic Fractures in Men (MrOS) and the Study of Osteoporotic Fractures (SOF) Research Groups, Insomnia with objective short sleep duration in community-living older persons: a multifactorial geriatric health condition. *J Am Geriatr Soc* 2023;71(4):1198–208. <https://doi.org/10.1111/jgs.18195>.
- [72] Fjola DS, Bertisch SM, Reid ML, deFilippi CR, Lima JAC, Redline S, Omland T. Association between insomnia phenotypes and subclinical myocardial injury: the Multi-Ethnic Study of Atherosclerosis. *Sleep* 2023;46(4). <https://doi.org/10.1093/sleep/zsac318>.
- [73] Canivet C, Nilsson PM, Lindeberg SI, Karasek R, Östergren PO. Insomnia increases risk for cardiovascular events in women and in men with low socioeconomic status: a longitudinal, register-based study. *J Psychosom Res* 2014;76(4):292–9. <https://doi.org/10.1016/j.jpsychores.2014.02.001>.
- [74] Chandola T, Ferrie JE, Perski A, Akbaraly T, Marmot MG. The effect of short sleep duration on coronary heart disease risk is greatest among those with sleep disturbance: a prospective study from the Whitehall II cohort. *Sleep* 2010;33(6):739–44. <https://doi.org/10.1093/sleep/33.6.739>.
- [75] Lu K, Chen J, Wu S, Chen J, Hu D. Interaction of sleep duration and sleep quality on hypertension prevalence in adult Chinese males. *J Epidemiol* 2015;25(6):415–22. <https://doi.org/10.2188/jea.je20140139>.
- [76] Sands-Lincoln M, Loucks EB, Lu B, Carskadon MA, Sharkey K, Stefanick ML, Ockene J, Shah N, Hairston KG, Robinson JG, Limacher M, Hale L, Eaton CB. Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the women's health initiative. *J Wom Health* 2013;22(6):477–86. <https://doi.org/10.1089/jwh.2012.3918>.
- [77] Johnson KA, Gordon CJ, Chapman JL, Hoyos CM, Marshall NS, Miller CB, Grunstein RR. The association of insomnia disorder characterised by objective short sleep duration with hypertension, diabetes and body mass index: a systematic review and meta-analysis. *Sleep Med Rev* 2021;59. <https://doi.org/10.1016/j.smrv.2021.101456>.
- [78] Miller CB, Bartlett DJ, Mullins AE, Dodds KL, Gordon CJ, Kyle SD, Kim JW, D'Rozario AL, Lee RSC, Comas M, Marshall NS, Yee BJ, Espie CA, Grunstein RR. Clusters of insomnia disorder: an exploratory cluster analysis of objective sleep parameters reveals differences in neurocognitive functioning, quantitative EEG, and heart rate variability. *Sleep* 2016;39(11):1993–2004. <https://doi.org/10.5665/sleep.6230>.
- [79] Neuhauser H, Diederichs C, Boeing H, Felix SB, Jünger C, Lorbeer R, Meisinger C, Peters A, Völzke H, Weikert C, Wild P, Dörr M. Hypertension in Germany - data from seven population-based epidemiological studies. *Deutsch Arztebl Int* 2016;113(48):809–15. <https://doi.org/10.3238/arztebl.2016.0809>.
- [80] Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiue SE, Cushman M, Delling FN, Deo R, De Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, MacKey JS, Matchar DB, Matsushita K, Mussolini ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL,

- Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JHY, Alger HM, Wong SS, Muntner P. Heart disease and stroke statistics - 2018 update: a report from the American Heart Association. *Circulation* 2018;137(12). <https://doi.org/10.1161/CIR.0000000000000558>.
- [81] Lichstein KL, Wilson NM, Noe SL, Aguillard RN, Bellur SN. Daytime sleepiness in insomnia: behavioral, biological and subjective indices. *Sleep* 1994;17(8):693–702. <https://doi.org/10.1093/sleep/17.8.693>.
- [82] Seidel WF, Ball S, Cohen S, Patterson N, Yost D, Dement WC. Daytime, alertness in relation to mood, performance, and nocturnal sleep in chronic insomniacs and noncomplaining sleepers. *Sleep* 1984;7(3):230–8. <https://doi.org/10.1093/sleep/7.3.230>.
- [83] Stepanski E, Zorick F, Roehrs T, Young D, Roth T. Daytime alertness in patients with chronic insomnia compared with asymptomatic control subjects. *Sleep* 1988;11(1):54–60. <https://doi.org/10.1093/sleep/11.1.54>.
- [84] Sugerman JL, Stern JA, Walsh JK. Daytime alertness in subjective and objective insomnia: some preliminary findings. *Biol Psychiatry* 1985;20(7):741–50. [https://doi.org/10.1016/0006-3223\(85\)90153-2](https://doi.org/10.1016/0006-3223(85)90153-2).
- [85] Lanfranchi PA, Pennestri MH, Fradette L, Dumont M, Morin CM, Montplaisir J. Nighttime blood pressure in normotensive subjects with chronic insomnia: implications for cardiovascular risk. *Sleep* 2009;32(6):760–6. <https://doi.org/10.1093/sleep/32.6.760>.
- [86] Chen IY, Jarrin DC, Ivers H, Morin CM. Investigating psychological and physiological responses to the Trier Social Stress Test in young adults with insomnia. *Sleep Med* 2017;40:11–22. <https://doi.org/10.1016/j.sleep.2017.09.011>.
- [87] Johansson JK, Kronholm E, Jula AM. Variability in home-measured blood pressure and heart rate: associations with self-reported insomnia and sleep duration. *J Hypertens* 2011;29(10):1897–905. <https://doi.org/10.1097/JHH.0b013e32834abcd>.
- [88] Nano M-M, Fonseca P, Vullings R, Aarts RM, van Wouwe JP. Measures of cardiovascular autonomic activity in insomnia disorder: a systematic review. *PLoS One* 2017;12(10):e0186716. <https://doi.org/10.1371/journal.pone.0186716>.
- [89] Cespedes EM, Dudley KA, Sotres-Alvarez D, Zee PC, Daviglus ML, Shah NA, Talavera GA, Gallo LC, Mattei J, Qi Q, Ramos AR, Schneiderman N, Espinoza-Giacinto RA, Patel SR. Joint associations of insomnia and sleep duration with prevalent diabetes: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *J Diabetes* 2016;8(3):387–97. <https://doi.org/10.1111/1753-0407.12308>.
- [90] Keckes M, Lattova Z, Maurovich-Horvat E, Beiting PA, Birkmann S, Lauer CJ, Wetter TC, Wilde-Frenz J, Pollmächer T, Finkelstein D. Impaired glucose tolerance in sleep disorders. *PLoS One* 2010;5(3):e9444. <https://doi.org/10.1371/journal.pone.0009444>.
- [91] Seelig E, Ulrich K, Klarhöfer M, Scheffler K, Brand S, Holsboer-Trachsler E, Hatzinger M, Bilz S, Coles JA. Neuroendocrine regulation and metabolism of glucose and lipids in primary chronic insomnia: a prospective case-control study. *PLoS One* 2013;8(4):e61780. <https://doi.org/10.1371/journal.pone.0061780>.
- [92] Jennings JR, Muldoon MF, Hall M, Buysse DJ, Manuck SB. Self-reported sleep quality is associated with the metabolic syndrome. *Sleep* 2007;30(2):219–23. <https://doi.org/10.1093/sleep/30.2.219>.
- [93] Okubo N, Matsuzaka M, Takahashi I, Sawada K, Sato S, Akimoto N, Umeda T, Nakaji S. Relationship between self-reported sleep quality and metabolic syndrome in general population. *BMC Public Health* 2014;14(1). <https://doi.org/10.1186/1471-2458-14-562>.
- [94] Hall MH, Okun ML, Sowers MF, Matthews KA, Kravitz HM, Hardin K, Buysse DJ, Bromberger JT, Owens JF, Karpov I, Sanders MH. Sleep is associated with the metabolic syndrome in a multi-ethnic cohort of midlife women: the swan sleep study. *Sleep* 2012;35(6):783–90. <https://doi.org/10.5665/sleep.1874>.
- [95] Kazman JB, Abraham PA, Zeno SA, Poth M, Deuster PA. Self-reported sleep impairment and the metabolic syndrome among African Americans. *Ethnicity and Disease* 2012;22(4):410–5.
- [96] Ikeda M, Kaneita Y, Uchiyama M, Mishima K, Uchimura N, Nakaji S, Akashiba T, Itami O, Aono H, Ohida T. Epidemiological study of the associations between sleep complaints and metabolic syndrome in Japan. *Sleep Biol Rhythms* 2014;12(4):269–78. <https://doi.org/10.1111/sbr.12071>.
- [97] Troxel WM, Buysse DJ, Matthews KA, Kip KE, Strollo PJ, Hall M, Drumheller O, Reis SE. Sleep symptoms predict the development of the metabolic syndrome. *Sleep* 2010;33(12):1633–40. <https://doi.org/10.1093/sleep/33.12.1633>.
- [98] Lin CL, Tsai YH, Yeh MC. The relationship between insomnia with short sleep duration is associated with hypercholesterolemia: a cross-sectional study. *J Adv Nurs* 2016;72(2):339–47. <https://doi.org/10.1111/jan.12844>.
- [99] Lin SC, Sun CA, You SL, Hwang LC, Liang CY, Yang T, Bai CH, Chen CH, Wei CY, Chou YC. The link of self-reported insomnia symptoms and sleep duration with metabolic syndrome: a Chinese population-based study. *Sleep* 2016;39(6):1261–6. <https://doi.org/10.5665/sleep.5848>.
- [100] Huang L, Zhou J, Sun Y, Li Z, Lei F, Zhou G, Tang X. Polysomnographically determined sleep and body mass index in patients with insomnia. *Psychiatry Res* 2013;209(3):540–4. <https://doi.org/10.1016/j.psychres.2012.12.012>.
- [101] Crönlein T, Langguth B, Busch V, Rupprecht R, Wetter TC. Severe chronic insomnia is not associated with higher body mass index. *J Sleep Res* 2015;24(5):514–7. <https://doi.org/10.1111/jsr.12294>.
- [102] Vgontzas AN, Fernandez-Mendoza J, Miksiewicz T, Kritikou I, Shaffer ML, Liao D, Basta M, Bixler EO. Unveiling the longitudinal association between short sleep duration and the incidence of obesity: the Penn State Cohort. *Int J Obes* 2014;38(6):825–32. <https://doi.org/10.1038/ijo.2013.172>.
- [103] Lou P, Chen P, Zhang L, Zhang P, Chang G, Zhang N, Li T, Qiao C. Interaction of sleep quality and sleep duration on impaired fasting glucose: a population-based cross-sectional survey in China. *BMJ Open* 2014;4(3):e004436. <https://doi.org/10.1136/bmjopen-2013-004436>.
- [104] Schwartz S, Anderson WMD, Cole SR, Cornoni-Huntley J, Hays JC, Blazer D. Insomnia and heart disease: a review of epidemiologic studies. *J Psychosom Res* 1999;47(4):313–33. [https://doi.org/10.1016/S0022-3999\(99\)00029-X](https://doi.org/10.1016/S0022-3999(99)00029-X).
- [105] Westerlund A, Bellocco R, Sundström J, Adami HO, Åkerstedt T, Trolle Lagerros Y. Sleep characteristics and cardiovascular events in a large Swedish cohort. *Eur J Epidemiol* 2013;28(6):463–73. <https://doi.org/10.1007/s10654-013-9802-2>.
- [106] Sivertsen B, Pallesen S, Glozier N, Bjorvatn B, Salo P, Tell GS, Ursin R, Øverland S. Midlife insomnia and subsequent mortality: the Hordaland health study. *BMC Public Health* 2014;14(1). <https://doi.org/10.1186/1471-2458-14-720>.

- [107] Lallukka T, Podlipskytė A, Sivertsen B, Andruškienė J, Varoneckas G, Lahelma E, Ursin R, Tell GS, Rahkonen O. Insomnia symptoms and mortality: a register-linked study among women and men from Finland, Norway and Lithuania. *J Sleep Res* 2016;25(1):96–103. <https://doi.org/10.1111/jsr.12343>.
- [108] Healey ES, Kales A, Monroe LJ, Bixler EO, Chamberlin K, Soldatos CR. Onset of insomnia: role of life-stress events. *Psychosom Med* 1981;43(5):439–51. <https://doi.org/10.1097/00006842-198110000-00007>.
- [109] Spielman A. Assessment of insomnia. *Clin Psychol Rev* 1986;6(1):11–25. [https://doi.org/10.1016/0272-7358\(86\)90015-2](https://doi.org/10.1016/0272-7358(86)90015-2).
- [110] Riemann D, Spiegelhalder K, Feige B, Ulrich V, Berger M, Perlis M, Nissen C. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 2010;14(1):19–31. <https://doi.org/10.1016/j.smrv.2009.04.002>.
- [111] Bonnet MH, Arand DL. Hyperarousal and insomnia: State of the science. *Sleep Med Rev* 2010;14(1):9–15. <https://doi.org/10.1016/j.smrv.2009.05.002>.
- [112] Monroe LJ. Psychological and physiological differences between good and poor sleepers. *J Abnorm Psychol* 1967;72(3):255–64. <https://doi.org/10.1037/h0024563>.
- [113] Tobaldini E, Nobili L, Strada S, Casali KR, Braghierioli A, Montano N. Heart rate variability in normal and pathological sleep. *Front Physiol* 2013;4:1–11. <https://doi.org/10.3389/fphys.2013.00294>.
- [114] Laugsand LE, Vatten LJ, Bjørngaard JH, Hveem K, Janszky I. Insomnia and high-sensitivity C-reactive protein: the HUNT study, Norway. *Psychosom Med* 2012;74(5):543–53. <https://doi.org/10.1097/PSY.0b013e31825904eb>.
- [115] Burgos I, Richter L, Klein T, Fiebich B, Feige B, Lieb K, Ulrich V, Riemann D. Increased nocturnal interleukin-6 excretion in patients with primary insomnia: a pilot study. *Brain Behav Immun* 2006;20(3):246–53. <https://doi.org/10.1016/j.bbi.2005.06.007>.
- [116] Clark AJ, Dich N, Lange T, Jennum P, Hansen ÅM, Lund R, Rod NH. Impaired sleep and allostatic load: cross-sectional results from the Danish Copenhagen aging and midlife biobank. *Sleep Med* 2014;15(12):1571–8. <https://doi.org/10.1016/j.sleep.2014.07.013>.
- [117] Floam S, Simpson N, Nemeth E, Scott-Sutherland J, Gautam S, Haack M. Sleep characteristics as predictor variables of stress systems markers in insomnia disorder. *J Sleep Res* 2015;24(3):296–304. <https://doi.org/10.1111/jsr.12259>.
- [118] de Zambotti M, Cellini N, Baker FC, Colrain IM, Sarlo M, Stegagno L. Nocturnal cardiac autonomic profile in young primary insomniacs and good sleepers. *Int J Psychophysiol* 2014;93(3):332–9. <https://doi.org/10.1016/j.ijpsycho.2014.06.014>.
- [119] Fernandez-Mendoza J. The insomnia with short sleep duration phenotype: an update on its importance for health and prevention. *Curr Opin Psychiatr* 2017;30(1):56–63. <https://doi.org/10.1097/YCO.0000000000000292>.
- [120] Buysse DJ. Sleep health: can we define it? does it matter? *Sleep* 2014;37(1):9–17. <https://doi.org/10.5665/sleep.3298>.
- [121] Strand LB, Laugsand LE, Wisloff U, Nes BM, Vatten L, Janszky I. Insomnia symptoms and cardiorespiratory fitness in healthy individuals: the Nord-Trøndelag health study (HUNT). *Sleep* 2013;36(1):99–108. <https://doi.org/10.5665/sleep.2310Norway>.
- [122] Castro-Diehl C, Wood AC, Redline S, Reid M, Johnson DA, Maras JE, Jacobs DR, Shea S, Allison C, St-Onge MP. Mediterranean diet pattern and sleep duration and insomnia symptoms in the Multi-Ethnic Study of Atherosclerosis. *Sleep* 2018;41(11). <https://doi.org/10.1093/sleep/zsy158>.
- [123] Grandner MA, Jackson N, Gerstner JR, Knutson KL. Sleep symptoms associated with intake of specific dietary nutrients. *J Sleep Res* 2014;23(1):22–34. <https://doi.org/10.1111/jsr.12084>.
- [124] Grandner MA, Kripke DF, Naidoo N, Langer RD. Relationships among dietary nutrients and subjective sleep, objective sleep, and napping in women. *Sleep Med* 2010;11(2):180–4. <https://doi.org/10.1016/j.smrv.2009.07.014>.
- [125] Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Barry MJ, Boyd C, Chow RD, Fitterman N, Harris RP, Humphrey LL, Manaker S, McLean R, Mir TP, Schünemann HJ, Vijan S, Wilt T. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American college of physicians. *Ann Intern Med* 2016;165(2):125–33. <https://doi.org/10.7326/M15-2175>.
- [126] St-Onge MP, Grandner MA, Brown D, Conroy MB, Jean-Louis G, Coons M, Bhatt DL. Sleep duration and quality: impact on lifestyle behaviors and cardiometabolic health: a scientific statement from the American heart association. *Circulation* 2016;134(18):e367. <https://doi.org/10.1161/CIR.0000000000000444>.
- [127] Li Y, Yang Y, Li Q, Yang X, Wang Y, Ku WL, Li H. The impact of the improvement of insomnia on blood pressure in hypertensive patients. *J Sleep Res* 2017;26(1):105–14. <https://doi.org/10.1111/jsr.12411>.
- [128] McGrath ER, Espie CA, Power A, Murphy AW, Newell J, Kelly C, Duffy N, Gunning P, Gibson I, Bostock S, O'Donnell MJ. Sleep to lower elevated blood pressure: a randomized controlled trial (slept). *Am J Hypertens* 2017;30(3):319–27. <https://doi.org/10.1093/ajh/hpw132>.
- [129] Bathgate CJ, Edinger JD, Krystal AD. Insomnia patients with objective short sleep duration have a blunted response to cognitive behavioral therapy for Insomnia. *Sleep* 2017;40(1). <https://doi.org/10.1093/sleep/zsw012>.

Chapter 35

Sleep apnea and cardiometabolic disease risk

Bernie Sunwoo^a and Atul Malhotra^{a, b}

^aDepartment of Medicine, Division of Pulmonary, Critical Care, Sleep Medicine and Physiology, University of California San Diego, San Diego, CA, United States; ^bUCSD, Medicine, La Jolla, CA, United States

What is OSA?

Obstructive sleep apnea (OSA) is the most common form of sleep disordered breathing. OSA is characterized by recurrent collapse of the soft tissues of the upper airway resulting in partial or complete cessation of airflow. Importantly, OSA is distinguished from central sleep apnea in that OSA patients continue to make respiratory efforts throughout the apnea. The mechanisms that cause OSA have been the subject of intense investigation over the last 20 years, during a surge in sleep apnea diagnoses, evolving treatment strategies, and a better understanding of sleep apnea's contribution to cardiovascular disease.

The upper airways, characterized by the oro- and nasopharyngeal spaces, are flexible multipurpose structures that accommodate mastication, deglutition of solids and liquids, clearance of secretions, phonation, and respiration. Instead of the rigid cartilaginous support structure that characterizes the first few generations of lower airways, the upper airway relies on a complex array of muscles for support. Complete and partial airway closure is an essential part of swallowing and phonation. However, this capacity becomes pathological when closure occurs repetitively during sleep. Although the threshold for normal versus abnormal is debated, patients with OSA have respiratory events in sufficient frequency to cause clinical consequences.

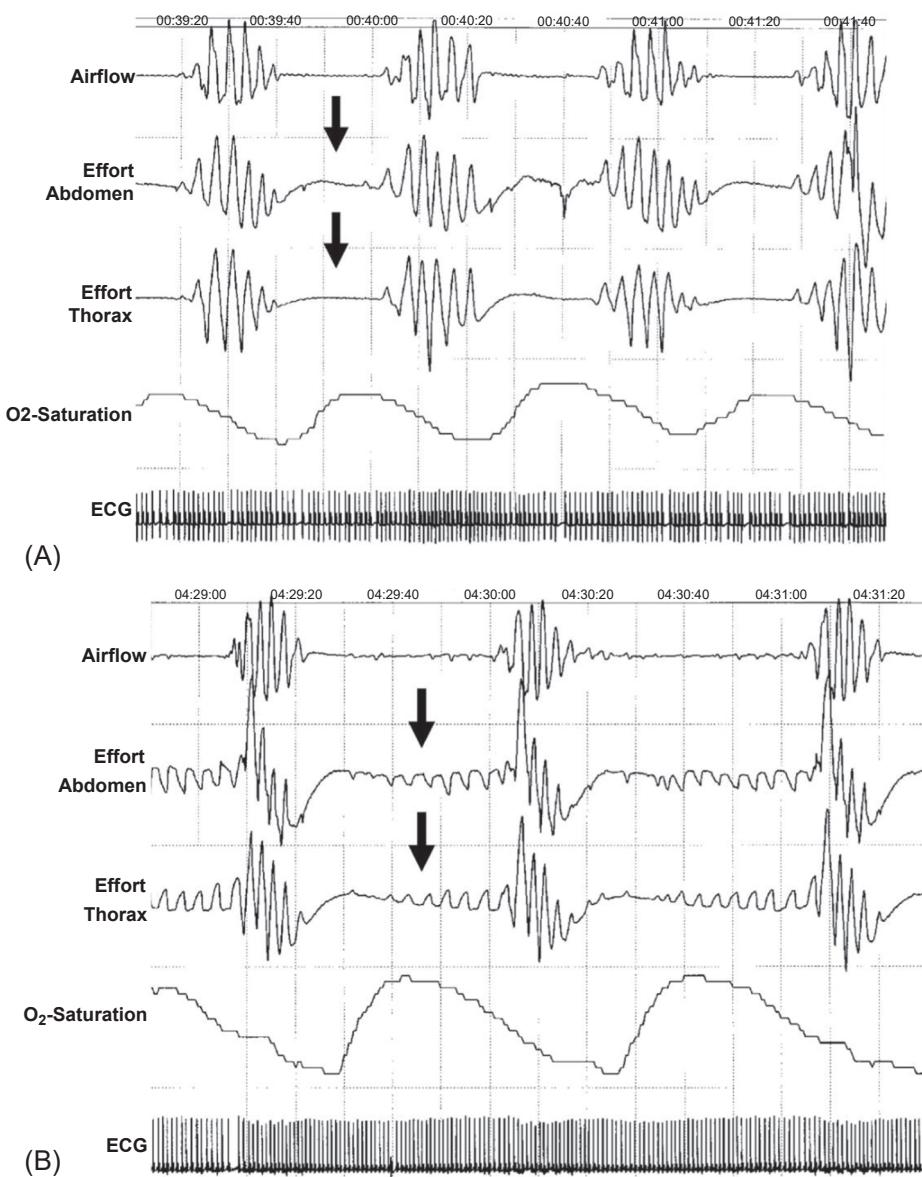
Patients with OSA have one or more anatomical or physiological predisposition to increase propensity for airway collapse. OSA patients may have crowded anatomy, with narrowing at different points of the upper airway. Obesity, with resultant increase in neck circumference and neck soft tissues, is associated with sleep apnea as well. Upper airway dilator muscle function is also important since OSA patients have increased activity of these muscles during wakefulness ostensibly in

compensation for anatomical deficiency [1], but a fall in dilator activity at sleep onset yields collapse of a vulnerable airway. Finally, sedative/hypnotic drugs and alcohol are all positively associated with worsening sleep disordered breathing, likely due to their depressive effect on airway muscle tone ([Fig. 35.1](#)).

Apnea itself is characterized by a steady rise in carbon dioxide and fall in oxygen as the patient makes ineffective respiratory efforts that do not result in adequate air flow. Were apnea to continue indefinitely, the patient would expire. However, by themselves, neither hypoxia nor hypercapnia is the primary trigger for the body to intervene during these failed efforts. Rescue from apnea, in the form of cortical arousal and engagement of the dilator muscles of the upper airway, is instead triggered by increasingly negative pleural pressures, generated by the actions of the muscles of inspiration to expand the lung in the absence of airflow [2]. Patients are not typically aware of these arousals, but the requisite muscles are engaged for airway opening and restoring adequate ventilation ([Fig. 35.2](#)).

Treatment of OSA has focused on correction of the anatomical and physiological predispositions listed above. Both dietary weight loss and exercise have been shown to improve and even cure sleep apnea, with weight loss surgery studies often using correction of sleep disordered breathing as an important outcome. Avoidance of sedating medications and abstinence from alcohol are encouraged in all patients with OSA. In positional therapy, a wedge pillow or some other prop is used to maintain side sleep and thus lessen the degree of airway collapse due to gravity. Mandibular advancement devices, dental orthotics that push the mandible forward and thus tether open the airway, are used in a subset of patients. Their use is limited by patient anatomy and comfort during sleep. Finally, surgical treatments, including the uvulopalatopharyngoplasty, have

FIGURE 35.1 Sleep study examples of (A) central sleep apnea and (B) obstructive sleep apnea, differentiated by respiratory effort signals.



mostly shown variable efficacy [3]. In more recent years, nocturnal hypoglossal nerve stimulation has shown promise as a method to maintain airway patency without triggering cortical arousal.

By far the most common and well-studied OSA treatment is the use of positive airway pressure (PAP) devices to stent open the airway by providing inspiratory and expiratory airway transmural pressure. Continuous positive airway pressure (CPAP) devices have evolved considerably in recent years, and now are capable of collecting data on apneic events, and adjusting applied pressure based on physiological needs. Modern CPAP machines also standardly heat and humidify the air being provided to the

patient. Three common masks are used: an oronasal mask sealing over the nose and mouth, a nasal mask that seals around the nose, and nasal “pillows,” a small chamber that rests on the upper lip, with fitted prongs that maintain a seal with the nares.

Who gets OSA?

Symptomatic OSA with daytime somnolence affects 3%–7% of adult men and 2%–5% of adult women. The most commonly recognized risk factors are weight, age, and male gender, with a male to female ratio of around 2–3:1 when population surveys are performed [4]. Because men

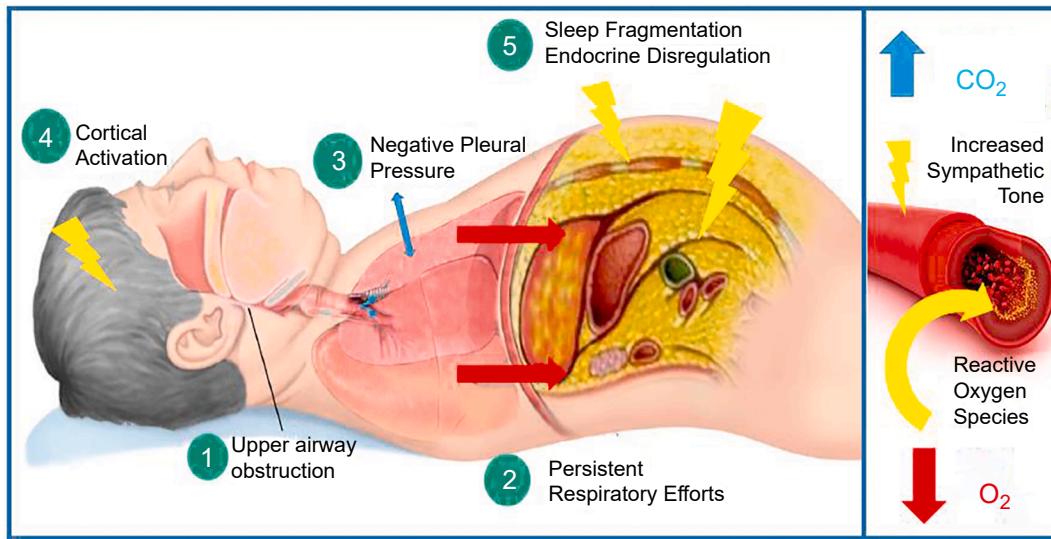


FIGURE 35.2 Pathophysiological mechanisms and consequences of obstructive sleep apnea.

are referred much more often for sleep apnea testing than women, the prevalence of sleep apnea diagnoses has a sex ratio between 5 and 8:1 [5]. It is unclear if this difference in referral patterns is due to differences in clinical suspicion in referring providers, differences in disease presentation, or other factors.

Both overweight and obese status are associated with increased risk of OSA, as is weight gain regardless of final BMI, with a 32% increase in AHI and sixfold increase in moderate/severe OSA symptoms with a weight gain of 10% [6]. Studies that have attempted to demonstrate an independent association of waist circumference or neck circumference have had mixed results [7,8]. Sleep apnea increases significantly with age; in men, an AHI >10 events per hour was present in 3.2% of patients aged 20–44 years, 11.3% of those ages 45–64 years, and 18.1% of those >65 years of age [9]. In women, the progression is equally dramatic: 0.6%, 2.0%, and 7.0% in the corresponding cohorts [10]. Interestingly, estrogen, progesterone, and testosterone may all play roles in the difference in sleep apnea prevalence between the sexes [10]. In general, both men and women have worsening sleep quality with age, with more interruptions and a decrease in the amount of sleep per night. With respect to sleep apnea, it is hypothesized that increased neck fat deposition and tissue laxity may additionally contribute [11,12].

In addition to the above, several medical conditions make sleep apnea more likely. Both snoring and apneas increase during pregnancy especially in the third trimester [13], despite a decrease in supine sleep. Alcohol use can induce apneas in otherwise healthy sleepers [14] and worsens apneas and hypoxia in those with existing sleep apnea [15]. Current smokers are more likely to snore and have OSA, at least in some studies [16]. Finally, PCOS in

women and Down's syndrome in both sexes are associated with very high (>60%) prevalence of OSA [17,18].

Does having OSA make you more likely to have cardiovascular disease?

Obstructive sleep apnea has been associated with hypertension, coronary artery disease, stroke, heart failure, and arrhythmias. In men with severe sleep disordered breathing, increased coronary and cerebrovascular morbidity and mortality have been reported [19,20]. Additionally, there is a dose response to this association, with worsening apnea-hypopnea indices being associated with greater cardiovascular morbidity, further suggesting a potential causal link. Nevertheless, the precise mechanisms by which OSA brings about cardiovascular disease remain unclear, and the presence of many common risk factors, such as obesity, age, and alcohol/cigarette use, further complicates distinguishing association from causation. Studies have explored the influence of OSA treatment on various cardiovascular end points to delineate better this relationship between OSA and cardiovascular disease.

Hypertension

An increased prevalence of hypertension has been consistently shown in OSA [21–24], and a dose-response effect between severity of OSA and blood pressure has been demonstrated [21]. 71% Of patients with resistant hypertension, defined as uncontrolled hypertension requiring at least three antihypertensive agents, have been shown to have OSA compared to 38% of patients with controlled hypertension, and OSA is a common cause of secondary hypertension [25–27].

A causal relationship between OSA and hypertension is supported by multiple studies now showing modest but clinically relevant reductions in blood pressure with OSA treatment. CPAP has been shown to improve nocturnal nondipping and daytime hypertension. A meta-analysis of 4888 patient showed CPAP reduced systolic blood pressure on average by 2.5 mmHg and diastolic blood pressure by 2.0 mmHg. Similar reductions in blood pressure have been shown with oral appliance therapies [28]. Studies have shown greater blood pressure improvement in patients with more severe OSA and in those with resistant hypertension [29,30]. This reduction in blood pressure has also been associated with increased CPAP adherence further strengthening the relationship between OSA and hypertension.

Coronary artery disease

OSA has been associated with cardiovascular events related to coronary artery disease [20,31]. Participants in the Wisconsin Sleep Cohort Study with severe sleep disordered breathing were 2.6 times more likely to have an incident coronary heart disease as defined by new reports of myocardial infarction, coronary revascularization procedures, congestive heart failure, and cardiovascular death, compared to participants without [31]. Similarly, Marin et al. demonstrated a higher incidence of fatal cardiovascular events and nonfatal cardiovascular events defined as nonfatal myocardial infarction, nonfatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography in patients with severe untreated OSA compared to milder OSA and healthy participants. CPAP treatment of OSA was associated with reduced cardiovascular risk compared to severe untreated OSA [19]. However, these observational studies fall short of proving cardiovascular benefits of CPAP.

Randomized trials exploring the effects of CPAP treatment on cardiovascular events including coronary artery disease are mixed. The SAVE trial was a multi-center randomized trial of 2717 adults with moderate to severe OSA and coronary or cerebrovascular disease randomized to CPAP therapy plus usual care or usual care alone. After a mean follow up of 3.7 years, CPAP did not significantly reduce the composite end point from death from cardiovascular causes, myocardial infarction, stroke or hospitalization for unstable angina, and heart failure of transient ischemic attack. No significant differences were observed in any of the cause-specific cardiovascular end points including myocardial infarction or hospitalization for unstable angina [32]. The RICCADS trial randomized 244 nonsleepy patients with newly revascularized coronary artery disease and moderate to severe OSA to CPAP or usual care. Over a median follow-up of 57 months, no statistically significant difference was

observed in the incidence of the primary end point of repeat vascularization, myocardial infarction, stroke, and cardiovascular mortality [33]. This study like the SAVE trial was limited by poor CPAP adherence, and when adjusted, on-treatment analysis showed a significant cardiovascular risk reduction in those who used CPAP ≥ 4 compared to <4 h per night.

A reverse causal pathway whereby coronary artery disease and myocardial infarction worsens sleep disordered breathing has also been proposed. In the Sleep Heart Health Study, participants without cardiovascular disease completed two polysomnograms 5 years apart. Participants who developed incident cardiovascular events including myocardial infarction, heart failure, and stroke had greater increases in both mean obstructive and central apnea indices compared with patients without incident cardiovascular disease [34].

Others have examined the association between OSA and identified atherogenic risk factors such as dyslipidemia, endothelial dysfunction, and inflammatory markers to try and better elucidate the relationship between OSA and coronary artery disease [35]. Despite experimental studies on mouse models showing increasing levels of triglyceride-rich lipoproteins with intermittent hypoxemia, cross-sectional human studies have not consistently supported a relationship between OSA and dyslipidemia. Studies on dyslipidemia are particularly challenged by the confounding effects of obesity [36,37]. Similarly studies looking at CPAP treatment on fasting lipid profiles have not shown a consistent improvement in the lipid profile but are methodologically limited. Studies on endothelial dysfunction, another recognized marker of atherosclerosis, largely support an association between OSA and endothelial dysfunction, strengthened by demonstration of improvement in endothelial dysfunction with CPAP therapy [35,38–42].

Cerebrovascular disease

Given shared atherogenic risk factors in cerebrovascular disease, it is not surprising that a high prevalence of sleep disordered breathing has been reported in stroke patients. Sleep-disordered breathing has been identified as both an independent risk factor for stroke and a consequence of strokes [43–46]. In one observational cohort study of 2011 consecutive adults who underwent polysomnography, OSA was significantly associated with incident stroke with a hazard ratio of 1.97 after adjusting for body mass index and cardiovascular risk factors [47]. A higher risk of stroke has been shown with higher apnea-hypopnea indices suggesting a dose-response relationship [44]. A dose-response relationship has been also been demonstrated between severity of sleep-disordered breathing and risk of recurrent vascular

events and all-cause mortality in stroke and TIA patients [48]. Following strokes, sleep-disordered breathing has been associated with worse cognitive and functional outcomes [49]. Consequently, a sleep study is recommended in TIA and stroke patients [50]. This is especially relevant given studies showing improvements in neurologic recovery and recurrent vascular events with CPAP treatment poststroke. There remains however conflicting evidence on the effects of CPAP therapy in reducing stroke risk and further studies are needed [45].

Heart failure

Sleep-disordered breathing, including OSA and central sleep apnea, is found in at least 50% of patients with heart failure [51]. A bidirectional relationship between sleep disordered breathing and heart failure exists. Gottlieb et al. followed a total of 1927 men and 2495 women aged ≥ 40 years free of heart failure over a median of 8.7 years. Men with severe OSA were 58% more likely to develop heart failure compared to those without OSA. This association was not observed in females [52]. In another cohort of community dwelling older men, central sleep apnea was also shown to be associated significantly with development of clinical heart failure and increased risk of decompensated heart failure [53]. Conversely, central sleep apnea and Cheyne-Stokes respiration have been shown to be a poor prognostic factor in heart failure, associated with increased postdischarge mortality and hospital readmission in acute heart failure [54–57].

CPAP treatment of OSA has been shown to improve symptoms and cardiac function and is the treatment of choice for OSA in heart failure [58–61]. However, the optimal management of central sleep apnea in heart failure, if any beyond medical optimization of the heart failure, is uncertain. The CANPAP trial randomized 258 heart failure patients (mean ejection fraction 24.5%) with CSA to CPAP or medical therapy alone and was stopped early due to lack of difference in transplant-free survival observed between the two groups [62]. This study was limited by variable CPAP adherence and posthoc subgroup analysis suggested a survival advantage in those effectively treated with CPAP to reduce the apnea-hypopnea index to below 15 events/h [63]. Adaptive servoventilation is a mode of PAP that adjusts the level of inspiratory support above an expiratory PAP with the goal of stabilizing ventilator instability. Smaller studies on ASV in heart failure with CSA have shown improvement in the apnea-hypopnea index and cardiac function, but a recent randomized controlled trial, the SERVE-HF trial ASV, has questioned the benefits of ASV in systolic heart failure patients with CSA [64,65].

SERVE-HF randomized 1325 heart failure with reduced ejection fraction $\leq 45\%$ patients with moderate to

severe, predominantly central sleep apnea to ASV or medical management. While ASV improved the apnea-hypopnea index, there was no difference in the incidence of the primary endpoint of all-cause mortality, lifesaving cardiovascular intervention, or unplanned hospitalization for heart failure with ASV. An unexpected 34% increase in all-cause and cardiovascular mortality was observed in the ASV group [66]. Various explanations have been postulated for this unexpected finding including methodological limitations, but the SERVE-HF resulted in an abrupt paradigm shift in the treatment of central sleep apnea in systolic heart failure including guidelines recommending against the use of ASV in systolic heart failure with predominantly central sleep apnea. Due to the results of SERVE-HF, a study of 126 hospitalized heart failure patients with moderate to severe SDB randomized to ASV, and optimized medical therapy or medical therapy alone was discontinued prematurely. A prespecified subgroup analysis suggested a positive effect of ASV in patients with heart failure with preserved ejection fraction, but this study was again limited by variable ASV adherence [67]. Ongoing studies [68] including the ADVENT-HF trial are in progress to try to delineate better the role of PAP in central sleep apnea.

Arrhythmias

While coronary artery disease and heart failure can result in arrhythmias, OSA itself has been associated with a higher frequency of arrhythmias. In the Sleep Heart Health Study, a multicenter cohort of approximately 6400 patients aged over 40 years with and without severe sleep-disordered breathing, individuals with severe sleep disordered breathing had four times the odds of atrial fibrillation, three times the odds of nonsustained ventricular tachycardia, and almost twice the odds of complex ventricular ectopy [69]. Additional studies have supported this association between OSA and atrial fibrillation with both an increased prevalence of atrial fibrillation described in patients with OSA and an increased prevalence of OSA described in patients with atrial fibrillation [69–75]. OSA has also been identified as a predictor for recurrence of atrial fibrillation following cardioversion or ablation. In a meta-analysis of 3995 patients who underwent pulmonary vein isolation, patients with OSA had a 25% greater risk of atrial fibrillation recurrence than those without OSA [76]. Treatment of OSA has been shown to reduce this risk of atrial fibrillation recurrence [77–79]. Studies exploring the association between OSA and bradycardias and sinus pauses are fewer and more mixed. However, improvement in bradycardia was demonstrated in a small subset of patients with moderate or severe OSA implanted with a loop recorder following CPAP treatment [80].

Why does OSA make you more likely to have cardiovascular disease?

The strong association between the presence of OSA and cardiovascular comorbidity prompts the question of how. Proposed mechanisms focus on the apneic event as the key stressor, with the hope of distinguishing the unique risks posed by OSA, independent of its common comorbidities. Each component of the apneic event (adrenergic response, hypoxia, and sleep fragmentation) has a body of evidence linking that element with worsening cardiovascular disease.

Apneas trigger a significant adrenergic response that has been correlated with daytime systemic hypertension. Patients with sleep apnea have heightened sympathetic tone throughout the day which only increases with sleep, in contrast to normal controls. Apneic events trigger further increases in sympathetic tone, yielding marked surges in blood pressure [81]. CPAP treatment abates these spikes in sympathetic activity and decreases the resting daytime and sleeping sympathetic tone [81,82].

The second deleterious consequence of apnea is pathological hypoxia. Most human beings have a slight decrease in oxygen levels during sleep, which corresponds with a slight drop in body temperature and oxygen consumption and is not deleterious. However, patients with moderate or severe sleep apnea or mild sleep apnea together with underlying pulmonary comorbidities can have profound desaturations during their apneic events. This intermittent hypoxia generates reactive oxygen species (ROS) that cause endothelial dysfunction through a variety of mechanisms. First, reactive oxygen species lead to increased lipid peroxidation [68] and oxidation of the protein side chains of endothelial cells [83]. The resulting endothelial dysfunction makes blood vessels less responsive to usual vasodilatory stimuli, such as nitric oxide [84], a phenomenon that partially reverses with CPAP therapy [85,86], and prolonged resistance to endothelial-mediated vasodilation leads to atherosclerotic changes [87], ultimately contributing to coronary artery disease and cerebrovascular disease. Reactive oxygen species also trigger endothelin release, which is associated with systemic hypertension and abates with treatment with CPAP [88].

A third consequence of obstructive apnea is sleep fragmentation, which in turn results in daytime symptoms and neurocognitive dysfunction. Arousals combined with hypoxemia and other stimuli are also thought to contribute to raised blood glucose and predisposition to diabetes. In healthy sleep, cortisol levels decline along with blood glucose levels, but when sleep periods are shortened or total sleep curtailed, multiple studies have demonstrated worsening glycemic control. Further studies have extended this observation to demonstrate similar findings in patients

with OSA [89]. Worsening apnea, as measured by hypoxic events and AHI, is correlated with both increased hyperglycemia on average [90] and glycemic variability [91]. These effects may be mediated by a reduction in glucagon-like peptide 1 response to feeding [90] or elevated fasting incretin levels (either glucagon-like peptide 1 or gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide) [92]. However, interventional studies using CPAP in OSA have shown somewhat variable effect on glucose control, perhaps related to variable PAP adherence in these studies.

What happens if we reduce apneic events?

The mainstay of OSA treatment is the use of continuous positive-airway pressure devices to maintain upper airway patency by providing a pneumatic splint. Patients beginning CPAP therapy often report getting their first restful night of sleep in years, and the data tend to back up these anecdotal reports. Sleep studies performed on CPAP demonstrate significant reduction in the apnea-hypopnea index and improvement in oxygenation, across the spectrum of OSA severity, as well as elimination of snoring and improvement in sleep fragmentation. Daytime sleepiness significantly improves, especially in severe OSA, as measured by patient self-assessment and/or by objective testing. Less subjectively, a reduction in road-traffic accidents has also been demonstrated, a major endpoint given the contribution of sleepiness to accidents. Patients also report improvement in their thinking and coordination, but the data here are more mixed, whether assessing via neuropsychological testing or functional neuroimaging. The Apnea Positive Pressure Long-term Efficacy Study (APPLES) was a 6-month randomized, double-blind, sham-controlled study assessing the effects of CPAP on neurocognitive variables in OSA patients and at 2 months significant improvements were seen only in the executive and frontal lobe function variable [93]. However, the study had a number of dropouts which limited power and the endpoints were questioned by some investigators, leading the results to be regarded as not definitive.

As discussed, studies exploring the impact on secondary cardiovascular endpoints, such as lipid metabolism, glycemic control, inflammatory markers, or blood pressure control, have all demonstrated significant improvement with CPAP use. The success of CPAP in improving these secondary markers, which are also part of the mechanistic explanation for the OSA/cardiovascular link, has led physicians and researchers to be hopeful for the impact of CPAP on cardiovascular morbidity and mortality. Until recently, this improvement was assumed, in the absence of large prospective studies to confirm it.

Unfortunately, with the reporting of the SAVE and RICCADSA trials, these expectations have been questioned [33,94,95]. The SAVE and RICCADSA trials showed no beneficial effect of CPAP on risk of cardiovascular disease in nonsleepy patients with moderate or severe OSA and established cardiovascular disease. This failure prompts the question of why. Was adherence to PAP too low? Was PAP therapy too late in this population with pre-existing cardiovascular disease, the endovascular damage having already been done? Is it necessary to eliminate apneas and hypopneas, rather than significantly reduce them? Regardless, as of yet, no randomized trial has demonstrated a mortality benefit with PAP therapy in OSA. Further well-designed studies are required to clarify the relationship between OSA and cardiovascular disease and the impact of CPAP therapy on overall cardiovascular disease. Until then, current clinical guidelines recommend CPAP for moderate to severe OSA with or without symptoms or mild OSA if accompanied by associated symptoms and/or cardiovascular disorders including hypertension, ischemic heart disease, or stroke [96].

Conclusion

OSA is an exciting topic with data rapidly evolving regarding its pathogenesis and potential treatment. In the future, randomized trials may need to stratify carefully which patients are likely to benefit from a particular intervention perhaps based on biomarkers. Personalized medicine approaches are also being developed to guide interventions for OSA based on the mechanism underlying apnea in a given individual. Only by further clinical and basic research are new therapies and approaches for OSA likely to emerge.

References

- [1] Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). *J Clin Investig* 1992;89(5):1571–9. <https://doi.org/10.1172/JCI115751>.
- [2] Gleeson K, Zwillich CW, White DP. The influence of increasing ventilatory effort on arousal from sleep. *Am Rev Respir Dis* 1990;142(2):295–300. <https://doi.org/10.1164/ajrccm/142.2.295>.
- [3] Ji HC, Cho SH, Kim S-N, Suh JD, Cho JH. Predicting outcomes after uvulopalatopharyngoplasty for adult obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2016;155(6):904–13. <https://doi.org/10.1177/0194599816661481>.
- [4] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328(17):1230–5. <https://doi.org/10.1056/NEJM199304293281704>.
- [5] Strohl KP, Redline S. Recognition of obstructive sleep apnea. *Am J Respir Crit Care Med* 1996;154(2):279–89. <https://doi.org/10.1164/ajrccm.154.2.8756795>.
- [6] Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000;284(23):3015–21. <https://doi.org/10.1001/jama.284.23.3015>.
- [7] Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol* 2005;99(4):1592–9. <https://doi.org/10.1152/japplphysiol.00587.2005>.
- [8] Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM. Predictors of sleep-disordered breathing in community-dwelling adults: the sleep heart health study. *Arch Intern Med* 2002;162(8):893–900. <https://doi.org/10.1001/archinte.162.8.893>.
- [9] Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men. I. Prevalence and severity. *Am J Respir Crit Care Med* 1998;157(1):144–8. <https://doi.org/10.1164/ajrccm.157.1.9706079>.
- [10] Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 2001;163(3 I):608–13. <https://doi.org/10.1164/ajrccm.163.3.9911064>.
- [11] Eikermann M, Jordan AS, Chamberlin NL, Gautam S, Wellman A, Lun Lo Y-, White DP, Malhotra A. The influence of aging on pharyngeal collapsibility during sleep. *Chest* 2007;131(6):1702–9. <https://doi.org/10.1378/chest.06-2653>.
- [12] Malhotra A, Huang Y, Fogel R, Lazic S, Pillar G, Jakab M, Kikinis R, White DP. Aging influences on pharyngeal anatomy and physiology: the predisposition to pharyngeal collapse. *Am J Med* 2006;119(1):72.e9. <https://doi.org/10.1016/j.amjmed.2005.01.077>.
- [13] Pien GW, Fife D, Pack AI, Nkwuo JE, Schwab RJ. Changes in symptoms of sleep-disordered breathing during pregnancy. *Sleep* 2005;28(10):1299–305. <https://doi.org/10.1093/sleep/28.10.1299>.
- [14] Carole W, Sherry L, Taasan VC, Block AJ, Boysen PG, Wynne JW. Alcohol increases sleep apnea and oxygen desaturation in asymptomatic men. *Am J Med* 1981;71(2):240–5. [https://doi.org/10.1016/0002-9343\(81\)90124-8](https://doi.org/10.1016/0002-9343(81)90124-8).
- [15] Remmers JE. Obstructive sleep apnea. A common disorder exacerbated by alcohol. *Am Rev Respir Dis* 1984;130(2):153–5. <https://doi.org/10.1164/arrd.1984.130.2.153>.
- [16] Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. *Thorax* 1991;46(2):85–90. <https://doi.org/10.1136/thx.46.2.85>.
- [17] Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2001;86(3):1175–80. <https://doi.org/10.1210/jc.86.3.1175>.
- [18] Trois MS, Capone GT, Lutz JA, Melendres MC, Schwartz AR, Collop NA, Marcus CL. Obstructive sleep apnea in adults with Down syndrome. *J Clin Sleep Med* 2009;5(4):317–23. <https://doi.org/10.5664/jcsm.27541>.
- [19] Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365(9464):1046–53. [https://doi.org/10.1016/S0140-6736\(05\)74229-X](https://doi.org/10.1016/S0140-6736(05)74229-X).
- [20] Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM, Patel A. Sleep-disordered breathing and mortality: a prospective cohort study.

- PLoS Med 2009;6(8):e1000132. <https://doi.org/10.1371/journal.pmed.1000132>.
- [21] Hou H, Zhao Y, Yu W, Dong H, Xue X, Ding J, Xing W, Wang W. Association of obstructive sleep apnea with hypertension: a systematic review and meta-analysis. *J Glob Health* 2018;8(1). <https://doi.org/10.7189/jogh.08.010405>.
- [22] Javier Nieto F. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA* 2000;283(14):1829. <https://doi.org/10.1001/jama.283.14.1829>.
- [23] O'Connor GT, Caffo B, Newman AB, Quan SF, Rapoport DM, Redline S, Resnick HE, Samet J, Shahar E. Prospective study of sleep-disordered breathing and hypertension: the sleep heart health study. *Am J Respir Crit Care Med* 2009;179(12):1159–64. <https://doi.org/10.1164/rccm.200712-1809OC>.
- [24] Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, Skatrud J. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med* 1997;157(15):1746–52. <https://doi.org/10.1001/archinte.157.15.1746>.
- [25] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ, Lenfant C, Carter BL, Cohen JD, Colman PJ, Cziraky MJ, Davis JJ, Ferdinand KC, Gifford RW, Glick M, Havas S, Hostetter TH, Kirby L, Kolasa KM, Linas S, Manger WM, Marshall EC, Merchant J, Miller NH, Moser M, Nickey WA, Randall OS, Reed JW, Shaughnessy L, Sheps SG, Snyder DB, Sowers JR, Steiner LM, Stout R, Strickland RD, Vallbona C, Weiss HS, Whisnant JP, Wilson GJ, Winston M, Karimbakas J. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *J Am Med Assoc* 2003;289(19):2560–72. <https://doi.org/10.1001/jama.289.19.2560>.
- [26] Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, De Paula LKG, Amaro ACS, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD, Lorenzi-Filho G. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension* 2011;58(5):811–7. <https://doi.org/10.1161/HYPERTENSIONAHA.111.179788>.
- [27] Gonçalves SC, Martinez D, Gus M, De Abreu-Silva EO, Bertoluci C, Dutra I, Branchi T, Moreira LB, Fuchs SC, De Oliveira ACT, Fuchs FD. Obstructive sleep apnea and resistant hypertension: a case-control study. *Chest* 2007;132(6):1858–62. <https://doi.org/10.1378/chest.07-1170>.
- [28] Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea a systematic review and meta-analysis. *JAMA J Am Med Assoc* 2015;314(21):2280–93. <https://doi.org/10.1001/jama.2015.16303>.
- [29] Pepperell JCT, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Jo Davies R. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002;359(9302):204–10. [https://doi.org/10.1016/S0140-6736\(02\)07445-7](https://doi.org/10.1016/S0140-6736(02)07445-7).
- [30] Liu L, Cao Q, Guo Z, Dai Q. Continuous positive airway pressure in patients with obstructive sleep apnea and resistant hypertension: a meta-analysis of randomized controlled trials. *J Clin Hypertens* 2016;18(2):153–8. <https://doi.org/10.1111/jch.12639>.
- [31] Khin MH, Young T, Hagen EW, Stein JH, Finn LA, Javier Nieto F, Peppard PE. Coronary heart disease incidence in sleep disordered breathing: the Wisconsin sleep cohort study. *Sleep* 2015;38(5):677–84. <https://doi.org/10.5665/sleep.4654>.
- [32] McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q, Lorenzi-Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *J Med* 2016;375(10):919–31. <https://doi.org/10.1056/NEJMoa1606599>.
- [33] Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSa randomized controlled trial. *Am J Respir Crit Care Med* 2016;194(5):613–20. <https://doi.org/10.1164/rccm.201601-0088oc>.
- [34] Chami HA, Resnick HE, Quan SF, Gottlieb DJ. Association of incident cardiovascular disease with progression of sleep-disordered breathing. *Circulation* 2011;123(12):1280–6. <https://doi.org/10.1161/CIRCULATIONAHA.110.974022>.
- [35] Drager LF, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: an emerging risk factor for atherosclerosis. *Chest* 2011;140(2):534–42. <https://doi.org/10.1378/chest.10-2223>.
- [36] Newman AB, Nieto FJ, Gidry U, Lind BK, Redline S, Shahar E, Pickering TG, Quan SF. Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. *Am J Epidemiol* 2001;154(1):50–9. <https://doi.org/10.1093/aje/154.1.50>.
- [37] Trzepizur W, Le Vaillant M, Meslier N, Pigeanne T, Masson P, Humeau MP, Bizeux-Thaminy A, Goupil F, Chollet S, Ducluzeau PH, Gagnadoux F. Independent association between nocturnal intermittent hypoxemia and metabolic dyslipidemia. *Chest* 2013;143(6):1584–9. <https://doi.org/10.1378/chest.12-1652>.
- [38] Chami HA, Keyes MJ, Vita JA, Mitchell GF, Larson MG, Fan S, Vasan RS, O'Connor GT, Benjamin EJ, Gottlieb DJ. Brachial artery diameter, blood flow and flow-mediated dilation in sleep-disordered breathing. *Vasc Med* 2009;14(4):351–60. <https://doi.org/10.1177/1358863X09105132>.
- [39] Mary SMI, Tse H-F, Lam B, Tsang KWT, Lam W-K. Endothelial function in obstructive sleep apnea and response to treatment. *Am J Respir Crit Care Med* 2004;169(3):348–53. <https://doi.org/10.1164/rccm.200306-767oc>.
- [40] Kohler M, Craig S, Pepperell JCT, Nicoll D, Bratton DJ, Nunn AJ, Leeson P, Stradling JR. CPAP improves endothelial function in patients with minimally symptomatic OSA: results from a subset study of the MOSAIC trial. *Chest* 2013;144(3):896–902. <https://doi.org/10.1378/chest.13-0179>.
- [41] Nieto FJ, Herrington DM, Redline S, Benjamin EJ, Robbins JA. Sleep apnea and markers of vascular endothelial function in a large community sample of older adults. *Am J Respir Crit Care Med* 2004;169(3):354–60. <https://doi.org/10.1164/rccm.200306-756OC>.
- [42] Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the cardiovascular health study. *Circulation* 2007;115(18):2390–7. <https://doi.org/10.1161/CIRCULATIONAHA.106.678276>.

- [43] Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med* 2005;172(11):1447–51. <https://doi.org/10.1164/rccm.200505-702oc>.
- [44] Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med* 2010;182(2):269–77. <https://doi.org/10.1164/rccm.200911-1746OC>.
- [45] Hermann DM, Bassetti CL. Role of sleep-disordered breathing and sleep-wake disturbances for stroke and stroke recovery. *Neurology* 2016;87(13):1407–16. <https://doi.org/10.1212/WNL.0000000000003037>.
- [46] Marshall NS, Wong KKH, Cullen SRJ, Knuiman MW, Grunstein RR. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the bus-selton health study cohort. *J Clin Sleep Med* 2014;10(04):355–62. <https://doi.org/10.5664/jcsm.3600>.
- [47] Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005;353(19):2034–41. <https://doi.org/10.1056/NEJMoa043104>.
- [48] Birkbak J, Clark AJ, Rod NH. The effect of sleep disordered breathing on the outcome of stroke and transient ischemic attack: a systematic review. *J Clin Sleep Med* 2014;10(1):103–8. <https://doi.org/10.5664/jcsm.3376Denmark>.
- [49] Aaronson JA, Van Bennekom CAM, Hofman WF, Van Bezeij T, Van Den Aardweg JG, Groet E, Kylstra WA, Schmand B. Obstructive sleep apnea is related to impaired cognitive and functional status after stroke. *Sleep* 2015;38(9):1431–7. <https://doi.org/10.5665/sleep.4984>.
- [50] Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45(7):2160–236. <https://doi.org/10.1161/STR.000000000000024>.
- [51] Arzt M, Woehrle H, Oldenburg O, Graml A, Suling A, Erdmann E, Teschler H, Wegscheider K. Prevalence and predictors of sleep-disordered breathing in patients with stable chronic heart failure: the SchlaHF registry. *JACC Heart Fail* 2016;4(2):116–25. <https://doi.org/10.1016/j.jchf.2015.09.014>.
- [52] Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122(4):352–60. <https://doi.org/10.1161/CIRCULATIONAHA.109.901801>.
- [53] Javaheri S, Blackwell T, Ancoli-Israel S, Ensrud KE, Stone KL, Redline S. Sleep-disordered breathing and incident heart failure in older men. *Am J Respir Crit Care Med* 2016;193(5):561–8. <https://doi.org/10.1164/rccm.201503-0536oc>.
- [54] Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007;49(20):2028–34. <https://doi.org/10.1016/j.jacc.2007.01.084>.
- [55] Khayat R, Jarjoura D, Porter K, Sow A, Wannemacher J, Dohar R, Pleister A, Abraham WT. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. *Eur Heart J* 2015;36(23):1463–9. <https://doi.org/10.1093/eurheartj/ehu522>.
- [56] Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, Giannuzzi P. Prognostic value of Nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation* 1999;99(11):1435–40. <https://doi.org/10.1161/01.CIR.99.11.1435>.
- [57] Khayat R, Abraham W, Patt B, Vincent B, Jacob W, Porter K, Jarjoura D. Central sleep apnea is a predictor of cardiac readmission in hospitalized patients with systolic heart failure. *J Card Fail* 2012;18(7):534–40. <https://doi.org/10.1016/j.cardfail.2012.05.003>.
- [58] Colish J, Walker JR, Elmayergi N, Almutairi S, Alharbi F, Lytwyn M, Francis A, Bohonis S, Zeglinski M, Kirkpatrick IDC, Sharma S, Jassal DS. Obstructive sleep apnea: effects of continuous positive airway pressure on cardiac remodeling as assessed by cardiac biomarkers, echocardiography, and cardiac MRI. *Chest* 2012;141(3):674–81. <https://doi.org/10.1378/chest.11-0615>.
- [59] Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S-I, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003;348(13):1233–41. <https://doi.org/10.1056/nejmoa022479>.
- [60] Kasai T, Narui K, Dohi T, Yanagisawa N, Ishiwata S, Ohno M, Yamaguchi T, Momomura S-I. Prognosis of patients with heart failure and obstructive sleep apnea treated with continuous positive airway pressure. *Chest* 2008;133(3):690–6. <https://doi.org/10.1378/chest.07-1901>.
- [61] Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. *Am J Respir Crit Care Med* 2004;169(3):361–6. <https://doi.org/10.1164/rccm.200306-752oc>.
- [62] Bradley TD, Logan AG, Kimoff RJ, Séries F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005;353(19):2025–33. <https://doi.org/10.1056/NEJMoa051001Canada>.
- [63] Arzt M, Floras JS, Logan AG, Kimoff RJ, Séries F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Ryan C, Tomlinson G, Bradley TD. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation* 2007;115(25):3173–80. <https://doi.org/10.1161/CIRCULATIONAHA.106.683482>.
- [64] Sharma BK, Bakker JP, McSharry DG, Desai AS, Javaheri S, Malhotra A. Adaptive servoventilation for treatment of sleep-disordered breathing in heart failure: a systematic review and meta-analysis. *Chest* 2012;142(5):1211–21. <https://doi.org/10.1378/chest.12-0815>.
- [65] Teschler H, Döhring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001;164(4):614–9. <https://doi.org/10.1164/ajrccm.164.4.9908114>.

- [66] Cowie MR, Woehrle H, Wegscheider K, Angermann C, D'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, Teschler H. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;373(12):1095–105. <https://doi.org/10.1056/NEJMoa1506459>.
- [67] O'Connor CM, Whellan DJ, Fiuzat M, Punjabi NM, Tasissa G, Anstrom KJ, Benjafield AV, Woehrle H, Blase AB, Lindenfeld JA, Oldenberg O. Cardiovascular outcomes with minute ventilation–targeted adaptive servo-ventilation therapy in heart failure: the CAT-HF trial. *J Am Coll Cardiol* 2017;69(12):1577–87. <https://doi.org/10.1016/j.jacc.2017.01.041>.
- [68] Kizawa T, Nakamura Y, Takahashi S, Sakurai S, Yamauchi K, Inoue H. Pathogenic role of angiotensin II and oxidised LDL in obstructive sleep apnoea. *Eur Respir J* 2009;34(6):1390–8. <https://doi.org/10.1183/09031936.00009709>.
- [69] Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S. Association of nocturnal arrhythmias with sleep-disordered breathing: the sleep heart health study. *Am J Respir Crit Care Med* 2006;173(8):910–6. <https://doi.org/10.1164/rccm.200509-1442OC>.
- [70] Braga B, Poyares D, Cintra F, Guilleminault C, Cirenza C, Horbach S, Macedo D, Silva R, Tufik S, De Paola AAV. Sleep-disordered breathing and chronic atrial fibrillation. *Sleep Med* 2009;10(2):212–6. <https://doi.org/10.1016/j.sleep.2007.12.007>.
- [71] Caples SM, Somers VK. Sleep-disordered breathing and atrial fibrillation. *Prog Cardiovasc Dis* 2009;51(5):411–5. <https://doi.org/10.1016/j.pcad.2008.06.004>.
- [72] Gami AS, Friedman PA, Chung MK, Caples SM, Somers VK. Therapy Insight: interactions between atrial fibrillation and obstructive sleep apnea. *Nat Clin Pract Cardiovasc Med* 2005;2(3):145–9. <https://doi.org/10.1038/ncpcardio0130>.
- [73] Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 2004;110(4):364–7. <https://doi.org/10.1161/01.CIR.0000136587.68725.8E>.
- [74] Mehra R, Stone KL, Varosy PD, Hoffman AR, Marcus GM, Blackwell T, Ibrahim OA, Salem R, Redline S. Nocturnal arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. *Arch Intern Med* 2009;169(12):1147–55. <https://doi.org/10.1001/archinternmed.2009.138>.
- [75] Monahan K, Storfer-Isser A, Mehra R, Shahar E, Murray M, Rottman J, Punjabi N, Sanders M, Quan SF, Resnick H, Redline S. Triggering of nocturnal arrhythmias by sleep-disordered breathing events. *J Am Coll Cardiol* 2009;54(19):1797–804. <https://doi.org/10.1016/j.jacc.2009.06.038>.
- [76] Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. *Am J Cardiol* 2011;108(1):47–51. <https://doi.org/10.1016/j.amjcard.2011.02.343>.
- [77] Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, Kramer DB, Zimetbaum PJ, Buxton AE, Josephson ME, Anter E. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2013;62(4):300–5. <https://doi.org/10.1016/j.jacc.2013.03.052>.
- [78] Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, Shamsuzzaman ASM, Somers VK. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation* 2003;107(20):2589–94. <https://doi.org/10.1161/01.cir.0000068337.25994.21>.
- [79] Naruse Y, Tada H, Satoh M, Yanagihara M, Tsuneoka H, Hirata Y, Ito Y, Kuroki K, Machino T, Yamasaki H, Igarashi M, Sekiguchi Y, Sato A, Aonuma K. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. *Heart Rhythm* 2013;10(3):331–7. <https://doi.org/10.1016/j.hrthm.2012.11.015>.
- [80] Simantirakis EN, Schiza SI, Marketou ME, Chrysostomakis SI, Chlouverakis GI, Klapsinos NC, Siafasas NS, Vardas PE. Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder. *Eur Heart J* 2004;25(12):1070–6. <https://doi.org/10.1016/j.ehj.2004.04.017>.
- [81] Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Investig* 1995;96(4):1897–904. <https://doi.org/10.1172/JCI118235>.
- [82] Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation* 1999;100(23):2332–5. <https://doi.org/10.1161/01.cir.100.23.2332>.
- [83] Vatansever E, Surmen-Gur E, Ursavas A, Karadag M. Obstructive sleep apnea causes oxidative damage to plasma lipids and proteins and decreases adiponectin levels. *Sleep Breath* 2011;15(3):275–82. <https://doi.org/10.1007/s11325-010-0378-8>.
- [84] Yamauchi M, Nakano H, Maekawa J, Okamoto Y, Ohnishi Y, Suzuki T, Kimura H. Oxidative stress in obstructive sleep apnea. *Chest* 2005;127(5):1674–9. <https://doi.org/10.1378/chest.127.5.1674>.
- [85] Jelic S, Le Jemtel TH. Inflammation, oxidative stress, and the vascular endothelium in obstructive sleep apnea. *Trends Cardiovasc Med* 2008;18(7):253–60. <https://doi.org/10.1016/j.tcm.2008.11.008>.
- [86] Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, Somers VK. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 2000;102(21):2607–10. <https://doi.org/10.1161/01.cir.102.21.2607>.
- [87] Li J, Savransky V, Nanayakkara A, Smith PL, O'Donnell CP, Polotsky VY. Hyperlipidemia and lipid peroxidation are dependent on the severity of chronic intermittent hypoxia. *J Appl Physiol* 2007;102(2):557–63. <https://doi.org/10.1152/japplphysiol.01081.2006>.
- [88] Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME, Somers VK. Effects of obstructive sleep apnea on endothelin-1 and blood pressure. *J Hypertens* 1999;17(1):61–6. <https://doi.org/10.1097/00004872-199917010-00010>.
- [89] Hui P, Zhao L, Xie Y, Wei X, Ma W, Wang J, Hou Y, Ning J, Zhou L, Guo Q, Zhou S. Nocturnal hypoxemia causes hyperglycemia in patients with obstructive sleep apnea and type 2 diabetes mellitus. *Am J Med Sci* 2016;351(2):160–8. <https://doi.org/10.1016/j.amjms.2015.12.002>.
- [90] Reutrakul S, Sumritsopak R, Saetung S, Chanprasertyothin S, Anothaisintawee T. The relationship between sleep and glucagon-like peptide 1 in patients with abnormal glucose tolerance. *J Sleep Res* 2017;26(6):756–63. <https://doi.org/10.1111/jsr.12552>.

- [91] Nakata K, Miki T, Tanno M, Ohnishi H, Yano T, Muranaka A, Sato T, Oshima H, Tatekoshi Y, Mizuno M, Abe K, Miura T, Romigi A. Distinct impacts of sleep-disordered breathing on glycemic variability in patients with and without diabetes mellitus. *PLoS One* 2017;12(12):e0188689. <https://doi.org/10.1371/journal.pone.0188689>.
- [92] Matsumoto T, Harada N, Azuma M, Chihara Y, Murase K, Tachikawa R, Minami T, Hamada S, Tanizawa K, Inouchi M, Oga T, Mishima M, Chin K. Plasma incretin levels and dipeptidyl peptidase-4 activity in patients with obstructive sleep apnea. *Ann Am Thorac Soc* 2016;13(8):1378–87. <https://doi.org/10.1513/annalsats.201510-697oc>.
- [93] Kushida CA, Nichols DA, Holmes TH, Quan SF, Walsh JK, Gottlieb DJ, Simon RD, Guilleminault C, White DP, Goodwin JL, Schweitzer PK, Leary EB, Hyde PR, Hirshkowitz M, Green S, McEvoy LK, Chan C, Gevins A, Kay GG, Bloch DA, Crabtree T, Dement WC. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the apnea positive pressure long-term efficacy study (APPLES). *Sleep* 2012;35(12):1593–602. <https://doi.org/10.5665/sleep.2226>.
- [94] Barbé F, Durán-Cantolla J, Sánchez-De-La-Torre M, Martínez-Alonso M, Carmona C, Barceló A, Chiner E, Masa JF, Gonzalez M, Marín JM, García-Rio F, Diaz De Atauri J, Terán J, Mayos M, De La Peña M, Monasterio C, Del Campo F, Montserrat JM. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA* 2012;307(20):2161–8. <https://doi.org/10.1001/jama.2012.4366>.
- [95] Medeiros AKL, Coutinho RQ, Barros IML, Costa LOBF, Leite APDL, Bittencourt MS, Lustosa TC, Carvalho MMB, Lira MPF, Ferreira MNL, Lorenzi-Filho G, Drager LF, Pedrosa RP. Obstructive sleep apnea is independently associated with subclinical coronary atherosclerosis among middle-aged women. *Sleep Breath* 2017;21(1):77–83. <https://doi.org/10.1007/s11325-016-1374-4>.
- [96] Epstein LJ, Kristo D, Strollo PJ, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5(3):263–76. <https://doi.org/10.5664/jcsm.27497>.

This page intentionally left blank

Chapter 36

Comorbid insomnia and sleep apnea (COMISA)

Alexander Sweetman

School of Psychological Science, University of Western Australia, Perth, WA, Australia

Abbreviations

AHI Apnea-hypopnea index

COMISA Comorbid insomnia and sleep apnea

CBT-I Cognitive behavioral therapy for insomnia

HNS Hypoglossal nerve stimulation

ISI Insomnia severity index

OSA Obstructive sleep apnea

PAP Positive airway pressure

Potential conflicts of interest

AS reports research equipment and/or funding support from the Australian Department of Health and Aged Care, National Health and Medical Research Council, Medical Research Future Fund, Flinders University, the Flinders Foundation, the Hospital Research Foundation, Big Health, Philips Respiration, Compumedics, the Western Australian Suicide Prevention and Resilience Research Centre, the American Academy of Sleep Medicine, Panthera, and commissioned/consultancy work for Australian Doctor, Sleep Review Mag, Re-Time Australia, Air Liquide and ResMed, and Honorarium from the American Academy of Dental Sleep Medicine, Taiwan Society of Sleep Medicine, TMJ Therapy Centres, Cerebra, and the Australian and New Zealand Academy of Orofacial Pain, and is co-developer of a digital CBT for insomnia program (Bedtime Window).

History of COMISA

The first peer-reviewed paper reporting on the cooccurrence of insomnia and sleep apnea was written by Guilleminault et al. in 1973 [1]. For the next 3 decades, a small

number of case studies, review articles, and experimental trials noted the potential overlap and consequences of insomnia and sleep apnea, but overall, there were very few publications focusing on the comorbidity during this time [2–7].

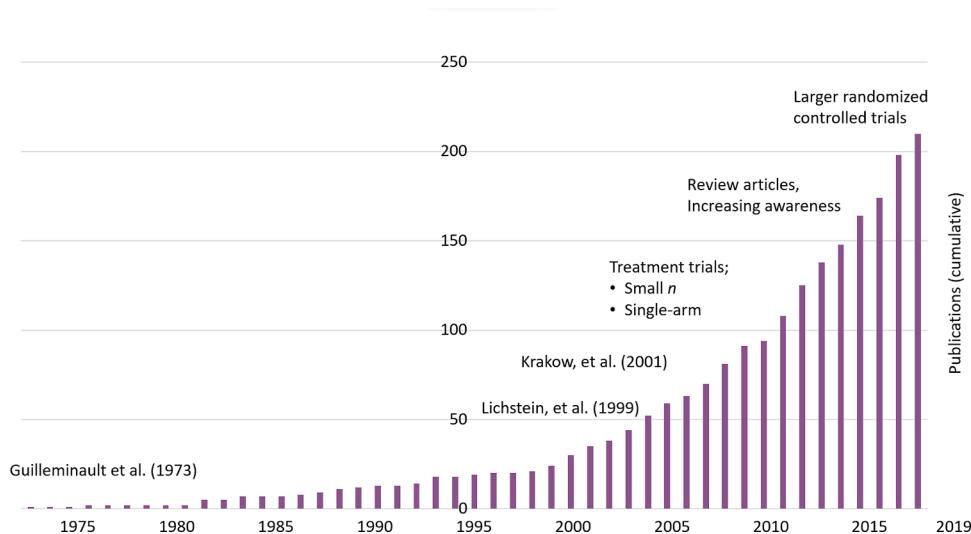
In 1999, Lichstein et al. [8] reported on the high prevalence of OSA in a sample of patients with insomnia symptoms, and in 2001, Krakow et al. [9] reported on the high prevalence of insomnia symptoms in a sample of patients with sleep disordered breathing. Following these two seminal publications, more research focusing on the high prevalence, characteristics, consequences, and treatment approaches in people with comorbid insomnia and OSA began to emerge [10–13] (Fig. 36.1).

By 2010, several studies reporting on the prevalence, consequences, and management of COMISA were reviewed by Luyster et al. [14], which drew further attention to the field. In 2017, we reviewed additional prevalence data published since 2010 and coined the term “COMISA” to draw more research and clinical attention to this prevalent and debilitating condition [15].

Behavioral sleep medicine researchers were at the forefront of COMISA research during this time, and between 2018 and 2021 several randomized controlled trials (RCTs) focusing on the use of behavioural treatment for insomnia symptoms in people with COMISA were published [16–19]. These RCTs collectively reported on the effectiveness of cognitive behavioral therapy for insomnia (CBT-I) from trained clinicians in people with COMISA, and the potential to administer CBT-I to improve subsequent management of the comorbid OSA.

Since this time, the COMISA field has expanded in several ways. Research activities focusing on underlying

FIGURE 36.1 Cumulative number of COMISA publications in scientific literature since first report in 1973. *Figure adapted from Sweetman A, Lack L, Bastien C. Co-morbid insomnia and sleep apnea (COMISA): prevalence, consequences, methodological considerations, and recent randomized controlled trials. Brain Sci 2019;9(12):371. <https://doi.org/10.3390/brainsci9120371>.*



mechanisms in COMISA have begun to emerge [20–23], a meta-analyses of COMISA prevalence published in 2019 confirmed the high comorbidity rates [24], and meta-analyses [25] and clinical trials of treatment approaches in patients with COMISA are emerging with increasing frequency [16–19,26–30]. Bidirectional relationships are a target of active research interest [23], as well as education [31] and implementation programs [26,27] to understand and improve the management of COMISA in the health system.

Characteristics

One reason for the limited widespread recognition of COMISA until the last 5–10 years may be because of historical differences in the stereotypical descriptions and presentations of insomnia and OSA [32]. For example, insomnia has historically been viewed as a sleep disorder impacting middle-aged to older adults, primarily females, and those with predisposition to anxiety or perfectionism. Alternatively, OSA has historically been viewed as a disorder also occurring in middle-to-older aged adults, but primarily impacting males presenting with excessive daytime sleepiness, overweight and obesity, and loud snoring. The heterogeneity in presenting features of both insomnia and OSA is now increasingly recognized, including the presence of clinically significant OSA without daytime sleepiness, different manifestations of OSA in males and females, and the high prevalence of insomnia in different genders, throughout the lifespan, and in the absence of anxiety or perfectionism. Both conditions present with many different combinations of personality types, occupations, and mental and physical health symptoms.

By definition, people with COMISA not only experience frequent self-reported difficulties initiating and/or maintaining sleep during the night (i.e., insomnia), but the sleep which is obtained is marked by frequent respiratory events, cortical arousals and awakenings (i.e., OSA) [33] (Fig. 36.2). Insomnia and OSA are each heterogeneous disorders, evidenced by descriptions of different presenting symptoms, phenotypes [34], subtypes [35], and clusters of different symptoms and presenting features [36,37]. Consequently, people with COMISA can also present with a variety of different manifestations of both insomnia and OSA, different reasons for seeking treatment, and previous treatment approaches and experiences.

For example, some patients with COMISA may present with a chief complaint of frequent and distressing difficulties initiating or maintaining sleep and no awareness of the presence of comorbid OSA [8], others may be aware of loud snoring and choking/gasping awakenings from sleep that precipitate prolonged awakenings. Some patients may be able to identify an initial physical or psychological stressor/s that precipitated their insomnia, while insomnia may have developed more gradually in other patients. Daytime manifestations of untreated COMISA are also diverse and may include increased physical or mental fatigue, concentration or memory difficulties, irritability or reduced mood, and daytime sleepiness. In addition, patients can also present with a diverse range and history of previous management experiences. A plethora of non-evidence-based recommendations are available online to improve symptoms of both insomnia and OSA, and many patients may have attempted a range of ineffective strategies to improve

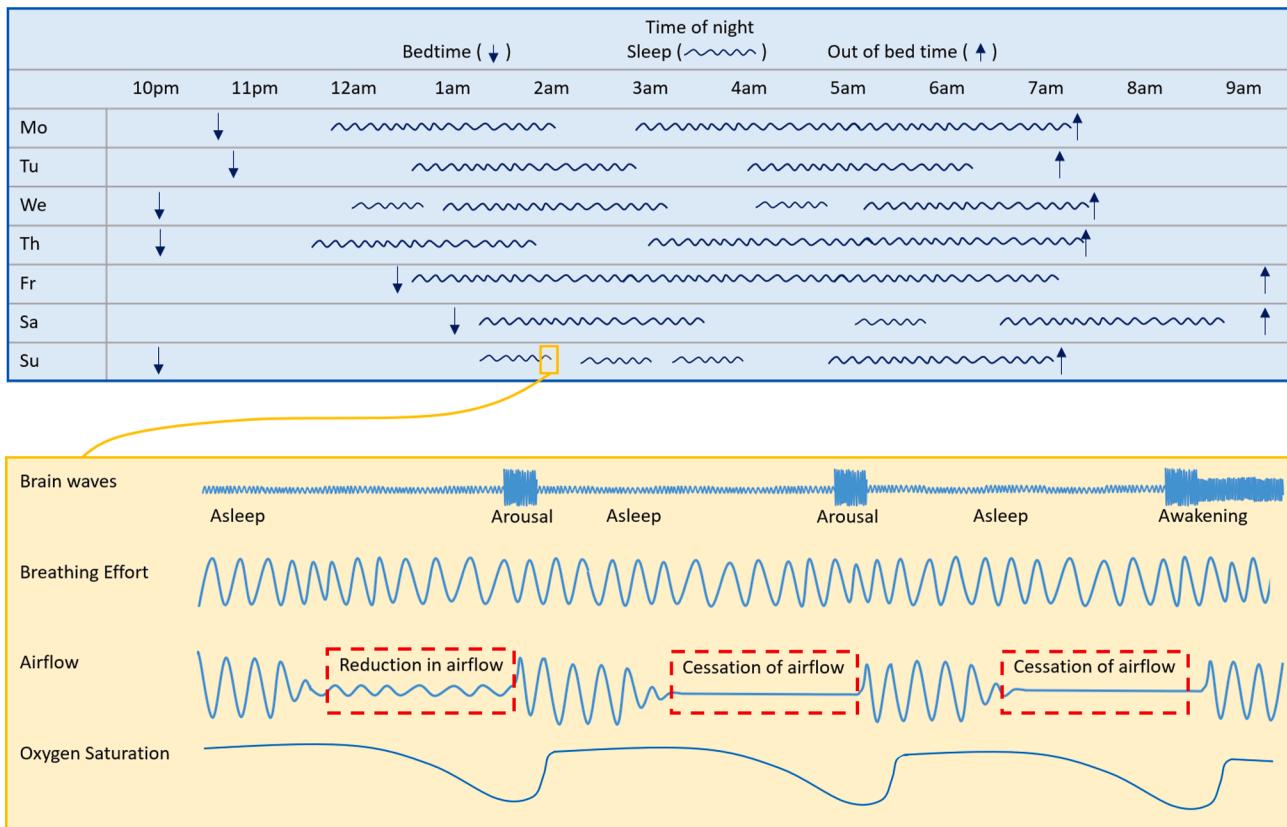


FIGURE 36.2 COMISA is characterized by sleep onset and/or maintenance difficulties (insomnia) that increase wake time and reduce sleep time, and frequent upper airway reduction and/or cessation (OSA) that often culminate in cortical arousals and awakenings and reduce sleep quality. For example, the top section shows example data from a 1-week baseline sleep-wake diary of a patient with difficulties initiating and maintaining sleep. The bottom section illustrates a snippet of sleep time interrupted by episodes of upper airway narrowing and collapse, cessation of airflow, cortical arousals, and an eventual awakening from sleep at approximately 2:00 a.m. Some awakenings may not be remembered the next morning when completing the sleep diary on the subsequent morning, and some periods of sleep that is marked by frequent respiratory events may be perceived as single long periods of wakefulness.

their sleep before presenting to healthcare settings. Some patients may have attempted and discontinued continuous positive airway pressure therapy for OSA due to negative initial experiences in the presence of untreated insomnia, while others may experience persistent insomnia symptoms despite adequate nightly use of continuous positive airway pressure therapy or other treatments for OSA. Some patients may present with a clear “chief complaint” (e.g., of either insomnia or OSA as the main factor motivating treatment-seeking) while other patients may present with general sleep difficulties/disturbance and be completely treatment naïve.

There is no single stereotypical presentation of a person with COMISA. Given the high prevalence and consequences of COMISA, it is important to assess for co-morbid OSA in all people with insomnia, and to assess for co-morbid insomnia in all people with OSA, regardless of age, gender, race, or the presence of co-morbidities.

Prevalence

Approximately 30%–50% of people with OSA report clinically significant insomnia symptoms and 30%–40% of people with insomnia have comorbid OSA. Articles by Luyster [14], Sweetman [15], Zhang [24], and Sweetman [38] have reviewed a large number of studies reporting on the high prevalence of COMISA in different settings, with varied sampling techniques, and different assessment tools and threshold for both insomnia and OSA. Most COMISA prevalence studies have been completed in sleep clinic populations, where assessment tools and patients are more readily available. Polysomnography is the “gold standard” measure of OSA presence and severity used in most COMISA prevalence studies, while insomnia is often assessed via self-report questionnaire, or diagnostic interview with a trained psychologist/clinician [15,24]. In population-based cohorts, COMISA is prevalent in approximately 1%–11% of people [39–43]. Variability

between studies is likely a result of varied sampling techniques, assessment tools, and threshold for two independent conditions.

One important implication of these high co-morbid prevalence estimates is that insomnia is generally more prevalent in people with OSA, compared with the prevalence of insomnia in the general population. In addition, the prevalence of OSA is generally higher in those with insomnia compared with the prevalence of OSA in the general population. This high co-morbid prevalence rate may indicate shared symptoms that complicate valid diagnosis of each disorder in the presence of the other [14], a referral bias in sleep clinic prevalence studies in which patients with more complex or overlapping sleep conditions are more likely to be referred to sleep clinics thereby inflating the measured prevalence of COMISA, or bi-directional relationships between insomnia and OSA that contribute to their frequent co-existence [23].

Consequences

Insomnia and OSA are each independently associated with impaired sleep, daytime function, quality of life, mental health, and physical health. Unsurprisingly, people with COMISA tend to experience worse consequences across each of these domains compared with people with neither disorder, and often compared with people with either insomnia alone or OSA alone.

Sleep

By definition, people with COMISA experience worse insomnia symptoms (e.g., self-reported difficulties initiating and/or maintaining sleep) compared with people with OSA alone, and people with COMISA experience greater severity of OSA compared with people with insomnia alone. Some studies have reported that comorbid insomnia is associated with worse OSA severity compared with OSA alone [44]; however, this association is not consistent across studies [45]. Symptoms of sleep disturbance that are nonspecific to each disorder such as nonrestorative sleep as well as general daytime impairments such as fatigue and lethargy may also be elevated in individuals with COMISA (as these symptoms may be attributable to either or both conditions in patients with COMISA) [14].

Daytime function

One of the earliest studies in the COMISA field reported no differences in neurocognitive functioning between participants with insomnia alone and COMISA [7]. However, numerous studies have since reported associations between COMISA and impairment of several domains of daytime functional performance, fatigue, and mood problems

including; neurocognitive performance [11,46], daytime sleepiness [47,48], concentration difficulties, irritability, and mood problems [9], and subscales of the Functional Outcomes of Sleep Questionnaire (intimacy, activity levels) [11]. Consequently, people with COMISA generally report worse daytime function compared with people with neither disorder and those with either disorder alone [32].

Mental health

Several studies have investigated mental health symptoms between people with neither disorder, insomnia alone, OSA alone, and COMISA. Lang et al. [49] reported that among 700 community-dwelling males, the severity and prevalence of depression symptoms were higher among people with COMISA compared with those with either disorder alone. A recent article by Jeon et al. [50] reviewed 15 studies investigating the association of COMISA and depression, and reported that the insomnia component of COMISA appears to play the predominant role in predicting cross-sectional associations with depression symptoms. Given that both insomnia and OSA are predictive of depression in longitudinal studies, it would also be of interest to investigate whether COMISA is associated with an increased risk of incident depression [51,52], and consequently, whether there is an opportunity to treat COMISA before depression develops to prevent the onset of depression or exacerbation of depression symptoms to major depressive disorder.

Physical health

Insomnia and OSA are each associated with reduced physical health [53,54]. COMISA is generally associated with a higher risk of cardiovascular disease compared with those with insomnia alone and neither condition [41,55]. However, research investigating risk of cardiovascular disease between people with COMISA and OSA alone is mixed [40,43,56,57].

Lechat et al. [58] recently used the Sleep Heart Health Study data to investigate the association between COMISA, insomnia alone, and OSA alone with prevalent cardiovascular disease and incident cardiovascular events, compared with people with neither condition (control). In fully controlled models, COMISA was associated with an increased risk of cardiovascular disease at baseline ($OR = 1.75$, 95% CI = 1.14–2.67), however OSA alone and insomnia alone were not associated with increased prevalence of cardiovascular disease compared with control. After excluding participants with preexisting cardiovascular disease, COMISA was also associated with an increased risk of experiencing a cardiovascular event in unadjusted models ($HR = 2.00$, 95% CI = 1.33–2.99), but not after controlling for all prespecified covariates

($HR = 1.37$, 95% CI = 0.91–2.06). Given that many patients with COMISA and preexisting cardiovascular disease were excluded from analyses of incident disease risk, it is possible that the lack of statistically significance was partly due to inadequate power.

Quality of life

The mental and physical health associations of COMISA may contribute to a reduced quality of life [41,47,59,60]. Bjornsdottir et al. [59] used data from the Icelandic Sleep Apnea Cohort study and a general population cohort study to investigate the association between OSA, insomnia symptoms, and quality of life (Short Form 12 questionnaire; physical and mental subscores). Among those with OSA, difficulties initiating sleep, sleeping pill use, and antidepressant use were associated with reduced physical and mental health subscores, and early morning awakening insomnia was associated with worse mental health scores. Alternatively, Sweetman et al. [41] used self-report data from an online survey of Australian adults to investigate the prevalence and health associations of COMISA, insomnia alone, OSA alone and neither disorder according to “symptom-level” threshold (reflecting self-report symptoms or a confirmed diagnosis of insomnia and/or OSA), and “disorder-level” threshold (more conservative threshold reflecting a confirmed diagnosis of OSA and strict diagnostic criteria for chronic insomnia disorder). Current health assessed on a 100-point visual analog scale was significantly lower in those with symptom-level COMISA ($M = 60.3$, $SD = 22.4$) compared with symptom-level insomnia alone ($M = 65.7$, $SD = 19.4$), OSA alone ($M = 69.9$, $SD = 21.3$) and neither condition ($M = 76.0$, $SD = 17.1$). However, there was no difference in current health levels between the three sleep disorder groups when using the disorder-level threshold (all three

groups reported worse current health than those with neither disorder).

Mortality

Given the associations between COMISA and reduced physical health, mental health, and quality of life, Sweetman, Lechat, Melaku et al. [42,43,61] recently sought to investigate the potential association of COMISA and all-cause mortality. Three population-based cohorts were investigated to identify individuals with COMISA, insomnia alone, OSA alone, and neither condition at baseline. Rates of mortality were assessed over 10–20 years of follow-up, controlling for socio-demographic characteristics, behavioral factors, chronic conditions, and potential mediators and moderators. Across all three studies, COMISA was associated with a 50%–70% increased risk of all-cause mortality, whereas insomnia alone and OSA alone were not associated with an increased risk of mortality in adjusted models, compared to those with neither condition (Fig. 36.3).

Bi-directional associations

Insomnia and OSA likely share bidirectional associations that contribute to their frequent comorbidity, morbidity, and response to different treatments (Fig. 36.4). The presence of bidirectional relationships is supported by several prevalence studies, treatment and experimental studies in the COMISA field.

Firstly, insomnia is more prevalent in people with OSA than would be expected based on the prevalence of insomnia in the general population. On the contrary, OSA is more prevalent in people with insomnia than would be expected given the population-based prevalence of OSA. Although the high prevalence of COMISA in sleep clinic

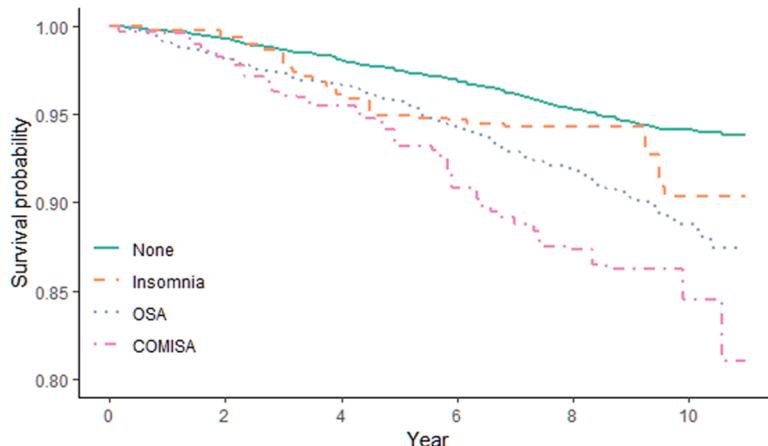


FIGURE 36.3 Association between COMISA, insomnia alone, OSA alone, and neither condition with all-cause mortality in the national health and nutrition examination survey data. Figure re-used with permission from Sweetman A, Lechat B, Appleton S, Reynolds A, Adams R, Adama Melaku Y. Association of co-morbid insomnia and sleep apnoea symptoms with all-cause mortality: analysis of the NHANES 2005–2008 data. *Sleep Epidemiol* 2022;2:100043. <https://doi.org/10.1016/j.slepe.2022.100043>.

settings may result from a referral bias (whereby patients with more severe or complex presentations such as COMISA are more likely to be referred to specialist sleep clinics), high co-morbid prevalence estimates have also been reported outside of sleep clinics. The high prevalence of COMISA may also reflect symptoms shared by both insomnia and OSA that can complicate the accurate assessment and diagnosis of each disorder in the presence of the other. For example, difficulties maintaining sleep may be a symptom of either insomnia (frequent and/or long awakenings during the night) or OSA (postapnea arousals/awakenings), or both conditions.

Second, the presence of bidirectional relationships is supported by clinical trials which have reported that A) treatment of OSA improves insomnia severity in some patients with COMISA [23,62], and b) treatment of insomnia improves OSA severity in some patients with COMISA [63] (Fig. 36.5). If insomnia and OSA were completely independent conditions, it would be expected that discrete treatments for each condition would have no impact on the co-morbid diagnosis.

Third, experimental trials have demonstrated that sleep deprivation/fragmentation (potentially mimicking some manifestations of insomnia) can reduce upper airway muscle activity and increase susceptibility to airway collapse [64–66]. Untreated OSA may also directly contribute to symptoms of insomnia through repeated respiratory events and arousals/awakenings being perceived as periods of wakefulness [67]. For example, respiratory events that culminate in awakenings from sleep can increase sympathetic activity and may exacerbate sleep maintenance difficulties and precipitate insomnia symptoms [68]. Over time, insomnia may continue to be a direct consequence of untreated OSA, or independent psychological and behavioral perpetuating factors may form resulting in the insomnia becoming a functionally independent co-morbid condition that requires targeted insomnia treatment [23].

Treatment

Although effective treatments exist for the management of insomnia alone and OSA alone, these treatments may be less appropriate, tolerated or effective in patients with COMISA. For example, specific features of insomnia may render treatments for OSA less acceptance/effective, while specific features of OSA may introduce feasibility or safety considerations for some treatments for insomnia.

OSA treatment

The recommended “first line” treatment for moderate and severe OSA is continuous positive airway pressure (CPAP) therapy, and lifestyle/weight management advice (where

indicated) [69,70]. Patients treated with CPAP wear nasal or oro-nasal masks for the duration of their sleep period, which deliver positive air pressure to pneumatically splint open the upper airway and prevent episodes of airway narrowing and collapse. Although CPAP is effective at stabilizing airflow during sleep and reversing many of the daytime symptoms of untreated OSA, patient acceptance and use of CPAP equipment for the duration of the sleep period is a major barrier to its effectiveness [71].

Indeed, comorbid insomnia symptoms have emerged as a predictor of reduced CPAP acceptance and use. A recent review of 25 studies investigating the effect of insomnia on CPAP use found that insomnia is associated with approximately a 30% reduction in rates of initial CPAP acceptance, and approximately 2 h less use of CPAP per night [72]. It is likely that many people with insomnia are protective of their sleep, and may view CPAP therapy as a “treat” to initiating and/or maintaining sleep throughout the night. CPAP therapy may precipitate awakenings in patients with insomnia [73], who may experience difficulties returning to sleep while wearing pressurized equipment. Those with COMISA may also spend more time awake throughout the night wearing pressurized masks, and therefore become more aware of the negative side effects of CPAP therapy (e.g., noise, air leaks, skin irritation, etc.), compared with people with OSA that do not have insomnia symptoms. Patients that experience persistent insomnia symptoms despite CPAP use may also perceive that CPAP is less effective at improving the overall sleep problem, and be more likely to reject treatment. Consequently, patients with OSA and comorbid insomnia are more likely to initially reject CPAP, use CPAP for a reduced portion of the sleep period each night, or discontinue CPAP therapy over time [72,74,75].

Although COMISA predicts reduced CPAP use overall, a subsample of people with COMISA tolerate CPAP well and report improvements in symptoms of both insomnia and OSA with CPAP therapy [23,62,76]. It is important for future research to attempt to prospectively identify this CPAP-responsive subgroup of patients with COMISA, that may be treated with CPAP alone. Difficulties maintaining sleep (i.e., frequent but brief awakenings) may be predictive of treatment response to CPAP therapy alone [77], although this has not been consistently reported [75]. One possible explanation for these conflicting findings is that multiple brief awakenings from sleep may indicate that insomnia symptoms result from untreated OSA, while patients with prolonged awakenings from sleep (e.g., awakenings that last for 20 min or more) may have evidence of conditioned insomnia that requires targeted treatment of insomnia in addition to CPAP therapy. Future studies are required to test this hypothesis.

Given the overall effect of comorbid insomnia symptoms on reduced CPAP acceptance and use, several

research groups have suggested that patients with COMISA should receive insomnia treatment prior to initiating CPAP therapy to A) improve comorbid insomnia symptoms, and B) facilitate a more positive initial experience with CPAP therapy in the absence of persistent insomnia symptoms [15,77,78].

Non-PAP therapies for OSA have also been investigated in the context of COMISA [79]. For example, several studies have recently investigated hypoglossal nerve stimulation (HNS) as a treatment for OSA in the presence of comorbid insomnia symptoms. There have been mixed initial reports of patient adherence to HNS between patients with OSA alone and COMISA. For example, both Patil et al. [28] and Wallace et al. [80] reported lower average adherence levels to HNS devices (of approximately 50 min/night) in Veterans with COMISA compared with those with OSA alone, which did not reach statistical significance (potentially due to sample sizes of 53 and 20 patients, respectively). Wallace et al. further reported a reduced treatment response in those with COMISA compared with patients with insomnia OSA alone [80]. Steffan et al. also reported that persistent insomnia was associated with lower satisfaction with HNS, and increased prevalence of depression symptoms compared with OSA alone [81]. Like CPAP therapy, HNS may also improve

manifestations of insomnia in a subsample of those with COMISA. For example, Pordzik et al. [82] reported an average 5-point improvement in the Insomnia Severity Index by posttreatment, falling close to the minimum clinically important difference for the ISI [83].

More research is required to investigate the effectiveness of other alternative treatments for OSA in the presence of insomnia symptoms including upper airway surgery, mandibular advancement devices, and positional devices in patients with insomnia symptoms and co-morbid supine-predominant OSA.

Insomnia treatment

Cognitive behavioral therapy for insomnia (CBT-I) is the recommended “first line” treatment for insomnia [84–87]. CBT-I is a multicomponent therapy that aims to identify and treat the underlying precipitating triggers and perpetuating factors of insomnia (Table 36.1). It has historically been delivered by suitably trained therapists over four to eight weekly or fortnightly sessions, but has also been adapted to other modalities including; group delivery [88], telehealth delivery [89], brief primary care interventions [90,91], and self-guided CBT-I books [92], eBooks, and interactive online programs [93]. Because CBT-I targets

TABLE 36.1 Core components of cognitive behavioral therapy for insomnia (CBT-I).

Component	Description
Sleep psychoeducation	Many CBT-I programs commence with an overview of insomnia, the nature of sleep during the night, and different processes that control the timing, duration and quality of sleep (e.g., the 2-process model). Normalizing brief awakenings during the night, describing the cyclic nature of sleep occurring in different stages throughout the night, and describing normal changes in “healthy” sleep across the lifespan can help to address any inaccurate expectations about sleep. Describing sleep pressure (the build-up of homeostatic sleep drive during sleep and reduction in sleep drive during sleep) can provide a good rationale for behavioral treatment components.
Stimulus control therapy	A set of simple instructions that aims to reassociate the bed with sleep and weaken any “learned” conditioned relationship between the bed/bedroom environment and an automatic state of alertness, wakefulness or anxiety.
Sleep restriction therapy	One of the most effective treatment components which aims to temporarily reduce time in bed over multiple consecutive nights, to reduce time spent awake during the night and consolidate sleep periods, before gradually extending time in bed from week-to-week. Patients are generally advised not to reduce time in bed below 5.5 h, and are provided advice on monitoring levels of daytime sleepiness during the acute sleep restriction phase.
Relaxation therapy	A series of therapies that aim to reduce cognitive and/or physiological arousal to facilitate sleep. Relaxation exercise should be practiced during the day/evening while out of bed to improve their effectiveness (like any new skill).
Cognitive therapy	Insomnia is often associated with strongly held beliefs about sleep, insomnia, and the consequences of sleep loss that can result in cognitive, behavioral or physiological patterns that exacerbate the insomnia condition. Cognitive therapies generally aim to identify specific mal-adaptive beliefs about sleep, test the validity of these beliefs, and replace potentially incorrect or mal-adaptive beliefs with more realistic alternatives that will reduce sleep-related anxiety, facilitate rest, relaxation and sleep.

the underlying factors that cause and maintain insomnia, it is associated with improvements in sleep, daytime function, and mental health, that are generally sustained long after treatment cessation [94]. CBT-i is effective in the presence of comorbid mental, physical, and sleep disorders and often improves symptoms or subsequent management of comorbidities including depression [95], pain [96], and OSA [25].

A recent systematic review and meta-analysis [25] investigated the effectiveness of CBT-I in people with COMISA. Of the 21 studies identified, nine were suitable for meta-analysis, with a pooled sample of 1,040 people with COMISA. It was reported that CBT-I is associated with large improvements in insomnia severity in the presence of untreated OSA (five studies, Hedges' $g = -1.19$, 95% CI = $-1.77, -0.61$) and treated OSA (four studies, Hedges' $g = -0.55$, 95% CI = $-0.75, -0.35$).

CBT-I may also improve the severity of untreated OSA. For example, we used data from an RCT to

investigate the effect of a four-session therapist-delivered CBT-I program, versus no-treatment control on changes in the apnea-hypopnea index (AHI) in participants with psychologist-diagnosed insomnia and sleep physician-diagnosed moderate and severe OSA [63] (Fig. 36.5). Given the established effects of sleep stage and sleep posture on AHI, we also examined and controlled for these variables [97]. Compared with the control group, CBT-I was associated with a significantly greater improvement in AHI from baseline to 6-week follow-up, after collapsing across sleep stage and posture. It is possible that CBT-I consolidates sleep periods throughout the night, reduces time spent in transitional sleep/wake periods, and reduces the arousal threshold to internal (e.g., respiratory arousal threshold) and external stimuli (e.g., sound and light cues) in patients with COMISA. The respiratory arousal threshold is a nonanatomical trait believed to contribute to OSA pathophysiology in approximately one third of patients and may be overrepresented in people with comorbid insomnia [22,23,34]. CBT-I (specifically sleep restriction

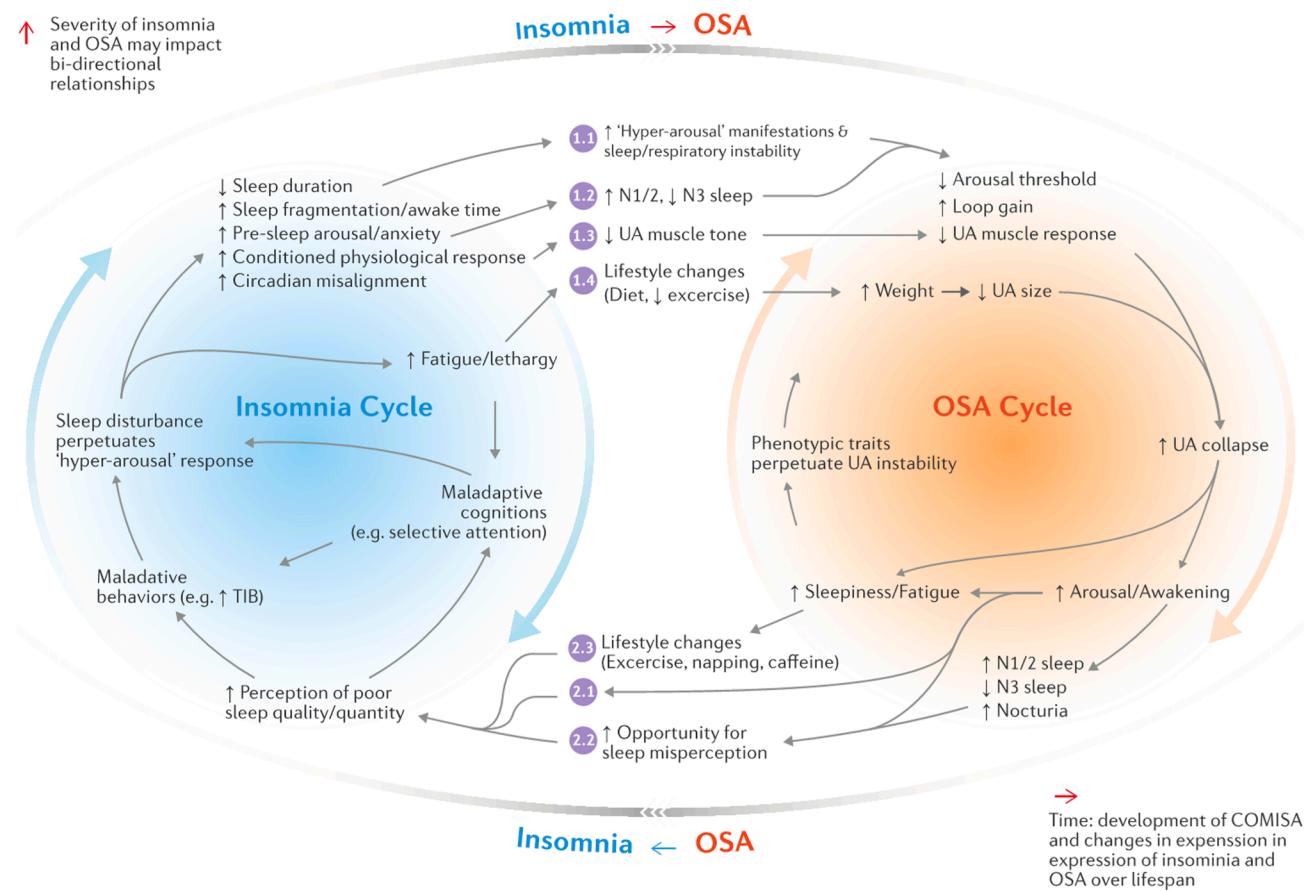


FIGURE 36.4 Insomnia and OSA likely share many bidirectional relationships that contribute to their frequent comorbidity, increased health consequences, and the effectiveness of different treatment approaches. Understanding these bidirectional relationships may be critical to guide the development and implementation of precision medicine approaches for COMISA. Used with permission from Sweetman A, Lack L, McEvoy RD, Smith S, Eckert DJ, Osman A, Carberry JC, Douglas W, Nguyen PD, Catcheside P. Bi-directional relationships between co-morbid insomnia and sleep apnea (COMISA). *Sleep Med Rev* 2021;60:101519. <https://doi.org/10.1016/j.smrv.2021.101519>.

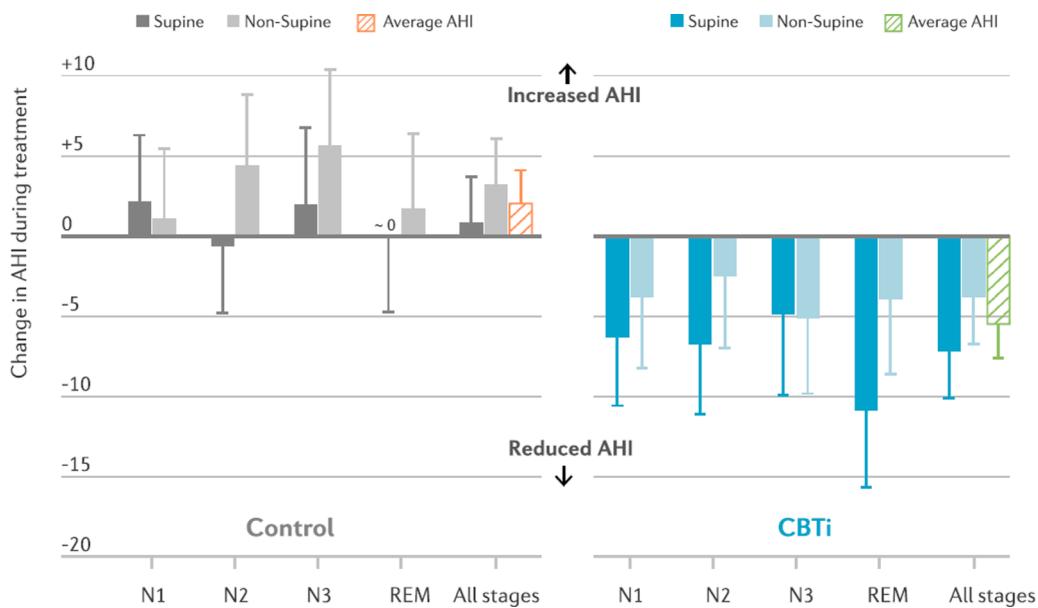


FIGURE 36.5 In a randomized controlled trial [63] of 145 people with untreated COMISA, cognitive behavioral therapy for insomnia (CBT-I) was associated with a greater reduction in the apnea-hypopnea index (AHI) by posttreatment after controlling for sleep stage and posture. Used with permission from Sweetman A, Lack L, McEvoy RD, Smith S, Eckert DJ, Osman A, Carberry JC, Douglas W, Nguyen PD, Catcheside P. Bi-directional relationships between co-morbid insomnia and sleep apnea (COMISA). *Sleep Med Rev* 2021;60:101519. <https://doi.org/10.1016/j.smrv.2021.101519>.

therapy) has recently been shown to reduce markers of arousal (cognitive arousal and markers of brain wave activity) [98], which may explain the effect of CBT-I on reducing OSA severity in those with COMISA [22,23].

Four RCTs have also investigated the effect of CBT-I versus no insomnia treatment, on improving subsequent acceptance and adherence to CPAP therapy in patients with COMISA [16–19]. While Sweetman [17] and Alessi [19] reported improvements in nightly CPAP adherence in those treated with CBT-I initially, Bjorvatn [16] and Ong [18] reported no between-group differences. Ongoing work aims to combine data from these and other trials to identify individual patient-level predictors of treatment response to CBT-I and CPAP therapy in patients with COMISA, to identify whether any reliable baseline symptoms are predictive of different patterns of treatment response.

Although effective, CBT-I is associated with a short-term increase in levels of daytime sleepiness during sleep restriction therapy [99,100]. People with COMISA may commence CBT-I programs with higher levels of daytime sleepiness compared with patients with insomnia alone [48] and may be at an increased risk of alertness failure [101] or exacerbation of daytime sleepiness during sleep restriction therapy [100]. For example, Sweetman et al. [100] reported that therapist-delivered CBT-I is associated with a small and short-lived increase in self-reported daytime sleepiness during the first week after commencing sleep restriction therapy in patients with co-

morbidity insomnia and moderate/severe untreated OSA. Another recent study by Turner et al. [102] also reported reduced neurocognitive performance immediately following therapist-delivered CBT-I in patients with COMISA. Collectively, these studies highlight the need for careful monitoring of sleepiness, and alertness during the first 2–3 weeks of sleep restriction therapy in patients with COMISA, or adaptation to standardized CBT-I programs and sleep restriction therapy protocols in COMISA samples. We have recently developed a self-guided digital C

The greatest barrier regarding the use of CBT-I in people with COMISA is suboptimal access. Despite hundreds of clinical trials and over 30 meta-analyses supporting the effectiveness of CBT-I, most people with insomnia do not access this effective nondrug treatment [103,104]. Instead, most patients are managed with suboptimal “sleep hygiene” advice (e.g., generic advice about healthy sleep practices/environmental conditions), or sleeping pills (which are generally not recommended for long-term use). In health settings that manage patients with COMISA, it is of critical importance to increase access to CBT-I. This may be achieved through developing and implementing suitable digital CBT-I programs tailored for COMISA [1,2], training additional therapists in sleep clinic/COMISA management settings in the delivery of CBT-I, establishing stronger referral networks between sleep clinics and behavioral sleep medicine providers or “sleep” psychologists, and establishing funding pathways for patients to access CBT-I.

Despite clinical guidelines recommending CBT-I as the “first line” treatment for insomnia, most patients are managed with sedative and hypnotic medicines [105]. In the context of COMISA, benzodiazepines are presently contraindicated in the presence of OSA [69], given earlier studies reporting exacerbation of respiratory events [106]. However, more recent clinical trials have reported that hypnotic medicines improve sleep parameters and have a suitable safety profile in the presence of specific subgroups of patients with OSA [107,108]. Dual orexin receptor antagonists have also been studied in patients with OSA [109] and COMISA [110,111], with adequate safety profiles and improvement in sleep parameters. Although CBT-I remains the recommended “first line” treatment for insomnia, it is not readily accessible to most patients with insomnia or COMISA. In addition to implementing strategies to improve access to CBT-I for COMISA [25], it is also important to continue to investigate the effectiveness and safety of nonpharmacological approaches in the management of COMISA [112], to guide the development of combination treatment approaches (e.g., with pharmacological and nonpharmacological interventions), and develop suitable treatment models for the minority of patients that do not respond to CBT-I as the “first line” treatment.

Conclusion

Comorbid insomnia and sleep apnea (COMISA) is a highly prevalent and debilitating condition that can be more difficult to effectively treat, compared with either disorder alone. Over the past 5–10 years, there has been an increase in research and clinical attention investigating the prevalence, consequences, characteristics, and treatments for COMISA.

A large body of research has established the high prevalence of COMISA in sleep clinic and population-based settings and documented various domains of mental health, physical health, daytime function, and quality of life that are impaired in people with both conditions.

Although a handful of treatment studies have documented the effectiveness of different single-arm treatment approaches for COMISA, substantial work is needed to understand the most effective treatment combinations, and specific subpopulations that are most responsive to different treatment sequences, combinations, and treatment delivery modalities. Translating evidence-based research into clinical settings requires targeted implementation research programs. Therefore, a future area of importance to the COMISA field will be to translate effective diagnostic and management approaches into sleep clinics and other healthcare settings that identify and treat patients with COMISA.

References

- [1] Guilleminault C, Eldridge FL, Dement WC. Insomnia with sleep apnea: a new syndrome. *Science* 1973;181(4102):856–8. <https://doi.org/10.1126/science.181.4102.856>.
- [2] Guilleminault C, Eldridge FL, Phillips JR, Dement WC. Two occult causes of insomnia and their therapeutic problems. *Arch Gen Psychiatry* 1976;33(10):1241–5. <https://doi.org/10.1001/archpsyc.1976.01770100103010>.
- [3] Lavie P, Zomer J, Eliaschar I, Joachim Z, Halpern E, Rubin A-HE, Alroy G. Excessive daytime sleepiness and insomnia: association with deviated nasal septum and nocturnal breathing disorders. *Arch Otolaryngol Head Neck Surg* 1982;108(6):373–7. <https://doi.org/10.1001/archotol.1982.00790540045013>.
- [4] Zorick FJ, Roth T, Hartzke KM, Piccione PM, Stepanski EJ. Evaluation an diagnosis of persistent insomnia. *Am J Psychiatr* 1981;138(6):1981.
- [5] Jacobs EA, Reynolds CF, Kupfer DJ, Lovin PA, Ehrenpreis AB. The role of polysomnography in the differential diagnosis of chronic insomnia. *Am J Psychiatr* 1988;145(3):346–9. <https://doi.org/10.1176/ajp.145.3.346>.
- [6] Ambrogetti A, Olson LG, Saunders NA. Differences in the symptoms of men and women with obstructive sleep apnoea. *J Med* 1991;21(6):863–6. <https://doi.org/10.1111/j.1445-5994.1991.tb01408.x>.
- [7] Stone J, Morin CM, Hart RP, Remsberg S, Mercer J. Neuropsychological functioning in older insomniacs with or without obstructive sleep apnea. *Psychol Aging* 1994;9(2):231–6. <https://doi.org/10.1037/0882-7974.9.2.231>.
- [8] Lichstein KL, Riedel BW, Lester KW, Neal Aguillard R. Occult sleep apnea in a recruited sample of older adults with insomnia. *J Consult Clin Psychol* 1999;67(3):405–10. <https://doi.org/10.1037/0022-006x.67.3.405>.
- [9] Krakow B, Melendrez D, Ferreira E, Clark J, Warner TD, Sisley B, Sklar D. Prevalence of insomnia symptoms in patients with sleep-disordered breathing. *Chest* 2001;120(6):1923–9. <https://doi.org/10.1378/chest.120.6.1923>.
- [10] Krakow B, Melendrez D, Lee SA, Warner TD, Clark JO, Sklar D. Refractory insomnia and sleep-disordered breathing: a pilot study. *Sleep Breath* 2004;8(1):15–29. <https://doi.org/10.1055/s-2004-822850>.
- [11] Gooneratne NS, Gehrmann PR, Nkwuo JE, Bellamy SL, Schutte-Rodin S, Dinges DF, Pack AI. Consequences of comorbid insomnia symptoms and sleep-related breathing disorder in elderly subjects. *Arch Intern Med* 2006;166(16):1732–8. <https://doi.org/10.1001/archinte.166.16.1732UnitedStates>.
- [12] Cherniack NS. Sleep apnea and insomnia: sleep apnea plus or sleep apnea minus. *Respiration* 2005;72(5):458–9. <https://doi.org/10.1159/000087667>.
- [13] Smith S, Sullivan K, Hopkins W, Douglas J. Frequency of insomnia report in patients with obstructive sleep apnoea hypopnoea syndrome (OSAHS). *Sleep Med* 2004;5(5):449–56. <https://doi.org/10.1016/j.sleep.2004.03.005>.
- [14] Luyster FS, Buysse DJ, Strollo PJ. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *J Clin Sleep Med* 2010;6(2):196–204. <https://doi.org/10.5664/jcsm.27772>.
- [15] Sweetman AM, Lack LC, Catcheside PG, Antic NA, Chai-Coetzer CL, Smith SS, Douglas JA, Doug McEvoy R.

- Developing a successful treatment for co-morbid insomnia and sleep apnoea. *Sleep Med Rev* 2017;33:28–38. <https://doi.org/10.1016/j.smrv.2016.04.004>.
- [16] Bjørn B, Thomas B, Lehmann S, Ståle P, Saxvig IW. No effect of a self-help book for insomnia in patients with obstructive sleep apnea and comorbid chronic insomnia – a randomized controlled trial. *Front Psychol* 2018;9. <https://doi.org/10.3389/fpsyg.2018.02413>.
- [17] Sweetman A, Lack L, Catcheside PG, Antic NA, Smith S, Chai-Coetzer CL, Douglas J, O’grady A, Dunn N, Robinson J, Paul D, Williamson P, McEvoy RD. Cognitive and behavioral therapy for insomnia increases the use of continuous positive airway pressure therapy in obstructive sleep apnea participants with comorbid insomnia: a randomized clinical trial. *Sleep* 2019;42(12). <https://doi.org/10.1093/sleep/zsz178>.
- [18] Ong JC, Crawford MR, Dawson SC, Fogg LF, Turner AD, Wyatt JK, Crisostomo MI, Chhangani BS, Kushida CA, Edinger JD, Abbott SM, Malkani RG, Attarian HP, Zee PC. A randomized controlled trial of CBT-I and PAP for obstructive sleep apnea and comorbid insomnia: main outcomes from the MATRICS study. *Sleep* 2020;43(9):1–10. <https://doi.org/10.1093/sleep/zsaa041>.
- [19] Alessi CA, Fung CH, Dzierzewski JM, Fiorentino L, Stepnowsky C, Tapia JCR, Song Y, Zeidler MR, Josephson K, Mitchell MN, Jouldjian S, Martin JL. Randomized controlled trial of an integrated approach to treating insomnia and improving the use of positive airway pressure therapy in veterans with comorbid insomnia disorder and obstructive sleep apnea. *Sleep* 2021;44(4). <https://doi.org/10.1093/sleep/zsaa235>.
- [20] Zheng JN, Tong B, Sweetman A, Eckert DJ, Osman A. The insomnia severity index is related to the respiratory arousal threshold in people with co-morbid insomnia and sleep apnoea (COMISA). *Sleep Adv* 2022.
- [21] Yanagimori M, Fernandes MD, Garcia ML, Scudeller PG, Carvalho CRR, Edwards B, Lorenzi-Filho G, Genta PR. Respiratory arousal threshold among patients with isolated sleep apnea and with comorbid insomnia (COMISA). *Sci Rep* 2023;13(1). <https://doi.org/10.1038/s41598-023-34002-4>.
- [22] Brooker EJ, Landry SA, Thomson LDJ, Hamilton GS, Genta PR, Drummond SPA, Edwards BA. Obstructive sleep apnea is a distinct physiological endotype in individuals with comorbid insomnia and sleep apnea. *Ann Am Thorac Soc* 2023;20(10):1508–15. <https://doi.org/10.1513/annalsats.202304-350oc>.
- [23] Sweetman A, Lack L, McEvoy RD, Smith S, Eckert DJ, Osman A, Carberry JC, Douglas W, Nguyen PD, Catcheside P. Bi-directional relationships between co-morbid insomnia and sleep apnea (COMISA). *Sleep Med Rev* 2021;60:101519. <https://doi.org/10.1016/j.smrv.2021.101519>.
- [24] Zhang Y, Ren R, Lei F, Zhou J, Zhang J, Wing Y-K, Sanford LD, Tang X. Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev* 2019;45:1–17. <https://doi.org/10.1016/j.smrv.2019.01.004>.
- [25] Sweetman A, Farrell S, Wallace DM, Crawford M. The effect of cognitive behavioural therapy for insomnia in people with co-morbid insomnia and sleep apnoea: a systematic review and meta-analysis. *J Sleep Res* 2023;32(6). <https://doi.org/10.1111/jsr.13847>.
- [26] Eldridge-Smith ED, Manber R, Tsai S, Kushida C, Simmons B, Johnson R, Horberg R, Depew A, Abraibesh A, Simpson N, Strand M, Espie CA, Edinger JD. Stepped care management of insomnia co-occurring with sleep apnea: the AIR study protocol. *Trials* 2022;23(1). <https://doi.org/10.1186/s13063-022-06753-4>. <https://trialsjournal.biomedcentral.com/>.
- [27] A. Sweetman, Effect of digital cognitive behavioural therapy for insomnia (dCBTi) in people with co-morbid insomnia and sleep apnoea: a randomised waitlist controlled trial.
- [28] Dhanda Patil R, Hong MP, Ishman SL. Hypoglossal nerve stimulation in veterans with comorbid insomnia and sleep apnea. *Otolaryngol Head Neck Surg* 2021;164(6):1345–53. <https://doi.org/10.1177/0194599820982638>.
- [29] Patil SP, Ayappa IA, Caples SM, John Kimoff R, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American academy of sleep medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med* 2019;15(2):301–34. <https://doi.org/10.5664/jcsm.7638>.
- [30] Krakow B, McIver ND, Ulibarri VA, Krakow J, Schrader RM. Prospective randomized controlled trial on the efficacy of continuous positive airway pressure and adaptive servo-ventilation in the treatment of chronic complex insomnia. *eClinicalMedicine* 2019;13:57–73. <https://doi.org/10.1016/j.eclim.2019.06.011>.
- [31] Sweetman A, Frank O, Stocks N, Mukherjee S, Lack L. General practitioner management of comorbid insomnia and sleep apnoea. *Aust J Gen Pract* 2023;52(9):607–12. <https://doi.org/10.31128/AJGP-12-22-6648>.
- [32] Sweetman A, Lack L, Bastien C. Co-morbid insomnia and sleep apnea (COMISA): prevalence, consequences, methodological considerations, and recent randomized controlled trials. *Brain Sci* 2019;9(12):371. <https://doi.org/10.3390/brainsci9120371>.
- [33] The American Academy of Sleep Medicine. International classification of sleep disorders. 2014.
- [34] Osman AM, Carter SG, Carberry JC, Eckert DJ. Obstructive sleep apnea: current perspectives. *Nat Sci Sleep* 2018;10:21–34. <https://doi.org/10.2147/NSS.S124657>.
- [35] Chung KF. Insomnia subtypes and their relationships to daytime sleepiness in patients with obstructive sleep apnea. *Respiration* 2005;72(5):460–5. <https://doi.org/10.1159/000087668>.
- [36] Ye L, Pien GW, Ratcliffe SJ, Björnsdóttir E, Arnardóttir ES, Pack AI, Benediktsdóttir B, Gislason T. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J* 2014;44(6):1600–7. <https://doi.org/10.1183/09031936.00032314>.
- [37] Crawford MR, Chirinos DA, Iurcotta T, Edinger JD, Wyatt JK, Manber R, Ong JC. Characterization of patients who present with insomnia: is there room for a symptom cluster-based approach? *J Clin Sleep Med* 2017;13(7):911–21. <https://doi.org/10.5664/jcsm.6666>.
- [38] Sweetman A, Osman A, Lack L, Crawford M, Wallace D. Co-morbid insomnia and sleep apnea (COMISA): recent research and future directions. *Curr Opin Pulm Med* 2023;29(6):567–73. <https://doi.org/10.1097/mcp.0000000000001007>.
- [39] Vozoris NT. Sleep apnea-plus: prevalence, risk factors, and association with cardiovascular diseases using United States population-level data. *Sleep Med* 2012;13(6):637–44. <https://doi.org/10.1016/j.sleep.2012.01.004>.
- [40] Sivertsen B, Björnsdóttir E, Øverland S, Bjorvatn B, Salo P. The joint contribution of insomnia and obstructive sleep apnoea on

- sickness absence. *J Sleep Res* 2013;22(2):223–30. <https://doi.org/10.1111/j.1365-2869.2012.01055.x>.
- [41] Sweetman A, Melaku YA, Lack L, Reynolds A, Gill TK, Adams R, Appleton S. Prevalence and associations of co-morbid insomnia and sleep apnoea in an Australian population-based sample. *Sleep Med* 2021;82:9–17. <https://doi.org/10.1016/j.sleep.2021.03.023>.
- [42] Lechat B, Kelly AL, Wallace DM, Reynolds A, Appleton SL, Scott H, Vakulin A, Lovato N, Adams R, Eckert DJ, Catcheside PG, Sweetman A. All-cause mortality in people with Co-occurring insomnia symptoms and sleep apnea: analysis of the Wisconsin sleep cohort. *Nat Sci Sleep* 2022;14:1817–28. <https://doi.org/10.2147/nss.s379252>.
- [43] Sweetman A, Lechat B, Appleton S, Reynolds A, Adams R, Adama Melaku Y. Association of co-morbid insomnia and sleep apnoea symptoms with all-cause mortality: analysis of the NHANES 2005–2008 data. *Sleep Epidemiol* 2022;2:100043. <https://doi.org/10.1016/j.sleep.2022.100043>.
- [44] Bianchi MT, Williams KL, McKinney S, Ellenbogen JM. The subjective-objective mismatch in sleep perception among those with insomnia and sleep apnea. *J Sleep Res* 2013;22(5):557–68. <https://doi.org/10.1111/j.1365-2869.2013.02046.x>.
- [45] Krell SB, Kapur VK. Insomnia complaints in patients evaluated for obstructive sleep apnea. *Sleep Breath* 2005;9(3):104–10. <https://doi.org/10.1007/s11325-005-0026-x>.
- [46] Philip R, Catcheside P, Stevens D, Lovato N, McEvoy D, Vakulin A. Comorbid insomnia and sleep apnoea is associated with greater neurocognitive impairment compared with OSA alone. *Sleep Med* 2017;40. <https://doi.org/10.1016/j.sleep.2017.11.762>.
- [47] Cho YW, Kim KT, Moon HJ, Korostyshevskiy VR, Motamedi GK, Yang KI. Comorbid insomnia with obstructive sleep apnea: clinical characteristics and risk factors. *J Clin Sleep Med* 2018;14(3):409–17. <https://doi.org/10.5664/jcsm.6988>.
- [48] Sweetman A, Lack L, Lambert S, Gradišar M, Harris J. Does comorbid obstructive sleep apnea impair the effectiveness of cognitive and behavioral therapy for insomnia? *Sleep Med* 2017;39:38–46. <https://doi.org/10.1016/j.sleep.2017.09.003>.
- [49] Lang CJ, Appleton SL, Vakulin A, McEvoy RD, Wittert GA, Martin SA, Catcheside PG, Antic NA, Lack L, Adams RJ. Co-morbid OSA and insomnia increases depression prevalence and severity in men. *Respirology* 2017;22(7):1407–15. <https://doi.org/10.1111/resp.13064>.
- [50] Jeon B, Luyster FS, Callan JA, Chasens ER. Depressive symptoms in comorbid obstructive sleep apnea and insomnia: an integrative review. *West J Nurs Res* 2021;43(11). <https://doi.org/10.1177/019345921989656>.
- [51] Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Ulrich V, Lombardo C, Riemann D. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord* 2011;135(1–3):10–9. <https://doi.org/10.1016/j.jad.2011.01.011>.
- [52] Peppard PE, Szklar-Coxe M, Hla KM, Young T. Longitudinal association of sleep-related breathing disorder and depression. *Arch Intern Med* 2006;166(16):1709–15. <https://doi.org/10.1001/archinte.166.16.1709UnitedStates>.
- [53] Li L, Gan Y, Zhou X, Jiang H, Zhao Y, Tian Q, He Y, Liu Q, Mei Q, Wu C, Lu Z. Insomnia and the risk of hypertension: a meta-analysis of prospective cohort studies. *Sleep Med Rev* 2021;56:101403. <https://doi.org/10.1016/j.smrv.2020.101403>.
- [54] Wang X, Ouyang Y, Wang Z, Zhao G, Liu L, Bi Y. Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. *Int J Cardiol* 2013;169(3):207–14. <https://doi.org/10.1016/j.ijcard.2013.08.088>.
- [55] Meira e Cruz M, Salles C, Gozal D. A reappraisal on the associations between sleep-disordered breathing, insomnia, and cardiometabolic risk. *Am J Respir Crit Care Med* 2021;203(12):1583–4. <https://doi.org/10.1164/rccm.202102-0337le>.
- [56] Luyster FS, Kip KE, Buysse DJ, Aiyer AN, Reis SE, Strollo PJ. Traditional and nontraditional cardiovascular risk factors in co-morbid insomnia and sleep apnea. *Sleep* 2014;37(3):593–600. <https://doi.org/10.5665/sleep.3506UnitedStates>.
- [57] Gupta MA, Knapp K. Cardiovascular and psychiatric morbidity in Obstructive Sleep Apnea (OSA) with Insomnia (sleep apnea plus) versus obstructive sleep apnea without insomnia: a case-control study from a nationally representative US sample. *PLoS One* 2014;9(3). <https://doi.org/10.1371/journal.pone.0090021>. <http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0090021&representation=PDF>.
- [58] Lechat B, Appleton S, Melaku YA, Hansen K, McEvoy RD, Adams R, Catcheside P, Lack L, Eckert DJ, Sweetman A. The association of co-morbid insomnia and sleep apnea with prevalent cardiovascular disease and incident cardiovascular events. *J Sleep Res* 2022. <https://doi.org/10.1111/jsr.13563>. [http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1365-2869](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2869).
- [59] Björnsdóttir BT, Eysteinsdóttir B, Arnardóttir ES, Janson C, Gislason T, Sigurdsson JF, Kuna ST, Pack AI, Benediktsdóttir B. Quality of life among untreated sleep apnea patients compared with the general population and changes after treatment with positive airway pressure. *J Sleep Res* 2014.
- [60] Tasbakan MS, Gunduz C, Pirildar S, Basoglu OK. Quality of life in obstructive sleep apnea is related to female gender and comorbid insomnia. *Turk Sleep Breath* 2018;22(4):1013–20. <https://doi.org/10.1007/s11325-018-1621-y>.
- [61] Lechat B, Appleton S, Melaku YA, Hansen K, McEvoy RD, Adams R, Catcheside P, Lack L, Eckert DJ, Sweetman A. Co-morbid insomnia and sleep apnoea is associated with all-cause mortality. *Eur Respir J* 2022;60(1). <https://doi.org/10.1183/13993003.01958-2021>. <http://erj.ersjournals.com/lookup/doi/10.1183/13993003.01958-2021>.
- [62] Lundström, Saxvig Irwa, Lehmann 1, Björvatn B. Sleep and breathing. 2021.
- [63] Sweetman A, Lack L, Doug McEvoy R, Antic NA, Smith S, Chai-Coetzer CL, Douglas J, O’Grady A, Dunn N, Robinson J, Paul D, Eckert D, Catcheside PG. Cognitive behavioural therapy for insomnia reduces sleep apnoea severity: a randomised controlled trial. *ERJ Open Res* 2020;6(2):00161–2020. <https://doi.org/10.1183/23120541.00161-2020>.
- [64] Bonnet MH, Arand DL. Clinical effects of sleep fragmentation versus sleep deprivation. *Sleep Med Rev* 2003;7(4):297–310. <https://doi.org/10.1053/smrv.2001.0245>.
- [65] Leiter JC, Knuth SL, Bartlett D. The effect of sleep deprivation on activity of the genioglossus muscle. *Am Rev Respir Dis* 1985;132(6):1242–5.
- [66] Parikh S, White D, Jordan, Merchia P, Malhotra E. 36 hours of sleep deprivation reduces genioglossus muscle activity during hypercapnia and inspiratory resistive loads during wakefulness. *AASM*; 2011.
- [67] Bensen-Boakes D-B, Osman A, Lack L, Catcheside P, Antic N, Smith SS, Chai-Coetzer CL, O’Grady A, Dunn N, Robinson J, McEvoy D, Alexander S. The effect of cognitive behavioural therapy for insomnia (CBT-I) on subjective-objective sleep

- discrepancy in individuals with Co-morbid insomnia and sleep apnoea: a randomised controlled trial. *Appl Sci* 2022;12(4):1787. <https://doi.org/10.3390/app12041787>.
- [68] Krakow B, Romero E, Ulibarri VA, Kikta S. Prospective assessment of nocturnal awakenings in a case series of treatment-seeking chronic insomnia patients: a pilot study of subjective and objective causes. *Sleep* 2012;35(12):1685–92. <https://doi.org/10.5665/sleep.2244UnitedStates>.
- [69] Sleep health primary care resource: evidence-based resources and information to assess and manage adult patients with obstructive sleep apnoea and insomnia. Australasian Sleep Association; 2023.
- [70] Epstein LJ, Kristo D, Strollo PJ, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5(3):263–76. <https://doi.org/10.5664/jcsm.27497>.
- [71] Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5(2):173–8. <https://doi.org/10.1513/pats.200708-119MGUnitedStates>.
- [72] Sweetman LL, Crawford D. Co-morbid insomnia and sleep apnea (COMISA): assessment and management approaches. *Sleep Med Clin* 2021.
- [73] Caetano Mota P, Morais Cardoso S, Drummond M, Santos AC, Almeida J, Winck JC. Prevalence of new-onset insomnia in patients with obstructive sleep apnoea syndrome treated with nocturnal ventilatory support. *Rev Port Pneumol* 2012;18(1):15–21. <https://doi.org/10.1016/j.rppne.2011.06.009>.
- [74] Smith S, Dunn N, Douglas J, Jorgensen G. Sleep onset insomnia is associated with reduced adherence to CPAP therapy. *Sleep Biol Rhythms* 2009;7:2009.
- [75] Wickwire EM, Smith MT, Birnbaum S, Collop NA. Sleep maintenance insomnia complaints predict poor CPAP adherence: a clinical case series. *Sleep Med* 2010;11(8):772–6. <https://doi.org/10.1016/j.sleep.2010.03.012>.
- [76] Tan D, Appleton A, Chai-Coetzer CL. Health and treatment correlates of obstructive sleep apnoea (OSA) alone and comorbid with insomnia (COMISA) in a community-based sample. Effect of COMISA on CPAP acceptance and use ASA Adelaide Meeting. 2022.
- [77] Björnsdóttir E, Janson C, Sigurdsson JF, Gehrman P, Perlis M, Juliusson S, Arnardottir ES, Kuna ST, Pack AI, Gislason T, Benediktsdóttir B. Symptoms of insomnia among patients with obstructive sleep apnea before and after two years of positive airway pressure treatment. *Sleep* 2013;36(12):1901–9. <https://doi.org/10.5665/sleep.3226Iceland>.
- [78] Ong JC, Crisostomo ML. The more the merrier? Working towards multidisciplinary management of obstructive sleep apnea and co-morbid insomnia. *J Clin Psychol* 2013;69(10):1066–77. <https://doi.org/10.1002/jclp.21958>.
- [79] Krakow B, Melendrez D, Sisley B, Warner TD, Krakow J, Leahigh L, Lee S. Nasal dilator strip therapy for chronic sleep-maintenance insomnia and symptoms of sleep-disordered breathing: a randomized controlled trial. *Sleep Breath* 2006;10(1):16–28. <https://doi.org/10.1007/s11325-005-0037-7>.
- [80] Douglas MW, Wohlgemuth WK. 0558 upper airway stimulation in US veterans with obstructive sleep apnea with and without insomnia: a preliminary study. *Sleep* 2019;42(Suppl. ment_1): A222. <https://doi.org/10.1093/sleep/zsz067.556>.
- [81] Steffen A, Baptista P, Ebner EM, Jeschke S, König IR, Bruchhage KL. Insomnia affects patient-reported outcome in sleep apnea treated with hypoglossal nerve stimulation. *Laryngoscope Investig Otolaryngol* 2022;7(3):877–84. <https://doi.org/10.1002/lio2.761>.
- [82] Pordzik J, Ludwig K, Seifen C, Huppertz T, Bahr-Hamm K, Matthias C, Gouveris H. Insomnia in patients undergoing hypoglossal nerve stimulation therapy for obstructive sleep apnea. *Biology* 2023;12(1):98. <https://doi.org/10.3390/biology12010098>.
- [83] Yang M, Morin CM, Schaefer K, Wallenstein GV. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. *Curr Med Res Opin* 2009;25(10):2487–94. <https://doi.org/10.1185/03007990903167415UnitedStates>. <http://www.informahealthcare.com/doi/pdf/10.1185/03007990903167415>.
- [84] Ree M, Junge M, Cunnington D. Australasian Sleep Association position statement regarding the use of psychological/behavioral treatments in the management of insomnia in adults. *Sleep Med* 2017;36:S43. <https://doi.org/10.1016/j.sleep.2017.03.017>.
- [85] Qaseem A, Holty JEC, Owens DK, Dallas P, Starkey M, Shekelle P. Management of obstructive sleep apnea in adults: a clinical practice guideline from the American college of physicians. *Ann Intern Med* 2013;159(7):471–83. <https://doi.org/10.7326/0003-4819-159-7-201310010-00704>.
- [86] Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008;4(05):487–504. <https://doi.org/10.5664/jcsm.27286>.
- [87] Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Groselj LD, Ellis JG, Espie CA, Garcia-Borreguero D, Gjerstad M, Gonçalves M, Hertenstein E, Fröjmark MJ-, Jennum PJ, Leger D, Nissen C, Parrino L, Paunio T, Pevernagie D, Verbraecken J, Weiß H-G, Wichniak A, Zavalko I, Arnardottir ES, Deleanu O-C, Strazisar B, Zoetmulder M, Spiegelhalder K. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res* 2017;26(6):675–700. <https://doi.org/10.1111/jsr.12594>.
- [88] Koffel EA, Koffel JB, Gehrman PR. A meta-analysis of group cognitive behavioral therapy for insomnia. *Sleep Med Rev* 2015;19:6–16. <https://doi.org/10.1016/j.smrv.2014.05.001>.
- [89] Arnedt JT, Conroy DA, Mooney A, Furgal A, Sen A, Eisenberg D. Telemedicine versus face-to-face delivery of cognitive behavioral therapy for insomnia: a randomized controlled noninferiority trial. *Sleep* 2021;44(1). <https://doi.org/10.1093/sleep/zsaa136>. <https://academic.oup.com/sleep>.
- [90] Buysse DJ, Germain A, Moul DE, Franzen PL, Brar LK, Fletcher ME, Begley A, Houck PR, Mazumdar S, Reynolds CF, Monk TH. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med* 2011;171(10):887–95. <https://doi.org/10.1001/archinternmed.2010.535UnitedStates>.
- [91] Sweetman A, Zwar NA, Grivell N, Lovato N, Lack L. A step-by-step model for a brief behavioural treatment for insomnia in Australian general practice. *Aust J Gen Pract* 2021;50(5):287–93. <https://doi.org/10.31128/ajgp-04-20-5391>.
- [92] Bjorvatn B, Fiske E, Pallesen S. A self-help book is better than sleep hygiene advice for insomnia: a randomized controlled comparative study. *Scand J Psychol* 2011;52(6):580–5. <https://doi.org/10.1111/j.1467-9450.2011.00902.x>.
- [93] Soh HL, Ho RC, Ho CS, Tam WW. Efficacy of digital cognitive behavioural therapy for insomnia: a meta-analysis of randomised controlled trials. *Sleep Med* 2020;75:315–25. <https://doi.org/10.1016/j.sleep.2020.08.020>.
- [94] van der Zweerde T, Bisdounis L, Kyle SD, Lancee J, van Straten A. Cognitive behavioral therapy for insomnia: a meta-

- analysis of long-term effects in controlled studies. *Sleep Med Rev* 2019;48:101208. <https://doi.org/10.1016/j.smrv.2019.08.002>.
- [95] Ye Y-Y, Zhang Y-F, Chen J, Liu J, Li X-J, Liu Y-Z, Lang Y, Lin L, Yang X-J, Jiang X-J, Courvoisier DS. Internet-based cognitive behavioral therapy for insomnia (ICBT-i) improves comorbid anxiety and depression—a meta-analysis of randomized controlled trials. *PLoS One* 2015;10(11). <https://doi.org/10.1371/journal.pone.0142258>.
- [96] Selvanathan J, Pham C, Nagappa M, Peng PWH, Englesakis M, Espie CA, Morin CM, Chung F. Cognitive behavioral therapy for insomnia in patients with chronic pain – a systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev* 2021;60:101460. <https://doi.org/10.1016/j.smrv.2021.101460>.
- [97] Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, Catcheside PG. Marked reduction in obstructive sleep apnea severity in slow wave sleep. *J Clin Sleep Med* 2009;5(6):519–24. <https://doi.org/10.5664/jcsm.27651>.
- [98] Maurer LF, Espie CA, Omlin X, Emsley R, Kyle SD. The effect of sleep restriction therapy for insomnia on sleep pressure and arousal: a randomized controlled mechanistic trial. *Sleep* 2022;45(1). <https://doi.org/10.1093/sleep/zsab223>. <https://academic.oup.com/sleep>.
- [99] Kyle SD, Miller CB, Rogers Z, Siriwardena AN, Macmahon KM, Espie CA. Sleep restriction therapy for insomnia is associated with reduced objective total sleep time, increased daytime somnolence, and objectively impaired vigilance: Implications for the clinical management of insomnia disorder. *Sleep* 2014;37(2):229–37. <https://doi.org/10.5665/sleep.3386UnitedKingdom>.
- [100] Sweetman A, McEvoy RD, Smith S, Catcheside PG, Antic NA, Chai-Coetzer CL, Douglas J, O’Grady A, Dunn N, Robinson J, Paul D, Williamson P, Lack L. The effect of cognitive and behavioral therapy for insomnia on week-to-week changes in sleepiness and sleep parameters in patients with comorbid insomnia and sleep apnea: a randomized controlled trial. *Sleep* 2020;43(7). <https://doi.org/10.1093/SLEEP/ZSAA002>. <https://academic.oup.com/sleep>.
- [101] Vakulin A, Baulk SD, Catcheside PG, Antic NA, Van Den Heuvel CJ, Dorrian J, McEvoy RD. Effects of alcohol and sleep restriction on simulated driving performance in untreated patients with obstructive sleep apnea. *Ann Intern Med* 2009;151(7):447–55. <https://doi.org/10.7326/0003-4819-151-7-200910060-00005>.
- [102] Turner AD, Ong JC, Jones AL, Tu A, Salanitro M, Crawford MR. Neurocognitive functioning in comorbid insomnia and sleep apnea patients is better after positive airway pressure therapy, but worse after cognitive behavioral therapy for insomnia: exploratory analysis of cognitive outcomes from the Multidisciplinary Approach to the Treatment of Insomnia and Comorbid Sleep Apnea study. *States Sleep* 2023;46(8). <https://doi.org/10.1093/sleep/zsad128>. <https://academic.oup.com/sleep>.
- [103] Miller CB, Valenti L, Harrison CM, Bartlett DJ, Glozier N, Cross NE, Grunstein RR, Britt HC, Marshall NS. Time trends in the family physician management of insomnia: the Australian experience (2000–2015). *J Clin Sleep Med* 2017;13(06):785–90. <https://doi.org/10.5664/jcsm.6616>.
- [104] Pfeiffer PN, Ganoczy D, Zivin K, Gerlach L, Damschroder L, Ulmer CS. Guideline-concordant use of cognitive behavioral therapy for insomnia in the Veterans Health Administration. *Sleep Health* 2023. <https://doi.org/10.1016/j.slehd.2023.07.002>. <http://www.journals.elsevier.com/sleep-health/>.
- [105] Sweetman A, Putland S, Lack L, Doug McEvoy R, Adams R, Grunstein R, Stocks N, Kaambwa B, Van Ryswyk E, Gordon C, Vakulin A, Lovato N. The effect of cognitive behavioural therapy for insomnia on sedative-hypnotic use: a narrative review. *Sleep Med Rev* 2021;56:101404. <https://doi.org/10.1016/j.smrv.2020.101404>.
- [106] Guilleminault C. Benzodiazepines, breathing, and sleep. *Am J Med* 1990;88(3):S25. [https://doi.org/10.1016/0002-9343\(90\)90282-i](https://doi.org/10.1016/0002-9343(90)90282-i).
- [107] Carter SG, Eckert DJ. Effects of hypnotics on obstructive sleep apnea endotypes and severity: novel insights into pathophysiology and treatment. *Sleep Med Rev* 2021;58:101492. <https://doi.org/10.1016/j.smrv.2021.101492>.
- [108] Messineo L, Eckert DJ, Lim R, Chiang A, Ali A, Carter SG, Carberry JC. Zolpidem increases sleep efficiency and the respiratory arousal threshold without changing sleep apnoea severity and pharyngeal muscle activity. *J Physiol* 2020;598(20):4681–92. <https://doi.org/10.1113/jp280173>.
- [109] Cheng JY, Filippov G, Moline M, Zammit GK, Bsharat M, Hall N. Respiratory safety of lemborexant in healthy adult and elderly subjects with mild obstructive sleep apnea: a randomized, double-blind, placebo-controlled, crossover study. *J Sleep Res* 2020;29(4). <https://doi.org/10.1111/jsr.13021>. [http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1365-2869](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2869).
- [110] Margaret M, Cheng J, Kumar D, Ramos B, Lowe A. Effect of lemborexant on sleep onset and maintenance in patients with co-morbid insomnia disorder and mild obstructive sleep apnea (P4-13.001). *Neurology* 2023;100(17_Suppl. ment_2). <https://doi.org/10.1212/WNL.00000000000202561>.
- [111] Kushida C, Zammit G, Cheng J, Kumar D, Moline M. 0354 effect of lemborexant on sleep architecture in subjects with comorbid insomnia and mild obstructive sleep apnea from a Ph 3 trial. *Sleep* 2023;46(Suppl. ment_1):A157. <https://doi.org/10.1093/sleep/zsad077.0354>.
- [112] Lowe AD, Lowe MS. Overview of medication treatment for Co-morbid insomnia and sleep apnea (COMISA) CPAP adherence: factors and perspectives. Canada: Springer International Publishing; 2022. p. 195–201. https://doi.org/10.1007/978-3-030-93146-9_18. <https://link.springer.com/book/10.1007/978-3-030-93146-9>.

Further readings

- [1] Sweetman Alexander, Richardson Cele, Smith Allan, Reynolds Chelsea. The effect of digital cognitive behavioural therapy for insomnia in people with co-morbid insomnia and sleep apnoea (COMISA): A pilot randomised controlled trial. *Journal of Sleep Research* 2025. In press.
- [2] Sweetman Alexander, Reynolds Chelsea, Lack Leon, Vakulin Andrew, Chai-Coetzer Ching Li, Wallace Douglas, et al. Effect of high-risk sleep apnea on treatment-response to a tailored digital cognitive behavioral therapy for insomnia program: a quasi-experimental trial. *Frontiers in Sleep* 2024;3. <https://doi.org/10.3389/frsle.2024.1355468>. In press.

Chapter 37

Sleep-wake disturbances and the cancer care continuum

Alexandria Muench^a, Krista Greeley^b and Sheila N. Garland^c

^aDepartment of Hematology Oncology, Penn Princeton, Princeton, NJ, United States; ^bDepartment of Psychology, Memorial University, St. John's, NL, Canada; ^cDepartment of Psychology and Discipline of Oncology, Memorial University, St. John's, NL, Canada

Prevalence of sleep disturbance and fatigue in cancer

Sleep-wake disturbance and insomnia are among the most prevalent and longest-lasting symptoms reported by cancer survivors. As defined, insomnia disorder is a dissatisfaction with sleep quality or quantity presenting as difficulty falling asleep or staying asleep, which occurs at least three times per week and has been present for at least 3 months with impairments in daytime functioning or significant psychological distress [1]. If a patient does not meet the frequency criteria of at least three nights per week for insomnia disorder but has disrupted sleep, they are considered to have insomnia symptoms. If a patient has the frequency but does not meet the duration criteria of more than 3 months for insomnia disorder, they are considered to have acute insomnia. A significant proportion of people diagnosed with cancer will begin treatment with insomnia symptoms. Out of 5702 patients presenting at a routine clinical visit prior to starting treatment, 12.5% reported severe sleep problems, 25.6% reported moderate problems, and 26.1% reported that sleep was a mild problem [2]. Nearly 60% of individuals with cancer will experience insomnia symptoms during or following cancer treatments [3]. Roughly one-third of these individuals will experience insomnia disorder.

CRF is also one of the most prevalent, distressing, and disabling side effects experienced by patients diagnosed with cancer, even more so than pain, nausea, or vomiting [4–6]. The experience of CRF involves physical symptoms (e.g., weakness, tiredness, and/or shortness of breath), mental health symptoms (e.g., depression and anxiety), motivational symptoms (lack of initiative or task completion), cognitive symptoms (impaired processing speed, short-term memory, and concentration), and social

symptoms (e.g., issues with body image, reduced interpersonal engagement, and fear of recurrence [7–9]). While CRF is a universal symptom in those receiving chemotherapy, radiation therapy, hematopoietic cell transplantation, or other biologic agents [6,10,11], CRF presents differently across cancer types and stages and often occurs prior to diagnosis, during treatment, and well after the completion of treatment [12,13]. Multiple studies indicate that up to 96% of patients undergoing chemotherapy report some form of CRF, ranging from mild to severe [7,9,14]. In addition, studies have shown that as many as 81% of survivors report persistent CRF more than 6 months after treatment completion [15,16], while approximately 33% still continue to experience CRF at 5 years posttreatment or even indefinitely for some individuals [17–19]. CRF is also a dose-limiting toxicity [20–23], as more than 30% of patients experience CRF so severe that it can affect their ability to tolerate chemotherapy [15,24] resulting in treatment discontinuation [9] and increased mortality [25].

Few studies have examined the prevalence of sleep disturbance and fatigue concurrently. Krupalija Davis et al. examined sleep disturbance and fatigue profiles in a heterogeneous sample of 1336 cancer outpatients receiving chemotherapy using latent variable monitoring [26]. Measurements of sleep disturbance and energy were completed over two cycles of chemotherapy. They identified three prevalence profiles relating to fatigue and sleep disturbance: (1) Low sleep disturbance and high morning energy (20.6%), (2) moderate sleep disturbance and low morning energy (52.1%), and (3) very high sleep disturbance and very low morning energy (27.3%). Based on this study, the most common profile of concurrent sleep disturbance and fatigue is when there is a moderate level of sleep disturbance and low morning energy.

Mechanisms of sleep disturbance and cancer-related fatigue

There are predisposing, precipitating, and perpetuating factors of both sleep disturbances and fatigue in cancer survivors, also referred to as “Spielman’s 3P model” [27]. These are risk factors, or variables relating to demographic information, symptomology, or comorbidities that may make someone more susceptible to developing and maintaining sleep disturbances or fatigue after a cancer diagnosis. Fig. 37.1 demonstrates these factors for sleep disturbance and fatigue individually, as well as the shared mechanisms. Predisposing factors are the underlying factors that may make one more susceptible to developing sleep disturbances or fatigue. Some predisposing factors shared of both sleep disturbances and fatigue in cancer populations are genetics and biological sex. Precipitating factors better

refer to a specific event/occurrence that may trigger the onset of sleep disturbances or fatigue. Mood disturbances, tumorigenesis, cancer treatment, and lifestyle changes are examples of precipitating factors for both sleep disturbances and fatigue. Perpetuating factors are behaviors that maintain or exacerbate the condition which include dysfunctional thoughts about sleep and fatigue, napping, and diet.

Predisposing factors

Genetics

Genetics have been identified as a predisposing factor for CRF and sleep disturbances in oncology populations. A study by Aouizerat et al. [28] studied the association of a proinflammatory cytokine, tumor necrosis factor-alpha (TNF- α), with sleep disturbance and fatigue in a sample of 185 cancer

Predisposing, Precipitating, and Perpetuating Factors of Insomnia and Cancer-Related Fatigue

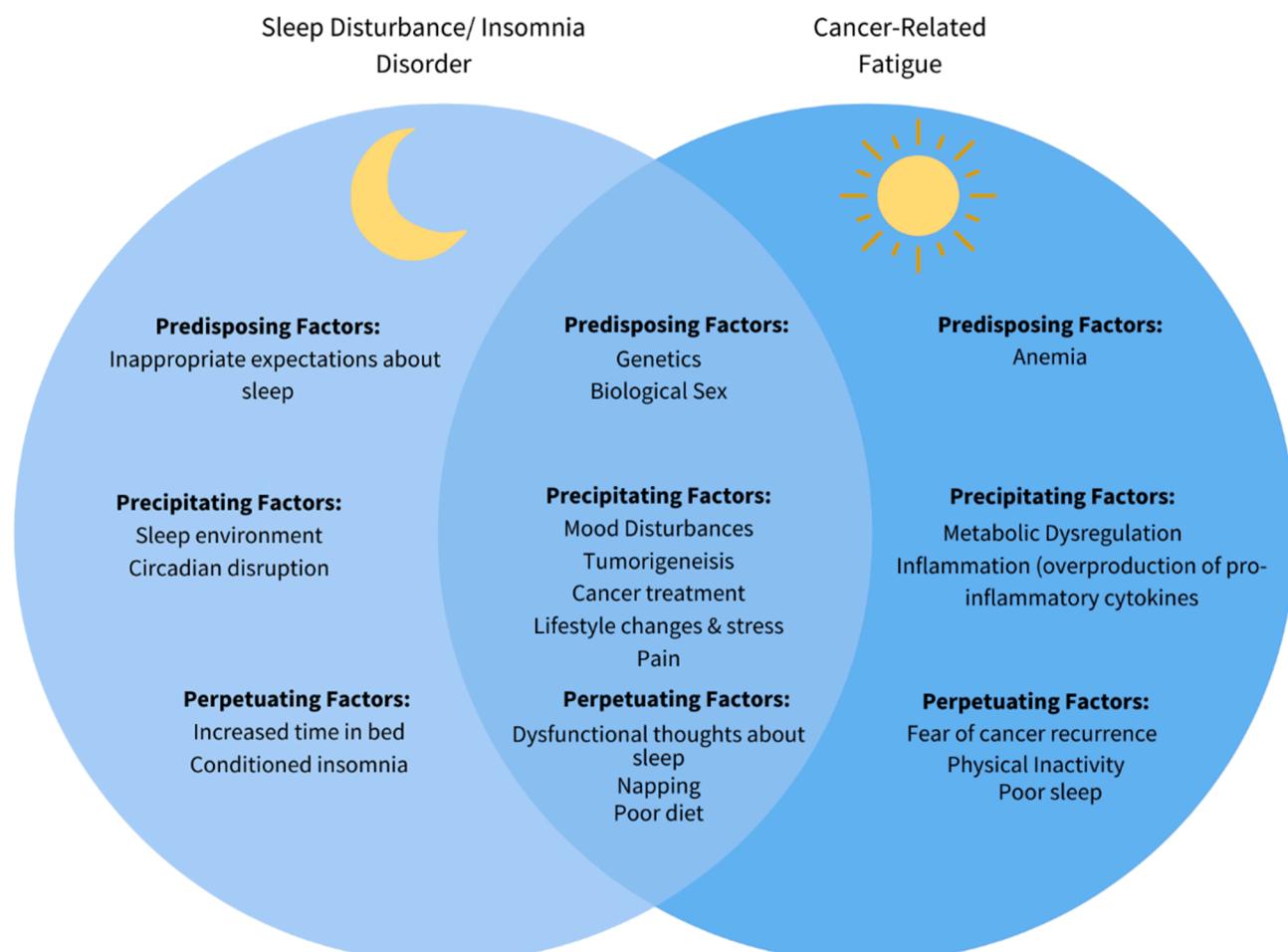


FIGURE 37.1 Diagram of predisposing, precipitating, and perpetuating factors of insomnia and cancer-related fatigue.

patients and found that those with the common allele homozygotes of TNFA had greater incidences of fatigue and sleep disturbances compared with minor allele carriers. Furthermore, a genetic variation of another proinflammatory cytokine, interleukin 6 (IL6) has also been associated with sleep disturbance and fatigue in oncology populations [29]. Those with the common allele homozygotes of IL6 reported higher levels of morning fatigue, evening fatigue, and sleep disturbance than those who carried minor alleles.

Biological sex

Evidence suggests that being female is a predisposing factor to developing fatigue and insomnia in cancer populations compared with being male [30–32]. This may be due to the fact that females have a lower capacity to carry oxygen due to lower levels of hemoglobin, which may result in fatigue [33]. There is also evidence that females may have a greater genetic predisposition to depression and anxiety which may predispose or increase the likelihood of experiencing insomnia and fatigue [34].

Precipitating factors

Tumorigenesis

There is a growing body of literature that suggests that the onset of sleep disturbance and fatigue may be a prodromal sign of cancer [35]. In fact, with respect to fatigue, Goedendorp et al. [36] conducted a study in 179 patients diagnosed with cancer, where the prevalence of fatigue was assessed prior to the initiation of treatment. Severe fatigue was found in 23.5% of the sample and varied between diagnoses, gastrointestinal cancer (28.1%) had the highest rates of fatigue, followed by breast cancer (20.3%), and prostate cancer (14.3%) [36]. With respect to insomnia, Ancoli-Israel et al. conducted a study in 68 women diagnosed with breast cancer. Results showed that, when compared with matched controls, these subjects had worse fatigue and quality of life at baseline (prechemotherapy) and, importantly, that insomnia is a contributing factor [37].

While the mechanisms of CRF and sleep disturbance in cancer still need to be elucidated, the leading hypothesis is that tumors lead to a dysregulation of cytokines, primarily proinflammatory cytokines [11,38]. Other potential mechanisms include, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, 5-hydroxytryptophan neurotransmitter dysregulation, anemia, and alterations in ATP and muscle metabolism [10,39–41].

Cytokine and HPA axis dysregulation

With respect to cytokine dysregulation, the basis of this research comes from basic science on the role of cytokines in sickness behaviors and neuro-immune signaling, where

tumorigenesis causes the signaling of peripheral inflammatory cytokines (e.g., IL6 and TNF- α) in the CNS, thus leading to fatigue. There is research to suggest that, given the role of the HPA axis in the regulation of cytokine production and antiinflammatory processes, it may be implicated in the development and maintenance of CRF and sleep disturbance. Dysregulation of the HPA axis may lead to alterations in glucocorticoid production and subsequent dysregulated circadian rhythms. Weinrib et al. evaluated diurnal cortisol rhythms in 177 patients diagnosed with ovarian cancer and found that higher levels of nocturnal cortisol and less cortisol variability were significantly associated with greater fatigue [42].

Dysregulation of central 5-HT

5-HT is involved in the regulation of many biologic functions, including but not limited to, sleep, mood, memory, and learning [43]. Dysregulation of brain serotonin (5-HT) levels is thought to be involved in the development and maintenance of fatigue across disorders, such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and CRF [44]. Prior research in exercise-induced fatigue and ME/CFS have shown changes and dysregulation in Central 5-HT [45,46]. In fact, patients diagnosed with chronic fatigue syndrome show increased serotonergic responses [47]. Maes et al. evaluated 5-HT antibodies in 117 patients diagnosed with ME/CFS. The authors found that 5-HT was elevated in ~61% in patients with ME/CFS, compared to 13% of patients just diagnosed with Chronic Fatigue [48]. Central 5-HT is also implicated in CRF. Proinflammatory cytokines, such as (TNF- α , can negatively affect the feedback loop between Central 5-HT and TNF- α [10]. This dysregulation in the loop causes increased 5-HT, which leads to more of this neurotransmitter and an over clearing at the synaptic level, thus leading to decreased mood and fatigue. Interestingly, this feedback loop is often found in response to cancer therapies.

Cancer treatment

Cancer treatment typically involves a combination of surgery, chemotherapy, radiation therapy, targeted therapies, immunotherapy, and/or hormone therapy, all of which have been shown to be a precipitating factor of sleep disturbance and fatigue because of their emotional impact, their direct physiologic effects, or their side effects [31,49]. Chemotherapy is thought to be particularly disruptive to circadian sleep–wake patterns [50,51]. Patients report more subjective sleep disturbance (e.g., lower sleep quality and duration) during the active phases of chemotherapy compared with rest periods [52]. Longitudinal studies using subjective measures have also shown gradual increases in sleep impairment with this treatment [53] as well as persistence

of elevated insomnia rates across chemotherapy cycles [54]. Moreover, cancer patients who completed chemotherapy and radiation therapy reported significantly higher levels of fatigue 2-years after finishing treatment [55]. A longitudinal study that followed the trajectory of women with breast cancer after radiotherapy found that fatigue levels increased significantly from baseline to posttreatment [56]. Fatigue levels remained high up to 2 years after treatment was finished. Women receiving endocrine adjuvant therapy for breast cancer, most commonly tamoxifen, report notable side effects, including hot flashes and nighttime sweating [57]. These symptoms cause frequent awakenings during the night, thus disrupting sleep.

Lifestyle changes and financial stress

Cancer often warrants many lifestyle changes and stress after a diagnosis, such as time off work, interruption of daily activities, or relocating for treatments. These interruptions can negatively impact sleep and cause the onset of fatigue or insomnia. A cancer diagnosis may disrupt a person's usual sleep/wake times and cause these sleep habits to become sporadic, thus disrupting sleep. In addition to lifestyle changes, a cancer diagnosis can be stressful financially. Cancer populations are especially prone to developing financial stress due to the costs associated with cancer treatment, travel, and loss of income [58]. In a study of 2458 prostate cancer survivors, cumulative financial stress (before and after diagnosis) was associated with fatigue [59]. In summary, the required lifestyle changes and stress from a cancer diagnosis can have detrimental impacts on the patient, thus being a precipitating factor for sleep disturbances and fatigue.

Mood disturbances

A diagnosis of cancer may cause anxiety and depression symptoms for the patient, which has the ability to disrupt sleep and contribute to the development of fatigue. This is especially true for those who have finished their cancer treatment, as feelings of loneliness, abandonment, fear, numbing of emotions, and avoidance behaviors are often experienced [60]. A meta-analysis identified three studies that assessed the relationship between fatigue and mood disturbances and found that anxiety and depression were significant risk factors [30]. Moreover, a longitudinal study of a heterogeneous sample of cancer patients found that greater depression and anxiety symptoms were predictive of sleep-wake disturbances [61].

Pain

Pain is experienced by approximately 40%–55% of cancer survivors after their diagnosis and can develop from cancer treatment, surgery, or the cancer itself [62,63]. Like fatigue and sleep disturbances in cancer populations, cancer-

related pain can persist after treatment is finished and can negatively contribute to quality of life and daily functioning [64,65]. Pain has been found to be associated with sleep disturbances and CRF [30,31,66]. In fact, pain is one of the most common symptoms that is associated with fatigue in cancer populations [67]. Experiencing pain can interrupt sleep-wake cycles as well as cause daytime fatigue due to its chronicity and severity in some cases. Evidence has shown that when pain levels are decreased, there is an improvement in insomnia severity [68].

Perpetuating factors

Dysfunctional thoughts about sleep and fatigue

Dysfunctional thoughts about sleep are unrealistic expectations about sleep that cause excessive worry, and often make sleep problems worse [69,70]. A study that examined 991 cancer patients found that dysfunctional thoughts about sleep, as well as maladaptive sleep behaviors, were involved in the maintenance of insomnia [32]. Some dysfunctional thoughts about sleep such as "I need to get 8 hours of sleep a night" or thinking that their sleep is "off track" due to a bad night's sleep can make insomnia symptoms worse [30,32,71]. Dysfunctional thoughts about fatigue are similar in that they often lead to behaviors that worsen the experience that they are trying to improve. For example, when fatigued, one might think that their fatigue must mean that they need to rest, when in fact increasing physical activity may be the key to symptom improvement. Other examples include the catastrophization of fatigue "My fatigue means I can't do what I enjoy" and "Once I feel fatigued, there is not much I can do but rest."

Napping and extending time in bed

Indeed, fatigued individuals tend to nap more during the day and extend their sleep periods during the night, which may in the long run impair their circadian rhythm and make their nighttime sleep less consolidated and lighter [72,73]. This may be particularly the case during cancer treatments, when patients suffer from higher levels of fatigue and are very likely and often encouraged to rest to recuperate [74,75]. Napping is also a factor that maintains insomnia. During the day, napping can interfere with sleeping during the night, and it may also worsen insomnia symptoms [76]. Having a later rise time in the morning does not allow for the accumulation of sufficient sleep pressure to fall and stay asleep at night.

Diet

Diet has been identified as a risk factor for sleep disturbances and fatigue in some studies. There is also evidence that

antiinflammatory foods, such as fruits, vegetables, and nuts, can help mitigate CRF and sleep quality symptoms by reducing inflammation [77,78]. In contrast, consumption of proinflammatory foods (processed meats, red meat, high sugar content, and refined grains) has been associated with the previously discussed inflammatory biomarkers (TNF- α and IL6) that contribute to fatigue and sleep disturbance [79].

Measurement of sleep-wake disturbance in cancer

Screening for cancer-related sleep disturbance and fatigue

It is recommended that all patients with cancer be screened for sleep disturbances and CRF at initial diagnosis, start of treatment, regular intervals during treatment, end of treatment, posttreatment survivorship, upon recurrence or progression, at end of life, or during times of personal transition (e.g., family crisis). The assessment process typically begins with a brief screening instrument such as the Edmonton Symptom Assessment Scale with a sleep item included [80] or questions such as, “Are you having problems falling asleep or staying asleep?; Are you experiencing excessive tiredness or fatigue during the day?; and Are you still fatigued and tired after sufficient rest and sleep?.” Individuals who screen positive are then recommended to complete a more focused assessment consisting of a semistructured clinical interview and validated measures.

Clinical interview

A semistructured clinical interview should cover the following content areas:

- Characterization of the insomnia and fatigue complaint:** It is helpful to have the patient describe the event or events that they believe to have precipitated their insomnia and fatigue. From here, one can easily assess the nature of the difficulty (i.e., difficulty falling asleep, staying asleep, or waking up too early), daytime tiredness and fatigue despite sleep and rest, the frequency and duration of the problem, the success, or lack thereof, of any previous attempts at treatment, the adequate opportunity is available for sleep, and whether their fatigue is proportional to their daytime activity.
- Typical sleep-wake pattern:** A characterization of a typical sleep-wake schedule can be accomplished by asking the patient to report on the following: What time do they typically go to bed at night and wake up in the morning? What time do they actually fall asleep and wake up? How many times do they tend to wake up at night and how long do these awakenings last? What activities do they engage in when they are awake

at night (e.g., checking social media and lying in bed and trying harder to sleep)? Do they nap and, if so, how frequently, for how long, and when? Does their fatigue improve with rest? Does their routine change on weekends?

- Individual and family history:** This section is useful to identify factors that might predispose an individual to experience insomnia and/or fatigue. Patients will often report that one or more of their immediate family members have past or present experience with insomnia [81]. They may also report past episodes of prolonged recovery and fatigue after a physical illness.
- Behavioral, cognitive, and environmental daytime and presleep conditions.** This includes an examination of what activities the individual engages in during the day and before bed. For example, patients may be very sedentary or have frequent naps to try and alleviate their fatigue. They may cancel activities because they don't feel like they have the energy to exert. In the evening, they may use distraction to cope with uncomfortable feelings and unwanted thoughts by watching television, working on the computer, or keeping busy with other tasks or going to bed earlier and trying harder to “force” sleep. Close attention to the behavioral, cognitive, and environmental daytime and pre-sleep conditions will identify relevant perpetuating factors and potential targets of behavioral and/or cognitive techniques.
- Perceived impact of insomnia and fatigue on next-day function, and compensatory behaviors:** Patients may report difficulty concentrating or paying attention, sleepiness, low motivation, and energy, or a worsening of comorbid physical or psychiatric conditions as consequences of their insomnia. They may also engage in, or discontinue, activities to try and cope with their daytime dysfunction. This may include daytime napping, stimulant use (e.g., caffeine), and canceling physical activity or social engagements. The behaviors, while intended to help them cope, actually perpetuate the persistence of the insomnia and fatigue and can be modified or eliminated to reduce their contribution to both disorders.
- The presence of other sleep disorders:** There are a number of other sleep disorders that may account for (or exacerbate) the presenting insomnia and fatigue symptoms or represent an additional comorbidity to be considered. To assess for these disorders, especially for clinicians less familiar with the signs and symptoms of the various intrinsic sleep disorders, it is recommended that a screening questionnaire be used. While many such instruments exist [82], only two are considered brief (The GSAQ [83] and the SDS-CL-25 [84]) and only one is both brief and comprehensive (the SDS-CL-25 [84]). If

the patient presents with symptoms suggestive of one or more of these disorders, a sleep study (PSG) may be warranted. If a patient has restless legs syndrome, the clinician should make sure that the patient does not have iron deficiency, which commonly occurs in gastrointestinal carcinomas. If the patient has developed movement disorders secondary to a chemotherapeutic agent, a trial of a dopaminergic agent should be initiated. If a patient has developed OSA, for example, secondary to enlarged lymph nodes in the pharynx, as might occur with lymphoma or with nasopharyngeal carcinoma, continuous positive airway pressure treatment as well as specific treatment directed at these areas should be initiated.

7. **Medical and psychiatric history:** A number of medical and psychiatric conditions, along with their treatments, can contribute to and complicate insomnia and fatigue [85]. Hypoxemia caused by spread of cancer to the lung or the development of lung fibrosis in response to chemotherapy or radiation therapy may require treatment, as patients with hypoxemia are known to have disturbed sleep. If the patient has clinical depression along with insomnia or fatigue, concurrent therapy for the mood disorder as well as for insomnia and fatigue should be initiated. If the cancer is causing pain that is disturbing sleep or increasing daytime fatigue, the pain needs to be treated concurrently with the sleep-wake disturbances. A thorough review of medications (both prescribed and over the counter) is necessary to identify any potential substances that may be contributing to their dysfunction. Attention should be paid to whether these are taken in the morning or evening depending on whether they impair or promote sleep. Anxiolytic medications are often used as a hypnotic/sedative to reduce presleep arousal, but this is not a recommended as a long-term solution for reasons of tolerance, dependence, and the potential for other negative outcomes [86,87].

Sleep only measures

Sleep can be measured both objectively (e.g., wrist actigraphy/wearables) and subjectively (e.g., sleep diaries and insomnia/sleep questionnaires [Insomnia Severity Index, the Pittsburgh Sleep Quality Index, and Epworth Sleepiness Scale] [88–90]). With respect to objective measures, wrist actigraphy can be used to delineate patterns in sleep/wake and to ascertain adherence to insomnia treatments (e.g., cognitive behavioral therapy for insomnia [CBT-I]). While actigraphy can be beneficial, there are some limitations, including that it is often not reimbursable by insurance, thus limiting patient and provider access. In addition, while an accurate measure of activity, actigraphy does not accurately

measure sleep. For example, a patient who lays very still in bed while awake, may have that wake time coded as sleep. In the context of behavioral treatments, patients are often asked to complete sleep diaries. The Consensus Sleep Diary is validated and is the most widely used version [91]. The diary is completed every morning and includes questions on sleep latency, wake-after-sleep onset, early morning awakenings, and sleep quality. Although there have been concerns raised regarding the subjective nature of the diary, especially with respect to how accurate it is, the sleep diary is integral to capturing the experience of the patient.

Fatigue only measures

Unlike sleep, there is currently no direct objective measure of fatigue, thus researchers and clinicians alike, rely on subjective questionnaires to diagnose CRF. There are quite a few self-report scales, including the PROMIS-7a, BFI, FACIT, FSI, and PFS [92–95]. These questionnaires assess an array of symptoms thought to be related to fatigue: physical symptoms (weakness, tiredness, shortness of breath), psychological symptoms (depression, anxiety), motivational symptoms (lack of initiative, task completion), cognitive symptoms (impaired processing speed, short-term memory, and concentration), and social symptoms (reduced ability to sustain interpersonal engagement, and fear of recurrence [7–9]). While these questionnaires are useful, the mechanisms of CRF have not yet been determined, thus limiting one's ability to accurately measure the phenomenon, ultimately hindering screening, prevention, and intervention efforts.

Sleep and wake measures

Measuring insomnia and fatigue in one measure can be accomplished by using a more general quality of life self-report measure such as the EORTC [96]. Actigraphy may be an effective way to measure 24-hour movement patterns and assess the absence of movement during the day (fatigue) and an excess of movement at night (sleep disturbance and insomnia). Some studies have looked at these 24-hour activity patterns using actigraphy. Most notably, Ancoli-Israel et al. used 24-hour actigraphy watches to study sleep and fatigue in women with breast cancer and found that women with breast cancer spent significantly more time napping during the day than their noncancer controls [37]. However, most commercially available and research software is designed to either look at physical activity during the day or sleep at night. More research needs to consider sleep-wake disturbances as a 24-hour phenomenon and more development is required to produce software that can efficiently analyze these rhythms.

Treatment of sleep-wake disturbances and fatigue in cancer

There is a large body of literature on treatment of sleep-wake disturbances and CRF as single symptoms, ranging from pharmacotherapy to behavioral interventions. This section will focus on those treatments with the most evidence for the management of both sleep-wake disturbance and fatigue: exercise, pharmacotherapy, mindfulness-based interventions, CBT-I, mindful movement interventions, and light therapy.

Exercise

To date, 31 studies (sample sizes ranging from 18 to 277) have examined the efficacy of exercise interventions for both sleep disturbances and CRF. The majority of these studies were RCTs/pilot RCTs [97–125]. Other study types included a comprehensive cohort study [126,127] and a randomized full factorial trial [128]. Cancer types studied included breast, multiple myeloma, lung, colorectal, solid tumors, prostate, ovarian, testicular, leukemia, pancreatic, and mixed types. CRF was measured using a myriad of self-report fatigue and sleep measures. In one study, sleep was measured objectively using actigraphy watches and sleep diaries [101].

The use of exercise to manage fatigue has been widely documented across the fatigue literature, most specifically in fibromyalgia and multiple sclerosis (MS), with effects ranging from small to moderate for fibromyalgia, and moderate to large for MS [129,130]. With respect to CRF, results on the effect of exercise, are small to moderate. Samuel et al. conducted a study in 148 patients diagnosed with head and neck cancer, in which they tested the effect of an exercise intervention (six-minute walking test) on CRF over an 11-week period. The authors found that, when compared with controls whose fatigue increased over time, those in the exercise intervention maintained their mild fatigue status and even showed greater decreases at 11 weeks [131]. Similarly, a recent meta-analysis reviewed 22 articles that evaluated exercise conducted during active cancer treatment [132]. The author findings provide strong evidence that exercise is at least moderately effective. Similarly, there is research to suggest that exercise is also effective for patients diagnosed with insomnia. Lowe et al. conducted a systematic review of 11 studies where the aim was to assess whether exercise improves objective and subjective sleep in people diagnosed with insomnia [133]. The findings indicate, that while exercise was shown to be helpful on both objective and subjective measures of insomnia, it had the greatest impact on sleep latency.

With respect to the studies that have assessed the efficacy of exercise for both CRF and sleep disturbance, the evidence suggests that exercise interventions can be

effective for both of these symptoms, but the literature varies. An RCT, conducted postchemotherapy, assessed the efficacy of low-to-moderate and high-intensity exercise in 277 cancer survivors (mixed types), found that both high-intensity and low-to-moderate intensity exercise significantly improved fatigue compared with a waitlist control [104]. However, no between-group differences were observed for sleep quality. Moreover, another RCT that assessed a home-based exercise program for lung and colorectal cancer survivors found that both fatigue and sleep quality significantly improved compared with the usual care control group [102]. Lastly, a study that used a sample of prostate cancer survivors (n = 80) found that there were no differences between the exercise treatment group and the control group in insomnia symptoms, but fatigue significantly improved in the treatment group after the intervention [118]. In sum, while exercise has been found to be helpful for both fatigue and sleep disturbance in cancer, limitations exist, especially with regard to patients undergoing active treatment who may be limited in their ability to engage in exercise.

Pharmacotherapy

Currently, there are 12 pharmacological interventions that use CRF and sleep disturbances as outcome variables (sample sizes ranging from 34–631). Some of these interventions were designed to target other symptoms in cancer survivors, such as hot flashes, but they still assessed CRF and sleep outcomes. The interventions were all RCTs that used different medications such as armodafinil [134–136], methylphenidate [137–140], venlafaxine [141], modafinil [142], and donepezil [143]. These studies have tested pharmacological treatments in breast cancer, brain tumors, multiple myeloma, lung cancer, and seven studies assessed mixed cancer types.

In general, 88% of the prescriptions written for the medical treatment of insomnia are for trazodone (Desyrel) or zolpidem (Ambien), with trazodone being the single most prescribed [144,145]. Remarkably, these prescription trends are not consistent with the clinical practice guidelines set forth by the American Academy of Sleep Medicine [146]. This organization recommended that clinicians use zolpidem (vs. no treatment) for sleep onset and sleep maintenance insomnia. A similar recommendation was made by the American College of Physicians [147]. These guidelines are based on the strength of evidence in published data and not on comparative efficacy or effectiveness data. In cancer, hypnotics are the most prescribed medication, despite the risk for deleterious side effects (e.g., dependence; palliation vs. cure) [148]. Other medications that are often prescribed are, benzodiazepines, anti-depressants, and melatonin receptor agonists [148]. While there are not many studies examining the use of

medications for insomnia in cancer, the literature that does exist suggests that benzodiazepines are superior to placebo with respect to shortening sleep latency and wake after sleep onset [149,150]. The NIH State of the Science (year) indicated that benzodiazepine receptor agonists (e.g., zolpidem) had a lower risk-benefit profile when compared with their benzodiazepine counterparts (e.g., Xanax), however, can be safe when used short-term [151]. Moreover, it was determined that antidepressants (e.g., trazodone) also carry potential side effects that may be cause for concern [151]. In sum, while medications for sleep disturbance can be efficacious, one should consider the side effect profile prior to prescribing.

Several medications have been studied for the treatment of CRF. Chow et al. [152] conducted a systematic review and network meta-analysis on pharmacologic interventions in CRF (18 studies and 2604 patients). The authors found that methylphenidate, modafinil, and paroxetine were superior to placebo. Methylphenidate and modafinil were equivalent to one another. Paroxetine was superior to modafinil. Overall, the use of pharmacological treatments for sleep disturbances and fatigue is not well documented, but the current literature demonstrates that they have increased risks for side effects than other interventions and they are not the most effective treatment for symptom relief.

The use of medications in the treatment of CRF and sleep disturbances has not been well documented in the literature. It is not surprising that there is a lack of pharmacological trials that target both daytime fatigue and nocturnal wakefulness as they would be acting on different systems. Jean-Pierre et al. assessed the use of modafinil in 631 cancer survivors after chemotherapy and found that sleep quality significantly improved after the intervention, and CRF improved only in those who had high CRF levels at baseline [142]. Only three RCTs available have been conducted with armodafinil, a wakefulness-promoting agent to daytime fatigue and sleepiness that may be a short-term side effect of CBT-I. Heckler et al. evaluated CBT-I with or without Armodafinil in 96 cancer survivors [134]. The authors found that, while CBT-I improved fatigue, armodafinil did not have a demonstrable effect. Similarly, they found that CBT-I improved insomnia but there were no improvements demonstrated from armodafinil. In a study that assessed the use of armodafinil compared with a placebo in 54 cancer patients, there were no significant improvements in either fatigue or sleep disturbances [135]. Other RCTs do not target both CRF and sleep disturbances, but they report both as secondary outcomes. For instance, Carpenter et al. [141] used venlafaxine (antidepressant) primarily to treat hot flashes in breast cancer survivors. They did not find any improvement in CRF or sleep after the intervention [141].

Mindfulness-based interventions

Mindfulness-based interventions are now widely used to treat a host of sequelae, including anxiety and insomnia [153,154]. Historically used in Buddhism, mindfulness has now been codified into a systematic practice, where the aim is to bring awareness and acceptance to one's feelings in the present moment [155]. More specifically, mindfulness interventions encourage moment-by-moment awareness, to develop a greater sense of emotional balance and well-being by disengaging oneself from strong attachment to beliefs, thoughts, or emotions [154,156].

The hyperarousal theory of insomnia hypothesizes that insomnia stems from anxiety surrounding sleep and that this anxiety often leads to fears that one won't be able to sleep, thus leading to sleep-related anxieties and a reaction in the sympathetic nervous system (e.g., the "fight or flight" response) [157]. Ong et al. developed the metacognitive model to explain how shifting from an outcome-oriented approach to a process-oriented approach may assist in decreasing sleep-related distress [158]. For instance, purely noticing that one is stressed versus trying to change the outcome, increases the likelihood that one will shift from maladaptive cognitions about sleep to an ability to cope better with sleep-related disturbance. Moreover, neurobiological models show that engagement in mindfulness practices influences brain regions associated with emotion regulation, attention regulation, body awareness, and self-perspective, thus leading to decreased distress and anxiety [159–165]. Gross et al. randomized 30 subjects diagnosed with chronic insomnia to a mindfulness based stress reduction (MBSR, [eight 2.5-hour long classes, a daylong retreat, and ongoing practice at home]) or pharmacotherapy (3 mg of eszopiclone) [166]. Results indicated that changes in both groups were of comparable magnitude, suggesting that MBSR may be an effective strategy for the treatment of insomnia. Similarly, a recent meta-analysis evaluated 330 subjects over 6 RCTS and found that Mindfulness significantly improved symptoms of insomnia, specifically decreasing total wake time and improving sleep quality, however sleep latency, total sleep time, and wake after sleep onset were not significantly impacted [167].

Cancer-related fatigue also seems to be improved by mindfulness-based interventions. Van der Lee et al. evaluated a 9-week mindfulness intervention in 100 cancer survivors (mixed diagnoses) [168]. When compared with the wait list control, subjects in the mindfulness-based group were significantly less fatigued (30% vs. 4%). Likewise, a recent systematic review (n = 15 studies, 1502 subjects), evaluated the effect of MBSR on fatigue in cancer patients. MBSR was found to significantly improve CRF, especially in patients diagnosed with lung cancer. Eight weeks of MBSR, with expert supervision, also seemed to be related to increased decreases in CRF.

Mindfulness interventions are also used to mitigate symptoms of sleep disturbance and fatigue concurrently in cancer [169,170]. To date, there are seven RCTs that assess the efficacy of mindfulness-based interventions in both CRF and sleep disturbances among cancer survivors (sample sizes ranging from 35–322). Five of these studies used a sample of breast cancer [170–174], while two studied mixed cancer types [169,175]. The FSI, BFI, MFSI [176], and the POMS were used to measure CRF, while the PSQI and ISI were used to measure sleep disturbances. Carlson and Garland used a mindfulness-based stress reduction program for cancer patients, and they found a significant change in sleep disturbance and fatigue after the intervention [169]. In a randomized controlled trial that examined the efficacy of a mindfulness-based treatment compared with survivorship education and a waitlist control found improvements in both insomnia and fatigue after the intervention in the mindfulness group [172]. Moreover, Reich et al. [170] used a sample of 322 breast cancer survivors to assess the efficacy of an MBSR intervention on different symptom clusters (pain, psychological, fatigue, and cognitive). They found that sleep quality and fatigue both significantly improved after the treatment, compared with usual care controls [170]. A randomized controlled trial assessed a mindfulness intervention group ($n = 85$) to a cancer survivor education group ($n = 81$) and a waitlist control group ($n = 81$) in breast cancer survivors. The mindfulness intervention and the survivorship education groups significantly improved in insomnia, but only the mindfulness group had significant improvements in fatigue after treatment. Overall, the literature suggests that mindfulness-based interventions can help improve CRF and sleep disturbances in cancer survivors.

Cognitive behavioral therapy for insomnia (CBT-I)

Currently, 20 studies have assessed the efficacy of CBT-I for the treatment of both CRF and sleep disturbances (sample sizes ranging from 10–255). Most of the studies are RCTs/pilot RCTs [134,177–193]. One study was a multiple baseline experimental design [194] and one study was a comprehensive cohort study [126]. The cancer types studied included breast, primary brain tumors, and some studies examined mixed types. The EORTC, MFSI, FSI, BFI, PFS [95], POMS, FACIT-F, and the CFS were used to measure fatigue. The ISI, PSQI, and sleep diaries were used to measure sleep disturbances.

There is now a large body of evidence to show that CBT-I is effective in the treatment of insomnia. In fact, CBT-I is equally as efficacious as sleep medication and is now considered the first-line treatment for insomnia [195]. While there are different variations in the application of CBT-I, in its standard form it is typically 6–8 sessions,

where the patient is instructed to use sleep diaries to track their sleep and the focus is on psycho-education on the use of stimulus control (e.g., using the bedroom only for sleep), sleep restriction (e.g., restricting time in bed), cognitive strategies (e.g., reframing maladaptive sleep thoughts), and sleep hygiene (e.g., limiting the use of stimulants before bed). A systematic and meta-analysis conducted by Johnson et al. [196] reviewed the literature on the use of CBT-I in people diagnosed with cancer ($n = 22$ studies, 1461 cancer survivors) [197]. Findings indicated improvements in insomnia severity (the primary outcome variable), sleep quality, total sleep time, sleep latency, wake after sleep onset, and sleep efficiency. The authors concluded that the evidence supports a strong recommendation for the use of CBT-I in patients diagnosed with cancer.

Although CRF has been thought to be distinct from sleep, there are at least eight studies evaluating the association between CRF and sleep disturbance [7,134,196–201]. Therefore, CBT-I has been assessed for its ability to manage CRF as well as insomnia. The CBT-I literature that assesses both insomnia and CRF is limited, but CBT-I seems to be efficacious for relieving CRF symptoms. For instance, Savard et al. assessed both insomnia and CRF in a sample of 57 breast cancer survivors and they found significant improvements in both symptoms after the intervention [179]. More recently, Zachariae et al. used virtually delivered CBT-I in 255 breast cancer survivors and found significant improvements in insomnia and CRF after the intervention [188]. Moreover, the improvements in insomnia and CRF were mostly maintained at the 3-year follow-up [202]. Heckler et al. evaluated the use of CBT-I (with and without armodafinil) for the treatment of CRF in 96 cancer survivors [134]. It was found that both groups showed statistically significant reductions in fatigue, suggesting that CBT-I may be useful for the treatment of CRF.

Mindful movement interventions

The use of mindful movement interventions for cancer-related symptoms is currently growing in the literature. To date, 16 studies have assessed the efficacy of these interventions on both CRF and sleep disturbances (sample sizes ranging from 30–226). All of these studies are RCTs/pilot RCTs. Most of these studies assess the efficacy in breast cancer [187,203–206], but other studies examined patients with lymphoma [207–209], prostate cancer [105], colorectal cancer [210], lung [116,125], head and neck [211], and three studies assessed mixed cancer types [115,212,213]. To measure CRF, the BFI, MFI, MFSI, EORTC, and the FSI were used. The PSQI, EORTC, and the Verran and Snyder-Halpern Sleep Scale were used to measure sleep disturbances.

Mindful movement interventions combine the use of low-impact, slow, exercise, and mindfulness techniques

(i.e., breathing and relaxation) to achieve deep states of relaxation [214]. These interventions typically include yoga, tai-chi, or qigong, which all involve slow, controlled movements with meditation. These interventions provide light movement that can be modified for physical limitations. In addition, meditative movement interventions may be a more accessible treatment option compared with cognitive behavioral or pharmacological interventions. Mindfulness movement interventions have also provided efficacy for CRF and sleep disturbances. Takemura et al. compared tai-chi to aerobic exercise and a control group in a sample of 226 lung cancer survivors [125]. They found that both tai-chi and aerobic exercise significantly improved sleep quality and CRF compared with the control. Moreover, Kiecolt-Glaser et al. used a yoga intervention in a sample of 200 breast cancer survivors [205]. They found that participants in the yoga intervention reported significant improvements in sleep compared with the control. However, at posttreatment, CRF did not experience a significant improvement compared with the control group.

Bright light therapy

There are currently nine studies that have assessed the efficacy of bright light therapy for both CRF and sleep disturbances (sample sizes ranging from 21–166). All of these studies are RCTs/pilot RCTs. The cancer types studied were primarily breast but lymphoma, hematological, or mixed cancer types were also studied. CRF was measured using the MFSI [215], FACIT-F [140,216,217], MFI [218], PROMIS-Fatigue [191,219,220], and the BFI [221]. Sleep disturbances were measured using the PSQI, ISI, PROMIS-Sleep, or objectively, using actigraphy watches.

Bright light therapy, which includes the use of a light box timed at a specified time of day, has some evidence of efficacy in both the treatment of insomnia and fatigue in cancer. An RCT by Starreveld et al. [218] assessed the efficacy of bright light therapy in a sample of 166 non-Hodgkin's lymphoma cancer survivors. They randomized 83 participants to the bright light group and 83 to a dim light control. They found that both groups experienced a significant improvement in sleep disturbances and CRF after the light therapy, but there were no significant differences between the two groups [218]. A study conducted by Bean et al. evaluated CBT-I plus light therapy in women receiving chemotherapy [191]. Subjects were randomized to either receive CBT-I bright light therapy ($n = 36$) or a treatment-as-usual ($n = 34$) condition. With respect to insomnia, women in the CBT-I and bright light condition showed a greater improvement (49%), when compared to the treatment as usual condition (15%). Results were similar with respect to fatigue, where there were

greater improvements in the CBT-I and bright light condition when compared to their treatment as usual counterparts. When examined on its own, light therapy appears to have stronger effects on fatigue than insomnia, but there were fewer trials that included sleep measures as additional outcomes [222]. In sum, bright light therapy may be useful for the treatment of insomnia and fatigue in cancer, especially when CBT-I is not available.

Future research and clinical recommendations

Sleep-wake disturbances, commonly in the form of insomnia, and fatigue frequently coexist throughout the cancer care trajectory and persist into survivorship. These two conditions share several similar predisposing, precipitating, and perpetuating factors suggesting that treatments for one may have beneficial effects on the other. Indeed, this is the case with treatments including exercise, mindfulness, and CBT-I. It is likely that these treatments all effect the shared mechanisms by improving mood, helping patients manage stress, and addressing lifestyle factors. These behavioral changes can help to provide new evidence and experiences to challenge and modify long-standing beliefs about sleep and fatigue.

Given that we have some evidence that certain interventions can improve both symptoms, it would be important for future trials to enroll patients with clinically significant fatigue and insomnia. Clinical trial designs should allow for the investigation of potential pathways and mediators of change. Furthermore, given that most of these interventions are multicomponent, for efficiency, it would be prudent to understand what components of the intervention are the most potent for which symptoms. This field of research also would benefit from more straightforward tools to assess sleep-wake disturbances and fatigue. These tools would vastly improve our ability to understand these overlapping symptoms.

In summary, the impact of sleep-wake disturbance and CRF on patients their families and society are substantial. A study that examined the impact of CRF found that 91% felt that their CRF symptoms prevented them from living a "normal" life [223]. Moreover, of the participants who were employed, 75% changed their occupation due to their CRF and/or took more time off work due to their symptoms. CRF has also been found to negatively impact mood, daily activities, and relationships [224]. Sleep-wake disturbances also negatively impact the quality of life, where women with ovarian cancer and insomnia experience a significantly lower quality of life including physical and functional wellbeing, compared with women without insomnia [225]. Given this burden, patients would benefit from regular screening and interventions that fit with their

respective diagnosis (e.g., either fatigue and/or insomnia). Unfortunately, this is not often the case and access remains a barrier for the majority of those people diagnosed with cancer. Thus, future research should focus on identifying mechanisms and treatments for both sleep disturbance and fatigue in cancer.

References

- [1] Association AP. Diagnostic and statistical manual of mental disorders (DSM-5). 5th ed. Washington, DC: Author; 2013.
- [2] Zhou ES, et al. Sleepless from the get go: sleep problems prior to initiating cancer treatment. *Int J Behav Med* 2018;25(5):502–16.
- [3] Savard J, et al. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. *J Clin Oncol* 2011;29(26):3580–6.
- [4] Berger AM, Gerber LH, Mayer DK. Cancer-related fatigue: implications for breast cancer survivors. *Cancer* 2012;118(8 Suppl 1):2261–9.
- [5] Hinds PS, et al. An evaluation of the impact of a self-care coping intervention on psychological and clinical outcomes in adolescents with newly diagnosed cancer. *Eur J Oncol Nurs* 2000;4(1):6–17.
- [6] NCCN Cancer-Related Fatigue Panel: National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Cancer-related fatigue. *J Natl Compr Canc Netw* 2016;1:56.
- [7] Roscoe JA, et al. Cancer-related fatigue and sleep disorders. *Oncologist* 2007;12(Suppl. 1):35–42.
- [8] Morrow GR. Cancer-related fatigue: causes, consequences, and management. *Oncologist* 2007;12(Suppl. 1):1–3.
- [9] Hofman M, et al. Cancer-related fatigue: the scale of the problem. *Oncologist* 2007;12(Suppl. 1):4–10.
- [10] Ryan JL, et al. Mechanisms of cancer-related fatigue. *Oncologist* 2007;12(Suppl. 1):22–34.
- [11] Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol* 2014;11(10):597–609.
- [12] Jim HS, et al. Risk factors for depression and fatigue among survivors of hematopoietic cell transplantation. *Cancer* 2016;122(8):1290–7.
- [13] Abrahams HJG, et al. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. *Ann Oncol* 2016;27(6):965–74.
- [14] Stasi R, et al. Cancer-related fatigue: evolving concepts in evaluation and treatment. *Cancer* 2003;98(9):1786–801.
- [15] Mustian KM, et al. Exercise and cancer-related fatigue. *US Oncol* 2009;5(2):20–3.
- [16] Mustian KM, et al. Exercise recommendations for cancer-related fatigue, cognitive impairment, sleep problems, depression, pain, anxiety, and physical dysfunction: a review. *Oncol Hematol Rev* 2012;8(2):81–8.
- [17] Celli D, et al. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol* 2001;19(14):3385–91.
- [18] Bower JE, et al. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol* 2000;18(4):743–53.
- [19] Minton O, et al. Drug therapy for the management of cancer related fatigue. *Cochrane Database Syst Rev* 2008;(1):CD006704.
- [20] Barsevick AM, et al. Recommendations for high-priority research on cancer-related fatigue in children and adults. *J Natl Cancer Inst* 2013;105(19):1432–40.
- [21] Saligan LN, et al. The biology of cancer-related fatigue: a review of the literature. *Support Care Cancer* 2015;23(8):2461–78.
- [22] Saligan LN, et al. Erratum to: the biology of cancer-related fatigue: a review of the literature. *Support Care Cancer* 2015.
- [23] Cornelison M, Jabbour EJ, Welch MA. Managing side effects of tyrosine kinase inhibitor therapy to optimize adherence in patients with chronic myeloid leukemia: the role of the midlevel practitioner. *J Support Oncol* 2012;10(1):14–24.
- [24] Wright F, Hammer MJ, D'Eramo Melkus G. Associations between multiple chronic conditions and cancer-related fatigue: an integrative review. *Oncol Nurs Forum* 2014;41(4):399–410.
- [25] Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. *J Natl Compr Cancer Netw* 2009;7(1):99–108.
- [26] Davis JK, et al. Sleep disturbance and decrements in morning energy contribute to a higher symptom burden in oncology patients. *Sleep Med* 2023;108:124–36.
- [27] Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. *Psychiatr Clin North Am* 1987;10(4):541–53.
- [28] Aouizerat BE, Dodd M, Lee K, West C, Paul SM, Cooper BA, et al. Preliminary evidence of a genetic association between tumor necrosis factor alpha and the severity of sleep disturbance and morning fatigue. *Biol Res Nurs* 2009;11(1):27–41.
- [29] Miaskowski C, et al. Preliminary evidence of an association between a functional interleukin-6 polymorphism and fatigue and sleep disturbance in oncology patients and their family caregivers. *J Pain Symptom Manag* 2010;40(4):531–44.
- [30] Huang ST, et al. Risk factors for cancer-related fatigue in patients with colorectal cancer: a systematic review and meta-analysis. *Support Care Cancer* 2022;30(12):10311–22.
- [31] Ma Y, et al. Prevalence and risk factors of cancer-related fatigue: a systematic review and meta-analysis. *Int J Nurs Stud* 2020;111:103707.
- [32] Savard J, et al. Prevalence, natural course, and risk factors of insomnia comorbid with cancer over a 2-month period. *J Clin Oncol* 2009;27(31):5233–9.
- [33] Celli D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol* 1998;25(3 Suppl. 7):43–6.
- [34] Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol* 2014;35(3):320–30.
- [35] Garland SN, et al. Are sleep continuity disturbance and fatigue prodromal symptoms of cancer development? *Med Hypotheses* 2018;120:72–5.
- [36] Goedendorp MM, et al. Severe fatigue and related factors in cancer patients before the initiation of treatment. *Br J Cancer* 2008;99(9):1408–14.
- [37] Ancoli-Israel S, et al. Sleep, fatigue, depression, and circadian activity rhythms in women with breast cancer before and after treatment: a 1-year longitudinal study. *Support Care Cancer* 2014;22(9):2535–45.
- [38] Bower JE. The role of neuro-immune interactions in cancer-related fatigue: biobehavioral risk factors and mechanisms. *Cancer* 2019;125(3):353–64.

- [39] Mitchell SA. Cancer-related fatigue: state of the science. *Pharm Manag PM R* 2010;2(5):364–83.
- [40] Barsevick A, et al. I'm so tired: biological and genetic mechanisms of cancer-related fatigue. *Qual Life Res* 2010;19(10):1419–27.
- [41] Morrow GR, et al. Fatigue associated with cancer and its treatment. *Support Care Cancer* 2002;10(5):389–98.
- [42] Weinrib AZ, et al. Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. *Cancer* 2010;116(18):4410–9.
- [43] Yennurajalingam S, et al. Meta-analysis of pharmacological, nutraceutical and phytopharmaceutical interventions for the treatment of cancer related fatigue. *Cancers (Basel)* 2022;15(1).
- [44] Morris G, Anderson G, Maes M. Hypothalamic-pituitary-adrenal hypofunction in myalgic encephalomyelitis (ME)/Chronic fatigue syndrome (CFS) as a consequence of activated immune-inflamatory and oxidative and nitrosative pathways. *Mol Neurobiol* 2017;54(9):6806–19.
- [45] Narita M, et al. Association between serotonin transporter gene polymorphism and chronic fatigue syndrome. *Biochem Biophys Res Commun* 2003;311(2):264–6.
- [46] Cao Y, Li Q. The variation of the 5-hydroxytryptamine system between chronic unpredictable mild stress rats and chronic fatigue syndrome rats induced by forced treadmill running. *Neuroreport* 2017;28(11):630–7.
- [47] Bakheit AM, et al. Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. *BMJ* 1992;304(6833):1010–2.
- [48] Maes M, et al. In myalgic encephalomyelitis/chronic fatigue syndrome, increased autoimmune activity against 5-HT is associated with immuno-inflammatory pathways and bacterial translocation. *J Affect Disord* 2013;150(2):223–30.
- [49] Savard J, Savard M-H. Insomnia and cancer: prevalence, nature, and nonpharmacologic treatment: prevalence, nature, and non-pharmacologic treatment. *Sleep Medicine Clinics* 2013;8(3):373–87.
- [50] Enderlin CA, et al. Sleep across chemotherapy treatment: a growing concern for women older than 50 with breast cancer. *Oncol Nurs Forum* 2010;37(4):461.
- [51] Beck SL, et al. Sleep quality after initial chemotherapy for breast cancer. *Support Care Cancer* 2010;18(6):679–89.
- [52] Chen ML, Yu CT, Yang CH. Sleep disturbances and quality of life in lung cancer patients undergoing chemotherapy. *Lung Cancer* 2008;62(3):391–400.
- [53] Van Onselen C, et al. Trajectories of sleep disturbance and daytime sleepiness in women before and after surgery for breast cancer. *J Pain Symptom Manag* 2013;45(2):244–60.
- [54] Palesh OG, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: university of rochester cancer center-community clinical oncology program. *J Clin Oncol* 2010;28(2):292–8.
- [55] Spratt DE, et al. Time course and predictors for cancer-related fatigue in a series of oropharyngeal cancer patients treated with chemoradiation therapy. *Oncologist* 2012;17(4):569–76.
- [56] Rosas JC, et al. (Pre)treatment risk factors for late fatigue and fatigue trajectories following radiotherapy for breast cancer. *Int J Cancer* 2023;153(9):1579–91.
- [57] Cella D, Fallowfield LJ. Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy. *Breast Cancer Res Treat* 2008;107(2):167–80.
- [58] Altice CK, et al. Financial hardships experienced by cancer survivors: a systematic review. *J Natl Cancer Inst* 2017;109(2).
- [59] Lu L, et al. Cumulative financial stress as a potential risk factor for cancer-related fatigue among prostate cancer survivors. *J Cancer Surviv* 2021;15(1):1–13.
- [60] Yi JC, Syrjala KL. Anxiety and depression in cancer survivors. *Med Clin North Am* 2017;101(6):1099–113.
- [61] Mark S, et al. Modifiable and non-modifiable characteristics associated with sleep disturbance in oncology outpatients during chemotherapy. *Support Care Cancer* 2017;25(8):2485–94.
- [62] Fassoulaki A, et al. Acute postoperative pain predicts chronic pain and long-term analgesic requirements after breast surgery for cancer. *Acta Anaesthesiol Belg* 2008;59(4):241–8.
- [63] Sheinfeld Gorin S, et al. Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. *J Clin Oncol* 2012;30(5):539–47.
- [64] Glare PA, et al. Pain in cancer survivors. *J Clin Oncol* 2014;32(16):1739–47.
- [65] Levy MH, Chwistek M, Mehta RS. Management of chronic pain in cancer survivors. *Cancer J* 2008;14(6):401–9.
- [66] Vena C, et al. Sleep-wake disturbances in people with cancer part I: an overview of sleep, sleep regulation, and effects of disease and treatment. *Oncol Nurs Forum* 2004;31(4):735–46.
- [67] Ruiz-Casado A, et al. Cancer-related fatigue in breast cancer survivors: a review. *Clin Breast Cancer* 2021;21(1):10–25.
- [68] Meuser T, et al. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain* 2001;93(3):247–57.
- [69] Espie CA. Insomnia: conceptual issues in the development, persistence, and treatment of sleep disorder in adults. *Annu Rev Psychol* 2002;53:215–43.
- [70] Harvey AG. A cognitive model of insomnia. *Behav Res Ther* 2002;40(8):869–93.
- [71] Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 2001;19(3):895–908.
- [72] Goldman SE, et al. Association between nighttime sleep and napping in older adults. *Sleep* 2008;31(5):733–40.
- [73] Owens JF, et al. Napping, nighttime sleep, and cardiovascular risk factors in mid-life adults. *J Clin Sleep Med* 2010;6(4):330–5.
- [74] Irvine DM, et al. Fatigue in women with breast cancer receiving radiation therapy. *Cancer Nurs* 1998;21(2):127–35.
- [75] Richardson A, Ream EK. Self-care behaviours initiated by chemotherapy patients in response to fatigue. *Int J Nurs Stud* 1997;34(1):35–43.
- [76] Stepanski EJ, Burgess HJ. Sleep and cancer. *Sleep Medicine Clinics* 2007;2(1):67–75.
- [77] Zick SM, et al. Examination of the association of diet and persistent cancer-related fatigue: a pilot study. *Oncol Nurs Forum* 2013;40(1):E41–9.
- [78] Scoditti E, Tumolo MR, Garbarino S. Mediterranean diet on sleep: a health alliance. *Nutrients* 2022;14(14).
- [79] Baguley BJ, et al. Mediterranean-style dietary pattern improves cancer-related fatigue and quality of life in men with prostate cancer treated with androgen deprivation therapy: a pilot randomised control trial. *Clin Nutr* 2021;40(1):245–54.

- [80] Savard J, Ivers H. Screening for clinical insomnia in cancer patients with the Edmonton Symptom Assessment System-Revised: a specific sleep item is needed. *Support Care Cancer* 2019.
- [81] Hammerschlag AR, et al. Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. *Nat Genet* 2017;49(11):1584–92.
- [82] Klingman KJ, Jungquist CR, Perlis ML. Questionnaires that screen for multiple sleep disorders. *Sleep Med Rev* 2017;32:37–44.
- [83] Roth T, et al. A new questionnaire to detect sleep disorders. *Sleep Med* 2002;3(2):99–108.
- [84] Klingman KJ, Jungquist CR, Perlis ML. Introducing the sleep disorders symptom checklist-25: a primary care friendly and comprehensive screener for sleep disorders. *Sleep Med Res* 2017;8(1):17–25.
- [85] Doufas AG, et al. Insomnia from drug treatments: evidence from meta-analyses of randomized trials and concordance with prescribing information. *Mayo Clin Proc* 2017;92(1):72–87.
- [86] Mallon L, Broman JE, Hetta J. Is usage of hypnotics associated with mortality? *Sleep Med* 2009;10(3):279–86.
- [87] McCall WV, et al. Hypnotic medications and suicide: risk, mechanisms, mitigation, and the FDA. *Am J Psychiatr* 2017;174(1):18–25.
- [88] Morin CM. Insomnia: psychological assessment and management. New York: Guilford Press; 1993.
- [89] Buysse DJ, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193–213.
- [90] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540–5.
- [91] Riemann D, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res* 2017;26(6):675–700.
- [92] Mendoza TR, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer* 1999;85(5):1186–96.
- [93] Webster K, Celli D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcome* 2003;1:79.
- [94] Hann DM, et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res* 1998;7(4):301–10.
- [95] Piper BF, et al. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncol Nurs Forum* 1998;25(4):677–84.
- [96] Aaronson NK, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365–76.
- [97] Payne JK, et al. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. *Oncol Nurs Forum* 2008;35(4):635–42.
- [98] Rogers LQ, et al. A randomized trial to increase physical activity in breast cancer survivors. *Med Sci Sports Exerc* 2009;41(4):935–46.
- [99] Dodd MJ, et al. A randomized controlled trial of home-based exercise for cancer-related fatigue in women during and after chemotherapy with or without radiation therapy. *Cancer Nurs* 2010;33(4):245–57.
- [100] Wang YJ, et al. Effects of a 6-week walking program on Taiwanese women newly diagnosed with early-stage breast cancer. *Cancer Nurs* 2011;34(2):E1–13.
- [101] Coleman EA, et al. Effects of exercise on fatigue, sleep, and performance: a randomized trial. *Oncol Nurs Forum* 2012;39(5):468–77.
- [102] Cheville AL, et al. A home-based exercise program to improve function, fatigue, and sleep quality in patients with Stage IV lung and colorectal cancer: a randomized controlled trial. *J Pain Symptom Manag* 2013;45(5):811–21.
- [103] Wenzel JA, et al. Impact of a home-based walking intervention on outcomes of sleep quality, emotional distress, and fatigue in patients undergoing treatment for solid tumors. *Oncologist* 2013;18(4):476–84.
- [104] Kampshoff CS, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the Resistance and Endurance exercise after ChemoTherapy (REACT) study. *BMC Med* 2015;13:275.
- [105] McQuade JL, et al. Qigong/tai chi for sleep and fatigue in prostate cancer patients undergoing radiotherapy: a randomized controlled trial. *Psychooncology* 2017;26(11):1936–43.
- [106] Zhang Q, et al. Effects of nurse-led home-based exercise & cognitive behavioral therapy on reducing cancer-related fatigue in patients with ovarian cancer during and after chemotherapy: a randomized controlled trial. *Int J Nurs Stud* 2018;78:52–60.
- [107] Adams SC, et al. Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. *Br J Cancer* 2018;118(10):1313–21.
- [108] Brown JC, et al. Dose-response effects of aerobic exercise among colon cancer survivors: a randomized phase II trial. *Clin Colorectal Cancer* 2018;17(1):32–40.
- [109] Bryant AL, et al. The effects of exercise on patient-reported outcomes and performance-based physical function in adults with acute leukemia undergoing induction therapy: exercise and quality of life in acute leukemia (EQUAL). *Integr Cancer Ther* 2018;17(2):263–70.
- [110] Chaoul A, et al. Randomized trial of Tibetan yoga in patients with breast cancer undergoing chemotherapy. *Cancer* 2018;124(1):36–45.
- [111] Huang HP, et al. The effect of a 12-week home-based walking program on reducing fatigue in women with breast cancer undergoing chemotherapy: a randomized controlled study. *Int J Nurs Stud* 2019;99:103376.
- [112] Paulo TRS, et al. The impact of an exercise program on quality of life in older breast cancer survivors undergoing aromatase inhibitor therapy: a randomized controlled trial. *Health Qual Life Outcome* 2019;17(1):17.
- [113] Steindorf K, et al. Quality of life, fatigue, and sleep problems in pancreatic cancer patients-A randomized trial on the effects of exercise. *Dtsch Arztebl Int* 2019;116(27–28):471–8.
- [114] Kim S, et al. Pre-post analysis of a social capital-based exercise adherence intervention for breast cancer survivors with moderate fatigue: a randomized controlled trial. *Support Care Cancer* 2020;28(11):5281–9.
- [115] Cheng D, et al. Effect of tai chi and resistance training on cancer-related fatigue and quality of life in middle-aged and elderly cancer patients. *Chin J Integr Med* 2021;27(4):265–72.

- [116] Cheung DST, et al. Feasibility of aerobic exercise and tai-chi interventions in advanced lung cancer patients: a randomized controlled trial. *Integr Cancer Ther* 2021;20.
- [117] Jarden M, et al. Longitudinal symptom burden in adult patients with acute leukaemia participating in the PACE-AL randomised controlled exercise trial—an explorative analysis. *Eur J Cancer Care* 2021;30(5):e13462.
- [118] Mardani A, et al. Effect of the exercise programme on the quality of life of prostate cancer survivors: a randomized controlled trial. *Int J Nurs Pract* 2021;27(2):e12883.
- [119] Piraux E, et al. Effects of high-intensity interval training compared with resistance training in prostate cancer patients undergoing radiotherapy: a randomized controlled trial. *Prostate Cancer Prostatic Dis* 2021;24(1):156–65.
- [120] Eisenhut L, et al. Effects of two types of exercise training on psychological well-being, sleep and physical fitness in patients with high-grade glioma (WHO III and IV). *J Psychiatr Res* 2022;151:354–64.
- [121] He X, et al. Effects of a 16-week dance intervention on the symptom cluster of fatigue-sleep disturbance-depression and quality of life among patients with breast cancer undergoing adjuvant chemotherapy: a randomized controlled trial. *Int J Nurs Stud* 2022;133:104317.
- [122] Boing L, et al. Mat Pilates and belly dance: effects on patient-reported outcomes among breast cancer survivors receiving hormone therapy and adherence to exercise. *Compl Ther Clin Pract* 2023;50:101683.
- [123] Mavropalias G, et al. The effects of home-based exercise therapy for breast cancer-related fatigue induced by radical radiotherapy. *Breast Cancer* 2023;30(1):139–50.
- [124] Leite B, et al. Effects of Pilates method on quality of life, fatigue and sleep quality among breast cancer women receiving hormone therapy - two-arm randomized clinical trial. *J Bodyw Mov Ther* 2024;37:18–24.
- [125] Takemura N, et al. Effectiveness of aerobic exercise and tai chi interventions on sleep quality in patients with advanced lung cancer: a randomized clinical trial. *JAMA Oncol* 2024;10(2):176–84.
- [126] Kroz M, et al. Impact of a combined multimodal-aerobic and multimodal intervention compared to standard aerobic treatment in breast cancer survivors with chronic cancer-related fatigue - results of a three-armed pragmatic trial in a comprehensive cohort design. *BMC Cancer* 2017;17(1):166.
- [127] Kroz M, et al. Four-year follow-up on fatigue and sleep quality of a three-armed partly randomized controlled study in breast cancer survivors with cancer-related fatigue. *Sci Rep* 2023;13(1):2705.
- [128] Solk P, et al. Effect of the Fit2Thrive intervention on patient-reported outcomes in breast cancer survivors: a randomized full factorial trial. *Ann Behav Med* 2023;57(9):765–76.
- [129] Estevez-Lopez F, et al. Effectiveness of exercise on fatigue and sleep quality in Fibromyalgia: a systematic review and meta-analysis of randomized trials. *Arch Phys Med Rehabil* 2021;102(4):752–61.
- [130] Razazian N, et al. The impact of physical exercise on the fatigue symptoms in patients with multiple sclerosis: a systematic review and meta-analysis. *BMC Neurol* 2020;20(1):93.
- [131] Samuel SR, et al. Effectiveness of exercise-based rehabilitation on functional capacity and quality of life in head and neck cancer patients receiving chemo-radiotherapy. *Support Care Cancer* 2019;27(10):3913–20.
- [132] Ehlers DK, DuBois K, Salerno EA. The effects of exercise on cancer-related fatigue in breast cancer patients during primary treatment: a meta-analysis and systematic review. *Expert Rev Anticancer Ther* 2020;20(10):865–77.
- [133] Lowe H, et al. Does exercise improve sleep for adults with insomnia? A systematic review with quality appraisal. *Clin Psychol Rev* 2019;68:1–12.
- [134] Heckler CE, et al. Cognitive behavioral therapy for insomnia, but not armodafinil, improves fatigue in cancer survivors with insomnia: a randomized placebo-controlled trial. *Support Care Cancer* 2016;24(5):2059–66.
- [135] Page BR, et al. Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue. *Neuro Oncol* 2015;17(10):1393–401.
- [136] Berenson JR, et al. A phase 3 trial of armodafinil for the treatment of cancer-related fatigue for patients with multiple myeloma. *Support Care Cancer* 2015;23(6):1503–12.
- [137] Bruera E, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol* 2006;24(13):2073–8.
- [138] Moraska AR, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: north Central Cancer Treatment Group NCCTG-N05C7 trial. *J Clin Oncol* 2010;28(23):3673–9.
- [139] Gehring K, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. *J Neuro Oncol* 2012;107(1):165–74.
- [140] Yennurajalingam S, et al. Sleep disturbance in patients with cancer: a feasibility study of multimodal therapy. *BMJ Support Palliat Care* 2021;11(2):170–9.
- [141] Carpenter JS, et al. Randomized, double-blind, placebo-controlled crossover trials of venlafaxine for hot flashes after breast cancer. *Oncologist* 2007;12(1):124–35.
- [142] Jean-Pierre P, et al. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program Research base study. *Cancer* 2010;116(14):3513–20.
- [143] Bruera E, et al. Donepezil for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol* 2007;25(23):3475–81.
- [144] Roy AN, Smith M. Prevalence and cost of insomnia in a state Medicaid fee-for-service population based on diagnostic codes and prescription utilization. *Sleep Med* 2010;11(5):462–9.
- [145] Beam AL, et al. Predictive modeling of physician-patient dynamics that influence sleep medication prescriptions and clinical decision-making. *Sci Rep* 2017;7:42282.
- [146] Sateia MJ, et al. Evaluation of chronic insomnia. An American Academy of sleep medicine review. *Sleep* 2000;23(2):243–308.
- [147] Wilt TJ, et al. Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med* 2016;165(2):103–12.
- [148] Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. *Sleep Med Rev* 2006;10(6):419–29.

- [149] Holbrook AM, et al. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ* 2000;162(2):225–33.
- [150] Walsh JKME, Erwin CW, Jamieson A, Mahowald M, Regestein Q, Ware JC. Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII-R primary insomnia. *Hum Psychopharmacol Clin Exp* 1998;13(3):191–8.
- [151] NIH State-of-the-Science Conference Statement on manifestations and management of chronic insomnia in adults. *NIH Consens State Sci Statements* 2005;22(2):1–30.
- [152] Chow R, Bruera E, Sanatani M, Chiu L, Prsic E, Boldt G, et al. Cancer-related fatigue—pharmacological interventions: systematic review and network meta-analysis. *BMJ Support. Palliat. Care.* 2021;13(3):274–80.
- [153] Ong J, Sholtes D. A mindfulness-based approach to the treatment of insomnia. *J Clin Psychol* 2010;66(11):1175–84.
- [154] Simkin DR, Black NB. Meditation and mindfulness in clinical practice. *Child Adolesc Psychiatr Clin N Am* 2014;23(3):487–534.
- [155] Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain, and illness. New York: Bantam Books trade paperback. xlv; 2013. p. 650.
- [156] Ludwig DS, Kabat-Zinn J. Mindfulness in medicine. *JAMA* 2008;300(11):1350–2.
- [157] Riemann D, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 2010;14(1):19–31.
- [158] Ong JC, Ulmer CS, Manber R. Improving sleep with mindfulness and acceptance: a metacognitive model of insomnia. *Behav Res Ther* 2012;50(11):651–60.
- [159] Goldin PR, Gross JJ. Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. *Emotion* 2010;10(1):83–91.
- [160] Holzel BK, et al. Differential engagement of anterior cingulate and adjacent medial frontal cortex in adept meditators and non-meditators. *Neurosci Lett* 2007;421(1):16–21.
- [161] Holzel BK, et al. Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Res* 2011;191(1):36–43.
- [162] Holzel BK, et al. Stress reduction correlates with structural changes in the amygdala. *Soc Cognit Affect Neurosci* 2010;5(1):11–7.
- [163] Brewer JA, et al. Meditation experience is associated with differences in default mode network activity and connectivity. *Proc Natl Acad Sci U S A* 2011;108(50):20254–9.
- [164] Farb NA, et al. Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. *Soc Cognit Affect Neurosci* 2007;2(4):313–22.
- [165] Holzel BK, et al. How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. *Perspect Psychol Sci* 2011;6(6):537–59.
- [166] Gross CR, et al. Mindfulness-based stress reduction versus pharmacotherapy for chronic primary insomnia: a randomized controlled clinical trial. *Explore* 2011;7(2):76–87.
- [167] Gong H, et al. Mindfulness meditation for insomnia: a meta-analysis of randomized controlled trials. *J Psychosom Res* 2016;89:1–6.
- [168] van der Lee ML, Garssen B. Mindfulness-based cognitive therapy reduces chronic cancer-related fatigue: a treatment study. *Psychooncology* 2012;21(3):264–72.
- [169] Carlson LE, Garland SN. Impact of mindfulness-based stress reduction (MBSR) on sleep, mood, stress and fatigue symptoms in cancer outpatients. *Int J Behav Med* 2005;12(4):278–85.
- [170] Reich RR, et al. Mindfulness-based stress reduction in post-treatment breast cancer patients: immediate and sustained effects across multiple symptom clusters. *J Pain Symptom Manag* 2017;53(1):85–95.
- [171] Bower JE, et al. Mindfulness meditation for younger breast cancer survivors: a randomized controlled trial. *Cancer* 2015;121(8):1231–40.
- [172] Bower JE, et al. Targeting depressive symptoms in younger breast cancer survivors: the pathways to wellness randomized controlled trial of mindfulness meditation and survivorship education. *J Clin Oncol* 2021;39(31):3473–84.
- [173] Witek Janusek L, Tell D, Mathews HL. Mindfulness based stress reduction provides psychological benefit and restores immune function of women newly diagnosed with breast cancer: a randomized trial with active control. *Brain Behav Immun* 2019;80:358–73.
- [174] Liu Q, et al. Mindfulness-based stress reduction with acupressure for sleep quality in breast cancer patients with insomnia undergoing chemotherapy: a randomized controlled trial. *Eur J Oncol Nurs* 2022;61:102219.
- [175] Johns SA, et al. Randomized controlled pilot study of mindfulness-based stress reduction for persistently fatigued cancer survivors. *Psychooncology* 2015;24(8):885–93.
- [176] Stein KD, et al. A multidimensional measure of fatigue for use with cancer patients. *Cancer Pract* 1998;6(3):143–52.
- [177] Davidson JR, et al. Nonpharmacologic group treatment of insomnia: a preliminary study with cancer survivors. *Psychooncology* 2001;10(5):389–97.
- [178] Simeit R, Deck R, Conta-Marx B. Sleep management training for cancer patients with insomnia. *Support Care Cancer* 2004;12(3):176–83.
- [179] Savard J, et al. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: sleep and psychological effects. *J Clin Oncol* 2005;23(25):6083–96.
- [180] Savard J, et al. Is a video-based cognitive behavioral therapy for insomnia as efficacious as a professionally administered treatment in breast cancer? Results of a randomized controlled trial. *Sleep* 2014;37(8):1305–14.
- [181] Savard J, et al. Efficacy of a stepped care approach to deliver cognitive-behavioral therapy for insomnia in cancer patients: a noninferiority randomized controlled trial. *Sleep* 2021;44(11).
- [182] Dirksen SR, Epstein DR. Efficacy of an insomnia intervention on fatigue, mood and quality of life in breast cancer survivors. *J Adv Nurs* 2008;61(6):664–75.
- [183] Ritterband LM, et al. Initial evaluation of an Internet intervention to improve the sleep of cancer survivors with insomnia. *Psychooncology* 2012;21(7):695–705.
- [184] Espie CA, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomnia in patients with cancer. *J Clin Oncol* 2008;26(28):4651–8.
- [185] Matthews EE, et al. Cognitive behavioral therapy for insomnia outcomes in women after primary breast cancer treatment: a randomized, controlled trial. *Oncol Nurs Forum* 2014;41(3):241–53.

- [186] Casault L, et al. A randomized-controlled trial of an early minimal cognitive-behavioural therapy for insomnia comorbid with cancer. *Behav Res Ther* 2015;67:45–54.
- [187] Irwin MR, et al. Tai chi chih compared with cognitive behavioral therapy for the treatment of insomnia in survivors of breast cancer: a randomized, partially blinded, noninferiority trial. *J Clin Oncol* 2017;35(23):2656–65.
- [188] Zachariae R, et al. Internet-delivered cognitive-behavioral therapy for insomnia in breast cancer survivors: a randomized controlled trial. *J Natl Cancer Inst* 2018;110(8):880–7.
- [189] Garland SN, et al. Acupuncture versus cognitive behavioral therapy for insomnia in cancer survivors: a randomized clinical trial. *J Natl Cancer Inst* 2019;111(12):1323–31.
- [190] Moon SY, et al. Comparative effectiveness of cheonwangbosimdan (Tian Wang Bu Xin Dan) versus cognitive-behavioral therapy for insomnia in cancer patients: a randomized, controlled, open-label, parallel-group, pilot trial. *Integr Cancer Ther* 2020;19.
- [191] Bean HR, et al. Light enhanced cognitive behavioral therapy for insomnia and fatigue during chemotherapy for breast cancer: a randomized controlled trial. *Sleep* 2022;45(3).
- [192] Hall DL, et al. The Survivorship Sleep Program (SSP): a synchronous, virtual cognitive behavioral therapy for insomnia pilot program among cancer survivors. *Cancer* 2022;128(7):1532–44.
- [193] Loughan AR, et al. Telehealth group Cognitive-Behavioral Therapy for Insomnia (CBT-I) in primary brain tumor: primary outcomes from a single-arm phase II feasibility and proof-of-concept trial. *Neuro Oncol* 2024;26(3):516–27.
- [194] Quesnel C, et al. Efficacy of cognitive-behavioral therapy for insomnia in women treated for nonmetastatic breast cancer. *J Consult Clin Psychol* 2003;71(1):189–200.
- [195] Edinger JD, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med* 2021;17(2):255–62.
- [196] Johnson JA, Rash JA, Campbell TS, Savard J, Gehrman PR, Perlis M, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. *Sleep Med Rev* 2016;27:20–8.
- [197] Squires LR, et al. Systematic review and meta-analysis of cognitive-behavioural therapy for insomnia on subjective and actigraphy-measured sleep and comorbid symptoms in cancer survivors. *Sleep Med Rev* 2022;63:101615.
- [198] Berger AM, Mitchell SA. Modifying cancer-related fatigue by optimizing sleep quality. *J Natl Compr Cancer Netw* 2008;6 (1):3–13.
- [199] Zee PC, Ancoli-Israel S, Workshop P. Does effective management of sleep disorders reduce cancer-related fatigue? *Drugs* 2009;69 (Suppl. 2):29–41.
- [200] Garland SN, et al. Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in cancer patients. *Neuropsychiatric Dis Treat* 2014;10:1113–24.
- [201] Li X, et al. Addressing cancer-related fatigue through sleep: a secondary analysis of a randomized trial comparing acupuncture and cognitive behavioral therapy for insomnia. *Integr Med Res* 2023;12(1):100922.
- [202] Amidi A, et al. Changes in sleep following internet-delivered cognitive-behavioral therapy for insomnia in women treated for breast cancer: a 3-year follow-up assessment. *Sleep Med* 2022;96:35–41.
- [203] Chen Z, et al. Qigong improves quality of life in women undergoing radiotherapy for breast cancer: results of a randomized controlled trial. *Cancer* 2013;119(9):1690–8.
- [204] Chandwani KD, et al. Randomized, controlled trial of yoga in women with breast cancer undergoing radiotherapy. *J Clin Oncol* 2014;32(10):1058–65.
- [205] Kiecolt-Glaser JK, et al. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. *J Clin Oncol* 2014;32(10):1040–9.
- [206] Larkey LK, et al. Randomized controlled trial of Qigong/Tai Chi Easy on cancer-related fatigue in breast cancer survivors. *Ann Behav Med* 2015;49(2):165–76.
- [207] Cohen L, et al. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. *Cancer* 2004;100(10):2253–60.
- [208] Yeh ML, Chung YC. A randomized controlled trial of qigong on fatigue and sleep quality for non-Hodgkin's lymphoma patients undergoing chemotherapy. *Eur J Oncol Nurs* 2016;23:81–6.
- [209] Chuang TY, Yeh ML, Chung YC. A nurse facilitated mind-body interactive exercise (Chan-Chuang qigong) improves the health status of non-Hodgkin lymphoma patients receiving chemotherapy: randomised controlled trial. *Int J Nurs Stud* 2017;69:25–33.
- [210] Lu Y, et al. Effect of Baduanjin qigong exercise on cancer-related fatigue in patients with colorectal cancer undergoing chemotherapy: a randomized controlled trial. *Oncol Res Treat* 2019;42 (9):431–9.
- [211] Wen L, et al. Effects of Baduanjin exercise in nasopharyngeal carcinoma patients after chemoradiotherapy: a randomized controlled trial. *Support Care Cancer* 2022;31(1):79.
- [212] Oh B, et al. Medical Qigong for cancer patients: pilot study of impact on quality of life, side effects of treatment and inflammation. *Am J Chin Med* 2008;36(3):459–72.
- [213] Namazinia M, et al. Effects of laughter yoga on health-related quality of life in cancer patients undergoing chemotherapy: a randomized clinical trial. *BMC Complement Med Ther* 2023;23 (1):192.
- [214] Larkey L, et al. Meditative movement as a category of exercise: implications for research. *J Phys Activ Health* 2009;6(2):230–8.
- [215] Ancoli-Israel S, et al. Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. *Support Care Cancer* 2012;20(6):1211–9.
- [216] Fox RS, et al. Feasibility and preliminary efficacy of a bright light intervention in ovarian and endometrial cancer survivors. *Int J Behav Med* 2021;28(1):83–95.
- [217] Wu LM, et al. Examining the efficacy of bright light therapy on cognitive function in hematopoietic stem cell transplant survivors. *J Biol Rhythms* 2022;37(5):471–83.
- [218] Starreveld DEJ, et al. Light therapy for cancer-related fatigue in (Non-)Hodgkin lymphoma survivors: results of a randomized controlled trial. *Cancers (Basel)* 2021;13(19).
- [219] Wu HS, et al. Evaluating chronotypically tailored light therapy for breast cancer survivors: preliminary findings on fatigue and disrupted sleep. *Chronobiol Int* 2022;39(2):221–32.
- [220] Wu HS, Davis JE, Chen L. Bright light shows promise in improving sleep, depression, and quality of life in women with

- breast cancer during chemotherapy: findings of a pilot study. *Chronobiol Int* 2021;38(5):694–704.
- [221] Celik A, Usta Yesilbalkan O. The effect of the bright white light application to cancer patients receiving palliative care on their fatigue level and sleep quality: a randomized control trial. *Omega* 2023;88(1):303–17.
- [222] Lin LY, Tam KW, Huang TW. Effect of bright light therapy on cancer-related fatigue and related symptoms: a systematic review and meta-analysis of randomized controlled trials. *J Psychosom Res* 2023;174:111501.
- [223] Curt GA, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist* 2000;5(5):353–60.
- [224] Lawrence DP, et al. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J Natl Cancer Inst Monogr* 2004;(32):40–50.
- [225] Ross TL, et al. Insomnia and its association with quality of life in women with ovarian cancer. *Gynecol Oncol* 2020;158(3):760–8.

This page intentionally left blank

Part VIII

Sleep health in children and adolescents

This page intentionally left blank

Chapter 38

Sleep, obesity, and cardiometabolic disease in children and adolescents

Teresa Arora^a and Ian Grey^b

^aZayed University, College of Natural and Health Sciences, Department of Psychology, Abu Dhabi, United Arab Emirates; ^bUnited Arab Emirates University, Abu Dhabi, United Arab Emirates

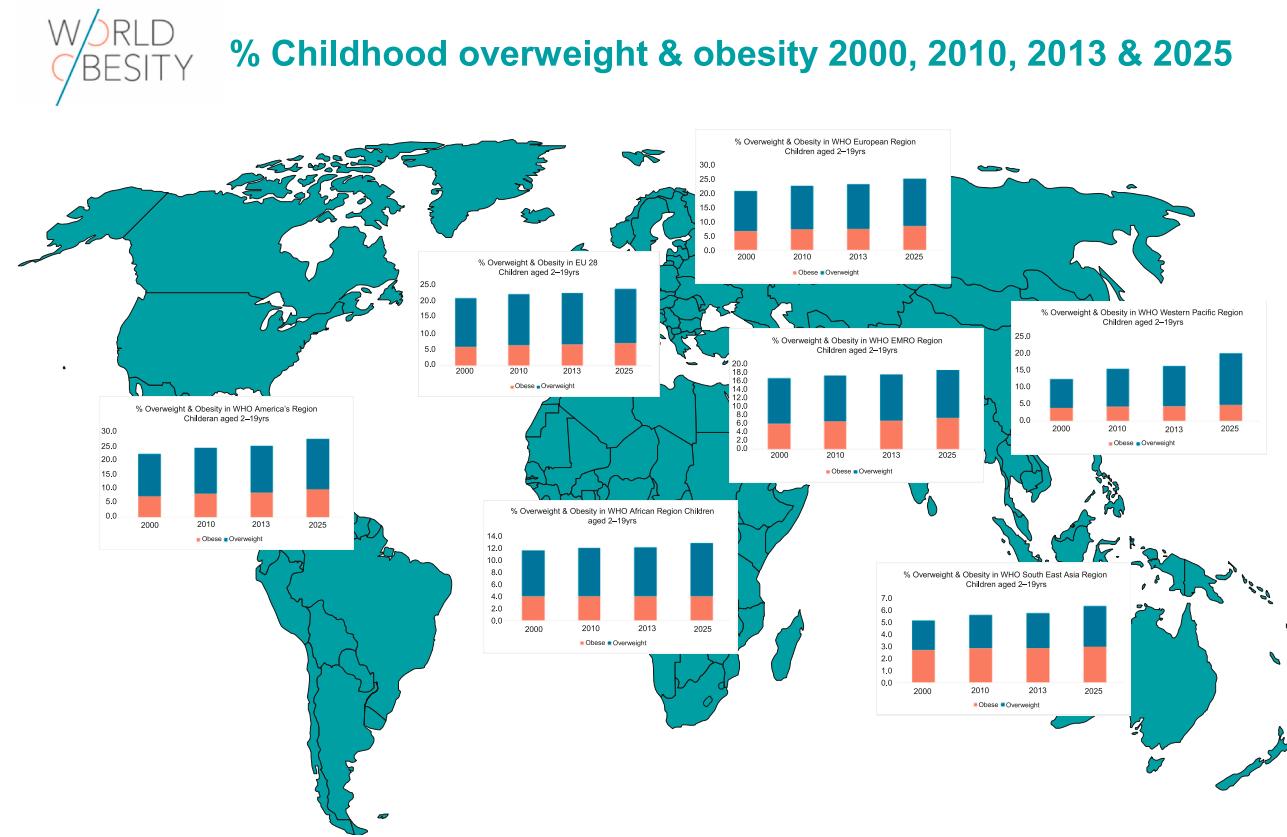
Introduction

The worldwide prevalence of obesity, cardiovascular, and metabolic disease has continued to rise in the 21st century. Previously, these diseases were mainly observed in adults, but they are now increasingly present in children. The abrupt increase in cardiovascular and metabolic disease as well as obesity has been largely attributed to noxious lifestyle behaviors. These include, but are not limited to, unhealthy diet, inadequate energy expenditure, increased levels of sedentariness, and excessive screen time. Very little was known about sleep behavior as a potential contributor to cardiometabolic health and obesity outcomes until the 1990s. This initial discovery has resulted in increased sleep research attention relating to multiple adverse mental and physical health consequences. There is a growing body of evidence surrounding the link between sleep and obesity, diabetes mellitus (DM), and markers of cardiovascular disease across all age groups and in multiple geographic locations. This chapter will focus on highlighting and discussing historical and contemporary evidence surrounding the associations between several important sleep features in relation to obesity and type 2 diabetes mellitus (T2DM), both of which are strongly correlated with cardiovascular disease, in pediatric populations. The possibility of improving sleep as a novel and contemporary approach to tackle the current epidemic of chronic health issues will also be discussed.

Defining overweight and obesity in children

Obesity is characterized as excessive adiposity and is one of the most concerning and serious public health concerns in the 21st century. The condition is complex and

multifactorial. Both genetic and environmental factors contribute to the onset and progression of obesity. Statistics from the World Health Organization (WHO) in 2016 estimated that 39% of men and women, aged 18 and over, were overweight or obese worldwide. Estimates for children and adolescents (5–19 years) were 18% in 2016. Data collected from 450 nationally representative surveys from 144 countries in the United Nations revealed a stark increase in obesity in preschool children (0–5 years) from 1990 to 2010 [1]. Fig. 38.1 highlights the prevalence of overweight and obesity among children (2–19 years) according to continent over time. In adults, obesity is usually characterized by body mass index (BMI; kg/m²). This method is used as a diagnostic tool to categorize individuals into underweight, healthy weight, overweight, or obese. It is a well-utilized method, given the ease of assessment for height and weight, but it has been criticized due to not directly assessing adiposity, which misrepresents the body weight outcome grouping. With children and adolescents, the application of BMI to compartmentalize body weight presents different challenges due to growth spurts and alterations in body fat and muscle. The tool is not usually used as a diagnostic tool in pediatric populations but is instead used to screen for potential weight and health-related conditions because BMI cannot determine if a child has excess adiposity unless assessed by a healthcare professional. The Centers for Disease Control and Prevention (CDC) states that BMI in children and adolescents can be calculated and then expressed as a percentile, which is plotted and directly compared, relative to other children in the United States who previously participated in national surveys conducted 1963–65 and 1988–94 [2]. These are based on age- and gender-specific percentiles with obesity, overweight, healthy weight, and underweight being defined as $\geq 95\text{th}$



© World Obesity Federation, London 2016. Email: obesity@worldobesity.org for permissions. Adapted from Lobstein, T., and Jackson-Leach, R. (2016) Planning for the worst: estimates of obesity and comorbidities in school-age children in 2025. *Pediatric Obesity*, 11: 321–325. doi: 10.1111/ijpo.12185. available at <http://onlinelibrary.wiley.com/doi/10.1111/ijpo.12185/full>

Knowledge Solutions Action

FIGURE 38.1 Prevalence of childhood overweight and obesity overtime.

percentile, >85th–94th percentile, 5th–85th percentile, and <5th percentile, respectively. Arguably, these data are now outdated, require revision, and are limited to US children. If the prevalence of childhood obesity continues to rise, then the condition could, over time, become the norm. In 2000, Cole et al. first proposed an alternative solution to classifying childhood overweight and obesity by developing a globally accepted definition taking into account age- and sex-specific cut points [3].

Causes and consequences of childhood obesity

Causes

The causes of obesity, both in adults and children, are well established. Weight gain and subsequent obesity onset are due to energy homeostasis imbalance, and there are multiple factors which drive this. Excessive energy intake and inadequate energy expenditure are driving factors of obesity, but other peripheral variables have also been

shown to influence energy balance. These include poverty, socio-economic status, exposure, and accessibility to fast food chains, mass media advertising, parental education, behavior and weight status, crime rates, excessive electronic device use, and sleep. While obesity does have a genetic component, it is a disease which is largely driven by a combination of lifestyle behaviors and socio-demographics.

Consequences

Excess adiposity is particularly concerning in pediatric populations, given that obesity now presents at a younger age. Childhood obesity has been associated with a wide range of adverse physiological and psychological health comorbidities at the individual level as well as severe social and economic implications. For example, obesity in children affects almost every major organ, and obesity at a young age is resulting in earlier onset of T2DM and other metabolic dysfunction, cardiovascular disease, some cancer types, respiratory disease, and sleep-disordered breathing,

some of which will be discussed in this chapter. The risk for noncommunicable diseases is positively correlated with BMI. Obesity in childhood is also associated with an increased risk of obesity and disability in adulthood as well as premature mortality. The psychological health of those with obesity occurring in childhood is also disquieting and includes depression, anxiety, social isolation, bullying, low self-esteem, confidence, and self-image. Suicide ideation is also common in those with obesity, with an increased number of attempted suicides documented among obese teenagers as compared to nonobese [4]. A systematic review which was published in 2009 revealed impaired health-related quality of life (HRQoL) in those with childhood obesity (<21 years old). Interestingly, this review also highlighted that the parent's perception was rated lower for HRQoL than the child's, suggesting that children may be learning to live with the condition from a young age [5]. Moreover, there are a host of neurocognitive impairments evident in obese children including reduced attention span, poorer memory recall, problem-solving abilities, and decision-making processes. Perhaps, it is not surprising then that obesity is linked to poorer academic attainment and aspiration [6]. Educational outcomes are among the strongest predictors of life and work satisfaction in adulthood [7]. Obesity also results in hypothalamic inflammation, which interestingly, is the neurological region where sleep-wake behaviors are regulated.

Attempts to reduce the obesity epidemic

Obesity is a global concern and childhood obesity is one of the leading causes of premature mortality. With this in mind, and taking into consideration the constellation of comorbidities, raising awareness and educating the public surrounding lifestyle-driven obesity-driven behaviors have been a major global priority. Efforts to reduce the childhood obesity epidemic have largely focused on educating children and parents about the causes and effects of obesity with a strong emphasis on energy homeostasis. The majority of attention has been concentrated on dietary behaviors including controlling portion sizes, consumption of healthy balanced meals, healthy food selection, reduced snacking behavior, and more. There have also been multiple interventions designed to promote adherence to healthy lifestyles, including increased physical activity and reduced screen time with the application of several innovative methods applied in school-based trials [8]. A recent review of the global literature surrounding trials aimed at tackling childhood obesity found that despite interventions being financially demanding, many have an inadequate follow up duration, have not involved parents, have largely focused on elementary school-aged children, and have not targeted low-income populations, and 50% the studies were

conducted in the United States (US) [9]. While some of the US studies generated positive outcomes (reduction in BMI), it was noted that different approaches were used, suggesting that what may work for one individual may not be successful for another. This emphasizes the need for tailored made interventions, based on individual circumstances, which will undoubtedly incur further financial penalties. National campaigns and intervention trials which raise awareness of the causes and consequences of childhood obesity have, in part, been successful in hampering a further rise with a plateau reported in some countries [10,11] but not in others [12]. The latest statistics gathered in the US from a nationally representative sample of 2–19 year olds in the US showed a 4.7% increase in overweight among children in a 2-year period (2014–16) [13].

What then, is not being incorporated into these obesity reduction trials that may be contributing to the ineffectiveness of such costly interventions? Sleep is an overlooked yet key factor and once the extensive evidence surrounding the relationship between sleep and obesity is better understood and integrated into obesity-reduction programs, this will enhance the efficacy of obesity interventions to tackle the current epidemic.

The importance of sleep in relation to health

The importance of sleep in relation to overall health, well-being, and extended mortality was recognized in 1972 in, what is now known as, the Alameda 7 study [14]. The study showed that acquiring 7–8 h of sleep per night, as well as other lifestyle behaviors, was protective against mortality. This early evidence triggered a number of further studies, which produced consistency across findings. For example, one of the largest US population studies reported a U-shaped relationship between number of sleeping hours and mortality as well as body mass index [15]. Mounting evidence has resulted in multiple systematic reviews and meta-analyses that consistently confirm the contribution of sleep duration in relation to mortality [16–20], obesity [20–25], as well as cardiovascular [17,20,26,27] and metabolic disease [20,28–32] across all age groups. So, what then is the evidence and the link between sleep and obesity? How then does sleep, a behavior associated with reduced consciousness, contribute to weight gain and subsequent obesity?

Evidence for a link between sleep duration and obesity in pediatric populations

One of the first studies to report a link between sleep duration and obesity in children was documented in France

[33]. A total of 704 controls were recruited and 327 cases of five-year-old school children with obesity. Anthropometric measurements were obtained within the school setting, and parents were interviewed to obtain information on multiple environmental factors, including sleep duration. The study showed that children with short sleep duration had an almost five-fold estimated relative risk of obesity [33]. Other demographic and lifestyle factors that predicted childhood obesity included the mother's origin, excessive television viewing and snacking but short sleep duration was, by far, the strongest predictor.

There is no shortage of population-based studies that have documented a dose-dependent association between the number of sleep hours and body weight in children. For example, a study of 6862 German children aged 5–6 years old, showed that 10.5–11 h sleep duration per night was protective against overweight and obesity as well as high body fat content with an estimated 23% reduced risk. Furthermore, those sleeping ≥11.5 h per night exhibited a further reduced risk (46%), compared to children who slept for 10 h or less per night [34]. These findings extend well beyond European children with similar observations noted in Japan [35], China [36], Turkey [37], America [38], Australia [39], the United Kingdom [40], and more. The majority of population in studies were initially cross-sectional and relied upon subjective sleep reports. Thus, the arguments were that there were no causal evidence and that sleep data may be inaccurate and subject to various biases. Over time, these limitations have been challenged and overcome. There is now considerable evidence from longitudinal studies which demonstrate that children who have inadequate sleep length, whatever the cause, gain more weight over time, compared to those who obtain sufficient sleep [40,41]. One of these studies also obtained objectively estimated sleep measures using a waist-worn accelerometer in free-living environment for 5 days and nights [40]. Moreover, recent systematic reviews and meta-analyses of prospective cohort studies verify that short sleep duration consistently contributes to an increased risk of the onset and progression of obesity among infants, children, and adolescents [21,22,24,25].

Other sleep parameters and childhood obesity

Just as obesity is a complex condition, sleep is also multifaceted and goes beyond duration. Historically, the majority of research has focused on the effects of sleep quantity in relation to health outcomes, but sleep has many additional features such as sleep quality, sleep-onset latency (time taken to initiate sleep), wake after sleep onset (a term used to quantify the amount of time spent awake throughout a sleep episode), sleep efficiency (an indicator of sleep quality which is based on the

proportion of time spent asleep and awake during a sleep episode), daytime napping, sleep architecture (proportion of specific sleep stages), and sleep–wake timings (onset and offset). Moreover, variability of these sleep features has recently become the focus of interest. Following the plethora of evidence surrounding the sleep–obesity link, the focus of research attention has recently shifted, and researchers have begun to investigate other components of sleep in relation to the condition, which will be subsequently discussed.

A recent systematic review and meta-analysis was conducted to assess the contribution of sleep duration and sleep quality in relation to childhood obesity [21]. The pooled estimates revealed that sleep quality was a stronger predictor of the condition compared to sleep duration. All studies included in the meta-analysis contained 26,533 participants and showed that those with insufficient sleep duration and poor sleep quality combined had a 27% increased risk of overweight/obesity. Poor sleep quality alone was associated with a 46% increased risk of the disease in children, adolescents and young adults. This suggests that other sleep features are important when attempting to understand the sleep–obesity relationship.

Circadian rhythms, also referred to as biological clocks, are controlled by the suprachiasmatic nucleus (SCN) located in the hypothalamus region of the brain. The SCN regulates sleep–wake timings. Interestingly, the timing of sleep, which is delayed in adolescents as a consequence of pubertal transition and exacerbated by lifestyle behaviors, has also been traced to obesity as well as poor dietary habits. A cross-sectional study of 511 young adolescents showed that late circadian preference was associated with higher BMI z-score. Interestingly, evening circadian preference (subjectively estimated and verified by wrist actigraphy) was also associated with a higher frequency of consuming unhealthy snacks and evening caffeine consumption as well as insufficient daily intake of fruit and vegetables [42]. This provides some mechanistic insight into how sleep may be contributing to weight gain and subsequent obesity by interfering with energy balance.

As previously mentioned, adolescents have a shifted circadian pattern which is characterized by delayed sleep initiation and later sleep onset. The recommended sleep duration for adolescents (13–18 years), based on consensus of the American Academy of Sleep Medicine (AASM), is 8–10 h per 24-hour period [43]. Given that a typical adolescent experiences sleep delays yet has academic attendance commitments on weekdays, this can significantly reduce sleep length in this age group. Many adolescents do not obtain 8–10 h of sleep during the week and weekend “catch-up” sleep is common. “Social jetlag” is a modern-day phenomenon, which is characterized by shorter and earlier sleep timings across the week with longer sleep quantity and later sleep timings on weekends

(weekend catch-up sleep). This occurs due to the incongruence between social patterns and the circadian clock. Social jetlag is usually determined by calculating the difference between the midpoint of sleep on weekdays versus weekends. This pattern of compensatory sleep at weekends to repay “sleep debt” accumulated across the week, however, has been associated with poorer neurocognitive capabilities [44], academic performance and psychological health consequences including depressive symptoms, suicide attempts, and self-injury [45]. Thus, sleep consistency seems to be crucial but challenging to achieve, particularly among adolescents. A recent study which acquired self-reported sleep data across 7 days in 307 first-year college students compared weekdays to weekend data, specifically in relation to BMI [46]. Greater day-to-day differences in wake timings, as well as standard deviation of wake time and sleep duration, were associated with higher BMI, after adjustment for possible confounders. Moreover, compared to those in the healthy weight BMI category, those who were classified as overweight or obese reported greater sleep variability. The authors also found that longer daytime napping was associated with a higher BMI. It is possible, although currently unknown, if daytime napping habits promote greater sleep variability and/or metabolic alterations. Another study, conducted in preadolescent children (8–10-year-olds), highlighted the contribution of social jetlag in the context of adiposity [47]. In this study, three sleep parameters were assessed (average sleep amount, sleep disturbances, and social jetlag) in relation to five adipose measures (body fat percent, fat mass, fat mass index, waist-to-hip ratio, and BMI). Interestingly, sleep duration was not associated with any adipose outcome. Sleep disturbances was associated only with fat mass index, but social jetlag was significantly associated with all five adipose measures. The key finding in this study was that each one hour of social jetlag was associated with 3% higher body fat percent. A normal, healthy developing adolescent will likely have more than one-hour of social jetlag, which is particularly concerning given these study findings. These findings are consistent with another study conducted in a large sample ($n = 3567$) of Chinese adolescents which showed that those with social jetlag are more likely to consume unhealthy food types, less likely to consume healthful foods and engage in moderate-to-vigorous physical activity, as well as have a higher BMI. They also found that those with 2 h of social jetlag were at greater risk of being overweight or obese [48].

Two recent studies by the same group have begun to explore the relationship between sleep inconsistency and energy intake [49] as well as abdominal obesity [49,50], which plays an important role in the development of insulin resistance (IR) and T2DM. The two studies recruited 305 adolescents and monitored their sleep with wrist actigraphy. They compared the effect of sleep duration

versus sleep variability in relation to subjective food and macronutrient intake as well as abdominal obesity, measured using dual-energy-x-ray absorptiometry scan. Those with higher sleep variability had more abdominal obesity, which was purported to be the result of increased energy intake, particularly from foods that are high in carbohydrates [50]. Another detailed study, conducted by a group in Sweden, assessed sleep characteristics each year using wrist actigraphy in 107 children from the age of 2 years until 6 years, in relation to adiposity [51]. Of the 107 children in the study, which was part of an obesity prevention program, 43 were deemed to be low risk of developing obesity as these children had normal-weight parents. The remaining 64 children were considered as high-risk for obesity development as they had overweight and/or obese parents. In this study, the authors focused efforts across five sleep features: 1) late sleep timing; 2) long sleep latency; 3) short sleep quantity; 4) poor sleep efficiency; and 5) irregular onset of sleep. Data were gathered from the wrist actigraphy each year and were compared across ages. The dependent variables, BMI z-scores and waist circumference, were objectively measured annually. The results of this study confirmed findings of previous studies suggesting shorter sleep duration was associated with higher BMI z-score across all ages. Children who slept later also had higher BMI z-scores as well as greater waist circumference compared to those who slept earlier. When comparing low-risk children who were not late sleepers, high-risk and late sleepers had significantly greater increases in both adipose measures. Thus, late sleep timing in early childhood years is likely to enhance the likelihood of obesity development in at-risk populations. These novel approaches provide a better understanding of how different features of sleep are partially contributing to the global epidemic of childhood obesity. Detailed mechanistic studies have also been conducted, which have revealed more clues about the involvement of sleep in obesity.

Sleep and energy homeostasis

Extensive research has been undertaken to better understand the influence that sleep has upon energy intake and expenditure, given that positive energy balance is known to cause obesity. There have been multiple experimental studies that have been conducted where sleep duration has been manipulated to examine the effect of this behavior upon energy balance. A recent systematic review identified 18 randomized controlled trials, four of which assessed the effect of sleep on food intake and another four which explored total energy expenditure [52]. The authors concluded that increases in energy intake as well as total energy expenditure were observed with sleep restriction. So why, if sleep restriction results in increased energy

intake as well as expenditure do people gain weight? The answer is simple. Energy expenditure does not adequately compensate for the increased amount of energy consumption, which results in positive energy and gradual weight gain when persistent.

It should be noted that the majority of experimental sleep studies to investigate alterations in body weight and metabolism have been conducted in adults with limited evidence available in pediatric populations. Sleep restriction studies that explore the mechanisms of obesity and metabolism are limited in children and adolescents. There have been multiple studies conducted in young, healthy adults, which have explored the effect of acute partial sleep restriction upon metabolic outcomes as a mechanistic approach to understanding the sleep–obesity link. One of the earliest studies showed that restricting adults sleep to 4 h per night for two consecutive nights resulted in alterations to appetite and hunger-regulating hormones, leptin and ghrelin. Specifically, leptin, which is a hormone that indicates satiety, was significantly reduced with sleep restriction, suggesting a delay in the hypothalamic signaling of satiety that can cause overeating. Ghrelin is commonly referred to as a hunger hormone, given that levels rise prior to food consumption and then decline afterward. Levels of ghrelin were increased following sleep restriction in this study suggesting that individuals may be hungrier. The authors obtained subjective reports of hunger in the study which confirmed this notion [53]. Moreover, participants were also asked to rate their appetite for different macronutrients (protein, fats, carbohydrates, sweet/salty foods, and more). Interestingly, not only did participants report higher levels of hunger, but they also indicated a stronger preference for carbohydrate and calorie-dense foods.

One of the few sleep-metabolism studies to be conducted in children investigated the effects of sleep restriction upon 24-hour food recall, levels of leptin and ghrelin as well as body weight [54]. The authors found that sleep restriction (1.5 h less than habitual sleep duration) for 1-week was associated with a significant increase in calorie intake per day as well as alterations to leptin. It should be noted that there were only 37 children in the sample, and thus generalizability to other populations is problematic. There are many adult studies that have consistently highlighted the relationship between sleep restriction and metabolic disruption. Leptin and ghrelin are neuroendocrine mediators in the sleep–obesity pathway, but there are fewer studies in children and the findings are less consistent, as noted in a recent review [55].

There are limited studies surrounding sleep in relation to energy output, meal timing, and macronutrients in children, but one in particular has provided a more detailed insight into this population [56]. A total of 87 children, aged 8–11 years, were part of a behavioral sleep improvement intervention. The children wore wrist

actigraphy for 1-week alongside waist accelerometers to estimate physical activity levels. Information pertaining to dietary intake and meal timings were obtained from 24-hour dietary recall. Later bedtimes were positively and significantly correlated with fat intake, later timing of first meal, as well as larger after dinner intake. Night-time sleep amount was correlated with BMI z-score, whereas bed timing was not. These findings provide further insights into the intricate relationships between sleep, feeding behaviors, and body weight, as well as highlighting the need to comprehensively examine sleep along with all of its features. Another study, a randomized cross-over trial of sleep manipulation, showed that while levels of hunger and food appeal were not affected during sleep restriction in adolescents, the overall amount of calories consumed was 11% higher, and serving and consumption of sweet foods was 52% greater during sleep restriction compared to when teens were in the healthy sleep condition [57].

A clear picture has emerged surrounding the importance of sleep in relation to obesity and metabolic regulation. The role for sleep curtailment-induced hormonal changes is a plausible mechanistic explanation for obesity in children and adults. Additional work is, however, needed to elucidate the precise role that leptin, ghrelin and other appetite-controlling hormones play in metabolic dysfunction that is associated with sleep alteration/imbalance. Unequivocally, sleep is fundamental to optimal metabolic regulation and provides a robust mechanistic explanation for short, or disrupted, sleep as a driver for obesity onset. Multiple causal pathways between sleep and obesity have been documented, which have highlighted a combination of behavioral and physiological drivers.

Neurological responses and cognitive control to food and the role of sleep

It is clear from the evidence that sleep alters the physiology of an individual. As sleep–wake behavior is regulated by the brain, it is perhaps not surprising that the brain responds differently to food cues when sleep is altered. In 2019, Jensen et al. [58] conducted a study, recruiting 52 adolescents between the ages of 12–18 year. They compared normal weight teens to overweight/obese participants, permitting them 5 h time in bed for five nights in their own environment followed by 9 h of sleep opportunity for five nights with each condition occurring 4 weeks apart. The morning after each sleep condition, participants underwent functional magnetic resonance imaging (fMRI) while completing a cognitive task to assess inhibition (go/no-go) task containing different food stimuli. The results of the study revealed that adolescents with normal weight had greater activation of brain pathways and regions, known to be associated with inhibition in response to food stimuli after sleep restriction as compared to overweight/obese

adolescents [58]. Overall, this implies that overweight/obese adolescents may experience disinhibition to specific food types, resulting in a loss of cognitive control and subsequent consumption, which may exacerbate their weight status. Indeed, this group also assessed participants who completed a food-related inhibitory control task, as well as other subjective measures to assess food reward after optimal and restricted sleep conditions. It was observed that sleep-restricted teens were more sensitive to food reward and had poorer cognitive control (more disinhibited) to food images compared to when in the optimal sleep condition [59]. A later study, by the same group, conducted a similar sleep protocol (6.5 h of sleep opportunity vs. 9.5 h for five consecutive nights) with 88 healthy adolescents [60]. They were asked to subjective report on five different food categories (sweets/desserts, fruits/vegetables, lean meats/eggs, fast food, processed snacks) in relation to food appeal and reinforcing value of food. It was concluded that sleep restriction increased the appeal of food as well as the reinforcing value to various food types, suggesting that just a small amount of sleep loss is needed to trigger alterations in the way food is perceived in the adolescent brain.

A more recent study, published in 2023, which also used fMRI and recruited 39 healthy teens (14–17 years old), showed how a relatively small amount of sleep loss can alter how the adolescent brain processes food stimuli. The sleep protocol included three stages: 1) sleep phase stabilization (baseline); 2) experimental sleep restriction set to approximately 6.5 h of sleep for five nights; and 3) optimal sleep duration of approximately 9 h per night. Participants completed a visual food paradigm while in the fMRI and results of food vs. nonfood responses were compared between the different sleep conditions in the same participants. The results showed that after sleep restriction, participants exhibited a greater response to food stimuli compared to when subjected to the optimal sleep condition. In particular, the dopaminergic drive of the brain regions associated with the reward pathways had greater activation, leading the authors to conclude that this may result in 1) an increased motivation to seek out food and 2) increased appeal for food, both of which are likely to impair cognitive control and possibly result in overfeeding [61].

Future directions

Given that there is now consistent, convincing evidence about the connections between sleep and body weight, hormone regulation, and altered brain responses to food, the next logical step seems to apply and incorporate this knowledge into interventions that target obesity reduction and prevention programs. Educating parents, children, and teachers about the downstream effects of sleep upon health

outcomes is the first step. Raising awareness about the importance of sleep on health at a population level is also imperative so that common myths, such as sleep being a waste of time, can be challenged. Recent efforts have begun, and sleep is now becoming more recognized as a pillar of health.

There have been multiple school-based interventions, which have specifically attempted to integrate sleep into the curriculum to optimize sleep in children and adolescents. Most of these trials have shown an increase in sleep knowledge when comparing baseline to follow up. This is good news as raising awareness among children and their parents is the first step, but knowledge alone is not sufficient to elicit behavior change. Unfortunately, improvements to sleep knowledge do not always translate into positive sleep behavior change. Some studies were designed to assess pre- and postsleep knowledge only, without exploring possible sleep behavior alteration. Others have shown that improved sleep knowledge does not positively influence subsequent behavior, although the evidence is somewhat heterogeneous. A recent narrative review surrounding sleep improvement as a possible tool for tackling obesity concluded that there are an insufficient number of adolescent studies to support this as a feasible method [62]. Thus, carefully designed studies which include longitudinal and objective assessments of sleep, as well as parental education and involvement, paired with intentional sleep behavior modification is now needed, particularly given the lack of long-term success and/or follow-up that other obesity-reduction trials have shown. When obesity researchers begin to recognize the contributions of sleep behavior, incorporating sleep improvement into future trials may enhance the success of these interventions.

Metabolic disease

The rising incidence of chronic health conditions in recent decades has resulted in a global public health concern. The occurrence of these diseases has been repeatedly and strongly linked to the presence of specific behavioral factors. The Centers for Disease Control and Prevention (CDC) estimated that eliminating three specific behavioral risk factors alone (poor diet, inactivity, and smoking) would prevent 80% of heart disease and stroke, 80% of type 2 diabetes, and 40% of cancer. In respect of diabetes, the prevalence of the disease has not only been rising steadily among the adult population but also more worryingly among children. The monetary cost alone of diabetes is astounding with estimates upwards of \$375 billion per year. Diabetes is not just expensive to treat, but it also reduces life expectancy by an average of 10 years. The rising prevalence of diabetes among children has intensified the search for a better understanding of the variables

associated with its onset and progression as well as how to best manage the disease. One promising line of research that has begun to gain traction concerns the nature of the relationship between aspects of sleep and heightened risk of diabetes. Research in this domain remains largely in its infancy, and the available research base is largely limited to primarily observational studies with limited experimental studies. Though research on the relationship between sleep and diabetes and children has followed on the coat-tails of research with adults, collectively it points to the role of sleep as a modifiable risk factor for the onset of diabetes in children [63]. As the quality and duration of sleep in children and adolescents appears to be decreasing similar to their adult counterparts, the implications for children may be as profound, if not more so, than for adults.

Mechanisms of diabetes

Diabetes mellitus (DM) is characterized by glucose dysregulation. The most frequently occurring are type 1 and type 2. Type 1 diabetes (T1D) occurs when the pancreas does not produce insulin, and T2D is driven by IR or insufficient insulin secretion. The key distinction between these two main types of DM revolves around the degree of insulin produced. In healthy individuals, the hormone insulin has a triggering effect on the cells of the body to absorb elevated levels of glucose in the bloodstream and therefore has a homeostatic type function. These cells of the body open special channels on their surface to absorb an influx of glucose, typically occurring after food intake. When cells do not effectively respond to insulin, or an insufficient amount is secreted, blood glucose levels become elevated. Interestingly, T2D was initially referred to as late-onset or adult-onset diabetes though this nosology has subsequently been dropped largely in response to the observation that an ever increasing number of children have developed the disease in recent years. Similar to diagnosis of the disease in adults, the criteria for disease in children are polydipsia, polyuria, and unexplained weight loss plus casual glucose concentration ≥ 200 mg/dL (11.1 mmol/L) in venous plasma, fasting glucose ≥ 126 mg/dL (7.0 mmol/L) in venous or capillary plasma, or two-hours glucose during OGTT ≥ 200 mg/dL (11.1 mmol/L) in venous plasma or capillary whole blood sample.

The consequences of diabetes can be severe, and it remains a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputation. The associated health, mortality, and quality of life costs associated with diabetes have provided the impetus for a, now substantial, research-base. Up until recently, among the most common causes identified have been poor quality diet, excessive body weight, and insufficient exercise. As of 2017, the

World Health Organization estimated that 422 million people had diabetes worldwide, which is approximately 8.5% of the adult population. According to the Global Burden of Disease report for 2015, the prevalence of diabetes increased by approximately 30% between 2005 and 2015 and during the same interval, the annual number of deaths from diabetes rose from 1.2 million to 1.5 million. Up until the 1990's, T2D had been considered a relatively rare occurrence in children and adolescents, but since that time, a number of industrialized countries such as the United States, Canada, Japan, and Germany have witnessed an increasing incidence of the disorder [64]. In the United States alone, overall unadjusted incidence rates of T2D are reported to have increased by 7.1% annually between 2002 and 2012 [65]. The increase in prevalence has unsurprisingly occurred in conjunction with an increase in prevalence and degree of obesity also among children and adolescents. However, some authors have noted a curious anomaly in the case of T2D in children—while incident obesity has stabilized in some countries, the prevalence of diabetes has increased three-fold. It also appears that prevalence statistics may be an underestimation of the true rates as several studies have reported that children were asymptomatic at diagnosis. Therefore, it is likely that, as with adults, undiagnosed T2D is a common condition in childhood. However, though the symptoms of the disease may be similar across children and adults, it appears the health consequences are not [66]. For example, one notable outcome of the UK Prospective Diabetes Mellitus Study was the observation that children and adolescents with T2D have a higher risk for disease-related complications, compared to adults with the same condition. In line with this, developing T2D at a younger age appears to be associated with a much higher risk of long-term cardiovascular disease than those who develop T2D in middle age [66]. Furthermore, young people with T2D appear to be at a much higher risk of developing associated complications than those with T1D. This higher level of risk does not appear to be related to overall levels of glycemic control or disease duration but to the occurrence of hypertension and dyslipidemia [67]. In addition, the negative effects of T2D extend beyond the traditional quantification of medical symptoms to quality of life; adolescents with T2D report poorer HRQoL scores compared to T1D counterparts [68]. Furthermore, the burden of psychological disorders in young people with T2D is high, with as many as one in five experiencing either psychological disorders or behavioral problems [69].

It is critical then for researchers to identify, as precisely as possible, all factors implicated in the onset of the disorder. In particular, emphasis should be placed upon the identification of preventative factors and early identification. Principal existing strategies for the prevention of T2D in children revolve around the role of the known factors

such as obesity and therefore reflect content surrounding teaching principles of good nutrition and the importance of adequate exercise. Family-based treatments for childhood obesity as a specific risk marker have also been subjected to empirical analysis, and support for their effectiveness is evident, particularly in the context of motivated families [64]. However, based on recent sleep research findings which will be discussed, the content of programs aimed at improving the management and reducing the current epidemic of T2D in children is likely to need rethinking with incorporation of effective sleep management strategies.

It is also worth noting that a number of existing reviews and guidelines for the prevention and management of T2D in children fail to mention sleep as a risk factor for the development, or management, of diabetes with the majority focusing on weight control. This is largely attributable to the recent emergence of research on the topic. While sleep may be implicated as a risk factor, it remains currently unclear about what precisely is the role of sleep in children in the development of T2D and whether optimal sleep functioning relates to improved quality of life and/or better symptom management. Furthermore, self-management programs may require modification in light of emerging research on the role of sleep. The role of sleep may add incremental benefits considering intervention studies have convincingly demonstrated that adoption of a healthy lifestyle characterized by healthy eating, regular physical activity, and subsequent modest weight loss can prevent the progression of impaired glucose tolerance to clinical DM [70].

Sleep and type 2 diabetes mellitus

Healthy sleep is gaining increasing recognition as an important lifestyle habit in the prevention of chronic diseases, and the evidence is striking. In addition to maintaining normal brain functioning, the importance of the role of sleep in controlling functions of multiple body systems is now well established. It is becoming clear that poor quality sleep including a reduction in the total hours of nocturnal sleep can lead to serious negative consequences for almost all bodily organs and systems. For example, immune function is compromised [71], systemic inflammation with increased inflammatory markers becomes apparent [72], and metabolic regulation is significantly disrupted [73]. Sleep deprivation has a profound effect on metabolic health. Specifically, sleep disturbance, insufficient or excessive sleep, and irregular sleep wake patterns have been associated with adverse outcomes such as obesity and impaired glucose metabolism [74], and emerging evidence has assigned an important role to sleep as a modulator of metabolic homeostasis [75]. In a healthy individual, insulin is produced in response to glucose,

which triggers the cells of the body to swiftly absorb glucose and regulate its level. Indicators of a substantial link between impaired sleep and abnormal blood glucose levels have emerged through several meta-analytic reviews and large-scale epidemiological studies [1,2]. Collectively, these studies indicate that sleeping less than 6 h a night is significantly associated with an increased risk of T2D. More importantly, this relationship remains evident when adjusted for previously identified risk factors for the development of T2D such as body weight, alcohol, smoking age, and even race. One specific recent meta-analysis of adult studies concluded that the risk of developing T2D was associated with insufficient sleep and that this was comparable to that of previously identified risk factors including family history of diabetes, excessive weight, and reduced levels of physical activity [32]. An additional large retrospective study involving over 80,000 prediabetic individuals reported that after adjustment for traditional risk factors, insomnia was associated with a 28% increased risk of developing T2D [3]. The authors argue that effective sleep should be considered as a modifiable risk factor in clinical guidelines for the management of T2D [3,32].

The relationship between sleep and T2D is more firmly established in adults with a U-shaped relationship being observed, indicating that both short- and long-sleep duration carry a risk for developing the disease. However, the specific endocrine and molecular mechanisms underlying this relationship are still not yet fully understood. The issue that arises with the evidence surrounding the link between sleep, T2D, and metabolic dysfunction is one of causality—specifically, does diabetes result in sleep reduction or does shorter sleep duration interfere with glucose regulation? The emerging consensus is that shortened sleep duration impairs glucose tolerance. Perhaps, the strongest evidence for this relationship stems from experimental studies inducing either total or partial sleep deprivation in healthy adult participants. Collectively, these studies indicate that the metabolic profile observed subsequent to sleep deprivation displays a number of similarities with T2D, including increased IR, decreased muscle glucose uptake, and increased liver glucose output and pancreatic β -cell dysfunction [4]. Additional research also suggests that specific sleep disorders considerably compromise glucose metabolism [76]. For example, Keckes et al. report that obstructive sleep apnea (OSA) is associated with an increased risk of impaired glucose tolerance and suggests that OSA is a likely specific risk factor for diabetes, regardless of concomitant obesity [76]. Finally, there is tentative evidence that reduced sleep is associated with changes in appetite regulation and may even operate as an independent risk factor for weight gain and the accumulation of abdominal fat. Sleep deprivation has been linked to an increased preference for fat- and carbohydrate-rich

food and a concomitant increase in daily caloric intake [5]. Additional supporting evidence for this relationship comes from recent experimental studies, which demonstrates that extending sleep duration to normal levels among overweight and sleep-deprived individuals is associated with a significant decrease in energy intake [6].

Epidemiological studies clearly point to a relationship between abnormalities in sleep duration and impaired glucose tolerance. These studies have demonstrated that difficulties in maintaining sleep or short sleep duration are associated with an increased incidence of diabetes [77,78]. However, the strongest evidence of a relationship between sleep duration and T2D derives from a number of meta-analytic studies conducted over the past 10 years involving very large numbers of participants. These meta-analyses demonstrate that short sleep duration increased the risk of T2DM and most indicate that long sleep duration was also associated with an increased risk [7]. In accounting for this relationship, one mechanism by which sleep deprivation might result in increased risk of IR and diabetes may be either by directly affecting parameters of glucose tolerance or indirectly through a disturbance in appetite regulation, leading to increased food intake and weight gain. Indeed, recent experimental research involving healthy nonobese participants has demonstrated that induced sleep restriction is associated with significantly increased calorie intake, body weight, and abdominal visceral fat [11]. With regard to short sleep duration and metabolic disorders, or weight gain, some have argued that sleep deprivation might simply result in increased opportunities to eat, and associated tiredness is likely to promote sedentary activities [79].

A number of experimental studies suggest that one pivotal mechanism in the relationship between sleep and T2D in adults is likely to be reduced insulin sensitivity. These studies which involve sleep deprivation ranging from one to 5 days report decreased insulin sensitivity in adult volunteers [8]. Of particular relevance are the results of studies which restrict sleep to between four and 5 h per night, thereby reflecting the sleep pattern of many individuals in contemporary society. This body of work demonstrates that glucose tolerance and/or insulin sensitivity are substantially impaired when sleep is restricted for a few days and up to several weeks [9,10]. Two possible lines of questions emerge from these findings. First, is it insufficient insulin or suppression of its release that is responsible? Second, do particular cells in the liver, muscles, and fat become unresponsive to an otherwise normal and present message of insulin? The available evidence suggests that cells become less responsive to insulin with the subsequent result of impaired glucose tolerance. A growing number of sleep restriction studies lend support to this claim, beginning with the landmark study published by Spiegel and colleagues in the late 1990s [80]. They found

that, in 11 healthy young men, restricting sleep from a baseline of 9–4 h for six consecutive nights, led to a significant decrease in glucose clearance [80]. A number of subsequent experimental sleep restriction laboratory-based adult studies have found that partial sleep restriction, or changes to sleep-wake timings (circadian desynchronization), leads to impaired glucose sensitivity without compensatory increases in insulin secretion, lower glucose effectiveness, and increased glucose levels [81]. For example, just 3 weeks of mild sleep restriction (1.5 h less than baseline sleep) in the home setting has been linked to transient impaired insulin sensitivity [82]. A more recent study demonstrated that 4 days of sleep restriction (involving a 40% reduction in habitual sleep duration) was related to reduced whole-body insulin sensitivity [12].

While the majority of research to date has explored sleep duration rather than sleep architecture, the latter also appears to have an impact on glucose homeostasis. Several studies have examined whether aspects of sleep architecture rather than quantity of sleep affect insulin sensitivity. A small number of studies suggest associations between various sleep stages and insulin sensitivity as well as insulin secretion. These point to positive associations between percentage of sleep time spent in slow wave sleep (SWS; stage 3) and insulin secretory measures as well as insulin sensitivity [83]. Another small study revealed an inverse association between percentage of total sleep time in stage 1 sleep (NREM1) and insulin sensitivity in adolescents, independent of total sleep duration [84]. Another study showed that SWS was positively associated with insulin sensitivity, whereas stage 1 sleep exerted the opposite effect on IR, after adjustment for age, gender, body mass index z-score, pubertal status, and apnea hypopnea index [85]. Greater sleep efficiency and longer total sleep were independently associated with lower glucose levels. This suggests that SWS, sleep efficiency, and total sleep duration are protective factors in maintaining glucose and insulin homeostasis.

A growing body of observational evidence points to a relationship between sleep duration and sleep quality and metabolic functioning in adults. These conclusions are supported by several meta-analyses [26,29,31,32], and some of the strongest evidence for sleep and glucose dysregulation come from experimental studies. In summary, the primary mechanisms in the development of impaired glucose metabolism appear to be changes in insulin secretion—the ability of the pancreatic beta-cells to respond to a glucose stimulus, insulin sensitivity, and the ability of peripheral tissues to respond to an insulin signal. Therefore, it seems that the results from these studies serve to confirm the associations observed in longitudinal epidemiological and cross-sectional between chronic sleep restriction and incidence of T2D are causally related—sleep restriction leads to increased IR, which without

increased insulin secretion to compensate can cause hyperglycemia eventually culminating in T2D even when traditional risk factors are accounted for and appear to be independent of age and gender.

Sleep and children

The consensus of a substantial body of research is that sleep quality and corresponding habits in children and adolescents have undergone a deterioration over recent decades. For example, data generated from the National Survey of Children's Health between 2003 and 2012 indicated that the prevalence of inadequate sleep (defined as 0–6 days of not getting enough sleep), increased across all age groups between 6 and 19 years of age [86]. Inadequate sleep duration increased from 23% to 35% for 6–9 year olds and from 30% to 41% for 10–13 year olds [86]. Data from the most recent survey administration (covering the period 2016–18) indicate that these increases have remained static with upwards of 35% of children experiencing chronic short sleep duration when compared against age group recommended hours of sleep per day [13]. These figures are similar to those reported elsewhere. For instance, more recently, it has been reported that upward of 42% of children had sleep durations shorter than the recommended amount [87].

These numbers contrast sharply with the most recent recommendations for sleep duration by the AASM [43]. Based on a review of 864 published articles, they recommended, by consensus, sleep duration in infants, children, and adolescents, which are shown in Table 38.1.

The AASM further stated that sleeping in the number of recommended hours on a regular basis is associated with better health outcomes including: improved cognition, attention, adaptive behavior, learning, memory, emotional regulation, quality of life, and mental and physical health. Furthermore, regularly sleeping fewer than the number of recommended hours is associated with attention, behavioral, and learning problems. Of particular relevance to this chapter is that insufficient sleep also increases the risk of accidents, injuries, hypertension, obesity, depression, and diabetes.

Sleep, diabetes, and children

Childhood diabetes is an increasing global health challenge, and the incidence of the disease among children appears to be rising. Recent epidemiological analysis indicates a 39% increase in the number of cases globally between 1990 and 2019 in children aged 0–14 years [14]. While some have pointed to methodological issues surrounding the reporting of reliable statistics [88], such reported increases are consistent with the findings of other regional research. For example, one large-scale study in the

TABLE 38.1 Recommended sleep duration for children and adolescents per 24-h period, as proposed by the American Academy of Sleep Medicine.

Age group	Recommended sleep duration
Infants (4–12 months)	12–16 h
Children (1–2 years)	11–14 h
Children (3–5 years)	10–13 h
Children (6–12 years)	9–12 h
Adolescents (13–18 years)	8–10 h

USA highlighted substantial increases in the estimated prevalence of both type 1 and type 2 diabetes in young people up to the age of 19 [89]. More specifically, from 2001 to 2017, significant increases in the number of young people diagnosed with T1D were observed among ages 5–9, 10–14, and 15–19 years. Across the same period, significant increases were also observed in those diagnosed with T2D aged 10–14 and 15–19 years old. Leaving aside for the moment the issue of causality in relation to sleep and diabetes, children with T1D experience more sleep disturbances, less time in deep sleep, increased daytime sleepiness, and shorter sleep durations compared to their healthy peers [15,16]. Additional research indicates that adolescents with T1D have significantly lower sleep efficiency and rapid eye movement sleep with significantly higher sleep onset latency, non-REM sleep, and arousal index [17]. Similar patterns have been reported in children diagnosed with T2D [18]. For example, one study reported that 67% of children living with T2D experienced poor sleep quality in contrast to only 8% for those with better glycemic control. It is not just older children that may be at potential risk as the relationship between sleep and risk appears to be present for children as young as 4–10 years. Furthermore, it has been reported that children in this age range routinely sleep less than 8 h per night and that variations in sleep may result in metabolic dysregulation [90]. In other words, the longer and more stable sleep duration is, the less likely a child is to exhibit metabolic dysfunction.

Although the pathophysiological mechanism of T2D in children is not completely understood, it is clear from adult studies that IR plays an important role. Evidence of this comes from cross-sectional and longitudinal studies demonstrating that IR may occur 10–20 years before the onset of the disease in adults and that it is an important predictor of whether or not an individual will later become diabetic [91]. In contrast, it appears that the disease in children is characterized by more a rapid onset of β -cell

failure compared with adults and dysregulation of glucose homeostasis. Therefore, identifying children at risk for T2D is of great importance in order to interrupt its progression and collateral diabetes-related health complications. Another implication of a period of IR (though shorter than in adults) is that children and adolescents with T2D may remain asymptomatic and undiagnosed for a long period of time. The consequences of the disease are as profound as for adults including accelerated development of cardiovascular disease, renal disease, and impaired visual functioning [64]. While adult studies have established a link between insufficient sleep and reduced insulin sensitivity, the presence of distinct developmental and physiological changes, which occur during adolescence, impact on the generalizability of this body of research to adolescents. Adolescence is characterized by complex endocrine, somatic, and nervous system changes including changes in sleep architecture, which can adversely affect sleep health [23]. One such change is the physiological shift in circadian rhythm that occurs in mid-adolescence resulting in later sleep onset and a reduction in total sleep time, shortening of the latency to REM sleep, a reduction in slow wave sleep and slow wave activity, and an increase in NREM 2 sleep [19,24]. These changes combined with school related early morning waking, increased social, and extra-curricular demands result in extended periods marked by insufficient sleep. This combination of factors may underpin reports such as almost half of teenagers report having less than 6 h sleep per night [21].

Research examining sleep health and risk for T2D in adolescence has followed by four broad lines of inquiry [1] sleep health and obesity [2], sleep health and dietary intake [3], sleep health and physical activity, and [4] sleep health and IR. The consensus of existing research is that insufficient sleep during adolescence increases the risk for T2D directly through an impact on insulin sensitivity and indirectly through other mechanisms such as increased dietary intake, sedentary activity, and weight gain [18]. Pediatric studies have reported associations between sleep duration, sleep architecture, and insulin sensitivity and glucose levels [92]. A number of studies report associations between short sleep duration and IR [83,92]. Similar to adult studies, others report a U-shaped relationship between sleep duration and glycemic measures, with increased glucose levels occurring at both higher and lower sleep duration independent of obesity [83]. In one large cross-sectional study of 4525 children, aged 9–10 years in the UK, each additional hour of sleep was found to be associated with less IR and associations between insulin and glucose remained after an adjustment for adiposity markers [93]. Another large cross-sectional study involving more than 2700 children conducted in South America reported similar results. Boys who met the recommended amount of

sleep had a decreased risk of elevated blood glucose levels compared to boys who had a short-sleep duration and the effect remained when controlling for potential confounding variables such as adiposity [94]. Self-reported insufficient sleep duration was also reported to be associated with IR via the use of fasting measures in youth ages 10–19 years [22]. To date, only a small number of experimental studies have examined the effects of sleep restriction or sleep disruption on glucose homeostasis in children and adolescents. One early study reported decreased insulin sensitivity in healthy male adolescents after three nights of sleep restriction (4 h per night) compared with three nights of recommended sleep duration (9 h per night) [86].

Aside from insulin resistance, it has been proposed that insufficient sleep may lead to decreased physical activity, increased food intake, and increased weight gain and obesity risk. One particular proposed indirect mechanism concerns the role of disinhibited eating behaviors and risk factors for T2D. Adult studies indicate that sleep restriction is associated with increased hunger, appetite, and food intake to compensate for increased energy expenditure during extended wakefulness [25]. Furthermore, alterations in appetite and energy intake are reported to be common following sleep deprivation [53,95]. For example, one study evaluated associations between sleep duration, daytime sleepiness, and eating patterns in 119 adolescent girls at risk for T2D [96]. The findings from this study indicated that subjective sleep duration and objectively determined energy intake were positively related. When age, race, puberty, body composition, depressive symptoms, and perceived stress were controlled for, sleep duration remained positively related to total energy intake [96]. Adjusting for the same covariates, daytime sleepiness was associated with a greater likelihood of binge eating in the previous month. Experimental studies with adolescents aged 14–16 years also indicate that insufficient sleep (6.5 h in bed) is associated with an increase in calorie consumption and that insufficient sleep is associated with food-related inhibitory control and increased subjective preference for sweet foods [26,27]. It has also been proposed that changes in appetite regulation may be mediated by two specific hormones related to sleep: Leptin and ghrelin. In sleep-restricted as opposed to well-rested individuals, leptin levels are decreased, while ghrelin levels increased promoting increased subjective hunger and food consumption [28].

Obesity is a well-established risk factor for T2D in adults, and a similar pattern has emerged in children with 85% of children with T2D being either overweight or obese at diagnosis [32]. Consequently, there has been increased focus on identifying the contributors to obesity in children including the potential role played by parameters of sleep health. Collectively, these studies suggest that impaired sleep is associated with obesity in children. For example, one study involving 240 toddlers observed that

decreases in sleep duration were significantly associated with obesity [29]. Other research with adolescents has reported that reductions in REM sleep by 1 h are associated with an approximately 3-fold increased odds of being overweight [30]. Perhaps, the strongest evidence comes from a comprehensive meta-analysis of prospective studies, which identified a causal relationship between short sleep duration and subsequent weight gain and obesity in children across development, including adolescence. Specifically, short sleep duration was found to be associated with a two-fold increased risk of developing obesity in infants, childhood, and adolescence [31]. However, the relationship between sleep and physical activity is somewhat less clear in part due to relatively few studies and validity issues of those studies. It has been hypothesized that decreased sleep at night leads to increased daytime sleepiness, which, in turn, may lead to reduced levels of physical activity. Several studies involving adolescents have reported that shorter sleep duration and poor sleep quality were associated with less physical activity, more electronics use, and higher sedentary behaviors in adolescents using both subjective and objective assessments [33].

One final additional proposed pathway from sleep imbalance to T2D relates to the role of endocrine stress, specifically increased cortisol and catecholamine levels. Elevated levels may result in impaired glucose metabolism. Sleep is a refractory period for three stress hormones—cortisol, norepinephrine, and epinephrine. These stress hormones are down-regulated at night; cortisol, in particular, is known to inhibit insulin production, and increased levels are related to IR [97]. Thus, delays to sleep or shortened sleep may cause cortisol levels to rise, which could result in IR. However, experimental data surrounding the respective roles of these hormones remain unclear in pediatric populations. In one key experimental study, three nights of moderate sleep restriction decreased insulin sensitivity in boys but was unrelated to endocrine stress markers [98].

Conclusion

Global statistics indicate an increasing prevalence of T2D among children and adolescents, which are, in part, attributable to traditional risk factors. However, poor sleep health, whether lifestyle driven or physiological, may also be contributing to the rising levels of childhood diabetes and obesity. Research to date indicates that we are just beginning to better understand the extent to which sleep deficiency impairs glucose metabolism in children. Additional research is, however, needed regarding about the extent, mechanisms, and dynamics of the relationship sleep has upon obesity and T2D. Overall, the data regarding sleep and metabolic disorders in children are more limited than for adults; short sleep duration may indeed predispose

the individual to IR and hyperglycemia. The magnitude (hours of sleep per night) and duration of sleep restriction (days to weeks) are likely to be important factors in determining the speed and extent of any diabetogenic changes, including elevations of circulating glucose levels caused by reduced insulin sensitivity of peripheral tissues and/or insufficient insulin secretion by the pancreas. The existing literature provides evidence that short sleep is associated with IR in adolescence, but additional research is still needed. Current experimental findings are consistent with recent epidemiological work, which demonstrates that lifestyle factors, including habitually short sleep duration, increase the risk of weight gain and obesity over all stages of childhood. It is noteworthy that no studies to date have attempted to determine whether improving the quality of sleep of children with T2D brings with it positive changes in glucose homeostasis. In respect of preventative efforts, sleep habits could be integrated into existing management programs that apply an evidence-based approach such as cognitive behavior therapy to reduce risk of the onset of diabetes in children.

References

- [1] de Onis M, Blössner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr* 2010;92(5):1257–64. <https://doi.org/10.3945/ajcn.2010.29786>.
- [2] Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat* 2000;11(246):1–190.
- [3] Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: International survey. *BMJ* 2000;320(7244):1240–3.
- [4] Van Wijnen LGC, Boluibijt PR, Hoeven-Mulder HB, Bemelmans WJE, Wendel-Vos GCW. Weight status, psychological health, suicidal thoughts, and suicide attempts in Dutch adolescents: results from the 2003 E-MOVO project. *Obesity* 2010;18(5):1059–61. <https://doi.org/10.1038/oby.2009.334>.
- [5] Tsilos MD, Olds T, Buckley JD, Grimshaw P, Brennan L, Walkley J, Hills AP, Howe PRC, Coates AM. Health-related quality of life in obese children and adolescents. *Int J Obes* 2009;33(4):387–400. <https://doi.org/10.1038/ijo.2009.42>.
- [6] Arora T, Hosseini-Araghi M, Bishop J, Yao GL, Thomas GN, Taheri S. The complexity of obesity in UK adolescents: relationships with quantity and type of technology, sleep duration and quality, academic performance and aspiration. *Pediatr Obes* 2013;8(5):358–66. <https://doi.org/10.1111/j.2047-6310.2012.00119.x>. <http://onlinelibrary.wiley.com/journal/10.1111/ISSN2047-6310/issues>.
- [7] Strenze T. Intelligence and socioeconomic success: a meta-analytic review of longitudinal research. *Intelligence* 2007;35(5):401–26. <https://doi.org/10.1016/j.intell.2006.09.004>.
- [8] Verrotti A, Penta L, Zenzeri L, Agostinelli S, De Feo P. Childhood obesity: prevention and strategies of intervention. A systematic review of school-based interventions in primary schools. *J Endocrinol Investig* 2014;37(12):1155–64. <https://doi.org/10.1007/s40618-014-0153-y>.

- [9] Ickes M, McMullen J, Haider T, Sharma M. Global school-based childhood obesity interventions: a review. *Int J Environ Res Publ Health* 2014;11(9):8940–61. <https://doi.org/10.3390/ijerph110908940>.
- [10] Schmidt Morgen C, Rokholm B, Sjöberg Brixval C, Schou Andersen C, Geisler Andersen L, Rasmussen M, Nybo Andersen AM, Due P, Sørensen TIA. Trends in prevalence of overweight and obesity in Danish infants, children and adolescents – are we still on a plateau? *PLoS One* 2013;8(7). <https://doi.org/10.1371/journal.pone.0069860Denmark>. <http://www.plosone.org/article/fetchObjectAttachment.action;jsessionid=DFA8DC717C194F025C5709F30C8A5C09?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0069860&representation=PDF>.
- [11] Keane E, Kearney PM, Perry IJ, Kelleher CC, Harrington JM. Trends and prevalence of overweight and obesity in primary school aged children in the Republic of Ireland from 2002–2012: a systematic review. *BMC Public Health* 2014;14(1). <https://doi.org/10.1186/1471-2458-14-974>.
- [12] Ranjani H, Mehreen TS, Pradeepa R, Anjana RM, Garg R, Anand K, Mohan V. Epidemiology of childhood overweight & obesity in India: a systematic review. *Indian J Med Res* 2016;143:160–74. <https://doi.org/10.4103/0971-5916.180203>.
- [13] Skinner AC, Ravankar SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of obesity and severe obesity in US children. *Pediatrics* 1999;141(3). <https://doi.org/10.1542/peds.2017-3459>.
- [14] Belloc NB, Breslow L. Relationship of physical health status and health practices. *Prev Med* 1972;1(3):409–21. [https://doi.org/10.1016/0091-7435\(72\)90014-X](https://doi.org/10.1016/0091-7435(72)90014-X).
- [15] Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry* 2002;59(2):131–6. <https://doi.org/10.1001/archpsyc.59.2.131>.
- [16] da Silva AA, de Mello RGB, Schaan CW, Fuchs FD, Redline S, Fuchs SC. Sleep duration and mortality in the elderly: a systematic review with meta-analysis. *BMJ Open* 2016;6(2). <https://doi.org/10.1136/bmjopen-2015-008119>.
- [17] Yin J, Jin X, Shan Z, Li S, Huang H, Li P, Peng X, Peng Z, Yu K, Bao W, Yang W, Chen X, Liu L. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc* 2017;6(9). <https://doi.org/10.1161/jaha.117.005947>.
- [18] Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep* 2010;33(5):585–92. <https://doi.org/10.1093/sleep/33.5.585>.
- [19] Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *J Sleep Res* 2009;18(2):148–58. <https://doi.org/10.1111/j.1365-2869.2008.00732.x>.
- [20] Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. *Sleep Med* 2017;32:246–56. <https://doi.org/10.1016/j.sleep.2016.08.006>.
- [21] Fatima Y, Doi SAR, Mamun AA. Longitudinal impact of sleep on overweight and obesity in children and adolescents: a systematic review and bias-adjusted meta-analysis. *Obes Rev* 2015;16(2):137–49. <https://doi.org/10.1111/obr.12245>.
- [22] Ruan H, Xun P, Cai W, He K, Tang Q. Habitual sleep duration and risk of childhood obesity: systematic review and dose-response meta-analysis of prospective cohort studies. *Sci Rep* 2015;5(1). <https://doi.org/10.1038/srep16160>.
- [23] Chen X, Beydoun MA, Wang Y. Is sleep duration associated with childhood obesity? A systematic review and meta-analysis. *Obesity* 2008;16(2):265–74. <https://doi.org/10.1038/oby.2007.63>.
- [24] Li L, Zhang S, Huang Y, Chen K. Sleep duration and obesity in children: a systematic review and meta-analysis of prospective cohort studies. *J Paediatr Child Health* 2017;53(4):378–85. <https://doi.org/10.1111/jpc.13434>.
- [25] Miller MA, Kruisbrink M, Wallace J, Ji C, Cappuccio FP. Sleep duration and incidence of obesity in infants, children, and adolescents: a systematic review and meta-analysis of prospective studies. *Sleep* 2018;41(4):1–19. <https://doi.org/10.1093/sleep/zsy018>.
- [26] Cappuccio FP, Cooper D, Delia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011;32(12):1484–92. <https://doi.org/10.1093/euroheartj/ehr007>.
- [27] Krittawong C, Tunhasirivet A, Wang Z, Zhang H, Prokop LJ, Chirapongsathorn S, Aydar M, Sun T, Kitai T. Association between short and long sleep duration and cardiovascular outcomes? A systematic review and meta-analysis. *J Am Coll Cardiol* 2017;69(11):1798. [https://doi.org/10.1016/s0735-1097\(17\)35187-2](https://doi.org/10.1016/s0735-1097(17)35187-2).
- [28] Shan Z, Ma H, Xie M, Yan P, Guo Y, Bao W, Rong Y, Jackson CL, Hu FB, Liu L. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care* 2015;38(3):529–37. <https://doi.org/10.2337/dc14-2073>.
- [29] Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33(2):414–20. <https://doi.org/10.2337/dc09-1124>.
- [30] Upala S, Sanguankeo A, Congrete S, Romphothong K. Sleep duration and insulin resistance in individuals without diabetes mellitus: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2015;109(3). <https://doi.org/10.1016/j.diabres.2015.06.003>.
- [31] Holliday EG, Magee CA, Krisharides L, Banks E, Attia J, Arias-Carrion O. Short sleep duration is associated with risk of future diabetes but not cardiovascular disease: a prospective study and meta-analysis. *PLoS ONE* 2013;8(11). <https://doi.org/10.1371/journal.pone.0082305>.
- [32] Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. *Sleep Med Rev* 2016;30:11–24. <https://doi.org/10.1016/j.smrv.2015.10.002>.
- [33] Locard E, Mamelle N, Billette A, Miginac M, Munoz F, Rey S. Risk factors of obesity in a five year old population. Parental versus environmental factors. *Int J Obes* 1992;16(10):721–9.
- [34] von Kries R, Toschke AM, Wurmser H, Sauerwald T, Koletzko B. Reduced risk for overweight and obesity in 5- and 6-y-old children by duration of sleep—a cross-sectional study. *Int J Obes* 2002;26(5):710–6. <https://doi.org/10.1038/sj.ijo.0801980>.
- [35] Sekine M, Yamagami T, Handa K, Saito T, Nanri S, Kawaminami K, Tokui N, Yoshida K, Kagamimori S. A dose-response relationship between short sleeping hours and childhood obesity: results of the Toyama Birth Cohort Study. *Child Care Health Dev* 2002;28(2):163–70. <https://doi.org/10.1046/j.1365-2214.2002.00260.x>.

- [36] Cao M, Zhu Y, He B, Yang W, Chen Y, Ma J, Jin J. Association between sleep duration and obesity is age- and gender-dependent in Chinese urban children aged 6–18 years: a cross-sectional study. *BMC Public Health* 2015;1471–2458(1):15. <https://doi.org/10.1186/s12889-015-2359-0>.
- [37] Ozturk A, Mazcioglu MM, Poyrazoglu S, Cicek B, Gunay O, Kurtoglu S. The relationship between sleep duration and obesity in Turkish children and adolescents. *Acta Paediatr* 2009;98(4):699–702. <https://doi.org/10.1111/j.1651-2227.2008.01169.x>.
- [38] Bell JF, Zimmerman FJ. Shortened nighttime sleep duration in early life and subsequent childhood obesity. *Arch Pediatr Adolesc Med* 2010;164(9):840–5. <https://doi.org/10.1001/archpediatrics.2010.143>.
- [39] Shi Z, Taylor AW, Gill TK, Tuckerman J, Adams R, Martin J. Short sleep duration and obesity among Australian children. *BMC Public Health* 2010;10. <https://doi.org/10.1186/1471-2458-10-609>.
- [40] Carter PJ, Taylor BJ, Williams SM, Taylor RW. Longitudinal analysis of sleep in relation to BMI and body fat in children: the FLAME study. *BMJ* 2011;(7809):342. <https://doi.org/10.1136/bmj.d2712>. <http://www.bmjjournals.org/content/342/bmj.d2712.full.pdf>.
- [41] Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, Steer C, Sherriff A. Early life risk factors for obesity in childhood: cohort study. *BMJ* 2005;330(7504):1357–9. <https://doi.org/10.1136/bmj.38470.670903.E0>.
- [42] Arora T, Taheri S. Associations among late chronotype, body mass index and dietary behaviors in young adolescents. *Int J Obes* 2015;39(1):39–44. <https://doi.org/10.1038/ijo.2014.157>.
- [43] Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, Malow BA, Maski K, Nichols C, Quan SF, Rosen CL, Troester MM, Wise MS. Consensus statement of the American Academy of sleep medicine on the recommended amount of sleep for healthy children: methodology and discussion. *J Clin Sleep Med* 2016;12(11):1549–61. <https://doi.org/10.5664/jcsm.6288>.
- [44] Kim SJ, Lee YJ, Cho SJ, Cho IH, Lim W, Lim W. Relationship between weekend catch-up sleep and poor performance on attention tasks in Korean adolescents. *Arch Pediatr Adolesc Med* 2011;165(9):806–12. <https://doi.org/10.1001/archpediatrics.2011.128>.
- [45] Kang SG, Lee YJ, Kim SJ, Lim W, Lee HJ, Park YM, Cho IH, Cho SJ, Hong JP. Weekend catch-up sleep is independently associated with suicide attempts and self-injury in Korean adolescents. *Compr Psychiatry* 2014;55(2):319–25. <https://doi.org/10.1016/j.comppsych.2013.08.023>.
- [46] Nicholson LM, Egbert AH, Moreno JP, Bohnert AM. Variability of sleep and relations to body weight among first-year college students. *Int J Behav Med* 2021;28(2):227–37. <https://doi.org/10.1007/s12529-020-09888-3>.
- [47] Lee S, Castro N, Signal L, Skidmore P, Faulkner J, Lark S, Williams MA, Muller D, Harrex H. Sleep and adiposity in preadolescent children: the importance of social jetlag. *Child Obes* 2018;14(3):158–64. <https://doi.org/10.1089/chi.2017.0272>.
- [48] Liang F, Fu J, Xu Y, Wang Y, Qiu N, Ding K, Zeng J, Moore JB, Li R. Associations of social jetlag with dietary behavior, physical activity and obesity among Chinese adolescents. *Nutrients* 2022;14(3):510. <https://doi.org/10.3390/nu14030510>.
- [49] He F, Bixler EO, Berg A, Imamura Kawasawa Y, Vgontzas AN, Fernandez-Mendoza J, Yanosky J, Liao D. Habitual sleep variability, not sleep duration, is associated with caloric intake in adolescents. *Sleep Med* 2015;16(7):856–61. <https://doi.org/10.1016/j.sleep.2015.03.004>.
- [50] He F, Bixler EO, Liao J, Berg A, Imamura Kawasawa Y, Fernandez-Mendoza J, Vgontzas AN, Liao D. Habitual sleep variability, mediated by nutrition intake, is associated with abdominal obesity in adolescents. *Sleep Med* 2015;16(12):1489–94. <https://doi.org/10.1016/j.sleep.2015.07.028>.
- [51] Xiu L, Ekstedt M, Hagström M, Bruni O, Bergqvist-Norén L, Marcus C. Sleep and adiposity in children from 2 to 6 years of age. *Pediatrics* 2020;145(3). <https://doi.org/10.1542/peds.2019-1420>.
- [52] Capers PL, Fobian AD, Kaiser KA, Borah R, Allison DB. A systematic review and meta-analysis of randomized controlled trials of the impact of sleep duration on adiposity and components of energy balance. *Obes Rev* 2015;16(9):771–82. <https://doi.org/10.1111/obr.12296>. <http://onlinelibrary.wiley.com/journal/10.1111/ISSN1467-789X>.
- [53] Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004;141(11):846–50. <http://annals.org/issues.aspx>. doi: 10.7326/0003-4819-141-11-200412070-00008.
- [54] Hart CN, Carskadon MA, Considine RV, Fava JL, Lawton J, Raynor HA, Jelalian E, Owens J, Wing R. Changes in Children's sleep duration on food intake, weight, and leptin. *Pediatrics* 2013;132(6):e1473. <https://doi.org/10.1542/peds.2013-1274>.
- [55] Hagen EW, Starke SJ, Peppard PE. The association between sleep duration and leptin, ghrelin, and Adiponectin among children and adolescents. *Curr Sleep Med Rep* 2015;1(4):185–94. <https://doi.org/10.1007/s40675-015-0025-9>.
- [56] Spaeth AM, Hawley NL, Raynor HA, Jelalian E, Greer A, Crouter SE, Coffman DL, Carskadon MA, Owens JA, Wing RR, Hart CN. Sleep, energy balance, and meal timing in school-aged children. *Sleep Med* 2019;60:139–44. <https://doi.org/10.1016/j.sleep.2019.02.003>.
- [57] Simon SL, Field J, Miller LE, DiFrancesco M, Beebe DW, Mistlberger RE. Sweet/dessert foods are more appealing to adolescents after sleep restriction. *PLOS ONE* 2015;10(2). <https://doi.org/10.1371/journal.pone.0115434>.
- [58] Jensen CD, Duraccio KM, Barnett KA, Carbine KA, Stevens KS, Muncy NM, Kirwan CB. Sleep duration differentially affects brain activation in response to food images in adolescents with overweight/obesity compared to adolescents with normal weight. *Sleep* 2019;42(4). <https://doi.org/10.1093/sleep/zsz001>. [www.journalsleep.org](http://journalsleep.org).
- [59] Duraccio KM, Zaugg K, Jensen CD. Effects of sleep restriction on food-related inhibitory control and reward in adolescents. *J Pediatr Psychol* 2019;44(6):692–702. <https://doi.org/10.1093/jpepsy/jzs008>.
- [60] Duraccio KM, Krietsch KN, Zhang N, Whitacre C, Howarth T, Pfeiffer M, Beebe DW. The impact of short sleep on food reward processes in adolescents. *J Sleep Res* 2021;30(2). <https://doi.org/10.1111/jsr.13054>. <http://onlinelibrary.wiley.com/journal/10.1111/ISSN1365-2869>.
- [61] DiFrancesco MW, Alsameen M, St-Onge M-P, Duraccio KM, Beebe DW. Altered neuronal response to visual food stimuli in adolescents undergoing chronic sleep restriction. *Sleep* 2023;0161–8105. <https://doi.org/10.1093/sleep/zsad036>.
- [62] Arora T, Taheri S. Is sleep education an effective tool for sleep improvement and minimizing metabolic disturbance and obesity in adolescents? *Sleep Med Rev* 2017;36:3–12. <https://doi.org/10.1016/j.smrv.2016.08.004>.

- [63] Dutil C, Chaput JP. Inadequate sleep as a contributor to type 2 diabetes in children and adolescents. *Nutr Diabetes* 2017;7(5). <https://doi.org/10.1038/nutd.2017.19>. <http://www.nature.com/nutd/index.html>.
- [64] Reinehr T. Type 2 diabetes mellitus in children and adolescents. *World J Diabetes* 2013;4(6):270. <https://doi.org/10.4239/wjd.v4.i6.270>.
- [65] Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ, Pihoker C, Saydah S, Wagenknecht L. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. *N Engl J Med* 2017;376(15):1419-29. <https://doi.org/10.1056/NEJMoa1610187>. <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1610187>.
- [66] Hillier TA, Pedula KL. Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. *Diabetes Care* 2003;26(11):2999-3005. <https://doi.org/10.2337/diacare.26.11.2999>.
- [67] Eppens MC, Craig ME, Cusumano J, Hing S, Chan AKF, Howard NJ, Silink M, Donaghue KC. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care* 2006;29(6):1300-6. <https://doi.org/10.2337/dc05-2470Netherlands>.
- [68] Naughton MJ, Ruggiero AM, Lawrence JM, Imperatore G, Klingensmith GJ, Waitzfelder B, McKeown RE, Standiford DA, Liese AD, Loots B. Health-related quality of life of children and adolescents with type 1 or type 2 diabetes mellitus: SEARCH for Diabetes in Youth Study. *Arch Pediatr Adolesc Med* 2008;162(7):649-57. <https://doi.org/10.1001/archpedi.162.7.649>.
- [69] Levitt Katz LE, Swami S, Abraham M, Murphy KM, Jawad AF, McKnight-Menci H, Berkowitz R. Neuropsychiatric disorders at the presentation of type 2 diabetes mellitus in children. *Pediatr Diabetes* 2005;6(2):84-9. <https://doi.org/10.1111/j.1399-543X.2005.00105.x>.
- [70] Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hamäläinen H, Ianne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344(18):1343-50. <https://doi.org/10.1056/NEJM200105033441801>.
- [71] Aldabal L, Bahamman AS. Metabolic, endocrine, and immune consequences of sleep deprivation. *Open Respir Med J* 2011;5(1):31-43. <https://doi.org/10.2174/1874306401105010031>.
- [72] Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. *Annu Rev Psychol* 2015;66:143-72. <http://arjournals.annualreviews.org/loi/psych>. doi: 10.1146/annurev-psych-010213-115205.
- [73] Kotronoulas G, Stamatakis A, Stylianopoulou F. Hormones, hormonal agents, and neuropeptides involved in the neuroendocrine regulation of sleep in humans. *Hormones (Basel)* 2009;8(4):232-48. <https://doi.org/10.14310/horm.2002.1239>.
- [74] Lee SWH, Ng KY, Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: a systematic review and meta-analysis. *Sleep Med Rev* 2017;31:91-101. <https://doi.org/10.1016/j.smrv.2016.02.001>.
- [75] Gozal D, Dumin M, Koren D. Role of sleep quality in the metabolic syndrome. *Diabetes, Metab Syndrome Obes Targets Ther* 2016;9:281-310. <https://doi.org/10.2147/DMSO.S95120>.
- [76] Keckeis M, Lattova Z, Maurovich-Horvat E, Beiting PA, Birkmann S, Lauer CJ, Wetter TC, Wilde-Frenz J, Pollmächer T, Finkelstein D. Impaired glucose tolerance in sleep disorders. *PLoS One* 2010;5(3). <https://doi.org/10.1371/journal.pone.0009444>.
- [77] Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM, Javier Nieto F. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med* 2005;165(8):863-8. <https://doi.org/10.1001/archinte.165.8.863>.
- [78] Nakamura Y, Katano N, Murakami Y, Tanaka T, Takebayashi T, Okayama A, Miura K, Okamura T, Ueshima H. Relationship between sleep duration and clustering of metabolic syndrome diagnostic components. *Diabetes, Metab Syndrome Obes Targets Ther* 2011;119. <https://doi.org/10.2147/DMSO.S16147>.
- [79] Sivak M. Sleeping more as a way to lose weight. *Obes Rev* 2006;7(3):295-6. <https://doi.org/10.1111/j.1467-789x.2006.00262.x>.
- [80] Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354(9188):1435-9. [https://doi.org/10.1016/s0140-6736\(99\)01376-8](https://doi.org/10.1016/s0140-6736(99)01376-8).
- [81] Leproult R, Holmbäck U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes* 2014;63(6):1860-9. <https://doi.org/10.2337/db13-1546>.
- [82] Denise Robertson M, Russell-Jones D, Margot Umpleby A, Dijk D-J. Effects of three weeks of mild sleep restriction implemented in the home environment on multiple metabolic and endocrine markers in healthy young men. *Metabolism* 2013;62(2):204-11. <https://doi.org/10.1016/j.metabol.2012.07.016>.
- [83] Koren D, Katz LEL, Brar PC, Gallagher PR, Berkowitz RI, Brooks LJ. Sleep architecture and glucose and insulin homeostasis in obese adolescents. *Diabetes Care* 2011;34(11):2442-7. <https://doi.org/10.2337/dc11-1093>.
- [84] Armitage R, Lee J, Bertram H, Hoffmann R. A preliminary study of slow-wave EEG activity and insulin sensitivity in adolescents. *Sleep Med* 2013;14(3):257-60. <https://doi.org/10.1016/j.sleep.2012.11.012>.
- [85] Zhu Y, Fenik P, Zhan G, Xin R, Veasey SC. Degeneration in arousal neurons in chronic sleep disruption modeling sleep apnea. *Front Neurol* 2015;6. <https://doi.org/10.3389/fneur.2015.00109>. <http://journal.frontiersin.org/article/10.3389/fneur.2015.00109/full>.
- [86] Hawkins SS, Takeuchi DT. Social determinants of inadequate sleep in US children and adolescents. *Public Health* 2016;138:119-26. <https://doi.org/10.1016/j.puhe.2016.03.036>.
- [87] Leger D, Beck F, Richard J-B, Godeau E, Goel N. Total sleep time severely drops during adolescence. *PLoS One* 2012;7(10). <https://doi.org/10.1371/journal.pone.0045204>.
- [88] Fazeli Farsani S, Van Der Aa MP, Van Der Vorst MMJ, Knibbe CAJ, De Boer A. Global trends in the incidence and prevalence of type 2 diabetes in children and adolescents: a systematic review and evaluation of methodological approaches. *Diabetologia* 2013;56(7):1471-88. <https://doi.org/10.1007/s00125-013-2915-z>.
- [89] Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, Liese AD, Merchant AT, Lawrence JM, Reynolds K, Dolan L, Liu LL, Hamman RF. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA* 2014;311(17):1778-86. <https://doi.org/10.1001/jama.2014.3201>.
- [90] Spruyt K, Molfese DL, Gozal D. Sleep duration, sleep regularity, body weight, and metabolic homeostasis in school-aged children. *Pediatrics* 2011;127(2). <https://doi.org/10.1542/peds.2010-0497>.
- [91] D'Adamo E, Caprio S. Type 2 diabetes in youth: epidemiology and pathophysiology. *Diabetes Care* 2011;34(Suppl. ment_2). <https://doi.org/10.2337/dc11-s212>.
- [92] Flint J, Kothare SV, Zihlif M, Suarez E, Adams R, Legido A, De Luca F. Association between inadequate sleep and insulin resistance

- in obese children. *J Pediatr* 2007;150(4):364–9. <https://doi.org/10.1016/j.jpeds.2006.08.063>.
- [93] Rudnicka AR, Nightingale CM, Donin AS, Sattar N, Cook DG, Whincup PH, Owen CG. Sleep duration and risk of type 2 diabetes. *Pediatrics* 2017;140(3). <https://doi.org/10.1542/peds.2017-0338>.
- [94] Pulido-Arjona L, Correa-Bautista JE, Agostinis-Sobrinho C, Mota J, Santos R, Correa-Rodríguez M, García-Hermoso A, Ramírez-Vélez R. Role of sleep duration and sleep-related problems in the metabolic syndrome among children and adolescents. *J Pediatr* 2018;144(1). <https://doi.org/10.1186/s13052-018-0451-7>.
- [95] Schmid SM, Hallschmid M, Jauch-Chara K, Born J, Schultes B. A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. *J Sleep Res* 2008;17(3):331–4. <https://doi.org/10.1111/j.1365-2869.2008.00662.x>.
- [96] Kelly NR, Shomaker LB, Radin RM, Thompson KA, Cassidy OL, Brady S, Mehari R, Courville AB, Chen KY, Galescu OA, Tanofsky-Kraff M, Yanovski JA. Associations of sleep duration and quality with disinhibited eating behaviors in adolescent girls at-risk for type 2 diabetes. *Eat Behav* 2016;22:149–55. <https://doi.org/10.1016/j.eatbeh.2016.06.019>. <http://www.elsevier.com/locate/eatbeh>.
- [97] Plat L, Byrne MM, Sturis J, Polonsky KS, Mockel J, Fery F, Van Cauter E. Effects of morning cortisol elevation on insulin secretion and glucose regulation in humans. *Am J Physiol Endocrinol Metab* 1996;270(1):E36. <https://doi.org/10.1152/ajpendo.1996.270.1.e36>.
- [98] Klingenbergs L, Chaput JP, Holmbadck U, Visby T, Jennum P, Nikolic M, Astrup A, Sjödin A. Acute sleep restriction reduces insulin sensitivity in adolescent boys. *Sleep* 2013;36(7):1085–90. <https://doi.org/10.5665/sleep.2816Denmark>.

Further readings

- [1] Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *J Appl Physiol* 2005;99(5):2008–19. <https://doi.org/10.1152/japplphysiol.00660.2005>.
- [2] Javaheri S, Caref EB, Chen E, Tong KB, Abraham WT. Sleep apnea testing and outcomes in a large cohort of medicare beneficiaries with newly diagnosed heart failure. *Am J Respir Crit Care Med* 2011;183(4):539–46. <https://doi.org/10.1164/rccm.201003-0406OC>.
- [3] Shaw ND, McHill AW, Schiavon M, Kangaroo T, Mankowski PW, Cobelli C, Klerman EB, Hall JE. Effect of slow wave sleep disruption on metabolic parameters in adolescents. *Sleep* 2016;39(8):1591–9. <https://doi.org/10.5665/sleep.6028>. <http://www.journalsleep.org/ViewAbstract.aspx?pid=30733>.
- [4] Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. *N Engl J Med* 1986;315(4):215–9. <https://doi.org/10.1056/NEJM198607243150402>.

This page intentionally left blank

Chapter 39

Sleep and mental health in children and adolescents

Michelle A. Short^a, Kate Bartel^a and Mary A. Carskadon^b

^aSchool of Psychology, Flinders University, Adelaide, SA, Australia; ^bE.P. Bradley Hospital, Brown University, Providence, RI, United States

Introduction

Mental illness poses one of the largest disease burdens of all conditions [1]. While the burden of diseases is felt most acutely among older adults, such psychiatry illnesses as depression and anxiety are prevalent across much of the human lifespan. Indeed, late childhood and adolescence are important developmental periods in terms of mental health, with a notable acceleration of the incidence of mood disorders, anxiety disorders, eating disorders, and psychosis occurring during this time [2]. Furthermore, these illnesses are frequently chronic and recurrent, and earlier age of onset is associated with a more severe and unremitting course, substantial impairments to educational and social functioning, and reduced quality of life [2]. Anxiety is the most common psychiatric disorder of childhood, affecting between 3.9% and 17.5% of children and adolescents, while depression affects between 2% and 8% [3,4]. Depression and anxiety disorders are frequently comorbid, with anxiety typically preceding depression [2]. Another affliction that often cooccurs with both conditions is sleep problems, including insufficient sleep, trouble falling asleep, and unrefreshing sleep, among others. As many as 90% of children with anxiety and/or depression report problems with their sleep [5]. As reviewed below, strong evidence indicates that sleep causally impacts a range of factors relating to mental health, including mood, emotion dysregulation, depression, anxiety, and suicide [6–8].

The importance of prevention and early intervention for mental health in youth is indisputable. Identifying sleep disturbances as a factor that contributes to deleterious alteration in mood, emotion regulation, and psychopathology is key because sleep is a target amenable to change. The amount of sleep children and adolescents obtain and the quality of sleep affect their mood and mental health [7,9–11]. This chapter focuses on the evidence

linking sleep and mental health with the aim to (a) review and summarize the literature regarding the impact of sleep duration and sleep quality in healthy school-age children and adolescents, and those with depression and anxiety and (b) identify approaches for families, school leaders, clinicians, and policymakers to improve child and adolescent sleep for optimal mental health functioning. It is important to note that this chapter focuses on the spectrum of mental health and not solely on mental illness. This is to acknowledge that mental health occurs on a spectrum that is much broader than simply the presence or absence of a diagnosable mental conditions. Thus, the included literature includes both healthy and clinical populations, and mood outcome measures include positive and negative mood states, emotion regulation, symptoms of depression and anxiety, and diagnoses of depression and anxiety.

Another important distinction to make at the outset is regarding the measures used to characterize sleep, which are varied across studies. Most studies use subjective self- or parent-reports of sleep, which are often included as items within a larger survey. These have the advantage of being time- and cost-effective and can be used for larger, epidemiological studies. The limitations of subjective survey measures of sleep include inaccuracy—especially when the reporter is a parent [12]—and reporting biases. Sleep diaries have widespread clinical use and involve recording sleep patterns each day. While this also relies upon self- or parent report, sleep diaries are not as susceptible to the reporting inaccuracies and biases as survey measures, as the reporting is anchored to the sleep of the previous night. To overcome some of the limitations of subjective reports, objective measures of sleep are also used, often actigraphy (using activity monitors) or polysomnography. Activity monitors are usually worn on the wrist like a wristwatch uses contain an accelerometer to measure movement. Algorithms are then applied to these

movement data to estimate sleep and wake. While this is an objective method, limitations include the reliance of concurrent sleep diaries to identify the time in bed period and any times that the device was not worn. In addition, there have been concerns regarding the accuracy of actigraphic algorithms when used with adolescents [13]. The gold standard of sleep measurement is polysomnography. Polysomnography uses electrodes applied to the scalp to directly measure brain activity and thus identify either wake or stage of sleep. While this method is the most accurate, it is time- and cost-intensive and is not often feasible for many studies. As such, few studies routinely include polysomnography to measure sleep.

Sleep duration and mental health

Much of the research on sleep and mental health has focused on how *much* sleep children and adolescents obtain. The recommended sleep duration in children ages 6–13 years is 9–11 h, while adolescents are recommended to sleep 8–10 h per night [14,15]. Recent studies with mood symptoms as an outcome have estimated that adolescents require between 7.5 and 9.5 h sleep per night for optimal mood [16,17]; however, many—if not most—teens sleep less [18]. A recent metaanalysis pooled data regarding normative sleep estimates from studies that included actigraphic estimates of sleep on school nights. Pooled results showed that most children and adolescents typically obtain sleep below these recommended amounts [19].

Much of the extant research linking sleep and mental health in children is cross-sectional [20–22], with short sleep linked to increased emotional lability [23]. For example, short sleep duration, objectively measured by actigraphy in a sample of 7-year-old children, was associated with heightened emotional reactivity [24]. Similarly, among 8–12-year-old children, shorter sleep durations were associated with heightened affective responses in domains including sadness, anger, fear, and disgust [25]. Of interest, sleep duration was not correlated with positive affective responses [25].

Sleep duration has also been linked to mental health symptomology and disorders such as anxiety and depression [20]. A telephone survey of parents of children aged 6–17 years revealed that as the number of nights per week of inadequate sleep increased, so did *symptoms* of depression. However, depression and anxiety *diagnoses* were not related to the number of nights of inadequate sleep [26]. Another study reported that, according to sleep diary measures, children with anxiety slept less than those without anxiety [27]. Sleep complaints, including insufficient sleep, also appear to feature highly among children with high levels of depression symptoms or a diagnosis of depression [28]. On the contrary, findings about the

association of *objectively* measured sleep to childhood depression are less consistent [20,28].

Experimental studies have shown a causal relation between sleep duration and a wide range of mood outcomes in children and adolescents [6,8,18,25,29–33], though experimental studies involving children are less abundant [21,22]. Nonetheless, these studies provide evidence that children with sufficient sleep experience better mood and are able to regulate their emotions better than those who are sleep restricted [34]. Metaanalytic data from studies of children aged 5–12 years indicate that sleep restriction is related to increased internalizing behavior problems, especially when experimentally shortened for two or more nights [22]. This association was demonstrated by Gruber and colleagues [32], who after a baseline of 5 days of habitual sleep (as measured via actigraphy), assigned 34 children, aged 7–11 years, to either 1 week of 1 h less time in bed per night or 1 week of 1 h more time in bed per night. When sleep was extended (by an average of 27 min per night), teacher ratings of the children's emotional lability decreased, whereas restriction of sleep (by an average of 54 min per night) led to increased teacher-reported emotional lability [32].

Another experimental study investigated the impact of sleep duration on teacher ratings of internalizing symptoms (e.g., anxious/sad affect and emotional lability) in children aged 6–12 years. Three sleep conditions were compared: 1 week of typical sleep (average 9.5 h' time in bed), 1 week of optimized sleep (minimum 10 h' time in bed), and 1 week of restricted sleep (8 h' time in bed for first and second graders; 6.5 h' time in bed for children in third grade or older) [33]. While attention and academic problems were negatively affected by restricting sleep, internalizing symptoms remained similar across the 3 weeks [33].

Vriend and colleagues used a similar experimental protocol to restrict and extend sleep in 32 children aged 8–12 years [25]. In this study reports of emotion regulation were obtained from parents and children, rather than teachers. All children experienced sleep restriction and sleep extension conditions in a counterbalanced order after 1 week of baseline sleep. Sleep period was extended by going to bed 1 h earlier and restricted by going to bed 1 h later, each condition for four consecutive nights; a three-night “washout” period occurred in between conditions [35]. Children slept an average of 74 min longer during the extended sleep condition compared with the short sleep condition. Positive affective in response to positive emotional images and parent-reported emotion regulation decreased following nights of short sleep. By contrast, negative affective response to negatively valenced images and child-reported emotion regulation did not differ between conditions [35].

While these experimental studies including children were all home-based studies, many studies of adolescents

have been laboratory based, thus enabling better adherence to study protocol regarding sleep and avoidance of countermeasures, such as caffeine. Measures of positive and negative affect are often used among adolescent studies. For example, adolescents consistently report feeling reduced positive affect following sleep restriction [18,29,30,36], suggesting that sleep loss diminishes their ability to feel positive affective states such as enthusiasm and excitement. The effects of restricted sleep on negative affect, however, are less consistent, with only one study showing significantly increased negative affect [36]. When considering discrete mood states, results from adolescent total sleep deprivation and chronic sleep restriction paradigms have shown reports of significantly increased anxiety, anger, confusion, and fatigue following sleep loss [6,8].

As well as affecting mood states, sleep loss modifies the ability to regulate mood and emotion. Emotion regulation refers to the ability of an individual to monitor, evaluate, and modulate emotional reactions in a way that helps individuals to achieve goals and function effectively across different contexts [37,38]. One hypothesis as to why emotions are affected by sleep duration proposes that short sleep disrupts the limbic system, which helps maintain emotion regulation [22]. Thus, impaired sleep renders a child vulnerable to emotional instability at a physiological level. This is clinically relevant, as emotion dysregulation is an important transdiagnostic factor that heightens the risk of a wide range of psychopathology outcomes [37]. Sleep loss is also implicated in suicidal ideation and suicide attempts, with one study finding a threefold increased risk of suicide attempt in adolescents who slept less than 8 h per night [22].

Experimental studies have found that adolescents' abilities to regulate their emotions are worsened with sleep loss [8,35,39]. For example, one study exposed adolescents aged 10–16 years to two night of sleep restriction (6.5 h on the first night and 2 h on the second night) and two nights with 7–8 h sleep per night. Conditions were separated by 1 week and the order was counterbalanced [39]. Following each sleep condition, participants completed an affective measurement battery. Adolescents reported increased anxiety during a catastrophizing task and rated the likelihood of potential catastrophes as higher following two night of restricted sleep when compared to when they had longer sleep opportunities. Furthermore, the younger adolescents, aged 10–13 years, found their main worry as more threatening when they were sleep deprived.

While experimental studies have been invaluable in demonstrating a causal relationship between sleep loss and many aspects of mood and emotion regulation, such brief sleep manipulations have not consistently shown direct effects of sleep loss on either depressed mood or anxiety symptoms. For example, although self-reported depressed mood symptoms increased with total sleep deprivation,

sleep restriction in two studies with adolescent participants did not show the same response [6,8]. Among intervention studies, adolescents randomly allocated to sleep extension, as well as adolescents who extended their sleep by 45 min following a delay to school start times, reported significantly fewer depressed mood symptoms [31,40], but not reduced anxiety [41].

While experimental studies have the advantage of experimental control, they often include highly screened, healthy participants without elevated depressed mood or anxiety symptoms, who are exposed to long sleep opportunities prior to sleep restriction, and their sleep is restricted over relatively short periods. Ecologically, children and adolescents typically restrict their sleep over multiple weeks and months during the school term. Thus, short-term in laboratory studies may not be able to capture effects of sleep that may appear only when sleep is chronically restricted over long periods. As a result, longitudinal studies are instrumental to indicating whether chronically restricted sleep is related to subsequent long-term deficits in mood and/or psychopathology and more effective for elucidating relationships between sleep, depression, and anxiety that are difficult to elicit in time-limited experimental studies. This approach often has the advantage of greater ecological validity by including a broader cross-section of participants. Among healthy adolescents, for example, evidence for a longitudinal association between sleep and subsequent depressed mood is reported in most [42,43], but not all [44], studies. One study of 12- to 15-year-old Dutch adolescents found that less time in bed at baseline was associated with greater severity of symptoms of depression/anxiety at follow-up, but not vice-versa [10]. Similarly, a study of 2259 US adolescents aged 12–15 years reported both concurrent and longitudinal associations between short sleep duration and lower self-esteem and higher depressive symptoms [43].

Another approach taken by recent studies is to examine the temporal relationship between sleep duration and next day mood in healthy samples and in adolescents with anxiety and depression disorders [16,45,46]. Fuligni and colleagues [16], for example, collected data on nightly sleep and daily mood over a 2-week period from 419 adolescents in grades 9 and 10. The analysis of nightly sleep and next-day depressed mood and anxiety symptoms determined the duration of sleep required for optimal next-day mood. This optimal sleep duration was estimated at 9.03 h (SD = 0.86) of sleep per night, similar to estimates of sleep need required for optimal daytime alertness and sustained attention [15,47]. The association between sleep duration and mood was U-shaped, with both long and short sleep associated with worse anxiety and depressed mood. These findings may explain why some studies do not find significant linear associations between sleep duration and mood, as nonlinear relationships are not always tested. In

addition, Fuligni and colleagues found that the relation of sleep duration to subsequent mood was not uniform but varied depending on sex and mental health status. Indeed, this study estimated that girls require more sleep than boys for optimal mood, and adolescents experiencing clinically significant internalizing symptoms require more sleep than adolescents below the clinical range [16]. These findings indicate differential vulnerability to the effect of short sleep in some populations and may explain why such associations are stronger in clinical groups compared with healthy controls [45]. A relationship between sleep duration and anxiety and depression symptoms has similarly been found in children and adolescents, aged 5–18 years (M age = 10.5 years), diagnosed with various psychiatric disorders. Among these clinical groups, parent-reported shorter sleep was associated with increased anxiety and depression symptoms [48].

Sleep quality and mental health

Sleep quality refers to a wide range of factors associated with the ease or difficulties with initiation and maintenance of sleep, as well as how subjectively refreshing or satisfying sleep is to the individual. A number of studies show that sleep quality and mental health are related, with longer sleep onset latencies, more frequent awakenings during the night, longer time spent awake after sleep onset, greater sleep disturbances, and poor subjective sleep quality predicting worse mood, poorer emotion regulation, and increased likelihood of mood disorders [9,49–51]. Sleep complaints pertaining to the quality of sleep are also common in children with anxiety, including difficulty falling asleep or staying asleep, refusing to go to bed, nightmares, and nighttime fears [52]. Similar to studies assessing sleep duration and mental health in children, those examining sleep quality are often cross-sectional [22].

Poor sleep quality has been shown to have a deleterious effect on mood beyond the effect that sleep quality variables may have on sleep duration [53]. Indeed, sleep quality shows unique associations with mental health functioning independent of sleep duration [54,55]. For example, in a cross-sectional study of nearly 100,000 Japanese high school students, results indicated that difficulty falling asleep, difficulty staying asleep, and subjective sleep quality showed dose-dependent relationships to mental health status, with worse sleep predicting worse mental health [50]. A review of 10–13-year-old children regarding sleep and anxiety demonstrated that subjective sleep complaints were common among children with anxiety, especially when parent report was used [27,56]. Furthermore, based on self and parent report, children who reported sleeping difficulties were more likely to have a diagnosis of anxiety than children who did not report trouble sleeping. Moreover, sleep issues are more likely to

persist as the child ages in those who experience anxiety [27]. Conversely, a recent metaanalysis found that decreased sleep efficiency was not associated with internalizing behavior problems [22].

Regarding specific components of sleep quality, children who experience anxiety may exhibit longer sleep latency. However, literature is inconsistent, as when objective measures of sleep are employed (actigraphy or polysomnography), some studies demonstrate this difference, whereas others find no difference between anxious children and controls [27,56,57]. Anxious children may have less slow-wave sleep and more nightly awakenings than those with depression or no psychiatric diagnoses [28]. The type of anxiety disorder may also relate to the sleep issue, with increased sleep latency, as measured by polysomnography, among children with general anxiety compared with those without any diagnosis. Furthermore, nightmares may be exhibited more frequently among children with separation anxiety [28].

Regarding sleep efficiency, data from a week's actigraphy measurements were not correlated with positive or negative affect [25]. In fact, anxious children may have higher objective sleep efficiency than controls [27]. Of note, when sleep is experimentally restricted, thus decreasing sleep fragmentation (i.e., improving sleep quality), the effects of shorted sleep are still evident—that is, despite improved sleep quality, emotional lability increased during a period of sleep restriction [32].

Overall, it appears that subjective sleep complaints are high among anxious children, yet objective sleep difficulties show less consistent evidence [56,57]. In part, the study's environment may play a role in different findings. That is, a comfortable home environment may facilitate sleep, compared with a novel laboratory environment exacerbating sleep issues in anxious children [27]. Moreover, some laboratory studies may not capture the home sleep environment, which enables difference in sleep patterns. For example, room sharing and changing beds during the night may occur at home in both anxious and nonanxious children, yet, these behaviors are not practiced in a laboratory [56].

Associations between aspects of sleep quality and mental health are also borne out longitudinally. Longitudinal studies demonstrate that sleep issues in childhood predict later anxiety and depression, in most, but not all studies [20]. In one study of 5-year-old children, sleep was measured at the age of 5 years using polysomnography and internalizing problems were measured 1 year later. Results showed that children who had poor sleep quality (indicated by sleep latency, sleep period time, and number of awakenings after sleep onset), reported more internalizing problems in their child 1 year later, when compared to parents of children with good/normal baseline sleep [58].

Longitudinal studies also indicate that sleep disturbances in early childhood increase the likelihood of

development of anxiety in adolescence and adulthood [28]. Stronger evidence suggests that sleep issues precede anxiety, however, the inverse relationship may also hold true [28,59]. That is, sleep issues and emotional disturbances are interrelated, and may predispose a child to future anxiety. It is likely that sleep and emotional functioning hold a bi-directional relationship, thus those with poor sleep are more likely to exhibit symptoms of anxiety and depression, and vice-versa, with each issue exacerbating the other [27,59,60]. More research employing objective measures is needed to clarify the strength and direction of associations [59]. When examining bidirectional relationships between sleep quality and anxiety disorders, one review found support for the role of sleep problems predicting anxiety disorders, but limited support for the role of anxiety as a predictor of sleep problems [11]. For example, Gregory and O'Connor assessed sleep problems and behavioral/emotional problems in a sample of 490 young people, assessed at age 4 years and again at mid-adolescence [9]. Sleep problems at age 4 predicted more attention problems, aggression, and depression/anxiety during mid-adolescence. Of note, the reverse relationship was not supported, as behavioral/emotional problems in early childhood did not predict sleep problems during adolescence. The authors also found that the concurrent association between sleep problems and anxiety/depression grew significantly stronger across this developmental period, increasing from $r = 0.39$ at 4 years to $r = 0.52$ during mid-adolescence [9]. This may be due to the greater prevalence of sleep problems among 4-year-olds, with sleep problem scores decreasing by approximately 50% between early childhood and mid-adolescence. As sleep problems are highly prevalent in young children, the presence of sleep problems may be less sensitive as a predictor of mental health in the very young.

In a study of 516 Japanese adolescents, Kaneita and colleagues assessed sleep and mental health at age 13 years and again after 2 years [51]. Concurrent with the reduction in sleep quality over this time was a reduction in mental health status. A new onset of poor sleep quality and chronically poor sleep quality both significantly predicted the development of poor mental health. Similar findings were reported from a longitudinal study of 3134 US adolescents, aged 11–18 years, who were assessed at baseline and approximately 1 year later [61]. Poor quality sleep was highly prevalent, with 60% experiencing nonrestorative sleep, 17% reporting difficulty falling asleep, and 12% waking frequently during the night either often or almost every day. After controlling for covariates, there was a dose-response relationship between insomnia symptoms at time 1 and depression at time 2. Specifically, greater insomnia symptom severity at baseline predicted worse mental health 1 year later [61].

One limitation in this literature is the reliance upon subjective self-report measures of sleep and mood. These associations may be inflated due to rater biases, whereby an adolescent who reports poor sleep may be more likely to report poor mood and vice versa. Objective measures of sleep are needed to mitigate against this and to determine whether subjectively short or poor-quality sleep is paralleled by objectively short or poor-quality sleep, or alternatively, whether youth with poorer mental health misperceive their sleep as being worse than it objectively is. Among the limited literature that has examined sleep and mental health using polysomnography, one study assessed objective sleep over two consecutive nights in youth aged 7–17 years with either anxiety disorders ($N = 24$), major depressive disorder without comorbid anxiety disorders ($N = 128$), or no history of psychiatric disorder ($N = 101$) [62]. Youth with anxiety disorders took longer to fall asleep on the second night than controls or youth with depression (longer sleep onset latencies are common on the first night of polysomnography, however, this typically resolves on subsequent nights among most individuals), and they experienced more awakenings than the depressed group [62]. Overall, it appears that sleep disturbances are related to childhood anxiety, possibly in a reciprocal fashion [63]. Similarly, children who experience depression symptoms to a large extent also experience sleep disturbances, such as insomnia [20,28]. However, this association is likely to be stronger in adolescents and adults [20,63].

A similar pattern of results was reported in a recent metaanalysis examining bidirectional relationships between sleep and adolescent depression. Specifically, they found that adolescents with depression took longer to fall asleep, had more frequent and longer awakenings during the night, had objectively lighter sleep (more stage 1 sleep), and reported worse sleep quality [7]. When examining prospective relationships over time, poor sleep quality was a predictor of subsequent major depression and suicide attempts, but not vice versa [7]. Among the various subjective and objective sleep predictors of concurrent and future depression, those variables associated with wakefulness in bed were most consistent in predicting depression. The authors propose a model of the relationship between sleep disturbances and depression. They suggest that increased time spent awake in bed due to long sleep onset latencies and wake periods during the night, coupled with poor subjective sleep quality leads to increased nighttime rumination, where adolescents lie in quiet wakefulness in bed and engage in negative repetitive thoughts focused on the symptoms, causes and consequences of their distress. This focus may be on their distress about their sleep, as is commonly witnessed among individuals with insomnia, or it may be about more general factors, such as relationships with others, issues related to school, mood, and tiredness [64]. This model is supported by research showing that such negative thoughts are associated

with poor sleep quality in both healthy adolescents, sleep-disordered adolescents, and children and adolescents with mood disorders [64–66]. Taken together, these findings highlight that the presence of sleep problems during adolescence is a “red flag” that teens are at heightened risk of psychopathology [36].

Improving sleep and mental health in children and adolescents

While insufficient and poor-quality sleep are extremely common among children and adolescents, the opportunities for change are many. Given the contribution of sleep to mental health, simple interventions to target sleep are likely to have broad beneficial impacts on how they experience and regulate mood and emotion, as well as the likelihood of developing mood and/or anxiety disorders. Bronfenbrenner’s ecological systems theory [67] posits that children’s development occurs in the context of several interacting ecosystems that include the self, the family, peers, school, community, and public policy. The sleep of children and adolescents is nested among, and impacted by, these different ecological systems. Thus, suggestions and strategies on how to improve sleep in children and adolescents are provided across four levels: families, schools, clinicians, and public policymakers.

Families

There are many ways that families can support better sleep. Limiting technology use, especially in the hour before bed, and removing access to technology overnight, helps to limit exposure to blue light, and allows the opportunity for sleep that is not broken by incoming calls and/or messages [68,69]. Reducing evening light and limiting or eliminating caffeine can help to ensure that children and adolescents are not being unnecessarily alerted by these exogenous alerting factors [69]. Exercising during the daytime can help children and adolescents to get to sleep faster and have more consolidated and refreshing sleep [70], as can maintaining a comfortable sleeping environment that is dark, cool, and quiet [69].

While adolescents can implement some of these behavioral changes, family involvement to implement, support, and model positive sleep habits to children and adolescents is beneficial [71,72]. Across the pediatric age range, families have an important role in supporting or harming sleep health. For example, setting limits around bedtime is associated with better sleep, better daytime functioning, and less depression and suicidal ideation [69,72,73]. Despite the numerous benefits to regulated bedtimes, research indicates that, even though many parents set limits around the bedtimes of their young children,

they relinquish limit-setting at a very early age [72,74]. A study of North American children and adolescents found that less than one in five children have a parent-set bed time at age 10 years, while less than 1 in 20 had a parent-set bedtime at age 13 [74]. Of note, however, this developmental shift did not reflect less parental involvement in regulating sleep patterns, overall. Rather, the focus of parental involvement shifted, with the reduction in parent-set bedtimes associated with a concurrent increase in the proportion of parents waking their children up for school in the morning [74].

While a small proportion of children and adolescents have a parent-set bedtime on school nights, this is largely not maintained across weekends. Thus, in older children and adolescents, even less regulation of bedtimes on weekends, coupled with sleep debt accrued across the school week and a delayed body clock, result in a pattern of even later bedtimes on weekends and wake times. Regular bedtimes and wake times across school nights and weekends are important for good sleep and for entrainment of circadian rhythms, or the body clock [75]. Children and adolescents who obtain sufficient sleep across the school week do not show the same pattern of “sleeping in” on weekends [76]. This catch-up sleep extends weekend wake time until later in the morning, or, for some, even into the afternoon. This pattern makes it very difficult for children and adolescents to then fit back into a healthy sleep pattern for school, as their body clocks are shifted later with this weekend catch-up sleep [75]. Maintaining a regular sleep pattern that allows for sufficient sleep across the week avoids these problems.

In addition to sleep-focused behaviors, general environmental factors impact sleep among families. As sleep requires the individual to disengage vigilance to the outside environment, it is important for children and adolescents to feel secure and safe at bedtime. Families can support sleep by maintaining a warm, supportive, and predictable family environment [71,77]. One study of adolescents found that adolescents who self-reported their families as being more disorganized had worse sleep hygiene, took longer to fall asleep, obtained less sleep, and were more sleepy during the day [71]. Conversely, among younger children, increased parental warmth was associated with more sleep [77]. These findings highlight the invaluable role of families in providing a home environment and family culture that supports good sleep.

Schools

Where schools are able to determine their start time, ensuring that the school day does not start before 8:30 a.m. is likely to have wide-ranging benefits to students in terms of enabling them to obtain more sleep, maintain alertness during the day, perform better in the classroom, have fewer

motor vehicle accidents, and have improved mood and less psychopathology [40,77,78]. A cross-cultural comparison between US adolescents, whose school days began at approximately 7:45 a.m., and Australian adolescents, whose school days started around 8:30 a.m., found that Australian adolescents obtained an average of 47 min more sleep per night sleep [79]. While several factors predicted this cross-cultural difference, the largest predictor was school start time. The American Medical Association and the American Academy of Pediatrics both recommend that schools start no earlier than 8:30 a.m. [80]. The RAND Corporation estimated that if all US schools were to delay school start time until 8:30 a.m., this would add \$US83 billion to the economy over the next decade due to higher high school graduation rates and thus better jobs, fewer costs associated with sleep-related car crashes, reduced obesity, and improved mental health [78].

While school start times receive most public attention, any school-related activities that require children and adolescents to wake earlier or stay up later can impinge on their ability to obtain sufficient sleep. Resultingly, school sport and school activities should not be scheduled before 8:30 a.m. Similarly, high academic workloads with large homework volumes and/or attending night school, and high levels of academic pressure can push bedtimes later and negatively impact sleep and mental health [77,81]. Thus, schools are urged to consider their policies regarding homework, and to question the assumption that homework *quantity* is important for academic achievement. Indeed, recent Programme for International Student Assessment results show that, while many of the countries ranked highest in academic performance are countries in which students start school early and have high academic workloads, such as Singapore, Japan, and Taiwan, countries like Finland, who consistently rank among the top academically performing countries, provide evidence that early start times and high volumes of homework are not necessary for academic success. Finnish schools do not start early, their students do not typically attend night school, nor do they have large homework volumes, yet their students rank among the highest in the world when it comes to academic achievement. Most tellingly, students from high-achieving countries with early start times and high academic workloads reported among the highest levels of school-work related anxiety, while Finnish students reported very low levels of school-work related anxiety [81]. Thus, high volumes of homework and night school are not necessary for high academic achievement and may come at a high cost to the children in those systems.

Clinicians

Clinicians can work with children and families to improve both sleep and mental health. It is imperative that basic

screening for sleep and mental health problems is routinely implemented. If children and adolescents are identified as having a sleep problem, the type of treatment used to improve sleep will depend largely on the sleep issue. Pharmacological interventions are not recommended as a first treatment approach [82], and are thus not reviewed here. Clinically, it is important to first assess the sleep issue. As well as a clinical interview, one means by which to do this is through a sleep diary, kept for at least 1 week [82]. Objective sleep measures, such as actigraphy, are desirable, but not always feasible [82,83]. Review of both the clinical interview and sleep diary allows definition of the sleep issue (e.g., whether issues falling asleep are due to insomnia or a circadian phase delay) and the goals the client wishes to achieve, both of which inform treatment. Regardless of the specific treatment chosen, psychoeducation for the parent and child regarding sleep is valuable [82,84]. Psychoeducation typically includes information about developmentally appropriate sleep duration recommendations, sleep hygiene, sleep pressure, sleep architecture, circadian rhythms, and the effects of light and darkness on the circadian rhythm.

Children benefit from sleep hygiene techniques, such as a consistent bedtime routine, and a safe, comfortable sleep environment [83]. Children who have difficulty initiating or maintaining sleep, and negative daytime consequences, in the absence of medical conditions, may have insomnia [82]. As well as good sleep hygiene, insomnia interventions may involve further behavioral treatment, such as cognitive behavior therapy. Both night awakenings and sleep efficiency are improved through behavioral interventions [84]. Adjusting a child's bedtime to a later time, to facilitate faster sleep initiation, may also be used. Once the child has associated bedtime with falling asleep, the bedtime is then moved earlier [82]. A list of resources for clinicians treating childhood insomnia can be found here [82] and here [85].

Concerning adolescents, there are two main psychological therapies which are implemented, again depending on the sleep disorder [82]. The first, bright light therapy, focuses on shifting the body clock of adolescents who have a delayed circadian rhythm. The adolescent is exposed to bright light for 30 min each morning, starting at the adolescent desired waking time, that is, the time at which they would naturally wake up if they did not have to go to school. The timing of this light exposure is then shifted earlier by 30 min each day until the adolescent is waking at their desired time. Appropriately timed morning bright light is prescribed in the morning, and dim light is used in the evening, to shift the circadian rhythm. As the light advances each day, so too does the circadian phase [86,87].

The other treatment widely used among adolescents is cognitive behavior therapy for insomnia, which is used to treat adolescents who experience insomnia. Cognitive

behavior therapy for insomnia is a multimodal treatment, which aims to reduce difficulties initiating or maintaining sleep, and the clinical distress associated with such sleep difficulties [86]. It incorporates sleep hygiene, relaxation, stimulus control, sleep restriction, and cognitive therapy, which all aim to reduce arousal associated with bedtime and sleep [86]. These treatments have effectively improved sleep latency, sleep duration, and awakenings after sleep onset in adolescents. Both depression and anxiety symptoms may also be diminished through this therapy [86].

Many other low-intensity treatment options exist, to improve the sleep of adolescents, especially those who do not experience disordered sleep. These include brief mindfulness and relaxation, and prebed phone restriction [82,88–90].

Policymakers

While delaying school start times until at least 8:30 a.m. and implementation of lighter extra-curricular homework loads are both discussed in greater detail in relation to how schools can improve sleep in children and adolescents, not all schools can act individually. Thus, public policy regarding these guidelines can have even wider benefit in supporting mental health of children and adolescents.

Health promotion and education regarding child and adolescent sleep may also help to improve sleep and mental health [42]. Health promotion could include information about how much sleep children and adolescents need, indicators of good or problematic sleep, sleep hygiene, and tips on how to improve sleep and where to seek resources. While the present focus has been on how sleep impacts mental health, sleep also affects cognitive performance, risk-taking, drug use, road safety, and delinquency, and so the potential benefits of sleep promotion are widespread.

Just as children sleep better in a safe home environment they also sleep better when they feel safe in their communities [91]. Children and adolescents who are exposed to community violence frequently experience sleep disturbances, nightmares, and reduced mental health [92]. Even if children and adolescents are not victims of community violence, the perception of safety in their neighborhoods can impact sleep [91]. One study of 252 adolescents from a wide range of socioeconomic backgrounds in the South-eastern United States asked adolescents about their concern regarding community violence and measured their sleep using actigraphy and self-report. Adolescents who were more concerned about community violence had lower sleep efficiency, woke more during the night, and reported more sleep-wake problems and daytime sleepiness. This effect was stronger among adolescent girls [91]. Thus, policy targeting community safety, especially

in areas containing a large proportion of families, is beneficial.

Lastly, paid employment is a factor that can negatively impact the sleep of adolescents [74,93]. High school students who work more than 20 h per week have later bedtimes and less sleep across the week. They also report more daytime sleepiness, are more likely to arrive late for school, have trouble staying awake at school, and are more likely to use caffeine, tobacco, and alcohol [94]. These deficits of sleep and daytime functioning were even more pronounced among adolescents who coupled more than 20 h of paid work with more than 20 h of extra-curricular activity [94]. Australian research indicates that, while most adolescents are aware of their rights at work in terms of declining shifts, they often report feeling pressured to accept shifts, or believe that declining shifts will result in less work being offered to them in the future [95]. Thus, there is scope for policy regarding paid employment for school students, for example, by placing limits around the finishing time of shifts offered to high school workers during school term time. This would mitigate the problem of adolescents finishing shifts so late that they are unable to obtain sufficient sleep before having to rise for school the next day to help support adolescent workloads, sleep, and mental health.

Conclusion

Summary

Overall, these findings suggest that while estimates of sleep need for optimal mood functioning are between 9 and 11 h per night for children and 8–10 h per night for adolescents, many young people chronically obtain sleep that is below this amount. Studies examining the relationship between sleep duration and mood suggest that sleep loss produces reductions in positive mood states and affect and increases in negative mood states and negative affect. Longitudinal studies support bidirectional relationships between sleep duration and mood and mood disorders; however, the link from sleep to mood/mental health has been reported more consistently than link from mood/mental health to sleep. Studies focusing on sleep quality have found similar results, with multiple aspects of sleep quality found to impact mental health, including how long it takes to fall asleep, waking during the night, and subjective sleep quality all impacting mental health.

Using Bronfenbrenner's ecological systems theory as a guiding explanatory framework, suggestions and recommendations for improving sleep, and thus mental health, were provided. These recommendations targeted families, schools, clinicians, and public policymakers, thus highlighting the importance of a multifaceted approach to support sleep and mental health in young people.

Limitations and future research directions

Overall, the present chapter provides an overview of the relationship between sleep duration and sleep quality and how they either support or diminish mental health in children and adolescents. In addition, we provide suggestions for how sleep (and thus mental health) can be supported across multiple ecological levels. It is important to note, however, that this overview is not exhaustive, and other factors, such as sleep regularity and the timing of circadian rhythms (or the body clock), affect mental health both directly or indirectly, through their influence on sleep duration and sleep quality [54,96].

While present findings support the importance of sleep for optimal mental health in children and adolescents, there remain gaps and limitations in the literature. First, multimodal assessment of sleep using both subjective and objective measures is needed to determine the degree to which subjectively reported insufficient or poor-quality sleep is also mirrored by objective data. While this is an important point across all developmental stages, it is particularly important among younger children, for whom research typically relies upon parent reports of sleep. Second, while there is a sizable body of work examining sleep quality and mental health outcomes, sleep quality is not unitary and the conceptual and operational definitions of sleep quality are often ill-defined. Research examining clearly defined and operationalized aspects of sleep quality, such as sleep onset latency, wake after sleep onset, number of nighttime awakenings, and subjective and objective sleep quality, is needed to determine how different facets of sleep quality affect mental health. Third, the literature consists largely of cross-sectional studies which cannot address the significant issue of causation or causal direction. This is important given the relationship between sleep and mental health is likely bidirectional. Future research would profit from more experimental studies to determine causation and directionality.

Several important areas remain under investigated. For example, studies to evaluate the efficacy of health promotion strategies aimed at sleep are needed to determine whether population-level interventions are effective. On a smaller scale, sleep intervention studies are urged to include mood and mental health outcomes to see how improving sleep on an individual level improves mental health. Finally, mood outcome measures need to include positive mood outcomes, such as happiness, as well as negative mood outcomes, such as depressed mood and anxiety. Emerging research suggests that positive emotion may be more sensitive to sleep loss and poor quality sleep than negative emotion [97]. While mood states relevant to mood disorders, such as depression and anxiety, are important to measure, reduction in positive mood, or anhedonia, is also a clinically relevant.

Concluding remarks

Sleep plays a crucial role in maintaining optimal mental health across the lifespan. Childhood and adolescence are critical developmental periods when the trajectories of many mental health conditions are begun and thus provide an optimal period for early intervention regarding sleep. Simple interventions to improve and safeguard sleep are thus important to benefit youth mental health and reduce the likelihood or severity of many mental health conditions.

References

- [1] Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. *Lancet Psychiatry* 2016;3(2):171–8. [https://doi.org/10.1016/s2215-0366\(15\)00505-2](https://doi.org/10.1016/s2215-0366(15)00505-2).
- [2] Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci* 2008;9(12):947–57. <https://doi.org/10.1038/nrn2513>.
- [3] Beeds K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *Psychiatr Clin* 2009;32(3):483–524. <https://doi.org/10.1016/j.psc.2009.06.002>.
- [4] Son SE, Kirchner JT. Depression in children and adolescents. *Am Fam Physician* 2000;62(10):2297–308.
- [5] Alfano CA, Gamble AL. The role of sleep in childhood psychiatric disorders. *Child Youth Care Forum* 2009;38(6):327–40. <https://doi.org/10.1007/s10566-009-9081-y>.
- [6] Short MA, Louca M. Sleep deprivation leads to mood deficits in healthy adolescents. *Sleep Med* 2015;16(8):987–93. <https://doi.org/10.1016/j.sleep.2015.03.007>.
- [7] Lovato N, Gradisar M. A meta-analysis and model of the relationship between sleep and depression in adolescents: recommendations for future research and clinical practice. *Sleep Med Rev* 2014;18(6):521–9. <https://doi.org/10.1016/j.smrv.2014.03.006>.
- [8] Baum KT, Desai A, Field J, Miller LE, Rausch J, Beebe DW. Sleep restriction worsens mood and emotion regulation in adolescents. *J Child Psychol Psychiatry Allied Discip* 2014;55(2):180–90. <https://doi.org/10.1111/jcpp.12125>.
- [9] Gregory AM, O'Connor TG. Sleep problems in childhood: a longitudinal study of developmental change and association with behavioral problems. *J Am Acad Child Adolesc Psychiatr* 2002;41(8):964–71. <https://doi.org/10.1097/00004583-200208000-00015>.
- [10] Meijer AM, Reitz E, Deković M, van den Wittenboer GLH, Stoel RD. Longitudinal relations between sleep quality, time in bed and adolescent problem behaviour. *J Child Psychol Psychiatry Allied Discip* 2010;51(11):1278–86. <https://doi.org/10.1111/j.1469-7610.2010.02261.x>.
- [11] Leahy E, Gradisar M. Dismantling the bidirectional relationship between paediatric sleep and anxiety. *Clin Psychol* 2012;16(1):44–56. <https://doi.org/10.1111/j.1742-9552.2012.00039.x>.
- [12] Short MA, Gradisar M, Lack LC, Wright HR, Chatburn A. Estimating adolescent sleep patterns: parent reports versus adolescent self-report surveys, sleep diaries, and actigraphy. *Nat Sci Sleep* 2013;5:23–6. <https://doi.org/10.2147/NSS.S38369Australia>.
- [13] Short MA, Gradisar M, Lack LC, Wright H, Carskadon MA. The discrepancy between actigraphic and sleep diary measures of sleep

- in adolescents. *Sleep Med* 2012;13(4):378–84. <https://doi.org/10.1016/j.sleep.2011.11.005>.
- [14] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Catesby Ware J, Adams Hillard PJ. National sleep foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 2015;1(1):40–3. <https://doi.org/10.1016/j.sleh.2014.12.010>.
- [15] Short MA, Weber N, Reynolds C, Coussens S, Carskadon MA. Estimating adolescent sleep need using dose-response modeling. *Sleep* 2018;41(4). <https://doi.org/10.1093/sleep/zsy011>.
- [16] Fuligni AJ, Bai S, Krull JL, Gonzales NA. Individual differences in optimum sleep for daily mood during adolescence. *J Clin Child Adolesc Psychol* 2017;53:1–11.
- [17] Ojio Y, Nishida A, Shimodera S, Togo F, Sasaki T. Sleep duration associated with the lowest risk of depression/anxiety in adolescents. *Sleep* 2016;39(8):1555–62. <https://doi.org/10.5665/sleep.6020>.
- [18] Lo JC, Ong JL, Leong RLF, Gooley JJ, Chee MWL. Cognitive performance, sleepiness, and mood in partially sleep deprived adolescents: the need for sleep Study. *Sleep* 2016;39(3):687–98. <https://doi.org/10.5665/sleep.5552>.
- [19] Galland BC, Short MA, Terrill P, Rigney G, Haszard JJ, Coussens S, Foster-Owens M, Biggs SN. Establishing normal values for pediatric nighttime sleep measured by actigraphy: a systematic review and meta-analysis. *Sleep* 2018;41(4). <https://doi.org/10.1093/sleep/zsy017>.
- [20] Gregory AM, Sadeh A. Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep Med Rev* 2012;16(2):129–36. <https://doi.org/10.1016/j.smrv.2011.03.007>.
- [21] Sadeh A. Consequences of sleep loss or sleep disruption in children. *Sleep Med Clin* 2007;2(3):513–20. <https://doi.org/10.1016/j.jsmc.2007.05.012>.
- [22] Astill RG, Van der Heijden KB, Van IJzendoorn MH, Van Someren EJW. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. *Psychol Bull* 2012;138(6):1109–38. <https://doi.org/10.1037/a0028204>.
- [23] Baglioni C, Spiegelhalder K, Lombardo C, Riemann D. Sleep and emotions: a focus on insomnia. *Sleep Med Rev* 2010;14(4):227–38. <https://doi.org/10.1016/j.smrv.2009.10.007>.
- [24] Nixon GM, Thompson JMD, Han DY, Becroft DM, Clark PM, Robinson E, Waldie KE, Wild CJ, Black PN, Mitchell EA. Short sleep duration in middle childhood: risk factors and consequences. *Sleep* 2008;31(1):71–8. <https://doi.org/10.1093/sleep/31.1.71>.
- [25] Vriend JL, Davidson FD, Corkum PV, Rusak B, McLaughlin EN, Chambers CT. Sleep quantity and quality in relation to daytime functioning in children. *Child Health Care* 2012;41(3):204–22. <https://doi.org/10.1080/02739615.2012.685039>.
- [26] Smaldone A, Honig JC, Byrne MW. Sleepless in America: inadequate sleep and relationships to health and well-being of our nation's children. *Pediatrics* 2007;119(1):S29. <https://doi.org/10.1542/peds.2006-2089F>.
- [27] Brown WJ, Wilkerson AK, Boyd SJ, Dewey D, Mesa F, Bunnell BE. A review of sleep disturbance in children and adolescents with anxiety. *J Sleep Res* 2018;27(3). <https://doi.org/10.1111/jsr.12635>.
- [28] Gregory AM, Sadeh A. Annual Research Review: sleep problems in childhood psychiatric disorders - a review of the latest science. *J Child Psychol Psychiatry* 2016;57(3):296–317. <https://doi.org/10.1111/jcpp.12469>.
- [29] Lo JC, Lee SM, Teo LM, Lim J, Gooley JJ, Chee MW. Neurobehavioral impact of successive cycles of sleep restriction with and without naps in adolescents. *Sleep* 2016;40(2):1–13.
- [30] Reddy R, Palmer CA, Jackson C, Farris SG, Alfano CA. Impact of sleep restriction versus idealized sleep on emotional experience, reactivity and regulation in healthy adolescents. *J Sleep Res* 2017;26(4):516–25. <https://doi.org/10.1111/jsr.12484>.
- [31] Dewald-Kaufmann JF, Oort FJ, Meijer AM. The effects of sleep extension and sleep hygiene advice on sleep and depressive symptoms in adolescents: a randomized controlled trial. *J Child Psychol Psychiatry* 2014;55(3):273–83. <https://doi.org/10.1111/jcpp.12157>.
- [32] Gruber R, Cassoff J, Frenette S, Wiebe S, Carrier J. Impact of sleep extension and restriction on children's emotional lability and impulsivity. *Pediatrics* 2012;130(5):e1155. <https://doi.org/10.1542/peds.2012-0564>.
- [33] Fallone G, Acebo C, Seifer R, Carskadon MA. Experimental restriction of sleep opportunity in children: effects on teacher ratings. *Sleep* 2005;28(12):1561–7. <https://doi.org/10.1093/sleep/28.12.1561>.
- [34] Chaput JP, Gray CE, Poitras VJ, Carson V, Gruber R, Olds T, Weiss SK, Connor Gorber S, Kho ME, Sampson M, Belanger K, Eryuzu S, Callender L, Tremblay MS. Systematic review of the relationships between sleep duration and health indicators in school-aged children and youth. *Appl Physiol Nutr Metab* 2016;41(6):S266. <https://doi.org/10.1139/apnm-2015-0627>.
- [35] Vriend JL, Davidson FD, Corkum PV, Rusak B, Chambers CT, McLaughlin EN. Manipulating sleep duration alters emotional functioning and cognitive performance in children. *J Pediatr Psychol* 2013;38(10):1058–69. <https://doi.org/10.1093/jpepsy/jst033>.
- [36] McMakin DL, Dahl RE, Buysse DJ, Cousins JC, Forbes EE, Silk JS, Siegle GJ, Franzen PL. The impact of experimental sleep restriction on affective functioning in social and nonsocial contexts among adolescents. *J Child Psychol Psychiatry Allied Discip* 2016;57(9):1027–37. <https://doi.org/10.1111/jcpp.12568>.
- [37] McLaughlin KA, Hatzenbuehler ML, Mennin DS, Nolen-Hoeksema S. Emotion dysregulation and adolescent psychopathology: a prospective study. *Behav Res Ther* 2011;49(9):544–54. <https://doi.org/10.1016/j.brat.2011.06.003>.
- [38] Thompson RA. Emotion regulation: a theme in search of definition. *Monogr Soc Res Child Dev* 1994;59(2–3):25–52. <https://doi.org/10.1111/j.1540-5834.1994.tb01276.x>.
- [39] Talbot LS, McGlinchey EL, Kaplan KA, Dahl RE, Harvey AG. Sleep deprivation in adolescents and adults: changes in affect. *Emotion* 2010;10(6):831–41. <https://doi.org/10.1037/a0020138>.
- [40] Owens JA, Belon K, Moss P. Impact of delaying school start time on adolescent sleep, mood, and behavior. *Arch Pediatr Adolesc Med* 2010;164(7):608–14. <https://doi.org/10.1001/archpediatrics.2010.96>.
- [41] Hasler JC. The effect of sleep extension on academic performance, cognitive functioning and psychological distress in adolescents. The University of Arizona; 2008.
- [42] Bonnar D, Gradisar M, Moseley L, Coughlin AM, Cain N, Short MA. Evaluation of novel school-based interventions for adolescent sleep problems: does parental involvement and bright light improve outcomes? *Sleep Health* 2015;1(1):66–74. <https://doi.org/10.1016/j.sleh.2014.11.002>.

- [43] Fredriksen K, Rhodes J, Reddy R, Way N. Sleepless in Chicago: tracking the effects of adolescent sleep loss during the middle school years. *Child Dev* 2004;75(1):84–95. <https://doi.org/10.1111/j.1467-8624.2004.00655.x>.
- [44] Lovato N, Short M, Micic G, Hiller R, Gradisar M. An investigation of the longitudinal relationship between sleep and depressed mood in developing teens. *Nat Sci Sleep* 2017;9:3–10. <https://doi.org/10.2147/NSS.S111521>.
- [45] Mullin BC, Pyle L, Haraden D, Riederer J, Brim N, Kaplan D, Novins D. A preliminary multimethod comparison of sleep among adolescents with and without generalized anxiety disorder. *J Clin Child Adolesc Psychol* 2017;46(2):198–210. <https://doi.org/10.1080/15374416.2016.1220312>.
- [46] Cousins JC, Whalen DJ, Dahl RE, Forbes EE, Olino TM, Ryan ND, Silk JS. The bidirectional association between daytime affect and nighttime sleep in youth with anxiety and depression. *J Pediatr Psychol* 2011;36(9):969–79. <https://doi.org/10.1093/jpepsy/jsr036>.
- [47] Carskadon MA, Harvey K, Duke P, Anders TF, Litt IF, Dement WC. Pubertal changes in daytime sleepiness. *Sleep* 1980;2(4):453–60. <https://doi.org/10.1093/sleep/2.4.453>.
- [48] Ivanenko A, Crabtree VML, O'Brien LM, Gozal D. Sleep complaints and psychiatric symptoms in children evaluated at a pediatric mental health clinic. *J Clin Sleep Med* 2006;2(1):42–8. <https://doi.org/10.5664/jcsm.26434>.
- [49] Short MA, Gradisar M, Lack LC, Wright HR, Dohnt H. The sleep patterns and well-being of Australian adolescents. *J Adolesc* 2013;36(1):103–10. <https://doi.org/10.1016/j.adolescence.2012.09.008>.
- [50] Kaneita Y, Ohida T, Osaki Y, Tanihata T, Minowa M, Suzuki K, Wada K, Kanda H, Hayashi K. Association between mental health status and sleep status among adolescents in Japan: a nationwide cross-sectional survey. *J Clin Psychiatr* 2007;68(9):1426–35. <https://doi.org/10.4088/jcp.v68n0916>.
- [51] Kaneita Y, Yokoyama E, Harano S, Tamaki T, Suzuki H, Muneyawa T, Nakajima H, Asai T, Ohida T. Associations between sleep disturbance and mental health status: a longitudinal study of Japanese junior high school students. *Sleep Med* 2009;10(7):780–6. <https://doi.org/10.1016/j.sleep.2008.06.014>.
- [52] Ivanenko A, Johnson K. Sleep disturbances in children with psychiatric disorders. *Semin Pediatr Neurol* 2008;15(2):70–8. <https://doi.org/10.1016/j.spen.2008.03.008>.
- [53] Kahn M, Fridenson S, Lerer R, Bar-Haim Y, Sadeh A. Effects of one night of induced night-wakings versus sleep restriction on sustained attention and mood: a pilot study. *Sleep Med* 2014;15(7):825–32. <https://doi.org/10.1016/j.sleep.2014.03.016>.
- [54] Short MA, Gradisar M, Lack LC, Wright HR. The impact of sleep on adolescent depressed mood, alertness and academic performance. *J Adolesc* 2013;36(6):1025–33. <https://doi.org/10.1016/j.adolescence.2013.08.007>.
- [55] Warner S, Murray G, Meyer D. Holiday and school-term sleep patterns of Australian adolescents. *J Adolesc* 2008;31(5):595–608. <https://doi.org/10.1016/j.adolescence.2007.10.005>.
- [56] McMakin DL, Alfano CA. Sleep and anxiety in late childhood and early adolescence. *Curr Opin Psychiatr* 2015;28(6):483–9. <https://doi.org/10.1097/YCO.0000000000000204>.
- [57] Ramtekkar U, Ivanenko A. Sleep in children with psychiatric disorders. *Semin Pediatr Neurol* 2015;22(2):148–55. <https://doi.org/10.1016/j.spen.2015.04.004>.
- [58] Hatzinger M, Brand S, Perren S, Von Wyl A, Stadelmann S, von Klitzing K, Holsboer-Trachsler E. pre-school children, sleep objectively assessed via sleep-EEGs remains stable over 12 months and is related to psychological functioning, but not to cortisol secretion. *J Psychiatr Res* 2013;47(11):1809–14. <https://doi.org/10.1016/j.jpsychires.2013.08.007>.
- [59] Sadeh A, Tikotzky L, Kahn M. Sleep in infancy and childhood: implications for emotional and behavioral difficulties in adolescence and beyond. *Curr Opin Psychiatr* 2014;27(6):453–9. <https://doi.org/10.1097/YCO.0000000000000109>.
- [60] Meltzer LJ, Mindell JA. Sleep and sleep disorders in children and adolescents. *Psychiatr Clin* 2006;29(4):1059–76. <https://doi.org/10.1016/j.psc.2006.08.004>.
- [61] Roberts RE, Roberts CR, Chen IG. Impact of insomnia on future functioning of adolescents. *J Psychosom Res* 2002;53(1):561–9. [https://doi.org/10.1016/s0022-3999\(02\)00446-4](https://doi.org/10.1016/s0022-3999(02)00446-4).
- [62] Forbes EE, Bertocci MA, Gregory AM, Ryan ND, Axelson DA, Birmaher B, Dahl RE. Objective sleep in pediatric anxiety disorders and major depressive disorder. *J Am Acad Child Adolesc Psychiatr* 2008;47(2):148–55. <https://doi.org/10.1097/chi.0b013e31815cd9bc>.
- [63] Chorney DB, Detweiler MF, Morris TL, Kuhn BR. The interplay of sleep disturbance, anxiety, and depression in children. *J Pediatr Psychol* 2007;33(4):339–48. <https://doi.org/10.1093/jpepsy/jsm105>.
- [64] Noone DM, Willis TA, Cox J, Harkness F, Ogilvie J, Forbes E, Sterr A, Gregory AM. Catastrophizing and poor sleep quality in early adolescent females. *Behav Sleep Med* 2014;12(1):41–52. <https://doi.org/10.1080/15402002.2013.764528>.
- [65] Hiller RM, Lovato N, Gradišar M, Oliver M, Slater A. Trying to fall asleep while catastrophising: what sleep-disordered adolescents think and feel. *Sleep Med* 2014;15(1):96–103. <https://doi.org/10.1016/j.sleep.2013.09.014>.
- [66] Alfano CA, Pina AA, Zerr AA, Villalta IK. Pre-sleep arousal and sleep problems of anxiety-disordered youth. *Child Psychiatr Hum Dev* 2010;41(2):156–67. <https://doi.org/10.1007/s10578-009-0158-5>.
- [67] U. Bronfenbrenner, Six theories of child development: revised formulations and current issues. Jessica Kingsley Publishers.
- [68] Gradišar M, Wolfson AR, Harvey AG, Hale L, Rosenberg R, Czeisler CA. The sleep and technology use of Americans: findings from the National Sleep Foundation's 2011 sleep in America poll. *J Clin Sleep Med* 2013;9(12):1291–9. <https://doi.org/10.5664/jcsm.3272Australia>.
- [69] Bartel KA, Gradišar M, Williamson P. Protective and risk factors for adolescent sleep: a meta-analytic review. *Sleep Med Rev* 2015;21:72–85. <https://doi.org/10.1016/j.smrv.2014.08.002>.
- [70] Brand S, Gerber M, Beck J, Hatzinger M, Pühse U, Holsboer-Trachsler E. High exercise levels are related to favorable sleep patterns and psychological functioning in adolescents: a comparison of athletes and controls. *J Adolesc Health* 2010;46(2):133–41. <https://doi.org/10.1016/j.jadohealth.2009.06.018>.
- [71] Billows M, Gradišar M, Dohnt H, Johnston A, McCappin S, Hudson J, Disorganization F. Sleep hygiene, and adolescent sleep disturbance. *J Clin Child Adolesc Psychol* 2009;38(5):745–52. <https://doi.org/10.1080/15374410903103635>.
- [72] Short MA, Gradišar M, Wright H, Lack LC, Dohnt H, Carskadon MA. Time for bed: parent-set bedtimes associated with improved sleep and daytime functioning in adolescents. *Sleep* 2011;34(6):797–800. <https://doi.org/10.5664/SLEEP.1052Australia>.

- [73] Gangwisch JE, Babiss LA, Malaspina D, Turner JB, Zammit GK, Posner K. Earlier parental set bedtimes as a protective factor against depression and suicidal ideation. *Sleep* 2010;33(1):97–106. <https://doi.org/10.1093/sleep/33.1.97>.
- [74] Carskadon MA. Patterns of sleep and sleepiness in adolescents. *Pediatrician* 1990;17(1):5–12.
- [75] Crowley SJ, Carskadon MA. Modifications to weekend recovery sleep delay circadian phase in older adolescents. *Chronobiol Int* 2010;27(7):1469–92. <https://doi.org/10.3109/07420528.2010.503293>.
- [76] Short MA, Arora T, Gradisar M, Taheri S, Carskadon MA. How many sleep diary entries are needed to reliably estimate adolescent sleep? *Emirates Sleep* 2017;40(3). <https://doi.org/10.1093/sleep/zsx006>.
- [77] Adam EK, Snell EK, Pendry P. Sleep timing and quantity in ecological and family context: a nationally representative time-diary study. *J Fam Psychol* 2007;21(1):4–19. <https://doi.org/10.1037/0893-3200.21.1.4>.
- [78] Hafner M, Stepanek M, Troxel WM. The economic implications of later school start times in the United States. *Sleep Health* 2017;3(6):451–7. <https://doi.org/10.1016/j.slehd.2017.08.007>.
- [79] Short MA, Gradisar M, Lack LC, Wright HR, Dewald JF, Wolfson AR, Carskadon MA. A cross-cultural comparison of sleep duration between U.S. And Australian adolescents: the effect of school start time, parent-set bedtimes, and extracurricular load. *Health Educ Behav* 2013;40(3):323–30. <https://doi.org/10.1177/1090198112451266>.
- [80] Rhoda A, Carskadon M, Millman R, Wolfson A, Braverman PK, Adelman WP, Breuner CC, Levine DA, Marcell AV, Murray PJ, O'Brien RF, Devore CD, Allison M, Ancona R, Barnett SE, Gunther R, Holmes B, Lamont JH, Minier M, Okamoto JK, Wheeler LSM, Young T. School start times for adolescents. *Pediatrics* 2014;134(3):642–9. <https://doi.org/10.1542/peds.2014-1697>.
- [81] OECD. PISA, results (volume I). OECD Publishing; 2015.
- [82] Corkum P, Vriend J. Clinical management of behavioral insomnia of childhood. *Psychol Res Behav Manag* 2011;4:69. <https://doi.org/10.2147/PRBM.S14057>.
- [83] Hill C. Practitioner review: effective treatment of behavioural insomnia in children. *J Child Psychol Psychiatry* 2011;52(7):731–40. <https://doi.org/10.1111/j.1469-7610.2011.02396.x>.
- [84] Meltzer LJ, Mindell JA. Systematic review and meta-analysis of behavioral interventions for pediatric insomnia. *J Pediatr Psychol* 2014;39(8):932–48. <https://doi.org/10.1093/jpepsy/jsu041>.
- [85] Hiller R, Gradisar M. Helping your child with sleep problems: a self-help guide for parents. Robinson; 2018.
- [86] Blake MJ, Sheeber LB, Youssef GJ, Raniti MB, Allen NB. Systematic review and meta-analysis of adolescent cognitive-behavioral sleep interventions. *Clin Child Fam Psychol Rev* 2017;20(3):227–49.
- [87] Richardson C, Cain N, Bartel K, Micic G, Maddock B, Gradisar M. A randomised controlled trial of bright light therapy and morning activity for adolescents and young adults with delayed sleep-wake phase disorder. *Sleep Med* 2018;45:114–23.
- [88] Bartel K, Richardson C, Gradisar M. Rapid review: sleep and mental wellbeing: exploring the links. Melbourne; 2018. p. 1–51. in press.
- [89] Bartel K, Scheeren R, Gradisar M. Altering adolescents' pre-bedtime phone use to achieve better sleep health. *Health Commun* 2018;9:1–7.
- [90] Bartel K, Huang C, Maddock B, Williamson P, Gradisar M. Brief school-based interventions to assist adolescents' sleep-onset latency: comparing mindfulness and constructive worry versus controls. *J Sleep Res* 2018;27:e12668.
- [91] Bagley EJ, Tu KM, Buckhalt JA, El-Sheikh M. Community violence concerns and adolescent sleep. *Sleep Health* 2016;2(1):57–62.
- [92] Duncan DF. Growing up under the gun: children and adolescents coping with violent neighborhoods. *J Prim Prev* 1996;16(4):343–56.
- [93] Laberge L, Ledoux E, Auclair J, Thuilier C, Gaudreault M, Gaudreault M, et al. Risk factors for work-related fatigue in students with school-year employment. *J Adolesc Health* 2011;48(3):289–94.
- [94] Carskadon M. Adolescent sleepiness: increased risk in a high-risk population. *J Saf Res* 1990;21(4):169.
- [95] House of representatives standing committee on education and training. Adolescent overload? Canberra: Commonwealth of Australia; 2009.
- [96] Pesonen A-K, Räikkönen K, Paavonen EJ, Heinonen K, Komsu N, Lahti J, et al. Sleep duration and regularity are associated with behavioral problems in 8-year-old children. *Int J Behav Med* 2010;17(4):298–305.
- [97] Watling J, Pawlik B, Scott K, Booth S, Short MA. Sleep loss and affective functioning: more than just mood. *Behav Sleep Med* 2017;15(5):394–409.

Chapter 40

Delayed school start times and adolescent health

Aaron T. Berger^a, Rachel Widome^a and Wendy M. Troxel^b

^aDivision of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, United States; ^bRAND Corporation, Santa Monica, CA, United States

Adolescence is a development period characterized by dramatic changes in neurobiological, physical, and socio-emotional development as well as changes in sleep-wake patterns. Most adolescents should optimally sleep a minimum of 8–9.5 h per night [1,2]. However, the majority fall substantially short of that mark as national surveillance shows that only 7% of US adolescents report getting at least 8.5 h of sleep on school nights [3]. Between ages 12 and 18, the probability of getting at least 7 h of sleep per night drops by about half [4]. The magnitude of the short sleep duration epidemic among adolescents is even larger than what we have observed in adults, with US high school-aged youth being more than twice as likely to report getting insufficient sleep compared with adults [2]. In addition, there are sleep disparities among adolescents, with girls, nonwhites, and those from lower socioeconomic status backgrounds, being more likely to report short sleep duration compared with other groups [4]. A particularly worrisome trend is the secular decline in adolescent sleep over the past 20 years, a trend that has been called a “great sleep recession” [4].

A variety of social and environmental factors pose significant obstacles to sufficient sleep for most US adolescents [5–9], including social pressures to stay up late, bright light from screens at and after bedtime, after school homework and employment, and caffeine use, to name a few. Even in the absence of these social and environmental contexts, there are powerful, hardwired biological factors that push teenagers toward later bedtimes and delayed wake-up times [10,11].

The circadian biological clock and sleep/wake homeostasis are two body systems that regulate sleep [12]. Early in puberty, in most adolescents, there is a neurobiological change to children’s circadian clocks that results in a 2 to 3-h delay in the release of the sleep-promoting hormone,

melatonin. This circadian timing persists through adolescence [13] and means that the time adolescents naturally fall asleep is deferred to a later hour. After this shift it is challenging, even for an adolescent who tries to get to bed at an early hour, to fall asleep prior to 11:00 p.m. and it follows that they will struggle to wake before 8:00 a.m. [11]. In addition, “sleep drive,” which accumulates over the waking hours and diminishes wakefulness as the day progresses, builds slower once children reach their teen years [14]. As adolescents get older, bedtime is delayed on both school and nonschool days [5]. This adolescent sleep timing shift has been observed both in the US and around the world, adding confirmatory evidence to this delay of sleep onset being a largely biological, and not purely social, normative, or cultural phenomenon [5,11,15]. Meanwhile, contrary to popular belief, adolescents require just as much sleep as they did when they were a few years younger [11] with 9.25 h of nightly sleep being considered optimal through the teen years [16].

Early school start times are perhaps the most potent and salient environmental constraint on adolescent sleep [1,17,18]. Although delayed sleep onset has many biological and social causes, delayed sleep onset does not necessarily result in truncated sleep duration, unless schedules dictate an untenable wake-up time. Unfortunately, this is nearly always the case in the US, where high schools, almost without exception, tend to start very early [18], leading adolescents to need to wake before they have finished sleeping. To meet the biological sleep needs of adolescents, over two dozen medical organizations, including the American Academy of Pediatrics and the Centers for Disease Control and Prevention, have recommended that middle and high schools start at 8:00:00 a.m., 8:30 a.m., or later [19]. Numerous examples in school districts from across the country have shown that high

schools can feasibly shift their start times to 8:30 a.m. or later [20]. Both cross-sectional [21] and longitudinal [22–24] evaluations of start time differences show that later start times allow teens to get more sleep, with each 1-h start time delay associated with 30–90 additional minutes of school night sleep duration. Yet <18% of US middle and high schools start at or after 8:30 a.m. and 42% start at 8:00 a.m. or earlier [18], start times which appear to most severely curtail sleep [25].

In this chapter, we aim to summarize the documented effects of delaying school start time on adolescent health. Given the strong evidence linking short sleep duration with numerous physical and mental health risks (covered in depth in the preceding chapters), delaying start times could be an effective population-level strategy to promote sleep and physical and mental health in adolescents. Our review covers those health outcomes that have been included in peer-reviewed literature, in relation to a K-12 school start time contrast (e.g., studies that have compared two or more schools with different start times, or one school before and after a start time change). We review the effects of school start times on sleep duration, academic outcomes and truancy, mental health and risky behavior, and unintentional injury. We conclude by discussing the obstacles communities face when delaying school start times.

Delaying high school start time improves sleep

Delaying school start time is a population-level intervention with the potential to affect sleep duration and sleep-related health during adolescence, a critical developmental period. Studies that have evaluated whether school start times are associated with more or better-quality sleep have overwhelmingly concluded that later school start times are associated with significantly longer school-night sleep duration [26,27]. Later school start times are associated with longer school-night sleep duration in all eight studies eligible for inclusion in a recent Cochrane review, and in 29 of 31 studies included in another recent systematic review [26,27]. Fig. 40.1 illustrates the distributions of school-night sleep duration for students at eight US high schools, with start times ranging from 7:35 a.m. to 8:55 a.m. [24]. Compared with students in the earliest-starting school, the entire distribution of sleep duration at later-starting schools shifts progressively toward longer sleep duration. Notably, approximately 10% of US high schools start before the earliest-starting high school in this sample [18].

Some have questioned whether a delayed school start time might be counterproductive, and only serve to delay bedtimes such that sleep duration is not lengthened. Contrary to this belief, most of the available evidence has

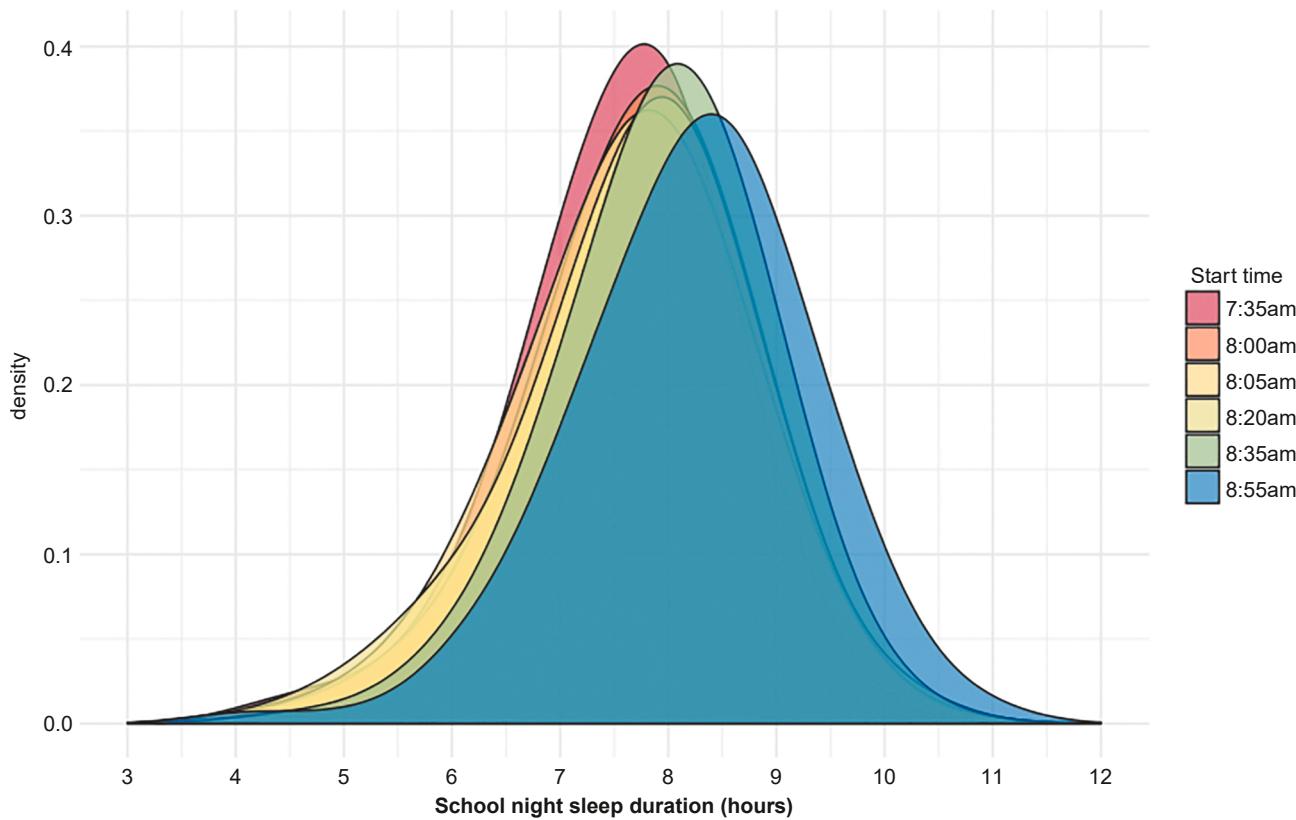
shown that later school start time leads to longer sleep duration because adolescent bedtimes are stable and likely not influenced much by artificially imposed wake-up times. In before-after studies of school start time changes, students typically maintain the same bedtimes after starting later than they had when their school started early [21,28,29], although one study showed that bedtimes actually shifted earlier when schools started later [22]. One recent cross-sectional study showed that students had modestly later bedtimes at schools with later start times; however, this study did not compare bedtimes before and after start time changes [25]. The stability of adolescent bedtimes across various school start times, early and late, is yet another piece of evidence reinforcing adolescents' circadian clocks are biologically set and rather inflexible.

Academic achievement, attention, and truancy

Students who do not get enough sleep have more difficulty concentrating in class, and are less likely to graduate high school or college than their better-rested peers [30]. Many sleepy adolescents find themselves unable to stay awake even while they are in class. A 2006 survey by the National Sleep Foundation found that 28% of high school students report falling asleep in school at least once a week [31]. Among high school students in a nationally representative survey, each additional hour of sleep was associated with 16% lower probability of attention problems in school, 15% lower probability of trouble completing homework, and a grade point average (GPA) increase of 0.2 points [30]. Moreover, when those students were followed through early adulthood, each additional hour of sleep was associated with 13% greater probability of graduating high school and a nearly 10% increase in probability of attending college [30].

Because delaying high school start time is recognized as an important strategy for promoting health sleep duration [1,19], researchers have worked to understand if later start times will improve adolescents' academic achievement. However, there are challenges in interpreting the effect of school start time on academic performance due to the nature of letter grades and standardized tests. Grade point averages may reflect the difficulty of a student's class schedule or the whims of a teacher, while standardized college entrance exams are not taken universally and may reflect only the population who intends to go to college [26]. In addition, students who struggle in school due to sleepiness might opt for, or be tracked into, less difficult courses.

Studies that have considered the effect of a 1-h school start time delay on standardized test scores have had mixed results [32,33]. Hinrichs compared ACT test scores of high



Data: Wahlstrom (2014)

FIGURE 40.1 Wahlstrom [24] collected self-reported sleep duration in eight US high schools with a range of start times. At later-starting schools, the entire distribution of school-night sleep duration is progressively shifted to the right, toward greater sleep.

school students in the Minneapolis and Saint Paul, Minnesota, public school districts before and after a start time delay in Minneapolis schools [32]. Hinrichs found no significant effects of school start time on ACT scores ($\beta = -0.024$, 95% confidence interval [CI] –0.23 to 0.18). In addition, Hinrichs conducted cross-sectional comparisons of high school student scores on the Kansas Reading Assessment by school start time. As with ACT scores, there was no association between school start time and reading score ($\beta = 0.95$, 95% CI –2.67 to 4.58). Meanwhile, Edwards conducted a similar study of the math and reading exam scores of middle school students in neighboring communities in North Carolina, one of which delayed its school start time during the study period [33]. Edwards found that students whose school was delayed by 1 h experienced a 1.8% point improvement in math scores (95% CI 1.19–2.37) and 0.98-point improvement in reading scores (95% CI 0.28–1.68) [33].

A few studies have also considered the effect of school start time on students' letter grades. Wahlstrom conducted a prepost study of student grades before and after start time delays in six school districts [24]. In four districts, the combined prepost change in all core courses (mathematics,

science, social studies, and/or English), and in two districts the core course grades were available for individual analysis. There was significant improvement in grades in three of the four school districts where all courses were analyzed collectively, and no significant difference in one school. In the two districts in which core course grades were analyzed separately, some courses had significant increases and others had significant decreases (although Wahlstrom did not report which specific courses showed letter grade improvements or setbacks) [24].

A considerable problem in causal inference for studies of school start times is that, due to the logistical complexity and multiple competing interests in setting school start times, researchers may never be able to randomize the start times that students receive. One noteworthy study, among first-semester freshmen at the US Air Force Academy (USAFA), was able to overcome that limitation [34]. Because the service academy randomly assigned students' academic schedules, including start time, course, and instructor, this study effectively recreates a randomized trial. The study found that when students are randomly assigned to take a class before 8:00:00 a.m., their academic performance in their first hour class was significantly

worse than those whose first hour class was assigned to 8:00:00 a.m. or later. In addition, having an early start to the academic day reduced performance throughout the entire day [34]. This study provides the highest-quality evidence that later school start times may play a causal role in improving academic outcomes. While the students at the USAFA are slightly older than high school students, most first-semester freshmen students are still biologically adolescents [34]. The average age of freshman cadets was not reported, but USAFA cadets are required to be between 17 and 23 years old in the year they enter [35], and 33% of all USAFA students are ages 18–19 years old, suggesting that a substantial majority of freshmen enter at age 18 [36].

Later school start times may improve learning and academic achievement by reducing sleepiness during the school day. Indeed, in a recent review of the school start time literature, 10 of the 12 studies that measured sleepiness found significantly less sleepiness in schools with later start times [26]. For example, Danner and Phillips used the Epworth Sleepiness Scale, a validated measure of daytime sleepiness [37], to measure changes in daytime sleepiness before and after a start time change in Kentucky [29]. Mean sleepiness declined from 8.9 to 8.2 ($P < .001$). Other longitudinal studies have also found lower levels of sleepiness following delays in start times [22,23]. Reduced sleepiness may also improve academic achievement by facilitating improved concentration and attention to school and after-school homework. An Israeli study used two different assessments to compare sustained attention in middle school students whose school start time was experimentally delayed by 1 h, compared with a group with consistently early start times [38]. The delayed start time group has a significantly better attention level, and made significantly fewer errors, than the early start time group.

Oversleeping students may be absent for all or part of a school day due to early start times. Edwards estimated that students at schools starting 1 h later average 1.3 fewer absences per year, with a median of five absences per year [33]. Wahlstrom identified the attendance of students who change schools more frequently as experiencing a particularly large benefit from later school start time [21]. While school attendance for continuously enrolled students was consistently high before and after a start time change, attendance for students who had changed schools during high school improved significantly following a start time delay, from 72% to 76% for ninth-grade students, and from 73.7% to 77.5% for 10th and 11th grade students [21]. This suggests that the largest gains in school attendance may be observed for the students at highest risk of absenteeism. Combined with reduced daytime sleepiness and better attention to school and homework, improved attendance may account for the increased academic achievement observed in later starting schools.

Mental health and risky behavior

Adolescence is known to be a highly vulnerable period for the onset of mental health issues and substance use disorders. For instance, 50% of all lifetime cases of depression begin by age 14 [39]. Furthermore, risky behavior in adolescence, including alcohol, tobacco, and other substance use and risky sexual behavior, are a cause of substantial morbidity, mortality, and social problems for youth and can lead to chronic lifelong health issues [40]. Thus, adolescence may be a critical period for preventing the lasting consequences of mental health and substance use-related morbidity and improving sleep health may be a key tactic in the armament of psychological and behavioral health promotion strategies.

Sleep loss and sleep disorders are commonly associated with reduced mental well-being and risky behaviors. Adults with psychiatric mood disorders such as major depression and post-traumatic stress disorder commonly experience sleep disturbances [41], inadequate or poor-quality sleep also co-occur with symptoms of depression [42], hopelessness and suicidal thoughts and attempts [42–44], irritability and impaired emotional regulation [45]. Sleep problems in childhood and adolescence may predict future mental health problems [46,47] and even suicide [47].

Experimental studies of sleep restriction provide further causal support for a role of sleep disturbance in contributing to mental health problems [45,48,49]. Experimentally sleep restricted adolescents exhibit higher levels of anxiety, anger, fatigue, and confusion compared with periods of sleep extension [45]. In addition, experimental sleep deprivation has been associated with reduced positive affect [48,49], and increased negative affect [48] in adolescents, which may increase adolescent vulnerability to depression. The role played by REM sleep in emotional processing [41] may explain these changes in affective response. When adolescents are woken prematurely they are deprived of rapid eye movement (REM) sleep (the stage of sleep known to be associated with emotional processing). This deficit hampers recovery from emotional conflict, and reduces emotional control by increasing reactivity to negative emotional stimuli [41].

Insufficient sleep may contribute generally to increased adolescent risk behaviors by diminishing teen's executive cognitive functioning and emotional regulation [50]. Early school start times cause many adolescents to live in a state of constant "circadian misalignment" due to the discrepancy between the school-imposed schedule and their own internal clock. Tired from the week, adolescents will sleep dramatically more hours on weekends to make up for school day sleep loss. Differences in weekend and weekday sleep hours have been associated with regulation of reward processing [51,52] which can manifest as increased

sensation-seeking and diminished regulatory control [50,53]. Sleep problems, including insomnia, short sleep duration, and inconsistencies in weekend versus weekday sleep, are associated cross-sectionally and longitudinally with increased use of alcohol, marijuana, and other drugs in adolescent samples [42,44].

Although much literature has been published on the associations between sleep and mental health in adolescence, comparatively little work has been done to identify the psychological effects of delayed school start time [54]. We recently conducted a recent systematic review of literature on school start time and psychological health, including substance use. We identified eight eligible studies conducted in the past 20 years. The most commonly studied outcome, symptoms of depression and anxiety, was assessed in four of the studies [21–23,55]. Positive and negative affect or attitudes were included in two more studies [56,57], and two other studies included nonspecific measures of mental health [58,59]. In both cross-sectional [21,55] and longitudinal studies [22,23], later school start time is consistently associated with fewer symptoms of depression and anxiety. One additional longitudinal study, with a control group, found that school start time was associated with improved general mental health and reduced psychologically relevant behavior problems, such as emotional problems and hyperactivity/inattention [59]. Although both studies assessing the effect of school start time on positive and negative affect [56,57] and one of the two studies of general mental health [58] did not find significant differences between earlier and later-starting schools, these studies were of short, 15-min differences in start times, a school with a late start on only 1 day of the week, and a highly unusual situation where a school was hosted during afternoon hours in another school building due to a fire. The highest quality studies uniformly found that later school start times are associated with better mental health in adolescents [22,23,59]. Notably lacking from the literature were studies of the impact of later start times on substance use or other risk-taking behaviors.

Unintentional injury

Sleep-deprived adolescents are more likely to be involved in car crashes, work-related injuries, and sports injuries [60]. High school students who get 7 h or less of sleep each night are more likely to take risks that can lead to serious injury or death, such as failing to wear bike helmets and seat belts, drinking and driving or riding with a drunk driver, and texting while driving, compared with students who get 9 or more hours of sleep [60]. Being in a car crash is the leading cause of death for US adolescents, resulting in nearly 4000 teen deaths in the US every year [61]. Nationally, one-fifth of fatal car crashes between 2009 and 2013 involved a drowsy driver [62]. Half of drowsy

driving crashes involve a driver aged 25 or younger [63]. By addressing widespread chronic sleep shortages among adolescents, delaying school start times has a clear link to reducing adolescent injuries and fatalities.

Several studies have analyzed the effect of school start time on car crash rates [24,29,64,65]. One longitudinal study compared car crash rates for 17- and 18-year-old drivers in a Kentucky school district to those in the state as a whole over the 2 years before and 2 years after a 1-h start time delay. Teens in the county with delayed start times had a 16.5% reduction in car crash rate over the study period, while teen crashes in the rest of the state increased by 7.8% [29]. Two cross-sectional studies compared crash rates for high school-aged drivers in adjacent communities in central [65] and eastern Virginia [64] with 85-min and 75- to 80-min start time differences, respectively. In each comparison, teen drivers in the communities with later start times were significantly less likely to be in crashes. As predicted, the teen crash peaks occurred during high school commute times in both communities, and teen drivers in the central Virginia community with earlier starting times were more likely to be in crashes where the car veered off the road to the right, a commonly sleep-related type of crash [65]. Finally, Wahlstrom compared the number of crashes involving 16- to 18-year-old drivers in four communities before and after a start time delay [24]. She found that there were fewer adolescent-involved crashes in three of the four communities following a start time delay, while one community had a slight increase in crashes after a start time delay. However, because the communities were not compared with a reference population, it is not possible to say if the observed trends were unique to communities in which start time was delayed.

Lengthening sleep duration could plausibly reduce these types of injuries by improving concentration, attention, and reaction time, and reducing fatigue and adolescent risk taking. For example, a Norwegian study compared reaction times among students whose start time is delayed 1 day of the week ($N = 33$), to high school students with consistently early start times ($N = 45$) [56]. Compared with the consistently early start students, students had significantly fewer reaction time lapses (response delays of over 500 ms) and faster average reaction times, on the late start day. These improvements in reaction time could reduce the risk of multiple types of injury. However, we are aware of no research to date assessing the effect of school start time on other types of accidental injury, including occupational and sports injuries. Another way school start times could be used to reduce the risk of child pedestrian injury is by staggering school start times with periods of high motor vehicle traffic to reduce exposure to traffic [66]. Future research is needed to identify what effect school start time may have on these and other injuries.

Conclusions

The evidence, which is based on pragmatic observational studies, some of which were natural experiment evaluations, suggests that delaying school start times can promote adolescent sleep and that this can have far reaching effects on healthy youth development. Numerous studies have overwhelmingly demonstrated that adolescents at later-starting schools are more likely get a healthy amount of sleep than their peers at earlier-starting schools. Limited evidence suggests that students at later-starting schools may learn more, and at worst perform no worse than their peers at earlier-starting schools, while an early start may hamper performance throughout the entire school day. There is also limited, but consistent, evidence that later school start times benefit both mental health and physical safety. Students starting school later demonstrate fewer symptoms of anxiety and depression and fewer behavioral problems. The risk of an adolescent being involved in a car crash appears to be reduced in communities with later-starting schools, possibly due to reduced sleepiness and improved reaction time among better-rested teens.

Given the consistency of these findings, with most studies showing clear benefits of later start times for adolescents and the absence of any studies showing harms for adolescents, it is striking that <20% of US middle and high schools start at 8:30 a.m. or later [18]. Although an increasing number of schools have made the change toward later start times or are currently in the process of considering the issue, there are many logistical challenges that deter school districts from making such a change, despite the robust evidence in support. Primary areas of concern include the potential impact on elementary school students (particularly if the schedules are “flipped” with elementary schools starting first and middle/high schools starting later to accommodate bussing), the impact on sports/extracurricular activities, and the impact on before or after-school childcare. Underlying many of these concerns is also a concern about the potential cost implications to school districts—a genuine concern in light of increasingly tightening school budgets. Countering this, however, the RAND Corporation recently published the first comprehensive investigation of the potential economic costs and benefits of a hypothetical state-wide shift in school start times to 8:30 a.m. or later across the US [67]. The study found that, even after just 2 years of such a policy change, the US economy would see an \$8.6 billion dollar gain, which would already outweigh the costs per student from delaying school start times to 8:30 a.m. The study projected even larger gains over a more protracted (e.g., 10-year) period of time, with benefits accrued through the improvement in academic outcomes and subsequent lifetime earnings of well-rested students as well as a reduction in adolescent drowsy driving motor vehicle crashes.

There are still important avenues for inquiry and a need to gain additional broad insight on the impacts of the timing of school days, as far as health and social impacts both in adolescence and later in the life course. In particular, there is a critical need for longitudinal studies with longer-term follow-up periods, as many potential benefits of later start times are likely to manifest over a longer period of time. Furthermore, there is a need to study the potential impact of start times changes on other members of the community, including parents, teachers, and elementary school students. In addition, there is a need to increase both the resolution the data on this topic via more objective measures as well as conduct research that would strengthen causal inference in this area. For this, innovative natural experiment evaluations are perhaps the best option given that randomizing schools to start time is highly infeasible. Strengthening the scientific base and disseminating such evidence to school districts and policy-makers is critical because school start times are likely one of the most readily modifiable major determinants of adolescent sleep and this relatively straightforward intervention can reach youth from various backgrounds.

References

- [1] Au R, Carskadon M, Millman R, Wolfson A, Braverman PK, Adelman WP, Breuner CC, Levine DA, Marcell AV, Murray PJ, O'Brien RF, Devore CD, Allison M, Ancona R, Barnett SE, Gunther R, Holmes B, Lerner M, Minier M, Okamoto JK, Young T. School start times for adolescents. *Pediatrics* 2014;134(3):642–9. <https://doi.org/10.1542/peds.2014-1697>.
- [2] Healthy people 2020 sleep health objectives. 2017. p. 2017.
- [3] Eaton DK, McKnight-Eily LR, Lowry R, Perry GS, Presley-Cantrell L, Croft JB. Prevalence of insufficient, borderline, and optimal hours of sleep among high school students - United States, 2007. *J Adolesc Health* 2010;46(4):399–401. <https://doi.org/10.1016/j.jadohealth.2009.10.011>.
- [4] Keyes KM, Maslowsky J, Hamilton A, Schulenberg J. The great sleep recession: changes in sleep duration among US adolescents, 1991–2012. *Pediatrics* 2015;135(3):460–8. <https://doi.org/10.1542/peds.2014-2707>.
- [5] Millman RP. Excessive sleepiness in adolescents and young adults: causes, consequences, and treatment strategies. *Pediatrics* 2005;115(6):1774–86. <https://doi.org/10.1542/peds.2005-0772>.
- [6] Maume DJ. Social ties and adolescent sleep disruption. *J Health Soc Behav* 2013;54(4):498–515. <https://doi.org/10.1177/0022146513498512>.
- [7] Maslowsky J, Ozer EJ. Developmental trends in sleep duration in adolescence and young adulthood: evidence from a national United States sample. *J Adolesc Health* 2014;54(6):691–7. <https://doi.org/10.1016/j.jadohealth.2013.10.201>.
- [8] Owens J, Au R, Millman R, Wolfson A, Braverman PK, Adelman WP, Breuner CC, Levine DA, Marcell AV, Murray PJ, O'Brien RF, Carskadon M. Insufficient sleep in adolescents and young adults: an update on causes and consequences. *Pediatrics* 2015;134:921–32.

- [9] Wing YK, Chan NY, Yu MWM, Lam SP, Zhang J, Li SX, Kong APS, Li AM. A school-based sleep education program for adolescents: a cluster randomized trial. *Pediatrics* 2015;135(3):e635. <https://doi.org/10.1542/peds.2014-2419>.
- [10] Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. *Sleep* 1993;16(3):258–62. <https://doi.org/10.1093/sleep/16.3.258>.
- [11] Carskadon MA, Acebo C, Jenni OG. Regulation of adolescent sleep: implications for behavior. *Ann N Y Acad Sci* 2004;1021(1):276–91. <https://doi.org/10.1196/annals.1308.032>.
- [12] Malley O', Malley. 7 School start time and its impact on learning and behavior. *Sleep Psychiatr Disord Child Adolesc*. 2008;5.
- [13] Frey S, Balu S, Greusing S, Rothen N, Cajochen C, Yamazaki S. Consequences of the timing of menarche on female adolescent sleep phase preference. *PLoS One* 2009;4(4):e5217. <https://doi.org/10.1371/journal.pone.0005217>.
- [14] Taylor DJ, Jenni OG, Acebo C, Carskadon MA. Sleep tendency during extended wakefulness: insights into adolescent sleep regulation and behavior. *J Sleep Res* 2005;14(3):239–44. <https://doi.org/10.1111/j.1365-2869.2005.00467.x>.
- [15] Sanya EO, Kolo PM, Desalu OO, Bolarinwa OA, Ajiboye PO, Tunde-Ayinmode MF. Self-reported sleep parameters among secondary school teenagers in middle-belt Nigeria. *Niger J Clin Pract* 2015;18(3):337–41. <https://doi.org/10.4103/1119-3077.151737>.
- [16] Adolescent Sleep Needs and Patterns: Research Report and Resource Guide. Published by the National Sleep Foundation. Authored by National Sleep Foundation Sleep and Teens Task Force. Co-chairs: Carskadon M, Roth T. Members: Benca R.M., Dahl R.E., Dement W.C., Mahowald M., Mindell J.A., Wahlstrom K.L., Wolfson A.R. Staff: Sagusti S.D., Spokas M., Gelula R.. 2000.
- [17] Barnes M, Davis K, Mancini M, Ruffin J, Simpson T, Casazza K. Setting adolescents up for success: promoting a policy to delay high school start times. *J Sch Health* 2016;86(7):552–7. <https://doi.org/10.1111/josh.12405>.
- [18] Wheaton AG, Ferro GA, Croft JB. School start times for middle school and high school students — United States, 2011–12 school year. *MMWR (Morb Mortal Wkly Rep)* 2015;64(30):809–13. <https://doi.org/10.15585/mmwr.mm6430a1>.
- [19] Position statements-start school later. 2018. <https://www.startschoollater.net/position-statements.html>.
- [20] Wahlstrom K. School start time and sleepy teens. *Arch Pediatr Adolesc Med* 2010;164(7):676–7. <https://doi.org/10.1001/archpediatrics.2010.122>.
- [21] Wahstrom K. Changing times: findings from the first longitudinal study of later high school start times. *NASSP Bull* 2002;86 (633):3–21. <https://doi.org/10.1177/019263650208663302>.
- [22] Owens JA, Belon K, Moss P. Impact of delaying school start time on adolescent sleep, mood, and behavior. *Arch Pediatr Adolesc Med* 2010;164(7):608–14. <https://doi.org/10.1001/archpediatrics.2010.96>.
- [23] Boergers J, Gable CJ, Owens JA. Later school start time is associated with improved sleep and daytime functioning in adolescents. *J Dev Behav Pediatr* 2014;35(1):11–7. <https://doi.org/10.1097/DBP.0000000000000018>.
- [24] Wahlstrom KL, Dretzke BJ, Gordon, Peterson K, Edwards K, Gdula J. Examining the impact of later high school start times on the health and academic performance of high school students: a multi-site study, 72; 2014.
- [25] Paksarian D, Rudolph KE, He JP, Merikangas KR. School start time and adolescent sleep patterns: results from the US National Comorbidity Survey-adolescent supplement. *Am J Publ Health* 2015;105(7):1351–7. <https://doi.org/10.2105/AJPH.2015.302619>.
- [26] Wheaton AG, Chapman DP, Croft JB. School start times, sleep, behavioral, health, and academic outcomes: a review of the literature. *J Sch Health* 2016;86(5):363–81. <https://doi.org/10.1111/josh.12388>.
- [27] Marx R, Tanner-Smith EE, Davison CM, Ufholz L-A, Freeman J, Shankar R, Newton L, Brown RS, Parpia AS, Cozma I, Hendrikx S. Later school start times for supporting the education, health, and well-being of high school students. *Cochrane Database Syst Rev* 2017;2017(7). <https://doi.org/10.1002/14651858.cd009467.pub2>.
- [28] Wahlstrom KL. Accommodating the sleep patterns of adolescents within current educational structures: an uncharted path Adolescent sleep patterns. Cambridge University Press; 2002.
- [29] Danner F, Phillips B. Adolescent sleep, school start times, and teen motor vehicle crashes. *J Clin Sleep Med* 2008;4(6):533–5. <https://doi.org/10.5664/jcsm.27345>.
- [30] Wang K., Sabia J.J., Cesur R. Sleepwalking Through School: New Evidence on Sleep and Academic Performance. IZA Discussion Paper No. 9829; 2016. Available at SSRN: <https://ssrn.com/abstract=2757919>
- [31] National Sleep Foundation. Sleep in America Poll. Washington DC: National Sleep Foundation; 2006.
- [32] Hinrichs P. When the bell tolls: the effects of school starting times on academic achievement. *Education Finance and Policy* 2011;6 (4):486–507. https://doi.org/10.1162/edfp_a_00045.
- [33] Edwards F. Early to rise? The effect of daily start times on academic performance. *Econ Educ Rev* 2012;31(6):970–83. <https://doi.org/10.1016/j.econedurev.2012.07.006>.
- [34] Carrell SE, Maghakian T, West JE. A's from Zzzz's? The causal effect of school start time on the academic achievement of adolescents. *Am Econ J Econ Pol* 2011;3(3):62–81. <https://doi.org/10.1257/pol.3.3.62>.
- [35] <https://www.academyadmissions.com/requirements/>.
- [36] Undergraduate age diversity at United States Air Force Academy. 2018. <https://www.collegefactual.com/colleges/united-states-air-force-academy/student-life/diversity/chart-age-diversity.html>.
- [37] Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: Failure of the MSLT as a gold standard. *J Sleep Res* 2001;9(1):5–11. <https://doi.org/10.1046/j.1365-2869.2000.00177.x>.
- [38] Lufi D, Tzischinsky O, Hadar S. Delaying school starting time by one hour: some effects on attention levels in adolescents. *J Clin Sleep Med* 2011;7(2):137–43. <https://doi.org/10.5664/jcsm.28100>.
- [39] Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* 2005;62 (6):617. <https://doi.org/10.1001/archpsyc.62.6.617>.
- [40] Anne Grunbaum J, Kann L, Kinchen SA, Williams B, Ross JG, Lowry R, Kolbe L. Youth risk behavior surveillance - United States, 2001. *J Sch Health* 2002;72(8):313–28. <https://doi.org/10.1111/j.1746-1561.2002.tb07917.x>.
- [41] Der MPW. Overnight therapy? The role of sleep in emotional. *Psychol Bull* 2010;135(5):731–48.
- [42] Wahlstrom KL, Berger AT, Widome R. Relationships between school start time, sleep duration, and adolescent behaviors. *Sleep Health* 2017;3(3):216–21. <https://doi.org/10.1016/j.slehd.2017.03.002>.

- [43] Daly BP, Paul Jameson J, Patterson F, McCurdy M, Kirk A, Michael KD. Sleep duration, mental health, and substance use among rural adolescents: developmental correlates. *J Rural Ment Health* 2015;39(2):108–22. <https://doi.org/10.1037/rmh0000033>.
- [44] Winsler A, Deutsch A, Vorona RD, Payne PA, Szklo-Coxe M. Sleepless in fairfax: the difference one more hour of sleep can make for teen hopelessness, suicidal ideation, and substance use. *J Youth Adolesc* 2015;44(2):362–78. <https://doi.org/10.1007/s10964-014-0170-3>.
- [45] Baum KT, Desai A, Field J, Miller LE, Rausch J, Beebe DW. Sleep restriction worsens mood and emotion regulation in adolescents. *J Child Psychol Psychiatry Allied Discip* 2014;55(2):180–90. <https://doi.org/10.1111/jcpp.12125>.
- [46] Gregory AM, Caspi A, Eley TC, Moffitt TE, O'Connor TG, Poulton R. Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *J Abnorm Child Psychol* 2005;33(2):157–63. <https://doi.org/10.1007/s10802-005-1824-0>.
- [47] Clarke G, Harvey AG. The complex role of sleep in adolescent depression. *Child Adolesc Psychiatr Clin N Am* 2012;21(2):385–400. <https://doi.org/10.1016/j.chc.2012.01.006>.
- [48] McMakin DL, Dahl RE, Buysse DJ, Cousins JC, Forbes EE, Silk JS, Siegle GJ, Franzen PL. The impact of experimental sleep restriction on affective functioning in social and nonsocial contexts among adolescents. *J Child Psychol Psychiatry Allied Discip* 2016;57(9):1027–37. <https://doi.org/10.1111/jcpp.12568>.
- [49] Lo JC, Ong JL, Leong RLF, Gooley JJ, Chee MWL. Cognitive performance, sleepiness, and mood in partially sleep deprived adolescents: the need for sleep Study. *Sleep* 2016;39(3):687–98. <https://doi.org/10.5665/sleep.5552>.
- [50] Edwards S, Reeves GM, Fishbein D. Integrative model of the relationship between sleep problems and risk for youth substance use. *Current Addict Rep* 2015;2(2):130–40. <https://doi.org/10.1007/s40429-015-0052-0>.
- [51] Hasler BP, Smith LJ, Cousins JC, Bootzin RR. Circadian rhythms, sleep, and substance abuse. *Sleep Med Rev* 2012;16(1):67–81. <https://doi.org/10.1016/j.smrv.2011.03.004>.
- [52] Hasler BP, Clark DB. Circadian misalignment, reward-related brain function, and adolescent alcohol involvement. *Alcohol Clin Exp Res* 2013;37(4):558–65. <https://doi.org/10.1111/acer.12003>.
- [53] Hasler BP, Soehner AM, Clark DB. Sleep and circadian contributions to adolescent alcohol use disorder. *Alcohol* 2015;49(4):377–87. <https://doi.org/10.1016/j.alcohol.2014.06.010>.
- [54] Berger AT, Widome R, Troxel WM. School start time and psychological health in adolescents. *Curr Sleep Med Rep* 2018;4(2):110–7. <https://doi.org/10.1007/s40675-018-0115-6>.
- [55] Wahlstrom KL. School Start Time Study Technical Report, Volume II: Analysis of Student Survey Data. Center for Applied Research & Educational Improvement, University of Minnesota; 1998.
- [56] Vedaa Ø, Saxvig IW, Wilhelmsen-Langeland A, Bjorvatn B, Pallesen S. School start time, sleepiness and functioning in Norwegian adolescents. *Scand J Educ Res* 2012;56(1):55–67. <https://doi.org/10.1080/00313831.2011.567396>.
- [57] Perkinson-Groo N, Lemola S, Grob A. Sleep duration, positive attitude toward life, and academic achievement: the role of daytime tiredness, behavioral persistence, and school start times. *J Adolesc* 2013;36(2):311–8. <https://doi.org/10.1016/j.adolescence.2012.11.008>.
- [58] Martin JS, Gaudreault MM, Perron M, Laberge L. Chronotype, light exposure, sleep, and daytime functioning in high school students attending morning or afternoon school shifts: an actigraphic study. *J Biol Rhythms* 2016;31(2):205–17. <https://doi.org/10.1177/0748730415625510>.
- [59] Chan NY, Zhang J, Yu MWM, Lam SP, Li SX, Kong APS, Li AM, Wing YK. Impact of a modest delay in school start time in Hong Kong school adolescents. *Sleep Med* 2017;30:164–70. <https://doi.org/10.1016/j.sleep.2016.09.018>.
- [60] Wheaton O, Miller GF, Croft JB. Sleep duration and injury-related risk behaviors among high school students—United States. *Morbidity and mortality weekly report* 2016;65:2007–13.
- [61] Fischer P, Schwartz S., Retting R., Hart A., Forker M., Adkins J., Macek K. Mission Not Accomplished: Teen Safe Driving, the Next Chapter. Report of Governors Highway Safety Association. 2016. Original URL: https://www.ghsa.org/sites/default/files/2016-12/FINAL_TeenReport16.pdf.
- [62] Tefft BC. Prevalence of motor vehicle crashes involving drowsy drivers. 2009.
- [63] Knippling R, Wang J-S. Crashes and Fatalities Related to Driver Drowsiness/Fatigue. U.S. Department of Transportation - National Highway Traffic Safety Administration. Office of Crash Avoidance Research. Research Note.; 1994. https://rosap.ntl.bts.gov/view/dot/2936/dot_2936_DS1.pdf.
- [64] Vorona RD, Szklo-Coxe M, Wu A, Dubik M, Zhao Y, Ware JC. Dissimilar teen crash rates in two neighboring southeastern Virginia cities with different high school start times. *J Clin Sleep Med* 2011;7(2):145–51. <https://doi.org/10.5664/jcsm.28101>.
- [65] Vorona RD, Szklo-Coxe M, Lamichhane R, Ware JC, McNallen A, Leszczyszyn AD. Adolescent crash rates and school start times in two Central Virginia Counties, 2009–2011: a follow-up study to a Southeastern Virginia study, 2007–2008. *J Clin Sleep Med* 2014;10(11):1169–77. <https://doi.org/10.5664/jcsm.4192>.
- [66] Yiannakoulias N, Bland W, Scott DM. Altering school attendance times to prevent child pedestrian injuries. *Traffic Inj Prev* 2013;14(4):405–12. <https://doi.org/10.1080/15389588.2012.716879>.
- [67] Hafner M, Stepanek M, Troxel WM. The economic implications of later school start times in the United States. *Sleep Health* 2017;3(6):451–7. <https://doi.org/10.1016/j.slehd.2017.08.007>.

Part IX

Economic and public policy implications of sleep health

This page intentionally left blank

Chapter 41

Sleep and health in the workplace

Soomi Lee^{a,b}, Chandra L. Jackson^c, Claire E. Smith^d, Rebecca Robbins^{e,f} and Orfeu Marcello Buxton^{b,g}

^aDepartment of Human Development and Family Studies, Pennsylvania State University, University Park, PA, United States; ^bCenter for Healthy Aging, Pennsylvania State University, University Park, PA, United States; ^cEpidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, United States; ^dDepartment of Psychology, University of South Florida, Tampa, FL, United States; ^eDivision of Sleep Medicine, Harvard Medical School, Boston, MA, United States; ^fDivision of Sleep and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital, Boston, MA, United States;

^gDepartment of Biobehavioral Health, Pennsylvania State University, University Park, PA, United States

Introduction

Work factors impact nighttime sleep

For most adults, over 60% of their daily time is spent either working or sleeping (U.S.) [1]. Work is necessary to sustain an economy and provide resources for essentials such as food and shelter that protect individual and family well-being. Ideally, work can also contribute to a sense of purpose, and is an important overall contributor to health and happiness. Yet work can also determine exposure to toxins, pollutants, workplace hazards, psychosocial risks, and other exposures. Work can shape health behaviors, including sleep, which have big-picture implications for organizations via employee performance, safety, attitudes, and health.

Most workers need to follow a cycle of work and rest in contemporary society, meaning work hours dictate times for rest (including sleep) more so than do workers' own needs for downtime and recovery [2]. Long work hours, shift work, and stress and worry from work limit the time and restful states needed for sufficient sleep, ultimately contributing to sleep deficiency among workers. Modifying risk factors for workers' sleep deficiency is a challenge when structural factors, work processes, and pressures are difficult to change. This challenge raises a serious concern for workers' health: sleep deficiency over an extended period of time may lead to increased allostatic load [3], and the excessive wear and tear of continual adaptation.

Sleep impacts work function and productivity

As noted below and elsewhere in this volume, poor sleep health can directly influence productivity by slowing mental activity, degrading cognition and decision-making, and increasing mistakes on the job. Sleep deficiency may also affect workers' affective and social functioning. For example, an experimental laboratory study found that sleep-deprived individuals have more difficulty recognizing nonverbal social cues (e.g., happy and angry faces) than do nonsleep-deprived individuals [4]. Moreover, poor sleep health (e.g., sleep loss, daytime sleepiness) leads to increased mistrust in others [5] by negatively biasing the interpretation of neutral or ambiguous events, which may decrease workplace morale and degrade work team dynamics. Substantial economic costs of untreated insomnia include absenteeism, or missing work [6,7], and presenteeism, or presence at work with low productivity [8], with the total price tag in the magnitude of tens to hundreds of billions annually. Furthermore, poor sleep health, such as short duration and poor quality sleep, circadian rhythm disruption, and sleep disorders may lead to withdrawal from work (i.e., lateness, absence, and turnover) and withdrawal or disengagement while at work (i.e., cognitive and emotional distraction, and work neglect) through daytime sleepiness [9]. As poor sleep reflects poor stress recovery and well-being [10], poor sleep may lead to compromised work productivity [11,12]. In fact, unhealthy sleep may contribute

to unethical behaviors at work by undermining the self-regulatory functioning needed for “right and ethical” decision-making and judgment [6]. Due to these severe and wide-ranging consequences, sleep health is considered a “strategic resource” [13] for organizational success across key indicators such as positive workplace relationships, employee health, and safety and productivity [14].

What theories of work can tell us about modifiable work factors influencing sleep

Despite the recently increasing focus on the work-sleep link, a comprehensive theoretical explanation of this link is lacking. Early organizational science theories, described in greater detail below, including the Job Demand Control (JD-C) model [15] and the Job Demand-Resources (JD-R) model [16,17] explain work characteristics influencing workers’ stress; yet do not focus on workers’ sleep. Several theoretical stress frameworks, such as the Effort-Recovery Model [18], the Cognitive Activation Theory of Stress [19,20], and the Allostatic Load Model [3,21] have also been invoked to explain the link between work experiences and sleep. Together, these theories suggest that time-based (e.g., work hours), thought-based (e.g., rumination), and arousal-based (e.g., anger and stress hormones) processes influence employees’ sleep quantity and quality [6]. Only recently has a theoretical model been proposed that considers work, nonwork (i.e., family and personal life), and sleep as the three major life domains and proposed related mechanisms, specifically time and energy, connecting each [22]. However, less attention has been paid to various contextual factors that may influence the stress and coping mechanisms of worker’s sleep health, such as life-course development, daily routines and activities, and broader societal context. Combining these relevant theories together, in this chapter, we present a novel, interdisciplinary, and comprehensive theoretical model for the mechanisms of stress and coping that influence workers’ sleep health (Fig. 41.2).

This chapter highlights the impact of increasing work demands and decreasing opportunities for good sleep, microlevel effects of work stressors on sleep, workplace intervention effects on sleep, sleep health and workers’ future health risks, work characteristics as a potential contributor to socioeconomic and racial/ethnic disparities in sleep health, potential reasons for and consequences of racial/ethnic disparities in work-sleep relationship, sleep-related workplace interventions, and future research directions.

Epidemiology of sleep and work

Epidemiological studies have shown the links between short self-reported sleep duration and negative health

outcomes, including obesity and metabolism [23,24], cardiovascular health [25–27], and mortality risk [28]. These topics are addressed in detail in chapters ## ##. Most of these studies, however, have examined sleep and health in the general adult population, rather than focusing on the working population. By doing so, there is a lack of knowledge about the prevalence and type of sleep issues among workers whose sleep may be particularly vulnerable. About 40% of workers report a few unwanted awakenings at night per week [29,30], and chapter ## points to directions for future research on sleep to bridge the gap between laboratory and epidemiological studies. While laboratory studies on sleep have tested the effects of sleep deprivation (or sleep restriction) on neurobehavioral performance, metabolism, and psychological health, epidemiological studies have examined the associations of habitual short sleep with mortality risk, obesity and metabolism, cardiovascular disease, and general health and psychosocial stress.

Focusing on sleep duration, there has been a lack of consensus until recently about the criteria for determining “short sleepers” among workers. The American Academy of Sleep Medicine and Sleep Research Society recommend that “adults obtain 7 or more hours of sleep per night on a regular basis to promote optimal health and functioning” [31]. However, according to the National Health Interview Survey in 2004–07, only about 30% of civilian-employed workers had 6 h or less sleep per night [32]. Many epidemiological studies have considered short sleep as less than 6 h per night.

There are hints that workers’ sleep varies by industry and occupation. In a rare study on this topic [32] found that self-reported short sleep duration (≤ 6 h per night) among US workers varied by industry and occupation within industry. Specifically, the prevalence of short sleep duration was greatest for management of companies and enterprises (40.5%), followed by transportation/warehousing (37.1%) and manufacturing (34.8%). Occupational categories with the highest prevalence of short sleep duration included production occupations in the transportation/warehousing industry and installation, maintenance, and repair occupations in both the transportation/warehousing industry and the manufacturing industry. Working in industries and occupations where nonstandard work schedules and long work hours are prevalent may increase the odds of short sleep duration.

Although not based on a national sample, another line of studies focusing on industry-specific implications of work and sleep also shows that the prevalence and nature of poor sleep health differ by industry (Fig. 41.1). The Work, Family, and Health Study [33] examined diverse sleep characteristics contributing to poor sleep health among employees in a Fortune 500 firm in the information

Panel A: Poor Sleep Health in IT Employees

(1 of any component; n=416, 65% N = 637)

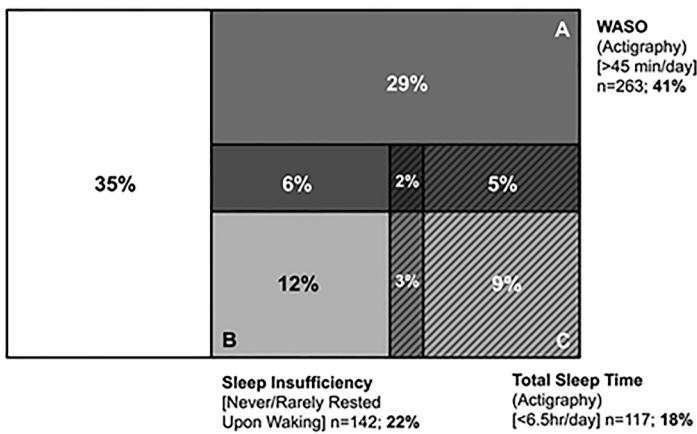
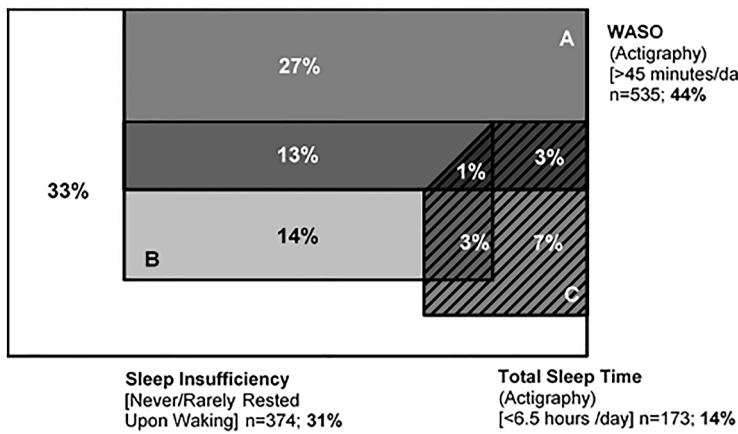


FIGURE 41.1 The prevalence and nature of poor sleep health in the IT (Ref. [33] and extended-care) (Ref. [34]) industry samples of employed adults.

Panel B: Poor Sleep Health in Extended-Care Employees

(1 of any component; n=822, 67% N = 1220)



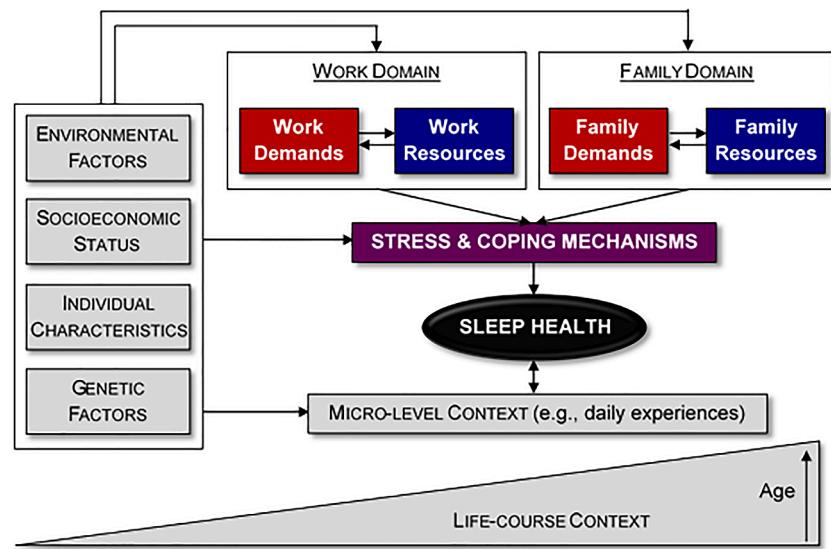
technology (IT) division. They defined poor sleep health as having at least one of the following three components: actigraphy total sleep time <6.5 h/day, actigraphy wake-after-sleep-onset (WASO) > 45 min/day, and self-reported sleep insufficiency (feeling never or rarely rested upon waking). As shown in Panel A of Fig. 41.1, 65% of the IT workers exhibited poor sleep health, including 18% with short sleep duration, 41% with long WASO (disturbed sleep), and 22% perceived sleep insufficiency. When examining these sleep characteristics among employees in the extended-care industry who provide direct care to older residents (Panel B, Fig. 41.1), 67% exhibited poor sleep health [34]. The prevalence of perceived sleep insufficiency (31%) among the extended-care workers was higher than among the IT workers (22%), which may suggest the qualitative aspect of their sleep is poor due to nonstandard and varying work shifts, less schedule control, and high work demands. These sleep

deficiency patterns were related to work-nonwork conflict, and in a randomized controlled trial of a supportive supervisor intervention, actigraph sleep and perceived sleep sufficiency of employees were improved [33], and biomarker-based measures of cardiovascular disease risk were also improved, 1 year later. [35].

The relationship between sleep and work in meta-analyses and representative surveys

Well-designed longitudinal studies reveal that work stress predicts changes in sleep over time, rather than vice versa. Van Laethem et al. [36] conducted a meta-analysis on workplace factors and sleep quality based on 16 of these longitudinal studies. They found strong evidence that high job demands were associated with decreases in sleep quality at follow-up after adjusting for baseline sleep quality. Evidence for high job demands predicting poor

FIGURE 41.2 A theoretical model for the mechanisms of stress and coping that influence workers' sleep health.



sleep (e.g., future sleep disturbances) was also observed in a more recent meta-analysis [37]. These studies suggest adverse effects of one specific workplace factor, effort-reward imbalance [38], on employee sleep, such that employees with higher effort-reward imbalance (i.e., effort invested into work greatly exceeds the rewards received) were more likely to experience sleep disturbances [37]. These findings highlight the importance of balance between demands and resources on the job for employees' sleep health, which closely relates to their stress and coping mechanisms. Results from the American Time Use Study (ATUS), a nationally representative longitudinal survey, suggest that sleep is routinely sacrificed to work tasks (and commuting time) across all sociodemographic strata. Compared to those who get a normal amount of sleep, short sleepers work 90 extra minutes on workdays and approaching 2 h more on non-workdays [39].

Theories of work and work stress that influence sleep

Work stress

Several theories attempt to explain the influence of work stress on workers' health and well-being—though, again, with health conceptualized generally rather than focused on sleep. The JD-C model [15] suggests that a workers' psychological and physical stress is a function of both job demands and job control (e.g., discretion and decision latitude), such that demands and control interactively predict strain. Specifically, the quadrant of high job demands and low job control may result in high-strain jobs. The JD-R model [16,17] expanded on this foundational premise to

(1) more comprehensively include a variety of job resources (i.e., including control but also other relevant resources) and (2) describe not only negative strain processes directly implicated in job demand exposure but also positive motivational process implicated in job resource exposure. The most recent iteration of JD-R also connects both the strain and motivational pathways to job performance [16]. Further, the buffering role of job resources (control) is consistent across JD-C and JD-R. These related perspectives suggest the importance of considering both positive resources and negative demands at work when attempting to understand employee health.

Work is not the only waking domain that affects and is affected by sleep [40]. Yet what is also important, but often forgotten, is the influence of the family home domain, sometimes called "family" or "nonwork." The Work-Home Resources model [41] describes that work and family are interrelated domains and work-family conflict (see the next section for this concept) may occur as a process whereby demands in one domain deplete personal resources (e.g., mood, attention, time, and energy) and impede performance and well-being in the other domain. The Work-Nonwork-Sleep framework echoes some of these same propositions but also extends them to sleep. In this model, attitudes, behaviors, and states across work, nonwork, and sleep are connected via time, a zero-sum resource, and personal energies, specifically physical energy and energetic activation. Extending upon previous theoretical models on work stress, Fig. 41.2 delineates inclusive mechanisms of stress and coping across work and family domains that influence workers' sleep.

Note. The life-course stage influences all aspects of the model. The family domain encompasses the nonwork

aspects of life, including all personal activities and responsibilities.

When work demands exceed work resources, it may create stress that may negatively affect sleep health. Although not specifically outlined in the theory, we propose that this process is transferable to the family domain and will be similar when family demands exceed family resources. On the contrary, when work resources exceed work demands, it may create coping mechanisms for stressful work conditions and thus workers' sleep health may be protected. These processes may affect and be affected by daily microlevel contexts, as well as by broader life-course contexts. For example, the dynamic associations of nightly sleep with daily stressors and physical activities have been reported [10,42]. Moreover, an individual's position in the life course influences sleep health, the extent of demands and resources in both work and family domains, and daily contexts. Environmental, social, individual, and genetic characteristics may also play roles in these mechanisms of stress and coping that influence workers' sleep health (Fig. 41.2).

Work demands and work-family conflict influence sleep

- Longer work hours and shorter sleep

As time is a finite resource, it is not surprising to find a negative association between work hours and sleep hours. In the analysis of the ATUS with a representative cohort of Americans 15+ years between 2003 and 2011, long hours at paid work were associated with shorter sleep hours on weekdays [43]. Further, in a study with medical interns who usually work extended work shifts, an intervention schedule that limited scheduled work hours to 16 or fewer consecutive hours (and encouraged pre-nightshift naps) increased interns' sleep duration on average by 5.8 h per week [44]. This intervention also resulted in fewer attentional failures while working during on-call nights. The timing of work can also affect workers' sleep. Shift work and variable work schedules involve disruptions of circadian rhythms and insufficient sleep during the day [45,46], when it is more difficult to sleep due to the wake-promoting signals from the central circadian pacemaker [47]. Of note, it is often the case for hourly paid employees on night shifts to be of lower socioeconomic status and minorities, reflecting disparities due to the selection process for these less favorably timed shifts [48,49]. Workers with multiple jobs (and multiple shifts) are more likely to be short sleepers (≤ 6 h per night); self-employed workers and those who can start work later in the morning are less likely to be short sleepers [43]. However, there is no linear relationship between socioeconomic status and work hours. Employees with higher education and higher incomes tend to work longer hours by exchanging their sleep time for economic incentives [43]

- The work-life interface and sleep

Work-nonwork "balance" has been shown to be cross-sectionally related to both workplace factors and employee health outcomes (for a systematic review, see Ref. [50]). Demands from both the work domain and the family domain can restrict the time available for sleep. Studies describe sleep as the "victim" in time-based conflict between work and family roles [40]. In particular, the extent to which demands from work permeate into the family domain and interfere with family and personal activities is called work-to-family conflict [51,52]. Note that the family domain includes any nonwork domains, so work-to-family conflict is not just an issue experienced by midlife, married, working parents [53]. Several studies consistently report that workers who experience higher work-to-family conflict have poorer sleep health measured by both self-reports and actigraphy [54–57].

- Interpersonal stressors at work

Some work-related stressors may have sustained effects on workers' sleep health beyond initial exposure. Stressors can leave cognitive stress residues and invoke worried rumination that may contribute to cognitive hyperarousal [58] and therefore lengthen sleep onset latency [59]. Interpersonal stressors are among the most frequent stressors for an average adult [60–63], and are predictive of both affective and physical well-being [64]. Interpersonal stressors may arise in the workplace, for example, in conflicts with colleagues or others, including supervisors [64]. These stressors may linger in workers' minds after work and interfere with their sleep at home. How workers' sleep health is associated with a variety of interpersonal stressors at work (e.g., perceived work inequality, workplace bullying, and job discrimination) is a key avenue for future research, especially with the rapidly changing nature of work as often remote (or not as much at one place as may have been common in the past). Work has also become more "always on," with electronic device-based communications and intrusive social media related to work invading almost any hour of the day and night [65]. Leadership also matters in the workplace; in an Italian workplace sample, leaders who devalue sleep have subordinate employees with lower-quality sleep [66]. There may also be racial/ethnic differences in the experience of interpersonal stressors at work and in sleep health. Later in this chapter, we discuss racial/ethnic disparities in the work-sleep relationship [Link to later section/chapter].

Micro-longitudinal (daily level) effects of work stressors on sleep

Most prior studies examining the associations between work stressors and sleep used cross-sectional data or

prospective data, focusing on between-person differences. For example, individuals who experience more work stressors overall may report poorer sleep than others, on average [54,55,67]. Examining between-person differences is meaningful, but cannot capture within-person differences, which may provide better insights on modifiable factors appropriate for future intervention strategies. For example, within an individual, some days may be more stressful than others, which may affect nightly sleep behavior. If we know the direction of the effect, we may be able to more effectively intervene in the causes and consequences of sleep deficiency in workers' daily context. Crucially, these within-person effects directly convey the range of possible "days" for a given individual, providing both insights and expectations about how and when a workplace intervention or a lifestyle change, for example, might be expected to improve an individual's sleep health.

A daily diary design allows researchers to examine temporal associations, such as day-to-night or night-to-next-day associations between work stressors and sleep [68]. Studies using multiple days' data report bidirectional associations between daily psychosocial experiences (positive and negative affect, positive events, and stressors) and nightly sleep [69]. A study focusing on work-derived stressors in midlife workers reveals more specific directions of the associations that differ across sleep measures [10]. In the aforementioned study, sleep duration and sleep quality were conceptualized as the previous night's sleep recovery, and sleep latency was conceptualized as bedtime rumination and worries that reflect today's stressors and conflicts. The study found that shorter sleep duration and lower sleep quality were associated with next-day consequences of more work-to-family conflict and time-based stressors, whereas longer sleep latencies were predicted by more stressors on that day. Another study found that on days following shorter sleep duration and poorer sleep quality, participants reported more cognitive interference (i.e., ruminating, off-task, and distracting thoughts) than their usual level [70]. With cognitive interference predicting nightly sleep, more same day's cognitive interference was associated with earlier shifts in sleep timing. Findings from this line of work show bidirectional temporal associations between sleep and stress in workers. Examining dynamic changes in sleep and stress is important because even minor consecutive sleep loss can impair daily affective and physical well-being [71].

An emerging line of research combines daily diary or more intensive ecological momentary assessment (EMA) with actigraphy sleep assessment [72,73]. There are still many unanswered questions that can be tested with microlongitudinal data. These data show that subjective sleep (reported through a daily diary or EMA) often does not correlate highly with objective sleep data (measured through actigraphy), suggesting that different sleep

measures may provide unique (nonredundant) information. These intensive data may provide promising avenues to test the mechanisms linking work stressors and nightly sleep. Daily physical activity, momentary dietary choices, and emotional residue are potential factors that may mediate the effect of work stressors on nightly sleep health in workers' everyday life.

Sleep health and workers' future health risks

Workers' sleep may influence their future health outcomes. Work environments can impose different sleep burdens on the workers, which may contribute to health disparities in the long-run context. A recent study shows that workers in extended-care settings (i.e., low-wage workers providing direct care in nursing homes) have poorer sleep health than more advantaged workers in the IT Fortune 500 firms [74]. Poorer sleep health is associated with higher cardiovascular disease risk [25,26,75], and such associations seem more evident for low-wage workers than for higher-wage workers [74]. This is in line with epidemiological evidence suggesting disparities in sleep and cardiovascular health by socioeconomic status [76–78].

Workers' poor sleep health may also predict their functional limitations in later life. Sleep deficiency is found to be associated with higher rates of pain and functional limitations among health care workers, after controlling for socioeconomic, individual, and workplace characteristics [79]. Note that poor sleep habits persist over time [80], and sleep problems usually increase with age [81]. In other words, disrupted sleep behaviors due to work stress may be sustained after retirement and continue to degrade health and functioning in later life. For example, having more insomnia symptoms and taking sleep medications (even physician-prescribed medications) at baseline predict the risk of falling at follow-up, after adjusting for known risk factors of falls [82]. These findings suggest that sleep-related behaviors are critical to understanding age-related changes in health and suggest possible ways to intervene in individuals' sleep and health problems during the second half of life.

Workplace intervention effects on sleep

Business case for sleep: Considering the evidence from the employer point of view

Poor sleep, both insufficient sleep duration and sleep disorders, is a pressing public health issue. The majority of adults in the US report sleeping for less than the recommended 7-h duration [31,83]. Further, research suggests that approximately 30% of adults in the US present with insomnia symptoms, and approximately 10% have received a clinical diagnosis for insomnia [84–86].

Estimates suggest total direct and indirect healthcare costs associated with insomnia to be between \$30 and \$40 billion annually [87,88]. Research also shows a significant healthcare burden of sleep deprivation, estimating total costs associated with insufficient sleep via direct and indirect healthcare cost expenditure to be between 250 and 415 billion US dollars annually [89]. One study found the presenteeism, productivity losses, and safety issues associated with insomnia and insufficient sleep cost an average of \$1967 per employee [90] while other research found presenteeism and productivity losses per employee with untreated insomnia to be equivalent to 11.3 days of lost work or \$2280 lost each year [7]. Using data from a statewide employee health program, research shows employee sleep difficulty is linked with absenteeism, lower workplace productivity, and increased healthcare costs (approximately \$350 more in healthcare costs per 1 unit of sleep difficulty) [91]. Thus poor sleep health is directly linked to adverse workplace outcomes with consequences for employers, including lower productivity and higher healthcare costs.

In addition to insufficient sleep and insomnia, obstructive sleep apnea (OSA) is an increasingly prevalent and costly disorder. According to the National Sleep Foundation, approximately one-third of adults in the US are at high risk for OSA [92], but it is estimated that approximately 80% of individuals with OSA are undiagnosed and untreated [93]. It is estimated that individuals with untreated OSA cost approximately 3.4 billion in medical costs each year [94]. In addition to the healthcare costs associated with untreated OSA, workers with untreated OSA are at significantly greater risk of accident or injury (OR 7.2, 95% confidence interval 2.4–21.8) [95]. Thus, it is evident that employee sleep duration, sleep quality, and treatment of existing sleep disorders are topics deserving the attention of employers from the standpoint of workplace productivity, presenteeism, and healthcare expenditure.

Healthcare spending was reported at 3.3 trillion US dollars and is estimated to continue to grow approximately 5.5% annually to over 5.5 billion US dollars by 2026 [96]. In the US, approximately 60% of the workforce has employer-based health insurance, creating an economic incentive for employers to develop thoughtful, effective workplace-based interventions to address sleep health and sleep disorder screening and care.

Worksite wellness, and the need for more attention to sleep

Most adults spend a large proportion of their waking lives at work or seeking work. For this reason, worksites represent a ready platform for reaching a potentially wide audience with sleep health promotional activities.

Accordingly, the American Heart Association, American Cancer Society, *Healthy People 2020*, National Institute for Occupational Safety and Health, and the Centers for Disease Control (CDC) have issued recommendations for comprehensive worksite health promotion efforts [97–101].

Meta-analysis suggests healthcare spending falls by approximately 3 dollars for every 1 dollar spent on wellness programs, and absenteeism and presenteeism costs fall by approximately 2 dollars for every 1 dollar spent on wellness programs [102]. With the growing attention to sleep as an important factor in overall health and well-being, and the role sleep plays in daytime productivity and cognition, incorporating sleep into employee health behavior change programs may be beneficial for employers.

In addition to reduced costs, worksite wellness efforts to address sleep are critical from the standpoint of injury and accident prevention. Employees on shift work are at particularly high risk for motor vehicle crashes due to drowsiness and circadian misalignment imposed by shift schedules [103]. After an extended work shift, research with medical residents showed a nearly 3 times greater risk for a car accident, and almost 6 times more likely to report a near-miss incident on their way home from an extended shift compared to a regular shift [104]. According to meta-analysis, sleepiness behind the wheel among nonshift workers was associated with approximately 2.5 times greater risk of a motor vehicle crash [105]. Accidents, such as motor vehicle crashes, could happen either at the workplace or on the way to or from work and are a particularly pressing concern for employees in driving-related occupations. Consequently, reducing fatigue among workers, particularly those at greater risk for insufficient sleep and circadian misalignment (such as shift workers), is a critical area of employee health promotion.

Interventions in the workplace to improve employee health outcomes are increasingly common. According to survey data, 90% of worksites in the US featured wellness offerings for employees [106]. According to the meta-analysis conducted by Baicker et al. (2010), the most common worksite wellness programs were weight loss and smoking cessation [102]. Further, in a nationally representative survey of workplaces, more than 20% of worksites reported exercise or nutrition programs, while fewer than 10% reported sleep or fatigue management programs [107]. Moreover, those worksites that had a sleep or fatigue management program for employees were typically larger and with bigger budgets for wellness interventions, suggesting that sleep and fatigue management programs may only be available to employees at well-resourced worksites. In summary, attention to sleep in health behavior change efforts at worksites is under-addressed, yet in workplace-based behavior change. However, in research

assessing readiness to change a variety of health behaviors (e.g., such as quitting smoking and implementing stress management practices), sleep quality was a strong predictor of readiness to change, suggesting sleep may play a role in the initiation of other health practices [91]. Consequently, while underexplored in worksite-based health promotion, employers stand to benefit from incorporating sleep in efforts to improve employee health and well-being. While sleep has many favorable associations with positive health outcomes, sleep is a relatively new component in some workplace-based health programming, especially because of motivating links to weight management, improved physical activity, and other health targets, as well as productivity and injury/accident prevention, along with the subsequent increase in liabilities for the workplace policies, practices and conditions that contribute to fatigue-related errors and mishaps.

To be completely clear, chronic sleep loss directly contributes to sleepiness and “fatigue.” Thus employee and employer motivations can be in alignment with the understanding that adequate restorative sleep is central to workplace readiness. Conversely, failure to enable adequate sleep or to obtain adequate sleep directly contributes to excessive sleepiness and fatigue, and thereby greater risks of accidents, mistakes, and reduced productivity. As one example, “drowsy driving,” which sounds potentially innocuous, is becoming more legally similar to drunken driving and constitutes a source of potential employer liability if fatigue and sleepiness management practices are not in place to counter elevated risks of accidents in sleep-deprived employees.

Worksite programs targeting sleep and sleep-related outcomes

According to the National Institutes of Health and Centers for Disease, comprehensive wellness programs play an important role in advancing population health and can take one of several forms, including efforts to address (1) the work environment’s physical, organizational, or psychosocial components; (2) the work-family-community interface; or (3) individual health-related behaviors [108]. Whereas the health-related behavioral contexts that have been focused on largely have included exercise, smoking, and weight control, there is a growing opportunity to integrate sleep and sleep-related interventions.

Sleep-related workplace initiatives are described in a growing body of literature. The taxonomy offered by Sorensen et al. [108] falls among the three different types of evidence-based workplace wellness programs of work environment, work-family-community interface, or individual health-related initiatives, listed in the examples below, not all of which have shown a favorable or replicated outcome [Table 41.1](#).

Racial ethnic disparities in sleep health and sleep disorders

As defined by the National Institutes of Health, a health disparity—discussed in more detail in Chapter XX—is considered “a health difference that adversely affects defined disadvantaged populations, based on one or more health outcomes” [109]. These health outcome differences (described later) are generally considered preventable and unjust [110]. Socially disadvantaged groups or populations disproportionately affected by health disparities include people who are Black/African American, Hispanic/Latino, Native American/Alaska Native, Asian American, Native Hawaiian and other Pacific Islander, socially disadvantaged populations, underserved rural communities, and minoritized sexual/gender groups [109]. Health outcome differences include a: “Higher incidence or prevalence of disease, including earlier onset or more aggressive progression; premature or excessive mortality from specific conditions; Greater global burden of disease, such as disability-adjusted life years as measured by population health metrics; poorer health behaviors and clinical outcomes related to the aforementioned information; or worse outcomes on validated self-reported measures that reflect daily functioning or symptoms from specific conditions.”

Many minoritized racial/ethnic groups, as well as immigrant groups to the US, are segregated within the labor market into lower-wage and lower-skilled jobs [49,111–114], and racial/ethnic disparities in the work-sleep relationship have been observed. Understanding the impact of occupational characteristics on sleep as a modifiable potential source of health inequity among ethnically diverse groups can help both identify drivers of poor sleep in the overall population and enable the development of more effective sleep-related interventions that improve population health while addressing health disparities. For instance, underresourced groups may have greater exposure to both traditional and unique job-related stressors/hazards (whether physical or social) that could help illuminate pathways linking suboptimal work-related factors to poor sleep. However, few studies have investigated the disparate impact of the apparent bidirectional relationship between sleep and work.

In addition to occupational segregation, racial differences in work-related factors that can affect sleep could arise for myriad reasons that may overlap or prove distinct across racial/ethnic minority groups. For instance, Black adults—who may be at particularly high risk for insufficient sleep-related morbidity and mortality [115]—are more likely than White adults to work nontraditional shifts with nonstandard work schedules (especially night shifts) and to have longer work hours, which can negatively affect health through insufficient sleep duration by, for example, disrupting circadian rhythms and increasing one’s appetite

TABLE 41.1 Examples of workplace interventions to improve sleep.

Workplace interventions	Intervention duration	Intervention components	Findings
Yoga/mindfulness			
de Bruin et al. [153]	1.5-month intervention	Weekly educational and practice sessions combined physical exercise, restorative yoga, and mindfulness meditation	Results showed exposure to the intervention was associated with positive effects for anxiety, depression, sleep quality
Fang & Li [154]	6-month intervention	Weekly yoga educational intervention	Results from participants exposed to the intervention showed improvements in self-reported sleep quality and work stress
Klatt et al. [155]	8-week intervention	Weekly sessions on mindfulness-based yoga and meditation	Results showed significant reductions in self-reported stress, overall sleep, and improved sleep quality
Blue light			
Jensen et al. [156]	10-day intervention	Employees were assigned to receive dynamic light exposure compared to ordinary institutional light	Results revealed no difference between intervention and control in monitored sleep efficiency and melatonin levels, but intervention nurses subjectively rated their sleep as more effective
Rahman et al. [157]	2 nights	Employees were assigned to either control lighting or intervention light	Results suggest objective sleep time was improved, sleep efficiency improved, and wake-after-sleep-onset decreased
Other interventions			
Takahashi et al. [158]	1-week intervention	Workers provided several nap sessions	Results show no significant improvement in nocturnal sleep but did demonstrate improved waking reaction time
Hakola & Harma (Shift timing) [159] Owens et al. [160]	10-day intervention	Shift workers were assigned to either backward-rotating or forward-rotating shift schedules for one shift schedule	Results suggest subjective and objective quality of sleep improved among older adults, and evidence for forward-rotating shift was evident
Olson et al. (Work-nonwork/family conflict) [33]	3-month intervention	Nonwork/family supportive supervisor behaviors in managers and improving schedule control of employees and focus group discussions, role-playing, and games intended to decrease work-nonwork/family conflict by	Results show sleep duration and sleep sufficiency improved in the intervention condition compared to the control usual practice group
Li et al. (CBTI) [161]	1-month intervention	Educational sessions on CBTI principles	Participants reported better subjective sleep quality, although no improvements were identified in sleep quality

for sweet and salty foods or causing the brain's effort-reward system to increase pleasure-seeking behaviors that disrupt sleep [116,117]. Compared with White individuals, Black individuals are also more likely to be employed in positions with low control/high demand and that involve low decision-making power. In addition to being more likely to report racial discrimination [113,118], Black adults are more likely to be among the working poor as defined by individuals with incomes that fell below the official poverty level despite spending at least 27 weeks in the labor force [119]. Among minoritized racial/ethnic groups (especially Hispanics/Latinos), assimilation and acculturation to standard US culture (work-related and beyond) also likely influence health beliefs and behaviors that can affect sleep quantity and quality [120]. Acculturative stress is considered the main pathway [121].

Experiences with voluntary or involuntary extended work hours likely vary across all racial/ethnic groups. For instance, a study using 2010 National Health Interview Study data found that White employees (20.9% [20.0%–22.0%]) were more likely than Asian employees (16.6% [13.9%–19.9%]) to formally work at least 48 h per week with a similar percentage (6.2% [5.6%–6.8%] for Whites and 6.7% [(5.0%–8.8%)] for Asians) working in temporary positions, and slightly more likely to work at least 60 h per week as well as engage in alternative shift work although these differences were nonsignificant [122]. With the potential for a differential impact by race/ethnicity, technology (e.g., internet with email capabilities and cellular phones) may have also increased the virtual accessibility of employees in ways that increase job strain as well as disrupt sleep [123,124]. For cultural reasons, some groups could be more likely than others to feel a particular pressure to be more responsive to succeed in workplace settings, which can conceivably increase psychosocial stress and displace sleep.

A prior study investigated whether short sleepers who worked nonstandard shifts other than day shift only were more likely to report hypertension and if the relationship varied by race among Black and White adults, where 11.0% reported rotating shift work and 4.0% reported night shift work. Shift work was associated with a 35% increased odds of hypertension among Black individuals (Odds Ratio = 1.35, Confidence Interval: 1.06–1.72), but not among White individuals (OR = 1.01, CI: 0.85–1.20), and Black shift workers sleeping less than 6 h had an 81% increased odds of reporting hypertension (OR = 1.81, CI: 1.29–2.54, $P < .01$), while White shift workers did not (OR = 1.17, CI: 0.90–1.52, NS) [125]. Furthermore, Jackson et al. found that Black adults, compared to White adults, were more likely to be short sleepers across occupational classes within various categories of employment industries such as manufacturing, education, and

healthcare [126,127]. The prevalence of short sleep duration was highest among professionals due to short sleep generally increasing with increasing professional roles based on occupational class (i.e., professional, support services, and laborers) within a given industry among Black individuals, whereas short sleep prevalence decreased with increasing professional roles for White individuals. Although short sleep duration among Hispanics/Latinos appeared generally similar to Whites, the occupational pattern observed among Black employees was, on average, similar among Hispanics/Latino employees [128]. Perhaps, the high prevalence of short sleep duration among professional Black adults and Hispanic/Latino adults can be attributed, in part, to limited professional/social networks that can provide emotional and financial support, discrimination in the workplace, the perceived high work ethic needed to succeed, and/or greater work-to-family conflict. When effort is not supported by potentially mitigating resources (e.g., financial and emotional support), a strong work ethic among marginalized groups may emerge as a coping strategy that causes strain in response to psychosocial and environmental stressors (e.g., career concerns and racism). This phenomenon, referred to as John Henryism, may be damaging to health through, among other factors, poor sleep that causes physiological dysregulation and adverse health outcomes [129,130].

Furthermore, the 2010 *Sleep in America* poll found that Hispanics/Latinos (38%) were the most likely compared to Blacks (33%), Whites (28%), and Asians (25%) to report being kept awake due to concerns related to employment, finances, personal relationship or health-related concerns [131]. Among 147 Latino farmworkers in North Carolina, most (83%) reported good sleep quality, and the association between working more than 40 h per week and reporting poor sleep quality approached statistical significance. A previous study has also found that short sleep was similar between Mexican-American and White adults, but that non-Mexican Latinos were more likely to be habitual short sleepers [132]. Similar to the "healthy worker" effect, Latino laborers could represent a highly select group of particularly healthy and young individuals with minimal sleep disturbances. Acculturation and cultural factors (e.g., religious beliefs and practices, strong work ethic) may influence factors (e.g., stress levels) that have been shown to influence sleep [133]. For some Latino heritages, traditional sleep habits such as "siestas" may still be practiced, thus increasing the quantity of total sleep [134]. Heterogeneity in sleep patterns of distinct Latino ethnic groups may also confound observed associations [135].

Another study that was nationally representative of the US and conducted among Asian and White individuals showed that Asian American adults had an overall age-adjusted prevalence of short sleep duration that was

higher than their White counterparts, which varied importantly by both industry and occupation with the largest gap observed in the Finance/Information industry, and that the socioeconomic pattern was similar to White adults with generally lower levels of short sleep among professionals [128]. A study among 3510 employees (2371 males and 1139 females) aged 20–65 years working in a local Japanese government evaluated whether work, family, behavioral, and sleep quality characteristics differed with varying time in bed (TIB). They found that high job demands, long work hours, and high work-to-family conflict were more prevalent among those with short TIB while those with long TIB had daily drinking habits. Participants with short TIB had poor sleep largely attributed to poor subjective sleep quality and daytime dysfunction, and those with long TIB had poor sleep largely due to long sleep latency, poor sleep efficiency, and sleep disturbances.

Previous studies also suggest that sleep patterns among employed immigrants to the US, regardless of race, may differ importantly from individuals born in the US [49,112,128,136,137], with immigrant status generally shown to be independently associated with a higher likelihood of short sleep [137]. For instance, a nationally representative sample of the US found that White immigrant workers had longer sleep durations than US-born White workers, and Black immigrant workers had a higher prevalence of short sleep than US-born Black workers, for whom the prevalence of short sleep was higher than other US-born groups. Certain immigrant populations could forgo sleep to work longer hours to, for instance, send remittances to their home country.

Overall, occupational factors may contribute to racial/ethnic disparities in sleep health because of differential access to power, prestige, and tangible/intangible resources across racial/ethnic groups [138,139]. For instance, occupational status is influenced by factors that have been shown to vary substantially by race. For example, differences in educational attainment create differential access to and use of information and knowledge (health related and beyond), and income creates differences through differential access to quality education, as well as to material goods and services. Racial/ethnic disparities in sleep may also be propagated through differential exposure to social hazards in the workplace that produce or further exacerbate stressors that impair sleep on a daily basis. For instance, exposure to everyday and major forms of racial/ethnic discrimination/harassment in the workplace and in society may play an important role in producing psychosocial stress related to job strain or limited control over job demands/prestige in ways that affect sleep [140,141]. In fact, a study by Lee et al. found that the social stressor of perceived racial/ethnic job discrimination, which may affect work productivity and decision-making, was related to degraded sleep health over time among employed

women [142]. Of note, most prior studies that include minoritized racial/ethnic groups have been cross-sectional, and disadvantaged groups may be generally more likely to have comorbid conditions (e.g., obesity, type 2 diabetes, sleep apnea) that could also result in less, poorer quality sleep, and these health conditions have been shown to influence one's working conditions [143].

In conclusion, poor sleep (mainly based on short sleep duration) has been shown to vary importantly by race, socioeconomic status, and immigrant status across various occupations and industries. These complex and preventable differences reflect the need to identify as well as understand structural and sociocultural factors that may influence differences in the work-sleep relationship to effectively address disparities in sleep or optimal health and productivity among workers in the US.

Future research topics and directions

We propose four key directions for future research on Sleep Health and the Workplace: (1) identifying how work characteristics and workers' sleep health are linked over time, (2) applying advanced research designs and methods for examining sleep health and work, (3) developing sleep-focused interventions for workers, and (4) examining sleep health disparities in the working population by industry, occupation, and socioeconomic status. As Litwiler et al. noted in their meta-analysis linking sleep duration and quality to a wide range of work-related antecedents and outcomes: "The demonstrated importance of sleep indicates that it should be a critical part of theory being developed about the biggest organizational challenges of our time" [144].

First, as many of the authors in this book have suggested, more longitudinal studies are needed to understand how work and sleep health are associated over time. Although nonexperimental longitudinal studies cannot determine causality, rigorously designed studies can provide information on the temporal association between a predictor and an outcome and rule out confounding variables. For example, when baseline level of sleep is controlled, we can test whether work demands predict changes in worker's sleep at a follow-up. Longitudinal studies that encompass multiple time points over a long period of time can also answer life-course-related questions, whether and how new employment, unemployment, and retirement affect individual sleep patterns. To better understand workers' sleep, it is also necessary to consider factors in the family and personal domains. Family researchers have begun to examine the interplay between sleep and family life [145]. Work and family are both the most salient contexts for adult health and well-being [146]. In particular, in couple relationships, a worker's sleep may affect and be affected by his/her partner's sleep [147,148].

As such, researchers are encouraged to take interdisciplinary perspectives to comprehensively capture work, family, and personal factors contributing to workers' sleep health.

Second, future research on work and sleep health may benefit from applying advanced research designs and methods. Most previous studies have used self-reported sleep measures. Self-reported sleep variables provide information on perceived sleep; however, they may be prone to self-report bias. This raises a concern about common-method bias when examining the relationship between reported work characteristics and reported sleep [149]. Actigraphy is an objective and nonintrusive method of monitoring sleep and activity patterns in population-based studies. Actigraphy has been increasingly used in sleep-related studies since the early 1990s [150]. Actigraphy offers valid and reliable results across studies that are highly correlated with those of polysomnography and has been used as a gold standard in the diagnosis of sleep disorders in laboratory settings [151]. Actigraphy is easy to use (e.g., wearing an accelerometer device on the nondominant wrist), interfering less with usual activities by participants. Thus, this method may be particularly valuable in studying the sleep health of workers who generally have a busy schedule around the clock. Moreover, actigraphy data can complement self-report data by providing in-depth information on various aspects of sleep health (e.g., sleep duration, the amount of WASO, sleep timing, daytime napping, and variability in sleep) [152]. This information becomes even more valuable when combined with diary data on participants' daily work and nonwork experiences [145]. Taken together, the use of multiple sophisticated methods may advance future research on work and sleep health.

Third, developing sleep-focused interventions for employees that draw on best practices in workplace-based health promotion and behavior change represents a promising future direction for research and practice. Directly considering the role of sleep in employee health and well-being, stress management, and personal impact on nonwork life is an engaging topic, fosters community and a commitment to the organization and coworkers, and demonstrates employers "get it." For productivity-focused employers (and who is not and likely to stay in business?), and especially those in safety-critical sectors, the essential role of adequate, restorative sleep on a regular basis can be an important component of workplace programs and policies to promote a safe workplace with fewer accidents and mistakes, and ultimately greater productivity. As noted by several national associations, including the American Heart Association and CDC, the workplace is a critical context for promoting health. Work is a place where many adults spend a large proportion of their waking lives, and employee sleep health is directly related to workplace-related outcomes,

including alertness and productivity, making sleep a potentially useful outcome for interventions. Future research drawing upon evidence-based approaches, such as cognitive behavioral therapy for insomnia, could improve employee sleep health and associated workplace productivity. It may be interesting to also consider approaches such as mindfulness-based stress reduction or yoga for improving health while also improving sleep. Targeting interventions toward improved employee sleep is a promising area for future research and practice.

References

- [1] Table 8B. Time spent in primary activities for the civilian population 18 years and over by presence and age of youngest household child and sex, 2023 annual averages, employed - 2023 A01 results. 2024.
- [2] Zijlstra FRH, Sonnentag S. After work is done: psychological perspectives on recovery from work. *Eur J Work Organ Psychol* 2006;15(2):129–38.
- [3] Ganster DC, Rosen CC. Work stress and employee health: a multidisciplinary review. *J Manag* 2013.
- [4] van der Helm E, Gujar N, Walker MP. Sleep deprivation impairs the accurate recognition of human emotions. *Sleep* 2010;33:335–42.
- [5] Anderson C, Dickinson DL. Bargaining and trust: the effects of 36-h total sleep deprivation on socially interactive decisions. *J Sleep Res* 2010;19(1-Part-I):54–63.
- [6] Driver HS. Sleep disorders at work. In: Barling J, Barnes CM, Carleton EL, et al., editors. *Work and sleep: research insights for the workplace*. New York, NY, US: Oxford University Press; 2016. p. 31–51.
- [7] Ozminkowski RJ, Wang S, Walsh JK. The direct and indirect costs of untreated insomnia in adults in the United States. *Sleep* 2007;30 (3):263–73.
- [8] Kessler RC, Berglund PA, Coulouvrat C, et al. Insomnia and the performance of US workers: results from the America insomnia survey. *Sleep* 2011;34(9):1161–71.
- [9] Mullins HM, Cortina JM, Drake CL, et al. Sleepiness at work: a review and framework of how the physiology of sleepiness impacts the workplace. *J Appl Psychol* 2014;99(6):1096–112.
- [10] Lee S, Crain TL, McHale SM, et al. Daily antecedents and consequences of nightly sleep. *J Sleep Res* 2017;26(4):498–509.
- [11] Christian MS, Ellis APJ. Examining the effects of sleep deprivation on workplace deviance: a self-regulatory perspective. *Acad Manag J* 2011;54(5):913–34.
- [12] Barnes CM, Schaubroeck J, Huth M, et al. Lack of sleep and unethical conduct. *Organ Behav Hum Decis Process* 2011;115 (2):169–80.
- [13] Barnes CM, Spreitzer G. Why sleep is a strategic resource. *Mit Sloan Manage Rev* 2015;56(2):19–21.
- [14] Barnes CM, Watson NF. Why healthy sleep is good for business. *Sleep Med Rev* 2019;47:112–8.
- [15] Karasek R. Job demands, job decision latitude and mental strain: implications for job redesign. *Adm Sci Q* 1979;24:285–308.
- [16] Bakker AB, Demerouti E. The Job Demands-Resources model: state of the art. *J Manag Psychol* 2007;22(3):309–28.

- [17] Demerouti E, Bakker AB, Nachreiner F, et al. The job demands-resources model of burnout. *J Appl Psychol* 2001;86(3):499–512.
- [18] Meijman TF, Mulder G. Psychological aspects of workload. In: Drenth PJD, Thierry H, de Wolff CJ, editors. *Handbook of work and organizational psychology*. Hove, East Sussex: Psychology Press Ltd; 1998.
- [19] Meurs JA, Perrewé PL. Cognitive activation theory of stress: an integrative theoretical approach to work stress. *J Manag* 2010;37(4):1043–68.
- [20] Ursin H, Eriksen HR. Cognitive activation theory of stress. *Psychoneuroendocrinology* 2010;34(6):877–81.
- [21] McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. *Ann N Y Acad Sci* 1998;840:33–44.
- [22] Crain TL, Brossot RM, Fisher GG. Work, nonwork, and sleep (WNS): a review and conceptual framework. *J Bus Psychol* 2018;33(6):675–97.
- [23] Hall MH, Muldoon MF, Jennings JR, et al. Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. *Sleep* 2008;31(5):635–43.
- [24] Knutson KL, Spiegel K, Penev P, et al. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007;11(3):163–78.
- [25] Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* 2006;47(5):833–9.
- [26] Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the sleep Heart health study. *Sleep* 2006;29(8):1009–14.
- [27] Meisinger C, Heier M, Löwel H, et al. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg Cohort study. *Sleep* 2007;30(9):1121–7.
- [28] Grandner MA, Drummond SP. Who are the long sleepers? Towards an understanding of the mortality relationship. *Sleep Med Rev* 2007;11(5):341–60.
- [29] Swanson LM, Arnedt JT, Rosekind MR, et al. Sleep disorders and work performance: findings from the 2008 National Sleep Foundation Sleep in America poll. *J Sleep Res* 2011;20(3):487–94.
- [30] Grandner MA, Patel NP, Gehrmann PR, et al. Problems associated with short sleep: bridging the gap between laboratory and epidemiological studies. *Sleep Med Rev* 2010;14(4):239–47.
- [31] Watson NF, Badr MS, Belenky G, et al. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of sleep medicine and sleep research society. *Sleep* 2015;38(6):843–4.
- [32] Luckhaupt SE, Tak S, Calvert GM. The prevalence of short sleep duration by industry and occupation in the National Health Interview Survey. *Sleep* 2010;33(2):149–59.
- [33] Olson R, Crain TL, Bodner TE, et al. A workplace intervention improves sleep: results from the randomized controlled Work, Family, and Health Study. *Sleep Health* 2015;1(1):55–65.
- [34] Marino M, Killerby M, Lee S, et al. The effects of a cluster randomized controlled workplace intervention on sleep and work-family conflict outcomes in an extended care setting. *Sleep Health* 2016;2(4):297–308.
- [35] Berkman LF, Kelly EL, Hammer LB, et al. Employee cardiometabolic risk following a cluster-randomized workplace intervention from the work, family and health network, 2009–2013. *Am J Publ Health* 2023;113(12):1322–31.
- [36] Van Laethem M, Beckers DG, Kompier MA, et al. Psychosocial work characteristics and sleep quality: a systematic review of longitudinal and intervention research. *Scand J Work Environ Health* 2013;39(6):535–49.
- [37] Linton SJ, Kecklund G, Franklin KA, et al. The effect of the work environment on future sleep disturbances: a systematic review. *Sleep Med Rev* 2015;23:10–9.
- [38] Siegrist J, Starke D, Chandola T, et al. The measurement of effort-reward imbalance at work: European comparisons. *Soc Sci Med* 2004;58(8):1483–99.
- [39] Basner M, Fomberstein KM, Razavi FM, et al. American time use survey: sleep time and its relationship to waking activities. *Sleep* 2007;30(9):1085–95.
- [40] Barnes CM, Wagner DT, Ghuman S. Borrowing from sleep to pay work and family: expanding time-based conflict to the broader nonwork domain. *Pers Psychol* 2012;65(4):789–819.
- [41] Stepnowsky Jr CJ, Moore PJ, Dimsdale JE. Effect of ethnicity on sleep: complexities for epidemiologic research. *Sleep* 2003;26(3):329–32.
- [42] Master L, Nye RT, Lee S, et al. Bidirectional, daily temporal associations between sleep and physical activity in adolescents. *Sci Rep* 2019;9(1):7732.
- [43] Basner M, Spaeth AM, Dinges DF. Sociodemographic characteristics and waking activities and their role in the timing and duration of sleep. *Sleep* 2014;37(12):1889–906.
- [44] Lockley SW, Cronin JW, Evans EE, et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. *N Engl J Med* 2004;351(18):1829–37.
- [45] Akerstedt T. Shift work and disturbed sleep/wakefulness. *Occup Med* 2003;53(2):89–94.
- [46] Sallinen M, Kecklund G. Shift work, sleep, and sleepiness - differences between shift schedules and systems. *Scand J Work Environ Health* 2010;36(2):121–33.
- [47] Czeisler CA, Buxton OM. The human circadian timing system and sleep-wake regulation. Elsevier; 2017.
- [48] Buxton OM, Okechukwu CA. Long working hours can be toxic. *Lancet Diabetes Endocrinol* 2015;3(1):3–4.
- [49] Ertel KA, Berkman LF, Buxton OM. Socioeconomic status, occupational characteristics, and sleep duration in African/Caribbean immigrants and US white health care workers. *Sleep* 2011;34(4):509–18.
- [50] Nijp HH, Beckers DG, Geurts SA, et al. Systematic review on the association between employee worktime control and work-non-work balance, health and well-being, and job-related outcomes. *Scand J Work Environ Health* 2012.
- [51] Netemeyer RG, Boles JS, McMurrian R. Development and validation of work-family conflict and family-work conflict scales. *J Appl Psychol* 1996;81(4):400–10.
- [52] Voydanoff P. Work demands and work-to-family and family-to-work conflict: direct and indirect relationships. *J Fam Issues* 2005;26(6):707–26.
- [53] Barnes CM. Working in our sleep: sleep and self-regulation in organizations. *Organ Psychol Rev* 2012;2:234–57.
- [54] Berkman LF, Liu SY, Hammer L, et al. Work-family conflict, cardiometabolic risk, and sleep duration in nursing employees. *J Occup Health Psychol* 2015;20(4):420–33.

- [55] Buxton OM, Lee S, Beverly C, et al. Work-family conflict and employee sleep: evidence from IT workers in the work, family and health study. *Sleep* 2016;39(10):1871–82.
- [56] Cummings DM, Adams A, Halladay J, et al. Race-specific patterns of treatment intensification among hypertensive patients using home blood pressure monitoring: analysis using defined daily doses in the Heart healthy lenoir study. *Ann Pharmacother* 2018.
- [57] Jacobsen HB, Reme SE, Sembajwe G, et al. Work-family conflict, psychological distress, and sleep deficiency among patient care workers. *Workplace Health Saf* 2014;62(7):282–91.
- [58] Espie CA. Insomnia: conceptual issues in the development, persistence, and treatment of sleep disorder in adults. *Annu Rev Psychol* 2002;53:215–43.
- [59] Åkerstedt T, Kecklund G, Axelsson J. Impaired sleep after bedtime stress and worries. *Biol Psychol* 2007;76(3):170–3.
- [60] Birditt KS, Fingerman KL, Almeida DM. Age differences in exposure and reactions to interpersonal tensions: a daily diary study. *Psychol Aging* 2005;20(2):330–40.
- [61] Bolger N, DeLongis A, Kessler RC, et al. Effects of daily stress on negative mood. *J Pers Soc Psychol* 1989;57(5):808–18.
- [62] Clark LA, Watson D. Mood and the mundane: relations between daily life events and self-reported mood. *J Pers Soc Psychol* 1988;54(2):296–308.
- [63] Repetti RL. Short-term effects of occupational stressors on daily mood and health complaints. *Health Psychol* 1993;12(2):125–31.
- [64] Potter PT, Smith BW, Strobel KR, et al. Interpersonal workplace stressors and well-being: a multi-wave study of employees with and without arthritis. *J Appl Psychol* 2002;87(4):789–96.
- [65] Pfeffer J. Dying for a paycheck: how modern management harms employee health and company performance—and what we can do about it. New York, NY: HarperBusiness; 2018.
- [66] Barnes CM, Awtry E, Lucianetti L, et al. Leader sleep devaluation, employee sleep, and unethical behavior. *Sleep Health* 2020;6(3):411–417 e415.
- [67] Berkman LF, Buxton O, Ertel K, et al. Managers' practices related to work-family balance predict employee cardiovascular risk and sleep duration in extended care settings. *J Occup Health Psychol* 2010;15(3):316–29.
- [68] Lee S, Almeida DM. Daily diary design. In: Whitbourne SK, editor. Encyclopedia of adulthood and aging. Oxford, UK: Wiley-Blackwell; 2016. p. 297–300.
- [69] Sin NL, Almeida DM, Crain TL, et al. Bidirectional, temporal associations of sleep with positive events, affect, and stressors in daily life across a week. *Ann Behav Med* 2017;51(3):402–15.
- [70] Lee S, Buxton OM, Andel R, et al. Bidirectional associations of sleep with cognitive interference in employees' work days. *Sleep Health* 2019;5(3):298–308.
- [71] Lee S. Naturally occurring consecutive sleep loss and day-to-day trajectories of affective and physical well-being. *Ann Behav Med* 2022;56(4):393–404.
- [72] Baron KG, Reid KJ, Zee PC. Exercise to improve sleep in insomnia: exploration of the bidirectional effects. *J Clin Sleep Med* 2013;9(8):819–24.
- [73] Russell C, Wearden AJ, Fairclough G, et al. Subjective but not actigraphy-defined sleep predicts next-day fatigue in chronic fatigue syndrome: a prospective daily diary study. *Sleep* 2016;39(4):937–44.
- [74] Buxton OM, Lee S, Marino M, et al. Sleep health and predicted cardiometabolic risk scores in employed adults from two industries. *J Clin Sleep Med* 2018;14(3):371–83.
- [75] Cappuccio FP, Stranges S, Kandala NB, et al. Gender-specific associations of short sleep duration with prevalent and incident hypertension: the Whitehall II Study. *Hypertension* 2007;50(4):693–700.
- [76] Canivet C, Nilsson PM, Lindeberg SI, et al. Insomnia increases risk for cardiovascular events in women and in men with low socioeconomic status: a longitudinal, register-based study. *J Psychosom Res* 2014;76(4):292–9.
- [77] St-Onge MP, Grandner MA, Brown D, et al. Sleep duration and quality: impact on lifestyle behaviors and cardiometabolic health: a scientific statement from the American Heart Association. *Circulation* 2016;134(18):e367–86.
- [78] Pillai V, Steenburg LA, Ciesla JA, et al. A seven day actigraphy-based study of rumination and sleep disturbance among young adults with depressive symptoms. *J Psychosom Res* 2014;77(1):70–5.
- [79] Buxton OM, Hopcia K, Sembajwe G, et al. Relationship of sleep deficiency to perceived pain and functional limitations in hospital patient care workers. *J Occup Environ Med* 2012;54(7):851–8.
- [80] Breslow L, Enstrom JE. Persistence of health habits and their relationship to mortality. *Prev Med* 1980;9(4):469–83.
- [81] Ohayon MM, Carskadon MA, Guilleminault C, et al. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep* 2004;27(7):1255–73.
- [82] Chen TY, Lee S, Buxton OM. A greater extent of insomnia symptoms and physician-recommended sleep medication use predict fall risk in community-dwelling older adults. *Sleep* 2017;40(11).
- [83] Liu Y, Wheaton AG, Chapman DP, et al. Prevalence of healthy sleep duration among adults - United States, 2014. *Morb Mortal Wkly Rep* 2016;65(6):137–41.
- [84] Morin CM, Bootzin RR, Buysse DJ, et al. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). *Sleep* 2006;29(11):1398–414.
- [85] Morin CM, Jarrin DC. Insomnia and healthcare-seeking behaviors: impact of case definitions, comorbidity, sociodemographic, and cultural factors. *Sleep Med* 2013;14(9):808–9.
- [86] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6(2):97–111.
- [87] Chilcott LA, Shapiro CM. The socioeconomic impact of insomnia. An overview. *Pharmacoeconomics* 1996;10(Suppl. 1):1–14.
- [88] Hafner M, Stepanek M, Taylor J, et al. Why sleep matters—the economic costs of insufficient sleep: a cross-country comparative analysis. *Rand Health Quarterly* 2017;6(4):11.
- [89] Rosekind MR, Gregory KB. Insomnia risks and costs: health, safety, and quality of life. *Am J Manag Care* 2010;16(8):617–26.
- [90] Rosekind MR, Gregory KB, Mallis MM, et al. The cost of poor sleep: workplace productivity loss and associated costs. *J Occup Environ Med* 2010;52(1):91–8.
- [91] Hui SK, Grandner MA. Trouble sleeping associated with lower work performance and greater health care costs: longitudinal data from Kansas state employee wellness program. *J Occup Environ Med* 2015;57(10):1031–8.

- [92] Hiestand DM, Britz P, Goldman M, et al. Prevalence of symptoms and risk of sleep apnea in the US population: results from the national sleep foundation sleep in America 2005 poll. *Chest* 2006;130(3):780–6.
- [93] Young T, Evans L, Finn L, et al. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 1997;20(9):705–6.
- [94] Kapur V, Blough DK, Sandblom RE, et al. The medical cost of undiagnosed sleep apnea. *Sleep* 1999;22(6):749–55.
- [95] Connor J, Whitlock G, Norton R, et al. The role of driver sleepiness in car crashes: a systematic review of epidemiological studies. *Accid Anal Prev* 2001;33(1):31–41.
- [96] Cuckler GA, Sisko AM, Poisal JA, et al. National health expenditure projections, 2017–26: despite uncertainty, fundamentals primarily drive spending growth. *Health Aff* 2018;37(3):482–92.
- [97] Katz DL, O'Connell M, Yeh MC, et al. Public health strategies for preventing and controlling overweight and obesity in school and worksite settings: a report on recommendations of the Task Force on Community Preventive Services. *Morb Mortal Wkly Rep* 2005;54(RR-10):1–12.
- [98] Maslowsky J, Ozer EJ. Developmental trends in sleep duration in adolescence and young adulthood: evidence from a national United States sample. *J Adolesc Health* 2014;54(6):691–7.
- [99] Koh HK. A 2020 vision for healthy people. *N Engl J Med* 2010;362(18):1653–6.
- [100] Sorensen G, Barbeau E. Steps to a healthier US workforce: integrating occupational health and safety and worksite health promotion: state of the science. In: National Institute of occupational safety and health steps to a healthier US workforce symposium; 2004.
- [101] Carnethon M, Whitsel LP, Franklin BA, et al. Worksite wellness programs for cardiovascular disease prevention: a policy statement from the American Heart Association. *Circulation* 2009;120(17):1725–41.
- [102] Baicker K, Cutler D, Song Z. Workplace wellness programs can generate savings. *Health Aff* 2010;29(2):304–11.
- [103] Garbarino S, De Carli F, Nobili L, et al. Sleepiness and sleep disorders in shift workers: a study on a group of Italian police officers. *Sleep* 2002;25(6):648–53.
- [104] Barger LK, Cade BE, Ayas NT, et al. Extended work shifts and the risk of motor vehicle crashes among interns. *N Engl J Med* 2005;352:125–34.
- [105] Bioulac S, Franchi JM, Arnaud M, et al. Risk of motor vehicle accidents related to sleepiness at the wheel: a systematic review and meta-analysis. *Sleep* 2017;40(10).
- [106] Linnan L, Bowling M, Childress J, et al. Results of the 2004 national worksite health promotion survey. *Am J Publ Health* 2008;98(8):1503–9.
- [107] Robbins R, Weaver MD, Quan SF, et al. Employee sleep enhancement and fatigue reduction programs: analysis of the 2017 CDC workplace health in America poll. *Am J Health Promot* 2021;35(4):503–13.
- [108] Sorensen G, Stoddard AM, Stoffel S, et al. The role of the work context in multiple wellness outcomes for hospital patient care workers. *J Occup Environ Med* 2011;53(8):899–910.
- [109] Duran DG, Perez-Stable EJ. Novel approaches to advance minority health and health disparities research. *Am J Publ Health* 2019;109(S1):S8–10.
- [110] Braveman P. What are health disparities and health equity? We need to be clear. *Publ Health Rep* 2014;129(Suppl. 2):5–8.
- [111] Chung-Bridges K, Muntaner C, Fleming LE, et al. Occupational segregation as a determinant of US worker health. *Am J Ind Med* 2008;51(8):555–67.
- [112] Hurtado DA, Sabbath EL, Ertel KA, et al. Racial disparities in job strain among American and immigrant long-term care workers. *Int Nurs Rev* 2012;59(2):237–44.
- [113] Krieger N, Waterman PD, Hartman C, et al. Social hazards on the job: workplace abuse, sexual harassment, and racial discrimination—a study of Black, Latino, and White low-income women and men workers in the United States. *Int J Health Serv* 2006;36(1):51–85.
- [114] Orrenius PM, Zavodny M. Do immigrants work in riskier jobs? *Demography* 2009;46(3):535–51.
- [115] Yoon IY, Song BG. Role of morning melatonin administration and attenuation of sunlight exposure in improving adaptation of night-shift workers. *Chronobiol Int* 2002;19(5):903–13.
- [116] Sharma S, Kavuru M. Sleep and metabolism: an overview. *Internet J Endocrinol* 2010;2010.
- [117] St-Onge MP, McReynolds A, Trivedi ZB, et al. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. *Am J Clin Nutr*. 2012;95(4):818–24.
- [118] Williams DR, Mohammed SA. Discrimination and racial disparities in health: evidence and needed research. *J Behav Med* 2009;32(1):20–47.
- [119] Statistics USBoL. A profile of the working poor, 2015. 2017.
- [120] Lara M, Gamboa C, Kahramanian MI, et al. Acculturation and Latino health in the United States: a review of the literature and its sociopolitical context. *Annu Rev Publ Health* 2005;26:367–97.
- [121] Aqua JK, White K, Johnson DA. A systematic review of acculturation and sleep health among adult immigrants in the United States. *Sleep Health* 2023;9(3):288–305.
- [122] Alterman T, Luckhaupt SE, Dahlhamer JM, et al. Prevalence rates of work organization characteristics among workers in the U.S.: data from the 2010 National Health Interview Survey. *Am J Ind Med* 2013;56(6):647–59.
- [123] Costa G. The 24-hour society between myth and reality. *J Human Erol* 2001;30(1–2):15–20.
- [124] Presser HB. Toward a 24-hour economy. *Science* 1999;284(5421):1778–9.
- [125] Ceide ME, Pandey A, Ravenell J, et al. Associations of short sleep and shift work status with hypertension among Black and White Americans. *Int J Hypertens* 2015;2015:697275.
- [126] Jackson CL, Kawachi I, Redline S, et al. Asian-White disparities in short sleep duration by industry of employment and occupation in the US: a cross-sectional study. *BMC Public Health* 2014;14:552.
- [127] Jackson CL, Hu FB, Redline S, et al. Racial/ethnic disparities in short sleep duration by occupation: the contribution of immigrant status. *Soc Sci Med* 2014;118:71–9.
- [128] Jackson CL, Redline S, Kawachi I, et al. Racial disparities in short sleep duration by occupation and industry. *Am J Epidemiol* 2013;178(9):1442–51.
- [129] James SA. John Henryism and the health of African-Americans. *Cult Med Psychiatry* 1994;18(2):163–82.
- [130] Markovic N, Bunker CH, Ukolli FA, et al. John Henryism and blood pressure among Nigerian civil servants. *J Epidemiol Community Health* 1998;52(3):186–90.

- [131] National Sleep Foundation. Summary of findings: 2005 sleep in America poll. 2005.
- [132] Hale L, Do DP. Racial differences in self-reports of sleep duration in a population-based study. *Sleep* 2007;30(9):1096–103.
- [133] Hale L, Rivero-Fuentes E. Negative acculturation in sleep duration among Mexican immigrants and Mexican Americans. *J Immigr Minority Health* 2011;13(2):402–7.
- [134] Loredo JS, Soler X, Bardwell W, et al. Sleep health in U.S. Hispanic population. *Sleep* 2010;33(7):962–7.
- [135] Redline S, Sotres-Alvarez D, Loredo J, et al. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds. The Hispanic community health study/study of Latinos. *Am J Respir Crit Care Med* 2014;189(3):335–44.
- [136] Seicean S, Neuhauser D, Strohl K, et al. An exploration of differences in sleep characteristics between Mexico-born US immigrants and other Americans to address the Hispanic Paradox. *Sleep* 2011;34(8):1021–31.
- [137] Voss U, Tuin I. Integration of immigrants into a new culture is related to poor sleep quality. *Health QualLife Outcomes* 2008;6:61.
- [138] Jackson CL, Walker JR, Brown MK, et al. A workshop report on the causes and consequences of sleep health disparities. *Sleep* 2020;43(8).
- [139] Etindele Sosso FA, Kreidlmayer M, Pearson D, et al. Towards A socioeconomic model of sleep health among the Canadian population: a systematic review of the relationship between age, income, employment, education, social class, socioeconomic status and sleep disparities. *Eur J Investig Health Psychol Edu* 2022;12(8):1143–67.
- [140] Thomas KS, Bardwell WA, Ancoli-Israel S, et al. The toll of ethnic discrimination on sleep architecture and fatigue. *Health Psychol* 2006;25(5):635–42.
- [141] Tomfohr L, Pung MA, Edwards KM, et al. Racial differences in sleep architecture: the role of ethnic discrimination. *Biol Psychol* 2012;89(1):34–8.
- [142] Lee S, Chang AM, Buxton OM, et al. Various types of perceived job discrimination and sleep health among working women: findings from the sister study. *Am J Epidemiol* 2020;189(10):1143–53.
- [143] Mensah GA, Mokdad AH, Ford ES, et al. State of disparities in cardiovascular health in the United States. *Circulation* 2005;111(10):1233–41.
- [144] Litwiller B, Snyder LA, Taylor WD, et al. The relationship between sleep and work: a meta-analysis. *J Appl Psychol* 2017;102(4):682–99.
- [145] Lee S, Lemmon M. Dynamic interplay between sleep and family life: review and directions for future research. In: McHale SM, King V, Buxton OM, editors. *Family contexts of sleep and health across the life course*. New York: Springer; 2017. p. 201–9.
- [146] Moen P, Wethington E. Midlife development in a life course context. In: Willis SL, Reid JD, editors. *Life in the middle*. San Diego: Academic Press; 1999. p. 3–23.
- [147] Sadeh A, McGuire JP, Sachs H, et al. Sleep and psychological characteristics of children on a psychiatric inpatient unit. *J Am Acad Child Adolesc Psychiatry* 1995;34(6):813–9.
- [148] Lee S, Martire LM, Damaske SA, et al. Covariation in couples' nightly sleep and gender differences. *Sleep Health* 2018;4(2):201–8.
- [149] Podsakoff PM, MacKenzie SB, Lee JY, et al. Common method biases in behavioral research: a critical review of the literature and recommended remedies. *J Appl Psychol* 2003;88(5):879–903.
- [150] Knutson KL, Buxton OM. Actigraphy as a tool for measuring sleep: pros, cons and secrets of the trade. 2011. p. 14–5.
- [151] Jean-Louis G, Kripke DF, Cole RJ, et al. Sleep detection with an accelerometer actigraph: comparisons with polysomnography. *Physiol Behav* 2001;72:21–8.
- [152] Buysse DJ. Sleep health: can we define it? Does it matter? *Sleep* 2014;37(1):9–17.
- [153] de Bruin EI, Formsmma AR, Frijstein G, et al. Mindful2Work: effects of combined physical exercise, yoga, and mindfulness meditations for stress relieve in employees. A proof of concept study. *Mindfulness* 2017;8(1):204–17.
- [154] Fang R, Li X. A regular yoga intervention for staff nurse sleep quality and work stress: a randomised controlled trial. *J Clin Nurs* 2015;24(23–24):3374–9.
- [155] Klatt M, Steinberg B, Duchemin AM. Mindfulness in motion (MIM): an onsite mindfulness based intervention (MBI) for chronically high stress work environments to increase resiliency and work engagement. *JoVE J* 2015;(101):e52359.
- [156] Jensen HI, Markvart J, Holst R, et al. Shift work and quality of sleep: effect of working in designed dynamic light. *Int Arch Occup Environ Health* 2016;89(1):49–61.
- [157] Rahman SA, Shapiro CM, Wang F, et al. Effects of filtering visual short wavelengths during nocturnal shiftwork on sleep and performance. *Chronobiol Int* 2013;30(8):951–62.
- [158] Takahashi M, Nakata A, Haratanai T, et al. Post-lunch nap as a worksite intervention to promote alertness on the job. *Ergonomics* 2004;47(9):1003–13.
- [159] Hakola T, Harma M. Evaluation of a fast forward rotating shift schedule in the steel industry with a special focus on ageing and sleep. *J Hum Ergol* 2001;30:315.
- [160] Owens J, Adolescent Sleep Working G, Committee on A. Insufficient sleep in adolescents and young adults: an update on causes and consequences. *Pediatrics* 2014;134(3):e921–32.
- [161] Li I, Mackey MG, Foley B, et al. Reducing office workers' sitting time at work using sit-stand protocols: results from a pilot randomized controlled trial. *J Occup Environ Med* 2017;59(6):543–9.

Chapter 42

Sleep and health equity

Judite Blanc^a, Jao Nunes^b, Natasha Williams^c, Rebecca Robbins^d, Azizi A. Seixas^{d,e} and Girardin Jean-Louis^{a,e,f}

^aUniversity of Miami Miller School of Medicine, Department of Psychiatry & Behavioral Sciences, Center for Translational Sleep and Circadian Sciences, Miami, FL, United States; ^bThe City College of New York, New York, NY, United States; ^cNYU Langone Health, Division of Health and Behavior, Department of Population Health, Center for Healthful Behavior Change, New York, NY, United States; ^dHarvard Medical School, Faculty of Arts & Sciences, Brigham and Women's Hospital, Harvard T.H. Chan School of Public Health, Boston, MA, United States; ^eNYU Langone Health, Department of Population Health, New York, NY, United States; ^fNYU Langone Health, Department of Psychiatry, New York, NY, United States

Introduction: Sleep and public health

Sleep is the “reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment” [8a,8b, p. 15]. Sleep is vital for optimal mental, emotional, and physical well-being and therefore has emerged as a pillar of health alongside nutrition, exercise, and smoking cessation. Leading scientific, clinical, and governmental organizations in the United States and internationally recognize the importance of sleep [1–3].

Despite this wide-scale recognition, schedules in America are inconsistent with healthy sleep habits [4]. For instance, career, social and lifestyle demands represent barriers to adequate sleep that have generated a sleep crisis of significant proportion with impact on individual outcomes (e.g., cognition, mental and physical health) and societal outcomes (e.g., productivity and safety). The Centers for Disease Control and Prevention (CDC) has made specific recommendations to meet daily needs: 9–12 h of sleep for school-aged children, 8–10 h of sleep for adolescents, and a minimum of 7 h for adults. However, the 2015 Youth Risk Behavior Surveillance System [5] shows an estimated nationwide prevalence of short sleep duration of 57.8% among middle school students and of 72.7% among high school students. Among adult respondents to the 2009 Behavioral Risk Factor Surveillance System, 41.3% reported 1–13 days of insufficient rest or sleep before the survey [6].

Poor sleep health has significant individual health and societal consequences. Poor sleep is associated with poor mental, emotional (e.g., anxiety, mood disturbance, and suicidal ideation), and physical health consequences (e.

g., accidents, illness, and pain). In addition, poor sleep health increases the risk for chronic conditions (e.g., high blood pressure, high body mass index [BMI], and obesity) and mortality. Poor sleep health extracts a significant cost in terms of dollars annually in medical expenses such as doctor visits, hospital services, prescriptions, and over-the-counter medications [7].

Conversely, research suggests that adequate sleep health has a protective effect for individual health and societal outcomes. Specifically, individuals who consistently report dimensions of sleep health, including good sleep quality, sufficient sleep duration, and absence of sleep disorder, are more likely to have better measures of mental, emotional, and physical health and longevity compared with those who cut their sleep short. But research also documents differences in sleep health along socio-economic lines, sleep health being out of reach for most individuals living in deprived social economic areas. Specifically, minority groups and individuals from disadvantaged economic backgrounds report lower sleep quality. Sleep, a precious resource in our society, this research suggests, may actually constitute a luxury most commonly practiced by majority race/ethnic groups and socio-economically advantaged individuals.

To tackle the sleep health crisis, the past 10 years has seen a dramatic increase in research that articulates these socio-economic limiting factors that affect sleep.

We argue there is a need for a paradigm shift in the way sleep medicine approaches this public health matter. We agree with Buysse [9] that the current focus mainly on sleep disorders should give way to a stronger emphasis on the notion of sleep health. This is crucial to the health of

individuals and of the population and stands to benefit sleep medicine itself.

What is sleep health?

While the body of knowledge on sleep patterns and associated public health outcomes is growing, there is no precise and specific definition of the concept of sleep health for use by sleep researchers and experts. When *sleep* and *health* are entered together in databases such as *PubMed* and *Google Scholar*, between 133,463 and 4,180,000 results are identified (October 22, 2025). Authors appear to use “sleep problems” and “sleep health” interchangeably in their titles. Buysse [9] noticed that not even in the 2006 Institute of Medicine Report and in the mission statement for sleep of The CDC, an explicit definition of sleep health was included. To fill the gap, in his recently published paper, “Sleep health: can we define it? Does it matter,” Buysse [9] articulated this comprehensive definition:

Sleep health is a multidimensional pattern of sleep-wakefulness, adapted to individual, social, and environmental demands, that promotes physical and mental well-being. Good sleep health is characterized by subjective satisfaction, appropriate timing, sufficient duration, high efficiency, and sustained alertness during waking hours. [9, p. 12]

And in contrast to the deficit model, this definition focuses on positive characteristics of sleep health which are physiologically quantifiable. Although adult-centered, it could be easily extrapolated to youth and cannot be conceived outside of its individual, social and environmental components, and offers specific anchors for these five dimensions of sleep health:

- Sleep duration: The number of sleep hours per day
- Sleep continuity or efficiency: The ability of falling asleep and staying asleep
- Timing: The placement of sleep within the 24-h day
- Alertness/sleepiness: The capacity of staying awake
- Satisfaction/Quality: The individual perception of “good” or “poor” sleep.

The following are questions of interest in the context of the present analysis: What is the relationship between the sleep health dimensions and physical and mental well-being? What are the mechanisms that influence sleep dimensions and related health outcomes? Overall, does the *presence* of sleep impairment affect all groups at the same level?

Social determinants of sleep health dimensions and associated health outcomes

During the last decades, factors affecting the five dimensions of sleep health, including age, sex, BMI, race/

ethnicity, education, environment, workplace, and economic position, have been widely documented [7,10–12]. In Table 42.1, we present a list of problems related to patients, providers, and the healthcare system that potentially undermine optimal sleep in disadvantaged communities.

As described in Table 42.1, there is a growing body of studies that show similar findings, not all categories are equally impacted by the sleep health crisis. How does this sleep deficiency vary across racial and ethnic groups? Are other individual, social and environmental components contributing to this variation of sleep patterns among different social groups? *These are valid questions that current research findings cannot yet answer in full.* At this point, we intend to explore another valid question: Can any role be attributed to the historical context, specifically to the race-based slavery system that underpins the birth of the American society?

Health differences and the historical sleep gap between blacks and whites

Identifying determinants of health differences

The debate is not a new one about the origin of historically ubiquitous health disparities/inequities and of the elusive health equity, but the tools of the debate remain faulty. Until now, there is little consensus regarding the meaning of the terms “health disparities/inequities” and “health equity.” An early articulated and widespread conceptualization of these notions is attributed to Margaret Whitehead in her famous article, “*The concepts and principles of equity and health*” [13]. She stated: “inequality in health is a term commonly used in some countries to indicate systematic, avoidable, and important differences.” In her discussion, she described seven critical determinants of health differentials: (1) Natural, biological variation; (2) Health-damaging behavior if freely chosen, such as participation in certain sports and pastimes; (3) The transient health advantage of one group over another when that group is first to adopt a health-promoting behavior (as long as other groups have the means to catch up fairly soon); (4) Health-damaging behavior where the degree of choice of lifestyles is severely restricted; (5) Exposure to unhealthy, stressful living and working conditions; (6) Inadequate access to essential health and other public services; and (7) Natural selection or health-related social mobility involving the tendency for sick people to move down the social scale.

According to Whitehead, these seven determinants of health differences are all interacting. Although the impact of biological factors and the effects of sick people moving down the social scale have been demonstrated, she underlined that the major role is to be attributed to socio-

TABLE 42.1 Summary of social determinants of sleep health and potential health outcomes.

Dimensions of sleep measured	Population studied	Social determinants/risk factors	Health outcomes	Source
Duration	BRFSS 2014 <i>N</i> = 444,306 American men and women aged ≤ 18 from 50 states and the District of Columbia	Location, employment status, education, black race, Hawaiians or other non-White/Hispanic ethnicities	N/A	[8]
	<i>N</i> = 474,684 participants of multiple studies from USA, Japan, UK, Sweden, Germany, Singapore, Israel, and Taiwan	N/A	Mortality of coronary heart disease, stroke CVD,	[14a]
	<i>N</i> = 29,818, aged 18–85 cross-sectional household interview survey 2005 national health interview survey (NHIS)	Black race	Obesity	[14b]
	<i>N</i> = 578 Chicago residents, aged 33–45 wrist actigraphy for three consecutive days from 2003 to 2005	Black race	Incident hypertension difference in diastolic and systolic blood pressure	[14c]
Sleep continuity/efficiency	<i>N</i> = 812 participants (36% African American; 67% female) Longitudinal and cross-sectional	Black race, sedentary life	Metabolic syndrome (increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels)	[14d]
Timing (shift work)	37 African American women and 62 women of other races. Day shift (<i>n</i> = 61), evening shift (<i>n</i> = 11), and night shift (<i>n</i> = 27)	Black race, evening and night shift	Nondipping blood pressure	[14e]
Alertness/sleepiness	<i>N</i> = 84,003 multiethnic female registered nurses aged 37–54 in 14 US states. Longitudinal analyses of data from the nurses' health study II	Shift work	Hypertension, diabetes, hypercholesterolemia, obesity, and depression	[14f]
Satisfaction/quality	<i>N</i> = 1139 including 520 whites, 586 African Americans, and 33 of Asian, native American, or Hispanic ethnicity	Female gender, age, education, income	Overall self-reported physical health	[14g]

economic and environmental factors, including lifestyles. Consequently, how may this fact hold explanations for the actual sleep health disparities?

History behind the black–white “sleep gap”

Biological imperatives to maintain homeostatic processes and social factors determine sleep in humans. The National Heart Lung and Blood Institute of the National Institutes of Health describes sleep as a fundamental requirement of living. Yet extensive scientific evidence revealed that social categories such as racial/ethnic minorities and *socioeconomically* disadvantaged groups do not attain the adequate and recommended amount, quality, and consistency of sleep. The associations between sleep quantity/quality and both demographic and socioeconomic factors have been widely reported in the literature [12,14,15]. Also, similar observations have been made for race/ethnicity that emerged as a significant determinant of individual variation in sleep phenotype. For instance, African Americans are more burdened with sleep health disparities [16]. White youth generally have better sleep than minority youth, Hispanics have more than Blacks, and there is inconclusive evidence for Asians and other minorities [17]. Depending on the definition adopted, sleep-disorder-breathing was 4–6 times more likely in 8- to 11-year-old black children compared with white children, and almost 3–5 times more likely in those born preterm than term children [18]. Moreover, on average, African–American adults report shorter sleep duration compared with other racial/ethnic groups [14].

This critical prevalence of suboptimal sleep in communities of African descent compared with those of European descent is of interest to this chapter. Traditionally and according to historians and national archives, people of African descent were the most affected compared with native-Americans and Hispanics by the slave trade and chattel enslavement in the United States. Sleep health disparities require to be investigated from a historical perspective, considering the birth context of this nation. The roots of the “blacks and whites sleep gap” are suspected by some historians to stretch back to the history of chattel enslavement and colonization in the United States. During this period, after people were kidnapped from the African continent and considered as chattel slaves by white European settlers, resting time control became an efficient weapon in the hands of the European masters to strengthen the race-based slavery system and allowed the maximum exploitation of the enslaved workforce [19,20]. Report on the sleep condition by the former enslaved abolitionist leader, Frederick Douglas echoes historian Benjamin Reiss’s analysis:

There were no beds given the slaves unless one coarse blanket be considered such, and none but the men and

women had these. This, however, is not considered a very great privation. They find less difficulty from the want of beds, than from the want of time to sleep; for when their day's work in the field is done, the most of them having their washing, mending, and cooking to do, and having few or none of the ordinary facilities for doing either of these, very many of their sleeping hours are consumed in preparing for the field the coming day; and when this is done, old and young, male and female, married and single, drop down side by side, on one common bed,—the cold, damp floor,—each covering himself or herself with their miserable blankets; and here they sleep till they are summoned to the field by the driver's horn. At the sound of this, all must rise, and be off to the field. There must be no halting; everyone must be at his or her post, and woe betides them who hear not this morning summons to the field; for if they are not awakened by the sense of hearing, they are by the sense of feeling: no age nor sex finds any favor. [19, pp. 8–9]

Reiss’s conception of the structure, ideology, practices, and policies that governed slave plantations and therefore enslaved people and their sleep phenotype might be very relevant for investigating sleep health disparities over a century later. All in all, socio-historical context has always been a significant determinant of who gets the best sleep, for:

If slaves helped build the modern world, they were never afforded sufficient rest from the toils involved. Nor were they afforded the privacy that, according to the sociologist Norbert Elias, was becoming a hallmark of Western bourgeois sleep. Once they were excluded from normal sleep, they were punished for failures to maintain alertness and productivity and branded as constitutionally lazy for any sign of exhaustion. Their supposedly different sleep patterns—those that marked them as belonging to an inferior race—were actually taken as a justification for race-based slavery by medical authorities and slavery propagandists [20, p. 122].

Sleep health as a contributor to health disparities in modern days

Regarding health differences in our contemporary society, sleep may play an important role among the factors that contribute to health and healthcare disparities [21], particularly cardiovascular health in the United States [22]. This idea of a mediating effect of sleep on health disparities can be analyzed based on the conceptual framework proposed by Jackson et al. [22], in their review of the multilevel determinants of sleep-cardiovascular health disparities via proximal, intermediate, and distal pathways.

1 Proximal factors include individual risk behaviors, biological/genetic pathways, and biological responses,

personal demographics such as acculturation, age, and sex that are recognized risks factors for Cardiovascular Diseases and impact sleep quality and quantity.

- 2 *Intermediate factors* comprise physical context, built environments, neighborhood and housing disadvantages, social relationships through family influences and social context such as racism. Data from the 2014 Census estimate the portion of Racial/ethnic minorities of US population at 37.8% [22a]. Approximately, $\frac{1}{4}$ of Blacks (mostly descendants of the former enslaved Africans, Africans, and Afro-Caribbean immigrants) (21.2%) and Hispanic persons (18.3%) lived in Poverty compared with non-Hispanic white (7.8%) (Descendants of the settlers and European immigrants) and Asian (10%) [22b]. Research has demonstrated that people living in disadvantaged neighborhoods have increased exposure to sleep disturbance risk factors such as inappropriate light, noise, allergens, tobacco, or air pollution. In addition to the higher rate of poverty, racial/ethnic minorities report more frequently objective and perceived discrimination. Results reported by Jackson et al. [22] have shown that experiences of racial discrimination and internalization of negative racial bias contribute to the acceleration of vascular aging in Black males.
- 3 *Distal factors* are occupational patterns, treatment access, and adherence, social conditions, and policies. For example, shift work is more current in African-Americans workers compared with their white counterparts and was reported to play a role in racial differences in sleep quantity. The proportion of job-related stress, low-wage jobs, and discrimination experiences was higher in black workers compared with whites ones.

From sleep health disparities toward sleep health equity

The CDC's Health Report from 1999 to 2014 indicates that trends in health were generally progressive for the overall population in the United States. Differences in life expectancy, infant mortality, cigarette smoking among women, influenza vaccinations among those aged 65 and over, and health insurance coverage narrowed among the racial and ethnic groups. Nonetheless, during 1980–2014, life expectancy at birth for males and females was longest for white persons and shortest for black persons. For both males and females, racial differences in life expectancy at birth lessened, but persisted during 1980–2014. Furthermore, disparities by racial and ethnic group in the rate of high blood pressure and smoking among adult men persisted throughout the study period, with non-Hispanic black adults more likely to have high blood pressure than

adults in other racial and ethnic groups throughout the period, and non-Hispanic black and non-Hispanic white males more likely to be current smokers than Hispanic and non-Hispanic Asian men. In summary, the authors of the report concluded that:

Despite improvements over time in many of the health measures presented in this Special Feature, disparities by race and ethnicity were found in the most recent year for all 10 measures,¹ indicating that although progress has been made in the 30 years since the Heckler Report, elimination of disparities in health and access to health care has yet to be achieved. ([23], p. 21)

Meanwhile, in the field of sleep medicine, although extensive efforts are being deployed by concerned clinicians and sleep researchers along with recommendations to develop research agenda and implement programs to decrease disparities in sleep health, the data presented previously suggest that there are still miles to go until society de facto attains sleep health equity [24]. Therefore, we conclude the chapter proposing a conceptual framework intended as a roadmap toward sleep health which incorporates findings from our group's research initiatives in the field of behavioral sleep research.

At the beginning of this chapter, we adopted Buysse's [9] definition of *sleep health* as a multidimensional pattern of sleep-wakefulness, adapted to the individual, social, and environmental demands, that promotes physical and mental well-being. Moreover, equity is the absence of avoidable, unfair, or remediable differences among groups of people, whether those groups are defined socially, economically, demographically or geographically or by other means of stratification [13]. Pursuing Equity in Health implies pursuing the elimination of health disparities/inequities [25]. To effectively move toward sleep equity, we believe a first step would be to define such a concept. Thus borrowing from the definitions of sleep health and health equity, we define *sleep health equity* as:

Equal opportunities that are given to each individual and/or communities based on their need, no matter their age, sex, race/ethnicity, geographic location, and socio-economic status, to obtain recommended, satisfactory, efficient amount of sleep with appropriate timing that promotes physical and mental well-being.

Similarly to the analogy of sacred circle that has the power to generate unity and to heal, we propose that sleep health equity practice is the constant effort to provide adequate sleep health resources to each group and individual, and to avoid sleep health disparities inherent to

1. a Measures of mortality, natality, health conditions, health behaviors, and health care access and utilization, by race, race and ethnicity, or by detailed Hispanic origin.a

socio-economic and environmental factors. Thus, moving toward sleep health equity implies to pay close attention to the importance of contextual factors such as culture, education, policies, funding, governance, institution, historic events, historic collaboration, community capacity and readiness, university capacity and readiness and the dynamic between them. In addition, the question of mutual respect and trust, cultural relevance, and sustained

partnerships should receive as much attention in the process (Fig. 42.1).

We identify a list of problems related to patients, providers, and the health-care-system that are undermining optimal sleep in disadvantaged communities, and then propose scientifically informed potential policy examples that may contribute to decrease sleep health disparities [5,22,24,26,27]. See Table 42.2.



FIGURE 42.1 Roadmap of policies toward the implementation of sleep health equity practices.

TABLE 42.2 Barriers to sleep health equity and policy solutions for reducing health disparities and advancing sleep health equity.

Sleep health equity barrier	Solution advancing sleep health equity
1. Higher prevalence of sleep-disordered-breathing (SBD) among African-American children	Implementation of programs for sleep health literacy, early screening and treatment for sleep disorders since elementary schools. Requirement for schools at all levels to include module on sleep health in their curriculum and refer at-risk youth to sleep health centers
2. Greater exposure to environmental risk factors for poor sleep among racial/ethnic minorities living in disadvantaged neighborhoods	Implementation of a multilevel approach to reducing environmental factors that disturb sleep such as inadequate light, noise, allergen and irritants, and air pollution. Limitations or suppression of all sources of inadequate light, noise, allergen, irritants and air pollution during the sleep time in identified communities
3. A higher rate of short sleep duration that increases cardiovascular risk among individuals of African-descents and other minorities	Adopt a multilevel community-oriented sleep health and promotion education campaign (Ex: PEERS-ED, TASHE, and MetSO). Provide incentives to corporate wellness programs that promote sleep and population health among racial/ethnic communities
4. Racial/ethnic minorities, particularly blacks are exposed to higher racial discrimination, which induces stress that undermines sleep	National campaign to raise awareness on the deleterious effects of racial bias, racial profiling, and discrimination on health. Increase severity of sanctions against racial discrimination nationwide
5. Blacks are disproportionately concerned with effects of shift work. Need stronger work schedule regulations	Limitations of shift length, regulation of time between shifts, regulation of degree of circadian phase changes in consecutive workdays
6. Culture and language barriers limit access to sleep health literacy among racial/ethnic minorities	Establishment of sleep centers with multiethnic and multilingual staff in vulnerable communities. Requirement for healthcare facilities in vulnerable communities to have a multiethnic and multilingual staff
7. Poor adherence to treatment of sleep disorders among minorities, particularly blacks at risk for obstructive sleep apnea (OSA)	A tailored behavioral intervention to increase adherence to physician recommendation (Ex: MetSO and PEERS-ED studies). Requirement for cultural competency training in sleep medicine programs
8. Lack of minority in the field of sleep medicine	Implementation of training programs from the high-school to faculty level to increase minority representation in sleep medicine (Ex: PRIDE and COMRADE programs). Requirement for a specific quota of racial/ethnic minorities in the recruitment of future sleep specialists
9. Lack of research on epigenetic factors associated with sleep problems among children and adults	Implementation of multilevel research that explores links of individual and household/neighborhood factors with poor sleep. Allocate funding to advance epigenetic studies on factors associated with poor sleep health
10. Lack of research on psychological resilience factors that are protective against factors that negatively affect sleep and CVD	Implementation of multilevel research that explores links among, stress exposure, individual, social, cultural and physical factors that affect sleep. Allocate funding to advance research on sleep health resilience

Conclusion

Although sleep is fundamental to general health, the American lifestyle and societal schedule are not consistent with healthy sleep patterns. Unfortunately, racial/ethnic minorities are the most affected by the sleep health crisis, which, for Blacks echoes of the historical context of the birth of America. Sleep medicine experts, specialists, practitioners, representatives, and policymakers have an ethical responsibility to help to eliminate sleep health inequities. Although recent data demonstrated that in general there was improvement in sleep health parameters in both privileged groups and disadvantaged ones, there is still a lot to be accomplished to eliminate health disparities. Youth and adults from disadvantaged communities would benefit if sleep medicine emphasizes the definition of sleep health dimensions and encourages the changes in practice they embody, in addition to identifying and treating sleep disorders. The positive aspect of sleep health as defined previously, and the ideal of equity in health comprise the anchors for our proposed definition of sleep health equity, and its associated conceptual framework toward the elimination of sleep health inequities.

References

- [1] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC, Adams Hillard PJ. National sleep foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 2015;1(1):40–3. <https://doi.org/10.1016/j.slehd.2014.12.010>.
- [2] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E, Twery M, Croft JB, Maher E, Barrett JA, Thomas SM, Heald JL. Recommended amount of sleep for a healthy adult: A joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep* 2015/06/01;38(6):843–4. <https://doi.org/10.5665/sleep.4716>. <http://www.journalsleep.org/ViewAbstract.aspx?pid=30027>.
- [3] Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T, Apnea S, Disease C. An American heart association/American college of cardiology foundation scientific statement from the American heart association council for high blood pressure research professional education committee, council on clinical cardiology, stroke council, and council on cardiovascular nursing. *J Am Coll Cardiol* 2008;52(8):686–717. <https://doi.org/10.1016/j.jacc.2008.05.002>.
- [4] Barnes CM, Drake CL. Prioritizing sleep health: public health policy recommendations. *Perspect Psychol Sci* 2015;10(6):733–7. <https://doi.org/10.1177/1745691615598509>.
- [5] Wheaton AG, Jones SE, Cooper AC, Croft JB. Short sleep duration among middle school and high school students — United States. *Mor Mortal Wkly Rep* 2018;67(3):85–90. <https://doi.org/10.15585/mmwr.mm6703a1>.
- [6] Perceived insufficient rest or sleep among adults - United States, 2008. *MMWR (Morb Mortal Wkly Rep)* 2009;58(42):1175–9. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5842a2.htm>.
- [7] Institute of Medicine. Sleep disorders and sleep deprivation: an unmet public health problem. The National Academies Press; 2006.
- [8] [a] Moore PJ, Adler NE, Williams DR, Jackson JS. Socioeconomic status and health: the role of sleep. *Psychosom Med* 2002;64(2):337–44. <https://doi.org/10.1097/00006842-200203000-00018>.
[b] Carskadon MA, Dement WC. Normal human sleep: an overview. In: Kryger TRM, editor. *Principles and practice of sleep medicine*. Elsevier; 2017.
- [9] Buysse D. Sleep health: can we define it? Does it matter? *Sleep* 2014;37(1):9–17. <https://doi.org/10.5665/sleep.3298>.
- [10] Johnson DA, Billings ME, Hale L. *Curr Epidemiol Rep* 2018;61:5. <https://doi.org/10.1007/s40471-018-0139-y>.
- [11] Grandner MA, Williams N, Knutson KL, Roberts D, Jean-Louis G. Sleep disparity, race/ethnicity, and socioeconomic position. *Sleep Med* 2016;18:7–18.
- [12] Grandner MA, Patel NP, Gehrmann PR, Xie D, Sha D, Weaver T, Gooneratne N. Who gets the best sleep? Ethnic and socioeconomic factors related to sleep complaints. *Sleep Med* 2010;11(5):470–8. <https://doi.org/10.1016/j.sleep.2009.10.006>.
- [13] Whitehead M. The concepts and principles of equity and health. *Health Promot Int* 1991;6(3):217–28. <https://doi.org/10.1093/heapro/6.3.217>.
- [14] [a] Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of healthy sleep duration among adults—United States, 2014. *MMWR Morb Mortal Wkly Rep* 2016;65(6):137–41. <https://doi.org/10.15585/mmwr.mm6506a1>.
[b] Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011;32(12):1484–92. <https://doi.org/10.1093/euroheartj/ehr007>.
[c] Donat M, Brown C, Williams N, Pandey A, Racine C, McFarlane SI, Jean-Louis G. Linking sleep duration and obesity among black and white US adults. *Clin Pract* 2013;10(5). <https://doi.org/10.2217/cpr.13.47>.
[d] Knutson KL, Van CE, Rathouz PJ, Yan LL, Hulley SB, Liu K, et al. Association between sleep and blood pressure in midlife: the CARDIA sleep study. *Arch Intern Med* 2009;169:1055–61.
[e] Troxel WM, Buysse DJ, Matthews KA, Kip KE, Strollo PJ, Hall M, Drumheller O, et al. Sleep symptoms predict the development of the metabolic syndrome. *Sleep* 2010;33(12):1633–40.
[f] Yamasaki F, Schwartz JE, Gerber LM, Warren K, Pickering TG. Impact of shift work and race/ethnicity on the diurnal rhythm of blood pressure and catecholamines. *Hypertension* 1998;32:417–23.
[g] Gangwisch JE, Rexrode K, Forman JP, Mukamal K, Malaspina D, Feskanich D. Daytime sleepiness and risk of coronary heart disease and stroke: results from the Nurses' health study II. *Sleep Med* 2014;15(7):782–8.
- [15] Adenekan B, Pandey A, McKenzie S, Zizi F, Casimir GJ, Jean-Louis G. Sleep in America: role of racial/ethnic differences. *Sleep Med Rev* 2013;17(4):255–62.
- [16] Petrov ME, Lichstein KL. Differences in sleep between black and white adults: an update and future directions. *Sleep Med* 2016;74–81. <https://doi.org/10.1016/j.sleep.2015.01.011>.

- [17] Guglielmo D, Gazmararian JA, Chung J, Rogers AE, Hale L. Racial/ethnic sleep disparities in US school-aged children and adolescents: a review of the literature. *Sleep Health* 2018. <https://doi.org/10.1016/j.sleh.2017.09.005>.
- [18] Rosen GM, Bendel AE, Neglia JP, Moertel CL, Mahowald M. Sleep in children with neoplasms of the central nervous system: case review of 14 children. *Pediatrics* 2003;112(1 Pt 1):e46–54. <https://doi.org/10.1542/peds.112.1.e46>.
- [19] Douglas F. Narrative of the life of Frederick Douglass, an American slave. New York: Penguin Classics; 1845.
- [20] Reiss B. Wild nights: how taming sleep created our restless world. Basic Books; 2017.
- [21] Williams NJ, Grandner MA, Snipes A, Rogers A, Williams O, Airhihenbuwa C, Jean-Louis G. Racial/ethnic disparities in sleep health and health care: importance of the sociocultural context. *Sleep Health* 2015;1(1):28–35.
- [22] [a] Jackson C, Redline S, Emmons KM. Sleep as a potential fundamental contributor to disparities in cardiovascular health. SSRN; 2015. <https://doi.org/10.1146/annurev-publhealth-031914-122838>.
[b] Colby SL, Ortman JM. Projections of the size and composition of the U.S. population: 2014 to 2060. In: Current population reports. Washington, DC: US Census Bureau; 2014. P25–1143.
- [c] US Census Bureau. Historical poverty tables: people and families—1959 to 2017. 2018. <https://www.census.gov/data/tables/time-series/demo/income-poverty/historical-poverty-people.html>.
- [23] National Center for Health Statistics. Health, United States, 2015: with special feature on racial and ethnic health disparities. Hyattsville, MD: National Center for Health Statistics; 2016.
- [24] Jean-Louis G, Grandner M. Importance of recognizing sleep health disparities and implementing innovative interventions to reduce these disparities. *Sleep Med* 2016;18:1–2. <https://doi.org/10.1016/j.sleep.2015.08.001>.
- [25] Braveman P. Health disparities and health equity: concepts and measurement. *Annu Rev Publ Health* 2006;27(1):167–94. <https://doi.org/10.1146/annurev.publhealth.27.021405.102103>.
- [26] Jean-Louis G, Newsome V, Williams NJ, Zizi F, Ravenell J, Ogedegbe G. Tailored behavioral intervention among blacks with metabolic syndrome and sleep apnea: results of the MetSO trial. *Sleep* 2017;40(1). <https://doi.org/10.1093/sleep/zsw008>.
- [27] Williams NJ, Robbins R, Rapoport D, Allegrante JP, Cohall A, Ogedegbe G, Jean-Louis G. Tailored approach to sleep health education (TASHE): study protocol for a web-based randomized controlled trial. *Trials* 2016;585(1):17. <https://doi.org/10.1186/s13063-016-1701-x>.

This page intentionally left blank

Chapter 43

Identifying and treating obstructive sleep apnea in commercial vehicle operators: A summary of guidance for clinicians

Indira Gurubhagavatula^{a, b}, Aesha M. Jobanputra^c and Miranda Tan^d

^aDepartment of Medicine, Division of Sleep Medicine, Perelman School of Medicine at the University Hospital of Pennsylvania Medical Center, Philadelphia, PA, United States; ^bSleep Disorders Clinic, Philadelphia VA Medical Center, Philadelphia, PA, United States; ^cDepartment of Medicine, Division of Pulmonary and Critical Care Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, United States;

^dDepartment of Psychiatry and Behavioral Services, Division of Sleep Medicine, Stanford University School of Medicine, Stanford, CA, United States

Drowsy driving has been likened to driving while intoxicated, with similar impairment in neurocognitive performance and driving capability [1]. Crash severity related to drowsy driving tends to be severe because the sleep-impaired driver is unable to attenuate impact by braking or steering away, resulting in heavier damages, serious injuries, or death [2,3]. The National Highway Traffic Safety Administration estimates that drowsy driving was responsible for 72,000 crashes, 41,000 injuries, and 800 deaths in 2013 [4]. These statistics, however, may be an underestimate [5,6] and recent data suggest that drowsy driving causes up to 9.5% of all motor-vehicle crashes [7], up to 10.8% of crashes that resulted in significant property damage, airbag deployment, or injury [7], and 16.5% of fatal crashes [6]. The key causes of drowsy driving include insufficient sleep, shift work disorder, medications, and untreated sleep disorders such as obstructive sleep apnea (OSA), chronic insomnia, and narcolepsy [8,9].

The association between OSA and daytime sleepiness increases the risk of collision by two- to fourfold [10–12]. OSA is characterized by repetitive collapse of the upper airway, causing breathing to stop or obstruct partially during sleep. As a result, oxyhemoglobin saturation falls briefly, which triggers a surge in sympathetic activity and arousal from sleep. Disruptions during sleep can confer symptoms of daytime sleepiness, fatigue, and inability to sustain attention—these deficits are amplified under mundane conditions or while doing overlearned activities that require sustained attention, such as, for example, driving long distances on a rural highway [13].

Untreated OSA has been associated with an increased risk of multiple health conditions, including cardiovascular diseases, neurocognitive impairment, and metabolic syndrome [14]. OSA tends to be more common in obese individuals, men, postmenopausal women, and middle-aged or older individuals [15]. Diagnosis can pose its own challenges, with the first obstacle being recognition of risk for the disease; it is estimated that up to 80% of people remain undiagnosed in the community [16]. Recent work has shown that OSA is highly prevalent in the population of commercial motor vehicle (CMV) operators [8]. This chapter will therefore focus on the prevalence, risks, and effects of OSA in the CMV operator.

Prevalence

OSA is much more common in CMV operators than in the general population [8,11,17,18]. A higher proportion of CMV operators carry the common risk factors for the disorder, including middle age, male gender, and central obesity [8,11]. Studies among CMV operators suggest OSA prevalence ranging from 28% [17,19] to 78% [8,11,17,18]; in contrast, the prevalence of OSA in the general population of employed workers is 10%–17% in men, and 9% in women aged 30–70 years [20]. Due to the rising prevalence of obesity, the overall prevalence of OSA continues to increase [21].

The Federal Motor Carrier Safety Administration (FMCSA) commissioned a study of 4280 CMV operators in Philadelphia, Pennsylvania; 1392 individuals responded

and 407 of the at-risk respondents underwent an in-laboratory polysomnography (PSG) [17]. This study estimated the OSA prevalence among commercial vehicle operators to be approximately 28% [17]. A similar study was conducted in Australia and a higher prevalence of 60% was found, compared with the American study, which was not explained by modestly lower body mass index (BMIs) in the latter group, but may be due to participant bias [8,15]. In a third study conducted by a large trucking company, 19,371 commercial drivers had employer-mandated screening for OSA with an online questionnaire [11]. Screening identified 30% (5908) drivers at high risk; of the drivers tested with PSG 80% had OSA [11]. These data support the value of systematic screening in identifying latent cases of OSA in this safety-sensitive population [22].

History of federally funded research and regulatory activity

The current regulation regarding OSA in CMV operators is vague and offers medical examiners little detail or specificity in evaluating for OSA. The rule states that the person being evaluated “has no established medical history or clinical diagnosis of [any] condition which is likely to cause loss of consciousness or any loss of ability to control a CMV.” [23] This rule has remained unchanged since 1970 [23], despite a series of meetings and publications to address regulation by the administration (Fig. 43.1).

In July 1988, the Department of Transportation and Federal Highway Administration convened at the Conference on Neurological Disorders and Commercial Drivers in Washington, D.C. and released the recommendation that anyone who would lose consciousness while driving should be excluded from operating a commercial vehicle [24]. Specific conditions that could contribute to such loss of consciousness were cited, including sleep disorders such as sleep apnea syndrome, which could cause excessive daytime sleepiness [24].

The FMCSA was later established, with the mission of reducing injuries and fatalities involving large trucks and buses [22]. The FMCSA authorized research to estimate the prevalence of OSA in CMV operators, which was published in 2002 [17]. In 2001, the FMCSA listed a single question on the Fitness for Duty Evaluation Form for OSA, which combined four items: sleep disorders, pauses in breathing while asleep, daytime sleepiness, and loud snoring [25]. Empiric evidence showed that over the course of the first year, responses to this question were rarely affirmative, raising questions about the accuracy of self-reported symptoms to identify risk during fitness-for-duty evaluations. To address this and other questions, the FMCSA convened a Medical Expert Panel to offer

guidance on screening and management of OSA in CMV operators in 2008, followed by additional meetings to update this information from its Medical Review Board (FMCSA-MRB) and its Motor Carrier Safety Advisory Committee in 2011 [19,26].

These meetings identified the lack of uniformity in fitness for duty evaluations, and the tendency of CMV operators to “doctor-shop” in gaining medical certification. To address this issue, in 2015, the administration required medical examiners to undergo training and certification to perform screening for OSA during fitness for duty evaluations of CMV operators (before and after hire) and created a National Registry for Certified Medical Examiners [27]. In March 2016, the FMCSA and Federal Road Administration issued a Notice of Proposed Rulemaking (NPRM) requesting prevalence data, cost, and benefits of OSA evaluation and treatment in CMV operators [28]. The American Academy of Sleep Medicine (AASM) convened a task force in response to address sleep and transportation safety awareness and published these recommendations for access to the larger sleep medicine community [29]. Based on this input and suggestions from other stakeholders, the FMCSA-MRB met in August 2016 to issue its latest recommendations [30]; these recommendations would apply to all truck and rail CMV operators with moderate to severe apnea and were intended to become law [31]. However, the plan to mandate the screening of truck and rail operators for OSA was abandoned in August 2017 when the NPRM was withdrawn by the new administration [32].

Screening

Guidance for screening has been offered by several groups [19,29,30]. In general, guidance documents emphasize the use of objective rather than subjective measures when assessing risk during the initial evaluation. Self-reported subjective measures have been shown to be unreliable in several studies, with a preponderance of negative responses [33–35]. Although some operators may admit to subjective symptoms of OSA (e.g., history of sleepiness-related accidents, fatigue, and sleepiness during duty hours) and typical symptoms of sleep apnea (e.g., snoring and gasping during sleep), research shows that such reporting is more commonly absent or unreliable [33–35]. In the study conducted by Dagan et al., OSA was detected in 77.7% of the drivers screened by PSG and 47.1% of them were sleepy according to the multiple sleep latency test (MSLT) [35]. None of the drivers, however, complained about sleep problems including snoring or excessive daytime sleepiness [35]. The absence of subjective reporting in the setting of objective findings consistent with OSA and sleepiness may be due to differential vulnerability to sleepiness based on genetic factors [36], or may be the result of

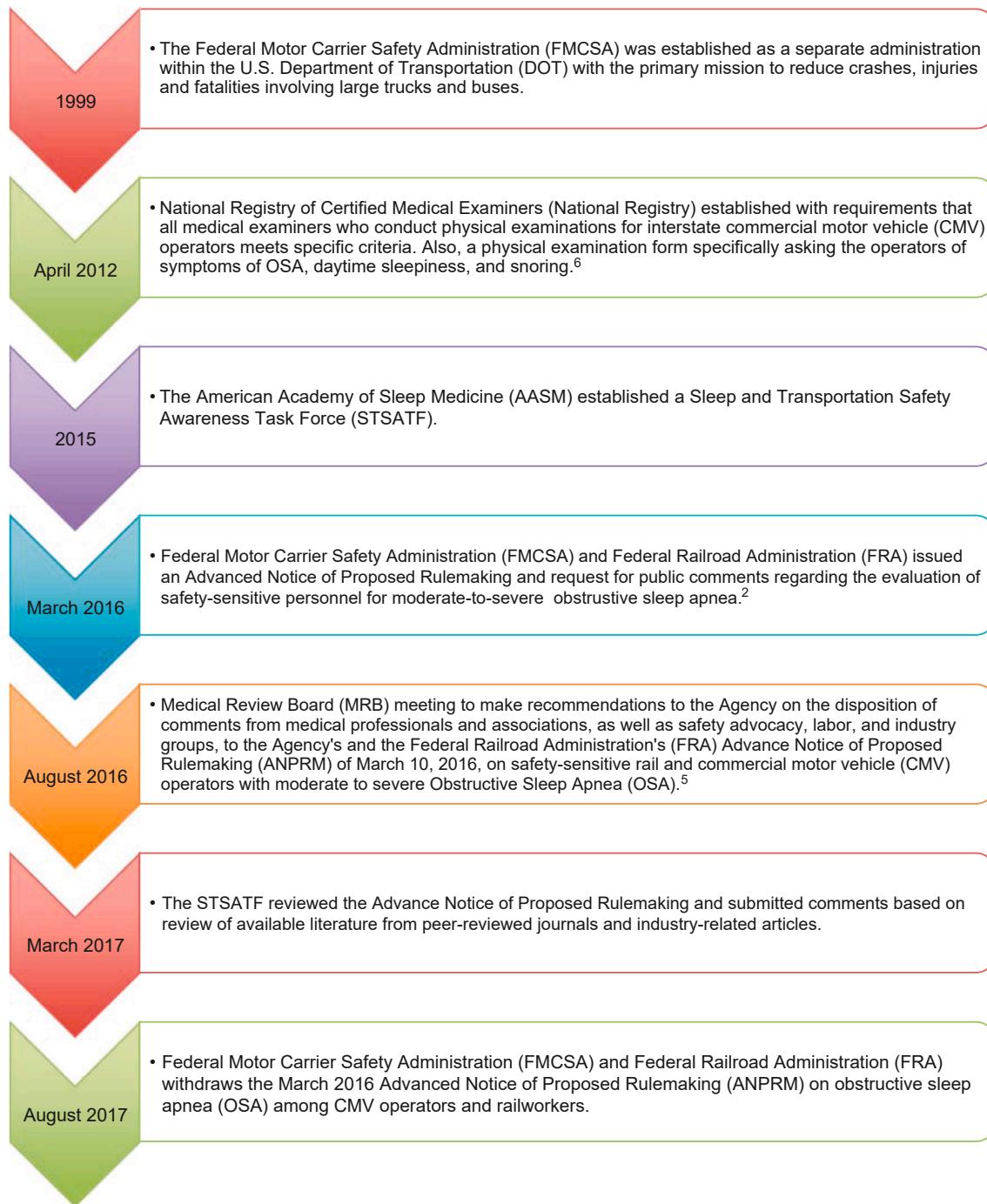


FIGURE 43.1 Timeline leading up to current regulations on commercial motor vehicle drives.

underreporting due to concerns about employment. Therefore, emphasis should be placed on objective criteria.

Due to the high prevalence of OSA and unreliability of subjective criteria, the AASM and Transportation Safety Awareness Task Force have put forth primary and secondary screening criteria that rely heavily on objective measures (Table 43.1) [29]. Primary criteria refer to high BMI, the

presence of resistant hypertension or diabetes, or a history of a drowsiness-related crash. If a CMV operator meets primary criteria, they should be referred to a board-certified sleep medicine physician for a thorough evaluation.

The use of BMI as a primary screening tool is well-supported. In a population-based prospective study conducted by Peppard et al., a 10% weight gain was associated

TABLE 43.1 Screening criteria for OSA recommended by AASM sleep and transportation safety awareness task force [11].

Primary criteria	Secondary criteria
1. BMI $\geq 40 \text{ kg/m}^2$	1. Symptoms of OSA
2. BMI $\geq 33 \text{ kg/m}^2$ and either a. Hypertension requiring ≥ 2 medications for control or b. Type 2 diabetes mellitus	2. BMI 28–33 kg/m ² with any of the following risk factors • Small or recessed jaw • Modified Mallampati classification 3 or 4 • Neck size ≥ 17 in. (Men), ≥ 15.5 in. (women) • Hypertension • Type 2 diabetes mellitus (especially if BMI $>30 \text{ kg/m}^2$) • Cardiovascular disease • Untreated hypothyroidism • Age ≥ 42 years • Family history of OSA • Male or postmenopausal female
3. Sleepiness-related crash or accident, off-road deviation, or rear-ending another vehicle by report or observation	
4. Fatigue or sleepiness during the duty period	

with sixfold increase in risk of developing moderate-to-severe OSA [37]. In another prospective study conducted in Brazil, 34.5% of those with BMI of 25 to $<30 \text{ kg/m}^2$ and 64.1% of those with BMI $\geq 30 \text{ kg/m}^2$ had OSA [38]. Lower BMI thresholds (such as 30 kg/m²) [39] for screening would require a larger number of operators to be tested and may result in fewer missed cases, but may result in higher costs. Most organizations recognize BMI $\geq 35 \text{ kg/m}^2$ as increased risk for OSA and advocate for testing using this parameter [19,35,40,41]; the higher BMI threshold limits the number of operators tested, but results in missed cases.

Initial evaluation

If a CMV operator presents with two or more of the factors listed in Table 43.1, (s)he should be referred for a comprehensive evaluation by a board-certified sleep physician for diagnostic testing. The likelihood of having OSA with these relatively high BMI thresholds may be $>80\%$ [28]—if for any reason an initial diagnostic test (such as home-based testing or PSG) is found to be inconclusive or negative, additional evaluation may be warranted.

Diagnosis

In 2008, the Medical Expert Panel advised the use of in-lab PSG to confirm the diagnosis of OSA in those who were at high risk for the condition upon screening [19]. PSG is the gold standard test for diagnosis of OSA [42] and can also help identify other sleep disorders, but is expensive and time-consuming. More recently, rapid advancements in diagnostic technologies have allowed home sleep apnea testing (HSAT) to become routine [43]. Typically, HSAT relies on three–four channels, rather than 12–16 used in PSG, to assess respiratory effort, airflow, oxygen saturation, and heart rate [43]. HSAT has many advantages, including portability, lower expense, convenience, and

accessibility. HSAT can be performed directly in the patient's preferred sleeping environment, rather than in a laboratory.

Despite the allure associated with HSAT, several limitations exist. HSAT is useful for confirming OSA in CMV operators with high preclinical suspicion, but is less useful for ruling out OSA and may be inconclusive [29]. In other words, a negative result is less useful than a positive, confirmatory result because of the high pretest probability of the chosen sample. In addition to inconclusive results on HSAT, AHI severity is underestimated and thus OSA may also be underestimated or missed [44]. Finally, this type of study is done in a home setting where there is a risk of a person other than the intended worker being evaluated wearing the device. HSAT should be performed in conjunction with a comprehensive sleep evaluation under a board-certified sleep physician [43].

Sleep studies (both PSG and HSAT) are considered positive for sleep apnea if the number of apneas (cessation in airflow) or hypopneas (reduction in airflow) per hour of sleep (if PSG) or test time (if HSAT) exceed a certain threshold. This measure, known as the apnea-hypopnea index (AHI, for PSG) or respiratory event index (REI, for HSAT), is used to grade the severity of illness according to the following thresholds: normal <5 events/h; mild = [5–15] events/h; moderate = [15–30] events/h; and severe AHI ≥ 30 events/h [42,43].

Treatment

CMV operators with AHI ≥ 20 events/h (i.e., in the moderate to severe range) should receive prompt, definitive treatment with positive airway pressure (PAP) therapy, as this cohort is more likely to experience a sleepiness-related crash [19,41]. Although data linking crashes to those with AHI between 5 and 15 events/h are less reliable, this group may also benefit from treatment with PAP or alternative modalities, such as a

mandibular advancement device, weight management, position therapy, or upper airway surgery [10].

Monitoring PAP therapy

If PAP is prescribed, treatment should be monitored in an ongoing fashion to assess for efficacy. Efficacy indicates adherence and effectiveness, both of which can be tracked using downloaded data from PAP devices [45–47]. Such data can now be obtained via wireless mechanisms [48], enabling prompt retrieval of information and intervention to improve efficacy, including correction of mask fit and addressing any side effects of PAP therapy (e.g., dry mouth and mask discomfort).

The three main criteria that must be addressed when evaluating the efficacy of treatment for OSA are [1]: resolution of OSA or residual AHI <5 events/h [2]; adherence to therapy for ≥4 h of PAP use per night for ≥70% of days; and [3] improvement in the symptoms of the intended CMV operator [29]. The assessment of sleepiness in CMV operators posttherapy can be challenging; symptom reporting is unreliable and objective measures of sleepiness (e.g., MSLT and Maintenance of Wakefulness Testing) have not been shown to correlate with on-the-road performance [49]. Therefore, most centers rely heavily on downloaded data from PAP devices to evaluate treatment efficacy of OSA.

Benefits of PAP therapy

Treatment of OSA with PAP improves daytime sleepiness within 2–7 days of treatment [50] and, more importantly, decreases the risk of motor vehicle accidents [8,10,51–55] based on simulated driving tests. A detailed cost analysis also found PAP therapy to be a cost-effective approach that reduces overall healthcare costs for individuals suffering from OSA [56]. Health payers and trucking companies using PAP to treat CMV operators with OSA save approximately \$2.88 billion and up to \$1.3–13.8 million annually, respectively [16,57]. Some studies contend that screening for and treating OSA with PAP results in major savings by reducing absenteeism and comorbidities, while increasing overall productivity [16]. Others have shown that the estimated costs of screening, diagnosis, and treatment for OSA are justified by the reduction in costs related to prevented crashes, provided that a high proportion of patients adhere to treatment [56]. A program to screen and diagnose commercial drivers for OSA using PSG was found to cost only half as much as not screening at all, or \$358–372 per driver [56]. This favorable cost analysis was attributed to the high cost of crashes, which would have otherwise occurred where screening, diagnosis, and treatment were not performed [56].

Education

CMV operators should be educated regarding symptoms, risk factors, and potential consequences of untreated OSA at the time of evaluation. Those who are found to be at low risk for OSA should be advised to seek reevaluation if they experience a weight gain of at least 10%, as such an increase has been correlated with an increase in AHI by 32% [37]. Rescreening is also advised if the CMV operator develops symptoms suggestive of OSA, or downstream consequences, such as hypertension or type 2 diabetes mellitus [29]. They should also be advised to avoid driving while sleepy for any reason, including insufficient sleep, circadian disorder, or medications.

Conclusion

OSA is more common among CMV operators than in general groups because individuals in this cohort have a higher prevalence of the three common risk factors for OSA: obesity, male gender, and middle age. If left unaddressed, OSA can lead to daytime sleepiness—often a contributing factor in vehicular crashes—as well as other health conditions, ultimately creating tremendous economic costs. Therefore, providing a permissive environment for CMV operators to seek help without fear of employment loss is paramount. Implementation of comprehensive case identification and treatment programs can facilitate management of OSA while maintaining employment. Sleep medicine clinicians should be aware of the high prevalence, potential risks, and specific challenges in identifying and treating OSA in this unique population. More specific guidance and a mandate from the federal government to diagnose and treat the condition are long overdue and may help mitigate the loss of life, injuries, property damage, and large financial costs that occur annually due to preventable accidents from untreated OSA in the transportation industry.

References

- [1] Williamson AM, Feyer AM. Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally prescribed levels of alcohol intoxication. *Occup Environ Med* 2000;57(10):649–55. <https://doi.org/10.1136/oem.57.10.649>.
- [2] Strohl KP, Brown DB, Collop N, George C, Grunstein R, Han F, Kline L, Malhotra A, Pack A, Phillips B, Rodenstein D, Schwab R, Weaver T, Wilson K. An official American thoracic society clinical practice guideline: sleep apnea, sleepiness, and driving risk in noncommercial drivers - an update of a 1994 statement. *Am J Respir Crit Care Med* 2013;187(11):1259–66. <https://doi.org/10.1164/rccm.201304-0726ST> undefined.
- [3] Mukherjee S, Patel SR, Kales SN, Ayas NT, Strohl KP, Gozal D, Malhotra A. An official American thoracic society statement: the importance of healthy sleep: recommendations and future priorities.

- Am J Respir Crit Care Med 2015;191(12):1450–8. <https://doi.org/10.1164/rccm.201504-0767ST>.
- [4] National Highway Traffic Safety Administration. (2016). NHTSA drowsy driving research and program plan. U.S. Department of Transportation. Retrieved September 2025, from: <https://www.nhtsa.gov/document/nhtsa-drowsy-driving-research-and-program-plan>
 - [5] Masten SV, Stutts JC, Martell CA. Predicting daytime and nighttime drowsy driving crashes based on crash characteristic models. In: 50th annual proceedings of the association for the advancement of Automotive medicine; 2006.
 - [6] Tefft BC. Prevalence of motor vehicle crashes involving drowsy drivers, United States, 1999–2008. Accid Anal Prev 2012;45:180–6. <https://doi.org/10.1016/j.aap.2011.05.028>.
 - [7] Owens JM, Dingus, Guo, Fang, Perez M, McClafferty J. Prevalence of drowsy driving crashes: estimates from a large-scale naturalistic driving study. AAA Foundation for Traffic Safety; 2018.
 - [8] Howard ME, Desai AV, Grunstein RR, Hukins C, Armstrong JG, Joffe D, Swann P, Campbell DA, Pierce RJ. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. Am J Respir Crit Care Med 2004;170(9):1014–21. <https://doi.org/10.1164/rccm.200312-1782OC>.
 - [9] Pack AI, Pack AM, Rodgman E, Cucchiara A, Dinges DF, Schwab CW. Characteristics of crashes attributed to the driver having fallen asleep. Accid Anal Prev 1995;27(6):769–75. [https://doi.org/10.1016/0001-4575\(95\)00034-8](https://doi.org/10.1016/0001-4575(95)00034-8).
 - [10] Tregear S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. J Clin Sleep Med 2009;5(6):573–81. <https://doi.org/10.5664/jcsm.27662>.
 - [11] Berger M, Varvarigou V, Rielly A, Czeisler CA, Malhotra A, Kales SN. Employer-mandated sleep apnea screening and diagnosis in commercial drivers. J Occup Environ Med 2012;54(8):1017–25. <https://doi.org/10.1097/JOM.0b013e3182572e16>.
 - [12] Burks SV, Anderson JE, Bombyk M, Haider R, Ganzhorn D, Jiao X, Lewis C, Levold A, Liu H, Ning J, Toll A, Hickman JS, Mabry E, Berger M, Malhotra A, Czeisler CA, Kales SN. Nonadherence with employer-mandated sleep apnea treatment and increased risk of serious truck crashes. Sleep 2016;39(5):967–75. <https://doi.org/10.5665/sleep.5734>.
 - [13] Gurubhagavatula I. Consequences of obstructive sleep apnoea. Indian J Med Res 2010;131(2):188–95.
 - [14] Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. Chest 2015;147(1):266–74. <https://doi.org/10.1378/chest.14-0500>.
 - [15] Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev 2017;34:70–81. <https://doi.org/10.1016/j.smrv.2016.07.002>.
 - [16] Hidden health crisis costing America billions. Underdiagnosing and undertreating obstructive sleep apnea draining healthcare system. American Academy of Sleep Medicine; 2016.
 - [17] Pack, Dinges, Maislin GA. Study of prevalence of sleep apnea among commercial truck drivers. Federal Motor Carrier Safety Administration; 2002.
 - [18] Stoohs RA, Bingham L, Itoi A, Guilleminault C, Dement WC. Sleep and sleep-disordered breathing, in commercial long-haul truck drivers. Chest 1995;107(5):1275–82. <https://doi.org/10.1378/chest.107.5.1275>.
 - [19] Ancoli-Israel S, Geroge CFP, Guilleminault C, Pack AI. Expert panel recommendations: obstructive sleep apnea and commercial vehicle driver safety, 14; 2008.
 - [20] Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013;177(9):1006–14. <https://doi.org/10.1093/aje/kws342>.
 - [21] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328(17):1230–5. <https://doi.org/10.1056/NEJM199304293281704>.
 - [22] Federal Motor Carrier Safety Administration. (2016, August 19). *Commercial motor vehicle drivers and obstructive sleep apnea*. U.S. Department of Transportation. Retrieved September 2025, from: <https://www.fmcsa.dot.gov/medical/Driver-medical-requirements/commercial-motor-vehicle-drivers-and-obstructive-sleep-apnea>
 - [23] U.S. Department of Transportation, Federal Motor Carrier Safety Administration. Medical Examiner's Handbook 2024.
 - [24] Booker HE. Conference on neurological disorders and commercial drivers. Administration UDoTaFH; 1988.
 - [25] Federal Motor Carrier Safety Administration. Medical examination report for commercial driver fitness determination (Form MCSA-5875). U.S. Department of Transportation; 2010. <https://www.fmcsa.dot.gov/regulations/medical/medical-examination-report-commercial-driver-fitness-determination>. [Accessed September 2025].
 - [26] Williams JR, AA, Tregear SJn. Evidence report: obstructive sleep apnea and commercial motor vehicle driver safety. 2011. updated review: 11.
 - [27] Federal Motor Carrier Safety Administration. (2019). National Registry of Certified Medical Examiners. U.S. Department of Transportation. September 2025, <https://nationalregistry.fmcsa.dot.gov>.
 - [28] U.S. Department of Transportation, Federal Motor Carrier Safety Administration, & Federal Railroad Administration. (2016). Evaluation of safety sensitive personnel for moderate-to-severe obstructive sleep apnea: Advance notice of proposed rulemaking. Federal Register, 81(111), 36397–36398. Retrieved September 2025, from: <https://www.federalregister.gov/d/2016-13564>
 - [29] Gurubhagavatula I, Sullivan S, Meoli A, Patil S, Olson R, Berneking M, Watson NF. Management of obstructive sleep apnea in commercial motor vehicle operators: recommendations of the AASM sleep and transportation safety awareness task force. J Clin Sleep Med 2017;13(05):745–58. <https://doi.org/10.5664/jcsm.6598>.
 - [30] American Academy of Sleep Medicine. (2016). FMCSA-FRA response — Comments on advance notice of proposed rulemaking: Evaluation of safety sensitive personnel for moderate-to-severe obstructive sleep apnea (Docket Nos. FMCSA-2015-0419 & FRA-2015-0111). Retrieved September 2025, from <https://aasm.org/resources/pdf/government/fmcsa-fra-response-aasm.pdf>
 - [31] Evaluation of Safety Sensitive Personnel for Moderate-to-Severe Obstructive Sleep Apnea: Advance Notice of Proposed Rulemaking; extension of comment period, 81 Fed. Reg. 36,858 (June 8, 2016)
 - [32] Evaluation of safety sensitive personnel for moderate-to-severe obstructive sleep apnea. Fed Regist 2017;82:37038–9.
 - [33] Talmage JB, Hudson TB, Hegmann KT, Thiese MS. Consensus criteria for screening commercial drivers for obstructive sleep apnea: evidence of efficacy. J Occup Environ Med 2008;50(3):324–9. <https://doi.org/10.1097/JOM.0b013e3181617ab8>.

- [34] Parks PD, Durand G, Tsismenakis AJ, Vela-Bueno A, Kales SN. Screening for obstructive sleep apnea during commercial driver medical examinations. *J Occup Environ Med* 2009;51(3):275–82. <https://doi.org/10.1097/JOM.0b013e31819eaaa4>.
- [35] Dagan Y, Doljansky JT, Green A, Weiner A. Body mass index (BMI) as a first-line screening criterion for detection of excessive daytime sleepiness among professional drivers. *Traffic Inj Prev* 2006;7(1):44–8. <https://doi.org/10.1080/15389580500412994>.
- [36] Van Dongen HPA, Bender AM, Dinges DF. Systematic individual differences in sleep homeostatic and circadian rhythm contributions to neurobehavioral impairment during sleep deprivation. *Accid Anal Prev* 2012;45:11–6. <https://doi.org/10.1016/j.aap.2011.09.018>.
- [37] Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000;284(23):3015–21. <https://doi.org/10.1001/jama.284.23.3015>.
- [38] Tufik S, Santos-Silva R, Taddei JA, Bittencourt LRA. Obstructive sleep apnea syndrome in the São Paulo epidemiologic sleep study. *Sleep Med* 2010;11(5):441–6. <https://doi.org/10.1016/j.sleep.2009.10.005>.
- [39] Gurubhagavatula I, Maislin G, Nkwuo JE, Pack AI. Occupational screening for obstructive sleep apnea in commercial drivers. *Am J Respir Crit Care Med* 2004;170(4):371–6. <https://doi.org/10.1164/rccm.200307-968OC>.
- [40] Hartenbaum N, Collop N, Rosen IM, Phillips B, George CFP, Rowley JA, Freedman N, Weaver TE, Gurubhagavatula I, Strohl K, Leaman HM, Moffitt GL. Sleep apnea and commercial motor vehicle operators: statement from the joint task force of the American college of chest physicians, the American college of occupational and environmental medicine, and the national sleep foundation. *Chest* 2006;130(3):902–5. <https://doi.org/10.1378/chest.130.3.902>.
- [41] DR Parker, *Motor carrier safety advisory committee and medical review board task: final report on obstructive sleep apnea (OSA)*.
- [42] Kapur VK, Ackley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, Harrod CG. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American academy of sleep medicine clinical practice guideline. *J Clin Sleep Med* 2017;13(3):479–504. <https://doi.org/10.5664/jcsm.6506>.
- [43] Collop NA, Anderson WMD, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, Hudgel D, Sateia M, Schwab R. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. *J Clin Sleep Med* 2007;3(7):737–47. <https://doi.org/10.5664/jcsm.27032>.
- [44] Bianchi MT, Goparaju B. Potential underestimation of sleep apnea severity by at-home kits: rescore in-laboratory polysomnography without sleep staging. *J Clin Sleep Med* 2017;13(4):551–5. <https://doi.org/10.5664/jcsm.6540>.
- [45] Berry RB, Kushida CA, Kryger MH, Soto-Calderon H, Staley B, Kuna ST. Respiratory event detection by a positive airway pressure device. *Sleep* 2012;35(3):361–7. <https://doi.org/10.5665/sleep.1696>.
- [46] Cilli A, Uzun R, Bilge U. The accuracy of autotitrating CPAP-determined residual apnea-hypopnea index. *Sleep Breath* 2013;17(1):189–93. <https://doi.org/10.1007/s11325-012-0670-x>.
- [47] Desai H, Patel A, Patel P, Grant BJB, Mador MJ. Accuracy of autotitrating CPAP to estimate the residual Apnea-Hypopnea Index in patients with obstructive sleep apnea on treatment with autotitrating CPAP. *Sleep Breath* 2009;13(4):383–90. <https://doi.org/10.1007/s11325-009-0258-2>.
- [48] Schwab RJ, Badr SM, Epstein LJ, Gay PC, Gozal D, Kohler M, Lévy P, Malhotra A, Phillips BA, Rosen IM, Strohl KP, Strollo PJ, Weaver EM, Weaver TE. An official american thoracic society statement: continuous positive airway pressure adherence tracking systems: the optimal monitoring strategies and outcome measures in adults. *Am J Respir Crit Care Med* 2013;188(5):613–20. <https://doi.org/10.1164/rccm.201307-1282ST>.
- [49] Antic NA, Catcheside P, Buchan C, Hensley M, Naughton MT, Rowland S, Williamson B, Windler S, McEvoy RD. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neuropsychological function in patients with moderate to severe OSA. *Sleep* 2011;34(1):111–9. <https://doi.org/10.1093/sleep/34.1.111>.
- [50] Tregear S, Reston J, Schoelles K, Phillips B. Continuous positive airway pressure reduces risk of motor vehicle crash among drivers with obstructive sleep apnea: systematic review and meta-analysis. *Sleep* 2010;33(10):1373–80. <https://doi.org/10.1093/sleep/33.10.1373>.
- [51] Shiomi T, Arita AT, Sasanabe R, Banno K, Yamakawa H, Hasegawa R, Ozeki K, Okada M, Ito A. Falling asleep while driving and automobile accidents among patients with obstructive sleep apnea-hypopnea syndrome. *Psychiatr Clin Neurosci* 2002;56(3):333–4. <https://doi.org/10.1046/j.1440-1819.2002.01004.x>.
- [52] Horstmann S, Hess CW, Bassetti C, Gugger M, Mathis J. Sleepiness-related accidents in sleep apnea patients. *Sleep* 2000;23(3):383–9. <https://doi.org/10.1093/sleep/23.3.1e>.
- [53] George CFP. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax* 2001;56(7):508–12. <https://doi.org/10.1136/thorax.56.7.508>.
- [54] Terán-Santos J, Jimenez-Gomez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. *N Engl J Med* 1999;340(11):847–51. <https://doi.org/10.1056/nejm199903183401104>.
- [55] Young T, Blustein J, Finn L, Palta M. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep* 1997;20(8):608–13. <https://doi.org/10.1093/sleep/20.8.608>.
- [56] Gurubhagavatula I, Nkwuo JE, Maislin G, Pack AI. Estimated cost of crashes in commercial drivers supports screening and treatment of obstructive sleep apnea. *Accid Anal Prev* 2008;40(1):104–15. <https://doi.org/10.1016/j.aap.2007.04.011>.
- [57] Watson NF. Health care savings: the economic value of diagnostic and therapeutic care for obstructive sleep apnea. *J Clin Sleep Med* 2016;12(8):1075–7. <https://doi.org/10.5664/jcsm.6034>.

This page intentionally left blank

Chapter 44

Value-based sleep and health: Health economic aspects of insomnia and obstructive sleep apnea

Emerson M. Wickwire^{a, b}

^aDivision of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, United States; ^bDepartment of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, United States

Among adults, the two most common sleep disorders encountered in clinical practice are insomnia disorder and obstructive sleep apnea (OSA). As discussed extensively throughout this volume, both conditions incur significant risks for various negative health outcomes and reduced health-related quality of life. In addition, these common sleep disorders impose significant economic burden borne by patients, insurers, employers, and the entire society [1,2]. Yet despite the tremendous volume of studies evaluating the pathophysiology, epidemiology, and outcomes of insomnia and OSA, relatively far fewer investigations have considered economic aspects of their treatment. Given ever-increasing costs and limited resources in the current healthcare environment, payers, employers, and policy-makers are in desperate need of these insights to guide informed decision-making regarding allocating healthcare resources. The aim of this chapter is to provide a brief overview of health economic concepts pertinent to insomnia and OSA and highlight several notable issues concerning the economic aspects of treatments for these two common sleep disorders.

Overview of sleep health economics

Direct and indirect costs of sleep disorders

In the broadest sense, the economic burden posed by sleep disorders can be broken into three domains: direct costs, indirect costs, and reduced health-related quality of life (HrQOL). Direct costs include assessment, diagnosis, treatment, and overall care for management. For example, in the case of insomnia, this might typically include a physician consultation, prescription sleep medication, and

ongoing outpatient care, or perhaps referral to a sleep psychologist or other provider for cognitive-behavioral treatment. In the case of OSA, direct costs could include physician consultation, diagnostic sleep testing, medical device supplies (e.g., positive airway pressure [PAP] or oral appliance therapy [OAT]), and ongoing medical oversight. Especially in the case of OSA, direct costs are heavily front-loaded and typically require longer time horizons to recapture following successful treatment.

Indirect costs are not directly related to treatment but can nonetheless be attributed to a given sleep disorder. For example, well-documented indirect costs of insomnia and OSA include increased healthcare resource utilization (HCRU) for comorbid conditions that are exacerbated by sleep disorders (e.g., cardiovascular disease or depression), diminished workplace productivity (e.g., absenteeism or presenteeism [being physically present at work, but underproductive]), and increased likelihood of workplace accidents and mistakes, including motor vehicle collisions (MVCs). While total aggregate societal costs are often cited to underscore the immense financial impact of sleep disorders, it is crucial to recognize that different stakeholders differentially shoulder various direct and indirect costs [3].

In the United States, estimates of the total costs of insomnia have ranged from \$28.1 billion to \$216 billion USD [4,5]. Notably, the majority of insomnia-related costs are borne by employers. In the Canadian province of Quebec, a well-conducted survey study found that workplace productivity losses (including absenteeism and presenteeism) accounted for over 90% of the total costs associated with insomnia [6]. In terms of OSA, a 2016 white paper commissioned by the American Academy of

Sleep Medicine estimated that the annual societal costs of OSA in the United States are greater than \$150 billion [7]. This sum included \$86.9 billion due to lost productivity in the workplace, \$30 billion due to increased healthcare resource utilization, \$26.2 billion due to MVCs, and \$6.5 billion resulting from workplace accidents and injuries [7].

From a sleep health economic perspective, it is essential to recognize that insomnia and OSA frequently coexist with other sleep, medical, and psychiatric conditions, often worsening or prolonging these chronic issues. For instance, sleep clinicians and researchers well understand the connections between insomnia and depression, as well as between OSA and cardiovascular disease (CVD). However, identifying the independent effects of sleep disorders from these comorbid conditions poses significant methodological challenges. Available data tend to be either highly detailed (i.e., randomized clinical trials or longitudinal, serial assessment cohort studies) or extensive (i.e., administrative claims data), but not both. Thus, even advanced techniques such as propensity-score matching and inverse probability of treatment weighting cannot fully eliminate residual confounding. As a result, economic stakeholders are likely to question whether the high costs attributed to sleep disorders are actually due to these comorbid chronic conditions, such as depression or CVD, which are themselves major drivers of elevated healthcare costs. Attribution of the unique contribution of comorbid sleep disorders to the economic burden of chronic medical conditions remains a significant focus for sleep scientists in the future.

Health-related quality of life

In addition to the direct and indirect costs of sleep disorders, health-related quality of life (HrQOL) is a critical economic outcome of interest. HrQOL encompasses both general as well as disease-specific components, each of which can be assessed using validated tools. Extensive evidence has shown that untreated insomnia and OSA can negatively impact HrQOL, while treatments are associated with improvements in HrQOL [1,2]. Typically, HrQOL measures evaluate an individual's subjective satisfaction with life and their capacity to function independently. General HrQOL tools such as the PROMIS [8], Short-Form 36 (SF-36) [9], and EuroQol-5D [10] assess overall satisfaction and functioning in areas such as mobility and vision. In contrast, disease-specific measures of HrQOL target impairments tied to particular conditions, such as fatigue for insomnia or sleepiness for OSA. Examples of disease-specific HrQOL measures include the Hotel-Dieu-16 (HD-16) for insomnia [11] and the Functional Outcomes of Sleep Questionnaire (FOSQ) for OSA [12].

An additional, important economic measure to quantify HrQOL is the quality-adjusted life year (QALY). QALYs

take into account both HrQOL and time, calculated as (quality on a 0–1 utility scale) multiplied by (time in years). QALYs, though strictly nonmonetary, provide a standardized metric that researchers and decision-makers can use to evaluate return-on-investment (ROI) across various disease states. For example, numerous cost-effectiveness analyses (CEAs) evaluate cost-effectiveness of sleep disorder treatments using the incremental cost-effectiveness ratio (ICER), which indicates the cost per QALY [13]. Of course, in the real world, the value of a QALY ultimately depends on what stakeholders (payers, employers, health systems, etc.) are willing to pay for improvement in HrQOL or health utility. Appropriately, this amount is known as willingness to pay (WTP). In terms of cost-effectiveness, costs per QALY below \$50,000 per QALY are generally considered cost-effective in the United States. However, this is only a rule of thumb and varies across health systems and nations.

Naturally, from a consumer standpoint, individual patients do not use advanced measures of HrQOL or analytical frameworks when assessing their personal willingness to pay (WTP). At the patient level, WTP is influenced by perceived benefits and costs, personal resources, available alternatives, and other factors. Although patients are a crucial stakeholder group and often place a high value on sleep, few empirical studies have explored WTP for treatments of insomnia or OSA from the patient perspective. A discrete-choice experiment conducted at a hospital in West Virginia revealed that among primary care patients with insomnia ($n = 82$), the willingness to pay (WTP) for a treatment that decreased sleep latency by 10 min, reduced wake after sleep onset (WASO) by 15 min, and increased total sleep time by 1 h was \$66.69 [14]. For individuals interested in consumer approaches to health care, examining the direct-to-consumer products and services available, along with their pricing and payment options, is likely to be highly informative and provide new knowledge to the sleep health economic field.

Economic perspective: Perceived value of sleep disorder treatments

The sleep medicine environment includes a variety of stakeholders. Patients, payers, providers, health systems, and equipment manufacturers incur varying costs, as well as potential savings or revenues associated with sleep disorder treatments. Consequently, it is not surprising that each stakeholder group perceives the value of sleep differently. Most important, patients prioritize HrQOL, which includes increased energy for work or leisure, and a smooth, hassle-free, streamlined care experience. Payers concentrate on cost savings, whereas employers focus on workplace productivity and minimizing accident risk. Providers appreciate testing and treatment options that are

valid, reliable, and easy to implement. Table 44.1 summarizes stakeholder perspectives in sleep medicine.

Economic benefit of sleep disorder treatments

Health economics of insomnia treatment

Multiple studies and several high-quality reviews have examined economic aspects of sleep disorder treatments. A detailed literature review revealed that both pharmacotherapy and cognitive-behavioral therapy for insomnia (CBTI) generally provided positive economic benefits, including in comorbid conditions [1]. Table 44.2 summarizes selected studies that have examined the economic impact of insomnia treatments. At the same time, it is essential to recognize that clinical settings, patient populations, study designs, and outcome measures have varied significantly across insomnia economic studies conducted so far. Generally, larger studies tend to overlook measures of insomnia severity, often relying instead on administrative diagnostic claims to define of insomnia. Such studies are also typically limited in assessments of how treatment affects specific insomnia-related changes, such as improvements in daytime functioning [15]. These limitations are especially relevant when evaluating real-world evidence. For instance, several analyses of administrative claims have indicated that insomnia medication treatments are linked to higher future costs [16–19]. While there are legitimate reasons that insomnia medications or CBT might lead to increased costs—such as accidents linked to residual sedation from medications or daytime sleepiness due to sleep restriction during CBT—the inability to accurately measure economic benefits and the perspective from which costs are evaluated are significant concerns. Ultimately, administrative claims data are unlikely to capture workplace productivity measures, which account for most insomnia-related costs and are entirely shouldered by employers. Another important factor to consider is

treatment costs, which are influenced by the format of the treatment (e.g., in-person, group, or digital insomnia care). Several recent studies have shown that CBTI approaches, including digital CBTI [20–23] and telephone-based CBTI in chronic pain [24] provide economic benefits.

Health economics of OSA treatment

Multiple studies have evaluated the economic impact of OSA (Table 44.3). A 2019 systematic review of treatments for OSA found that 15 out of 18 comparisons yielded positive economic benefits [2]. Very recently, several additional studies have indicated positive economic benefits from PAP, particularly in patients with cardiovascular disease [25–29]. These data not only provide further evidence for the association of OSA and CVD [30], but they also underscore the significance of patient selection in clinical and health economic research. In other words, some patients are more likely than others to benefit from OSA treatment and to demonstrate economic benefit from OSA treatment. In a study of older adults with cardiovascular disease (CVD) and comorbid OSA, adherence to PAP was linked to a total cost reduction of \$4477 over 12 months, representing a 40% decrease (\$6825 vs. \$11,302, $P < .05$) [25]. In another study involving older adult Medicare beneficiaries with CVD and comorbid OSA, high adherence to PAP was linked to a 59% decrease in 30-day hospital readmissions [29]. While the cost of readmissions was not estimated in this study, readmissions are a key outcome and highly relevant to patients, payers, and health systems. From the perspective of health policy, 30-day readmissions also incur significant financial penalties from the Centers for Medicare and Medicaid Services in the United States. It is important to note that these studies utilized similar analytic frameworks based on Medicare administrative claims data. Nevertheless, these findings align with earlier reports and encourage future sleep health economic research across diverse populations, employing different study designs, research methodologies, and outcome measures.

In terms of OSA economics, several issues warrant mention. First, costs associated with OSA include costs of diagnostic testing, which can vary widely (e.g., HSAT/APAP to hospital-based, fully attended PSG and separate titration). Overall, OSA care pathways are underexplored in sleep medicine and are shaped by factors at the patient, provider, and health system levels. Second, different stakeholders experience different costs in distinct ways. For instance, Kim and colleagues performed an economic analysis of a multisite OSA clinical trial [31]. From the payer perspective, relative to in-lab OSA treatment, in-home OSA treatment resulted in savings of \$264 over a 3-month period. On the contrary, from the provider perspective, the operating margin fell from \$142 to $-\$161$,

TABLE 44.1 Health economic perspectives in sleep medicine.

Aspect	Perceived value/Desired outcome
Patient	Quality of life, ease of treatment experience
Payer	Cost savings (profit)
Employer	Workplace productivity, reduced accident risk
Health system	Revenue (profit), population health
Society	Total costs and health economic outcomes

TABLE 44.2 Economic aspects of insomnia treatment: Summary of select empirical studies.

Ref	Sample	Design	Insomnia treatment	Economic outcome	Key findings
Snedecor et al. [34]	434 adults w/depression and comorbid insomnia	RCT	Eszopiclone	QALY, drug costs	versus PBO + FLX, ESZ + FLX gained 0.0058 QALY at direct cost of \$110. Incremental cost per QALY was \$19,026.
Watanabe et al. [35]	37 patients w/refractory depression and insomnia	RCT	CBTI	QALY, CBTI costs	versus TAU, CBT gained 0.019 QALY at cost of \$316. Incremental cost per QALY was \$17,121.
Savard et al. [36]	111 Canadian women w/breast cancer, M age = 54.3y	RCT	In-person CBTI versus vCBTI	Costs	versus vCBTI, CBTI cost \$186.95 CAD for each 1-point reduction in insomnia severity
Kale et al. [37]	18,919 w/prevalent insomnia (64.8% female), M age = 64.5y, 5939 w/incident insomnia (63.2% female), M age = 62.8y	Retrospective cohort study	Suvorexant	HCRU, costs	versus baseline, suvorexant was associated with reduced HCRU over 12 months. Total costs were reduced by \$72.66 and \$112.07 in the prevalent cohort and incident groups, respectively.
Forma et al. [38]	252 (57.5% female), M age = 54.2y	Retrospective cohort study	dCBTI	HCRU, costs	Versus baseline, dCBTI was associated with a significant reduction in ER visits (-56.2% ; $P = .001$) and sleep medication use (-8.9% ; $P = .377$) at 2 years. Total cost reduction was \$1963 per patient.
Wickwire et al. [39]	Medicare beneficiaries w/comorbid ADRD, cancer, depression, menopause, T2DM; sample sizes ranged from 23,168 (T2DM) to 3015 (ADRD)	Retrospective cohort study	Zolpidem, trazodone, or benzodiazepines	HCRU, costs	Versus no insomnia, insomnia was associated with increased HCRU and costs. Versus untreated insomnia, treated insomnia was associated with increased HCRU and costs.

Costs for earlier studies (prior to 2022) have been updated to 2022 US dollars using the inflation calculator provided by the U.S. Bureau of Labor Statistics (when needed, costs were first translated from international currencies to USD in the year of publication, then adjusted for inflation). *ADRD*, Alzheimer's disease and related dementia; *CBTI*, cognitive behavioral treatment for insomnia; *dCBTI*, digital CBTI; *FLX*, fluoxetine; *HCRU*, healthcare resource utilization; *m*, months; *MAPI*, mindful awareness practices-insomnia; *OA*, osteoarthritis; *PBO*, placebo; *PCBT*, professionally based CBTI; *RCT*, randomized controlled trial; *T2DM*, type 2 diabetes mellitus; *QALY*, quality-adjusted life year; *USD*, U.S. dollars; *VCBT*, video-based CBTI

signifying a loss of profitability and sustainability during the same period [31]. In addition to perspective, it is important to consider the time horizon when evaluating potential economic benefit of sleep disorder treatments, since the costs for treating insomnia and OSA are often paid up front, while the economic benefits accrue gradually over time.

Transition to value-based care

In the United States and worldwide, healthcare costs are rising at an alarming pace. Nonetheless, as emphasized in this chapter, healthcare costs are borne differentially by various stakeholder groups. To reduce costs and mitigate financial risk, stakeholders attempt to shift these costs to others. For instance, employers and insurance plan sponsors frequently impose higher copayments or implement high-deductible health plans, effectively transferring upfront costs to employees and patients. Fig. 44.1 illustrates the tensions associated with cost-shifting.

Another strategy for managing financial risk is to adjust payment structures. Within the larger healthcare landscape, alternative payment models (APMs) have been introduced to facilitate the shift from fee-for-service (FFS) to value-based care, moving away from volume-based approaches. The objectives of value-based frameworks are to enhance quality while reducing costs. The continuum of shared risk spanning from fee-for-service (FFS) at the most conservative end to comprehensive population health management at the most integrated end is shown in Fig. 44.2. In a traditional fee-for-service (FFS) model, healthcare providers (such as providers, health systems, and durable medical equipment providers) receive a prenegotiated fee for each specific service rendered. While this approach offers predictability, it commoditized healthcare services, disconnects billable activities from health outcomes, and lacks financial incentives for delivering high-quality patient care. As depicted in Fig. 44.2, the next step on the value-based continuum retains the core characteristics of FFS but adds a quality metric. For instance, a durable medical equipment (DME) provider might receive a given fee for PAP masks and resupply.

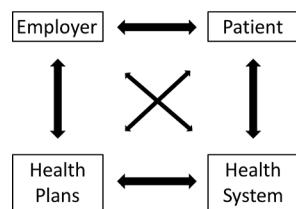


FIGURE 44.1 Cost-shifting is an approach used by payers, employers, health systems, and patients to reduce costs and minimize financial risk. Each stakeholder seeks to “shift” costs, often up-front costs such as copays or deductibles, to another. *Figure from Wickwire EM, Verma T. Value and payment in sleep medicine. J Clin Sleep Med. 2018;14(5):881–884. <https://doi.org/10.5664/jcsm.7130>. Copyright American Academy of Sleep Medicine. Reproduced with permission.*

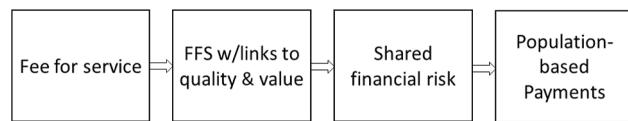


FIGURE 44.2 Alternate payment models (APMs) are designed to support the transition from volume-based fee-for-service (FFS) payments to value-based care. Incremental steps transition from exclusive FFS payments, to FFS payments with links to quality, then to shared financial risk, and finally to total population health. Interested readers are referred to the excellent white paper published by the Health Care Payment & Learning Action Network at www.hcp-lan.org. Figure from Wickwire EM, Verma T. Value and payment in sleep medicine. *J Clin Sleep Med*. 2018;14(5):881–884. <https://doi.org/10.5664/jcsm.7130>. Copyright American Academy of Sleep Medicine. Reproduced with permission.

However, for each patient who adheres to PAP, this fee could be increased by 10%. For a more in-depth discussion, including cost-shifting among stakeholders using HSAT as an example, interested readers are encouraged to refer to a more detailed discussion [3]. While alternative payment models (APMs) are still in their infancy within sleep medicine, astute sleep medicine providers are mindful of the potential for bundled payments and shared risk, as these are likely to influence the field in the future.

Future research directions

To increase the perceived value of the field, sleep clinicians and scientists should adopt a value-based framework. First, sleep researchers should incorporate well-chosen economic endpoints in all insomnia and OSA clinical trials and indeed, throughout sleep research. Second, considering that insomnia and OSA are often comorbid with numerous medical and psychiatric conditions, it is crucial to assess the economic aspects within these various disease subgroups. As described above, although methodological challenges persist, disentangling the effects of comorbid sleep disorders in multiple chronic conditions is essential for accurate attribution [32]. Third, to ensure comprehensive assessment of economic aspects of insomnia and OSA, researchers need to take into account the varied perspectives of the stakeholders we serve, including employers. Since a significant portion of costs related to insomnia and OSA are borne by employers, it is surprising that very few studies have examined these economic outcomes from the employer perspective; this is a vital area for future research. Fourth, key gaps in knowledge exist regarding the potential economic benefit of treatment adherence, as well as on the economic aspects of interventions aimed at improving adherence [2,32,33]. Finally, especially in light of the rapid adoption of telehealth during COVID-19, increasing understanding regarding the economic aspects of telehealth and remote monitoring are essential. Table 44.4 presents these and other recommendations to advance sleep health economic science.

TABLE 44.3 Economic aspects of OSA treatment: Summary of select empirical studies.

Ref	Sample	Design	OSA treatment	Economic outcome	Key findings
Bahammam et al. [40]	344 Canadian men (M age = 49y)	Prospective cohort study	CPAP or BPAP	Physician costs, hospitalizations	Versus 2y prediagnosis, CPAP adherence was associated with reduced physician costs and hospitalizations over 2y
Bailey et al. [29]	1301 U.S. Medicare beneficiaries w/ CVD and comorbid OSA	Retrospective cohort study	CPAP	30-day hospital readmissions	Versus low adherence, high CPAP adherence was associated with 59% reduction in 30-day readmissions.
Cistulli et al. [41]	4237 w/HF and preserved EF, (54.0% female), M age 64.1 y	Retrospective cohort study	CPAP	All-cause hospitalizations and ER visits	PAP adherence reduced hospitalizations by 57% and ER visits by 36% over 1 y. Reduced inpatient costs (\$12,732 vs. \$15,610, $P < .001$) and ER visits (\$717 vs. \$1008, $P < .001$).
Hoffman et al. [42]	248, M age = 44y, 99% men, commercial drivers in US	Retrospective cohort study	CPAP or BPAP	Total costs	Versus prediagnosis, CPAP was associated with reduced HCRU costs over 2 y (y 1: \$3706 y 2: \$4194).
Kirsch et al., 2019 [27]	1,098, M age = 55.7y, 63% men in US	Retrospective cohort study	CPAP	Acute care HCRU and costs	CPAP adherence was associated with reduced inpatient (RR = 0.92, 95% CI: 0.86–0.98) and acute care visits (RR = 0.96, 95% CI: 0.92–0.99).
Malhotra et al. [43]	3182 w/HF and reduced EF, (69.9% male), M age 59.7 y	Retrospective cohort study	CPAP	Hospital costs	PAP adherence was associated with reduced composite costs (\$3500 vs. \$5879, $P = .031$).
Tarasiuk et al. [44]	740 children <18y, M age = 5.6y, 37% boys in Israel	Prospective, longitudinal case-control study	TA	Total costs	CPAP was associated with 32.5% reduced total costs over 1y.
Wickwire et al. [45]	1921 U.S. Medicare beneficiaries w/ CVD and comorbid OSA	Retrospective cohort study	CPAP	Inpatient HCRU	High CPAP adherence was associated with 25% reduction in inpatient visits (HR = 0.75; 95% CI 0.57, 0.97).
Wickwire et al. [46]	37,459 w/depression and comorbid OSA, (62% female), M age = 52.9y	Retrospective cohort study	PAP	HCRU, costs, self-harm events	CPAP adherence was associated with reductions in HCRU and costs over 2y, and self-harm events over 1y.

Costs for earlier studies (prior to 2022) have been updated to 2022 US dollars using the inflation calculator provided by the U.S. Bureau of Labor Statistics (when needed, costs were first translated from international currencies to USD in the year of publication, then adjusted for inflation). APAP, auto-titrating positive airway pressure; BPAP, bilevel positive airway pressure; CI, confidence interval; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; EF, ejection fraction; HCRU, healthcare resource utilization; HF, heart failure; HR, hazard ratio; M, mean; m, months; PAP, positive airway pressure; RCT, randomized controlled trial; QALY, quality-adjusted life year; TA, tonsillectomy and adenoidectomy; USD, U.S. dollars; UPPP, uvulopalatopharyngoplasty; y, years

TABLE 44.4 Recommendations for future sleep health economic research.

Domain	Recommendation
Incorporate health economic outcomes	Measure direct and indirect costs of sleep disorders in all clinical trials
Assess HrQOL	Include measures of generic and disease-specific HrQOL
Target key subpopulations	Perform health economic analyses among demographic groups, including racial groups, women, older adults, and children
Investigate comorbid sleep disorders	Evaluate economic impact of insomnia and OSA treatments in key comorbid disease states (e.g., cardiovascular disease, depression)
Increase PAP adherence	Evaluate cost-benefit of interventions to increase treatment adherence, including behavioral approaches, telehealth and remote monitoring, and automated approaches
Adopt stakeholder perspectives	Consider especially the employer perspective (e.g., study workplace productivity and accident and injury risk)
Consider global impact	Study sleep disorder treatments in various health-care delivery systems globally
Compare established treatments	Compare economic effectiveness of established sleep disorder treatments to guide allocation of limited health-care resources

Conclusions

Sleep disorders, such as insomnia and OSA, impose substantial economic burden on patients, payers, employers, health systems, and other key stakeholders. A growing body of scientific literature indicates that successful treatment of sleep disorders can yield positive economic benefits. Sleep clinicians should familiarize themselves with the relevant findings, and sleep scientists should incorporate economic endpoints in all future clinical trials. All in the sleep field should increase attention to the economic perspectives of the various stakeholders we serve. These recommendations will become increasingly important as economic factors increasingly influence health policy and resource allocation moving forward.

Acknowledgments

The author thanks Emmanuel Agaba, MBBS, MPH for his editorial assistance.

References

- [1] Wickwire EM, Shaya FT, Scharf SM. Health economics of insomnia treatments: the return on investment for a good night's sleep. *Sleep Med Rev* 2016;30:72–82. <https://doi.org/10.1016/j.smrv.2015.11.004>.
- [2] Wickwire EM, Albrecht JS, Towe MM, Abariga SA, Diaz-Abad M, Shipper AG, Cooper LM, Assefa SZ, Tom SE, Scharf SM. The impact of treatments for OSA on monetized health economic outcomes: a systematic review. *Chest* 2019;155(5):947–61. <https://doi.org/10.1016/j.chest.2019.01.009>.
- [3] Wickwire EM, Verma T. Value and payment in sleep medicine. *J Clin Sleep Med* 2018;14(05):881–4. <https://doi.org/10.5664/jcsm.7130>.
- [4] Martin SA, Aikens JE, Chervin RD. Toward cost-effectiveness analysis in the diagnosis and treatment of insomnia. *Sleep Med Rev* 2004;8(1):63–72. <https://doi.org/10.1016/j.smrv.2003.08.001>.
- [5] S. Wake up America a national sleep alert : report of the national commission on sleep disorders research. The Commission, The Commission; 1993.
- [6] Daley M, Morin CM, LeBlanc M, Grégoire JP, Savard J, Baillargeon L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. *Sleep Med* 2009;10(4):427–38. <https://doi.org/10.1016/j.sleep.2008.04.005>.
- [7] American Academy of Sleep M. Hidden health crisis costing America billions. Underdiagnosing and undertreating obstructive sleep apnea draining healthcare system Mountain View. 2016. CA: Frost & Sullivan, CA: Frost & Sullivan.
- [8] Hanmer J, Feeny D, Fischhoff B, Hays RD, Hess R, Pilkonis PA, Revicki DA, Roberts MS, Tsevat J, Yu L. The PROMIS of QALYs. *Health Qual Life Outcome* 2015;13(1). <https://doi.org/10.1186/s12955-015-0321-6>.
- [9] Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. conceptual framework and item selection. *Med Care* 1992;30(6):473–83. <https://doi.org/10.1097/00005650-199206000-00002>.
- [10] Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37(1):53–72. [https://doi.org/10.1016/0168-8510\(96\)00822-6](https://doi.org/10.1016/0168-8510(96)00822-6).
- [11] Leger D, Scheuermaier K, Raffray T, Metlaine A, Choudat D, Guilleminault C. HD-16: a new quality of life instrument specifically designed for insomnia. *Sleep Med* 2005;6(3):191–8. <https://doi.org/10.1016/j.sleep.2005.03.013>.
- [12] Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI, Dinges DF.

- An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20(10):835–43.
- [13] Mohit B, Cohen JT. Trends of cost-effectiveness studies in sleep medicine. *Sleep Med* 2019;53:176–80. <https://doi.org/10.1016/j.sleep.2018.06.001>.
- [14] Roy AN, Suresh Madhavan S, Lloyd A. A discrete choice experiment to elicit patient willingness to pay for attributes of treatment-induced symptom relief in comorbid insomnia. *Manag Care* 2015;42–50. http://www.managedcaremag.com/sites/default/files/imported/1504/ManagedCare_2015-04.pdf.
- [15] Wickwire EM, Morin CM. Advancing a value framework for sleep: update on economic aspects of cognitive-behavioral treatments for insomnia. *Sleep Med Rev* 2020;54:101387. <https://doi.org/10.1016/j.smrv.2020.101387>.
- [16] Amari DT, Juday T, Frech FH, Wang W, Wu Z, Atkins N, Wickwire EM. Falls, healthcare resources and costs in older adults with insomnia treated with zolpidem, trazodone, or benzodiazepines. *BMC Geriatr* 2022;22(1). <https://doi.org/10.1186/s12877-022-03165-6>.
- [17] Wickwire EM, Amari DT, Juday TR, Frech F, Gor D, Malhotra M. Incremental health care resource use and costs among adult patients with depression and treated for insomnia with zolpidem, trazodone, or benzodiazepines. *Curr Med Res Opin* 2022;38(5):711–20. <https://doi.org/10.1080/03007995.2022.2047537>.
- [18] Wickwire EM, Amari DT, Juday TR, Frech FH, Gor D, Malhotra M. Cardiac events and economic burden among patients with hypertension and treated insomnia in the USA. *Future Cardiol* 2022;18(9):731–41. <https://doi.org/10.2217/fca-2022-0009>.
- [19] Wickwire EM, Vadlamani A, Tom SE, Johnson AM, Scharf SM, Albrecht JS. Economic aspects of insomnia medication treatment among Medicare beneficiaries. *Sleep* 2020;43(1). <https://doi.org/10.1093/sleep/zsz192>.
- [20] Baka A, van der Zweerde T, Lancee J, Bosmans JE, van Straten A. Cost-effectiveness of guided internet-delivered cognitive behavioral therapy in comparison with care-as-usual for patients with insomnia in general practice. *Behav Sleep Med* 2022;20(2):188–203. <https://doi.org/10.1080/15402002.2021.1901708>.
- [21] Buntrock C, Lehr D, Smit F, Horvath H, Berking M, Spiegelhalder K, Riper H, Ebert DD. Guided internet-based cognitive behavioral therapy for insomnia: health-economic evaluation from the societal and public health care perspective alongside a randomized controlled trial. *J Med Internet Res* 2021;23(5):e25609. <https://doi.org/10.2196/25609>.
- [22] Darden M, Espie CA, Carl JR, Henry AL, Kanady JC, Krystal AD, Miller CB. Cost-effectiveness of digital cognitive behavioral therapy (Sleepio) for insomnia: a Markov simulation model in the United States. *Sleep* 2021;44(4). <https://doi.org/10.1093/sleep/zsaa223>.
- [23] Sampson C, Bell E, Cole A, Miller CB, Marriott T, Williams M, Rose J. Digital cognitive behavioral therapy for insomnia and primary care costs in England: an interrupted time series analysis. *BJGP Open* 2022;6(2). <https://doi.org/10.3399/BJGPO.2021.0146>.
- [24] Yeung K, Zhu W, McCurry SM, Von Korff M, Wellman R, Morin CM, Vitiello MV. Cost-effectiveness of telephone cognitive behavioral therapy for osteoarthritis-related insomnia. *J Am Geriatr Soc* 2022;70(1):188–99. <https://doi.org/10.1111/jgs.17469>.
- [25] Bock JM, Needham KA, Gregory DA, Ekono MM, Wickwire EM, Somers VK, Lerman A. Continuous positive airway pressure adherence and treatment cost in patients with obstructive sleep apnea and cardiovascular disease. *Mayo Clin Proc Innov Qual Outcomes* 2022;6(2):166–75. <https://doi.org/10.1016/j.mayocpiqo.2022.01.002>.
- [26] Chhatre S, Chang YHA, Gooneratne NS, Kuna S, Strollo P, Jayadevappa R. Association between adherence to continuous positive airway pressure treatment and cost among medicare enrollees. *Sleep* 2020;43(1). <https://doi.org/10.1093/sleep/zsz188>.
- [27] Kirsch DB, Yang H, Maslow AL, Stolzenbach M, McCall A. Association of positive airway pressure use with acute care utilization and costs. *J Clin Sleep Med* 2019;15(09):1243–50. <https://doi.org/10.5664/jcsm.7912>.
- [28] Wickwire EM, Doyinsola Bailey M, Somers VK, Oldstone LM, Srivastava MC, Johnson AM, Scharf SM, Albrecht JS. CPAP adherence is associated with reduced inpatient utilization among older adult edicare beneficiaries with pre-existing cardiovascular disease. *J Clin Sleep Med* 2022;18(1):39–45. <https://doi.org/10.5664/jcsm.9478>.
- [29] Bailey MD, Wickwire EM, Somers VK, Albrecht JS. Adherence to continuous positive airway pressure reduces the risk of 30-day hospital readmission among older adults with comorbid obstructive sleep apnea and cardiovascular disease. *J Clin Sleep Med* 2022;18(12):2739–44. <https://doi.org/10.5664/jcsm.10196>.
- [30] Jacob C, Lettieri C, Wickwire E, Holley A. Obstructive sleep apnea and cardiovascular disease, a story of confounders. *Sleep Breath* 2020;24(4):1299–313. <https://doi.org/10.1007/s11325-019-01945-w>.
- [31] Kim RD, Kapur VK, Redline-Bruch J, Rueschman M, Auckley DH, Benca RM, Foldvary-Schafer NR, Iber C, Zee PC, Rosen CL, Redline S, Ramsey SD. An economic evaluation of home versus laboratory-based diagnosis of obstructive sleep apnea. *Sleep* 2015;38(7):1027–37. <https://doi.org/10.5665/sleep.4804>.
- [32] Wickwire EM. Making dollars and sense of SAVE. *J Clin Sleep Med* 2017;13(5):765–6. <https://doi.org/10.5664/jcsm.6606>.
- [33] Wickwire EM, Lettieri CJ, Cairns AA, Collop NA. Maximizing positive airway pressure adherence in adults: a common-sense approach. *Chest* 2013;144(2):680–93. <https://doi.org/10.1378/chest.12-2681>.
- [34] Snedecor SJ, Botteman MF, Schaefer K, Sarocco P, Barry N, Pickard AS. Economic outcomes of eszopiclone treatment in insomnia and comorbid major depressive disorder. *J Ment Health Pol Econ* 2010;13(1):27–50.
- [35] Watanabe N, Furukawa TA, Shimodera S, Katsuki F, Fujita H, Sasaki M, Sado M, Perlis ML. Cost-effectiveness of cognitive behavioral therapy for insomnia comorbid with depression: analysis of a randomized controlled trial. *Psychiatr Clin Neurosci* 2015;69(6):335–43. <https://doi.org/10.1111/pcn.12237Japan>.
- [36] Savard J, Ivers H, Morin CM, Lacroix G. Video cognitive-behavioral therapy for insomnia in cancer patients: a cost-effective alternative. *Psychooncology* 2021;30(1):44–51. <https://doi.org/10.1002/pon.5532>.
- [37] Kale HP, Qureshi ZP, Shah R, Khandker R, Botteman M, Meng W, Benca R. Changes in healthcare resource use and costs in commercially insured insomnia patients initiating suvorexant. *Adv Ther* 2021;38(10):5221–37. <https://doi.org/10.1007/s12325-021-01891-8>.
- [38] Forma F, Knight TG, Thorndike FP, Xiong X, Velez FF, Maricich YA, Malone DC, Baik R. Real-world evaluation of clinical response and long-term healthcare resource utilization patterns

- following treatment with a digital therapeutic for chronic insomnia. *Clin Outcomes Res* 2022;14:537–46. <https://doi.org/10.2147/CEOR.S368780>.
- [39] Wickwire EM, Juday TR, Kelkar M, Heo J, Margiotta C, Frech FH. Economic burden of comorbid insomnia in 5 common medical disease subgroups. *J Clin Sleep Med* 2023;19(7):1293–302. <https://doi.org/10.5664/jcsm.10592>.
- [40] Bahammam A, Delaive K, Ronald J, Manfreda J, Roos L, Kryger MH. Health care utilization in males with obstructive sleep apnea syndrome two years after diagnosis and treatment. *Sleep* 1999;22(6):740–7. <https://doi.org/10.1093/sleep/22.6.740>.
- [41] Cistulli PA, Malhotra A, Cole KV, Malik AS, Pépin JL, Kuniyoshi FHS, Benjafield AV, Somers VK. Positive airway pressure therapy adherence and health care resource use in patients with obstructive sleep apnea and heart failure with preserved ejection fraction . American heart association inc. Australia Journal of the American Heart Association 2023;12(14). <https://doi.org/10.1161/JAHA.122.028733>.
- [42] Hoffman B, Wingenbach DD, Kagey AN, Schaneman JL, Kasper D. The long-term health plan and disability cost benefit of obstructive sleep apnea treatment in a commercial motor vehicle driver population. *J Occup Environ Med* 2010;52(5):473–7. <https://doi.org/10.1097/JOM.0b013e3181dbc8ab>.
- [43] Malhotra A, Cole KV, Malik AS, Pépin JL, Kuniyoshi FHS, Cistulli PA, Benjafield AV, Somers VK. Positive airway pressure adherence and health care resource utilization in patients with obstructive sleep apnea and heart failure with reduced ejection fraction. *J Am Heart Assoc* 2023;12(10). <https://doi.org/10.1161/JAHA.122.028732>.
- [44] Tarasiuk A, Simon T, Tal A, Reuveni H. Adenotonsillectomy in children with obstructive sleep apnea syndrome reduces health care utilization. *Pediatrics* 2004;113(2):351–6. <https://doi.org/10.1542/peds.113.2.351>.
- [45] Wickwire EM, Doyinsola Bailey M, Somers VK, Oldstone LM, Srivastava MC, Johnson AM, Scharf SM, Albrecht JS. CPAP adherence is associated with reduced inpatient utilization among older adult Medicare beneficiaries with pre-existing cardiovascular disease. *J Clin Sleep Med* 2022;18(1):39–45. <https://doi.org/10.5664/jcsm.9478>.
- [46] Wickwire EM, Cole KV, Dexter RB, Malhotra A, Cistulli PA, Sterling KL, Pépin JL. Depression and comorbid obstructive sleep apnea: association between positive airway pressure adherence, occurrence of self-harm events, healthcare resource utilization, and costs. *J Affect Disord* 2024;349:254–61. <https://doi.org/10.1016/j.jad.2023.12.055>.

This page intentionally left blank

Chapter 45

Sleep and athletes*

Michael A. Grandner^a and Amy Athey^b

^aSleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine – Tucson, Tucson, AZ, United States;

^bAthey Performance, Virginia Beach, VA, United States

Prevalence of sleep concerns in athletes

Sleep problems among elite athletes are relatively common. In a report by the PAC-12 athletics conference of the National Collegiate Athletic Association (NCAA), 66% of students indicated that lack of flexible time is the hardest thing about being an athlete—harder than the academic work [1]. This report also noted that sleep is the activity that students reported that their athletic time commitments mostly prevented them from doing. Other findings from this report support the discrepancy between perceived sleep needs among students and their opportunity for sleep. Among respondents, 77% reported that they perceive that they get less sleep than nonathletes at their institutions, and over 50% reported that if they had an extra hour of the day that it would be used for sleep. Some athletes reported waking up at 5:00:00 a.m., or earlier to report to practice or training activities, which is inconsistent with developmental circadian rhythms [2]. Also noted in this report, when asked, many students reported that they needed a break of approximately 2–3 weeks just to catch up on sleep and relieve stress. Finally, this report noted that students requested that nonpractice hours be extended to make more time for sleep and studying [1].

Further data from the NCAA indicate that only about one in five student athletes achieve the recommended sleep duration of at least 8 hours [3]. In addition, this same report found that approximately half of student athletes report six or fewer hours of sleep on a typical night, which is associated with a wide range of health and functional deficits [4,5]. This prevalence of insufficient sleep is greater than that seen in the

general population, where approximately one third of young adults aged 18–30 report six or fewer hours [6].

A recent survey of collegiate varsity student athletes reported that 33% had received information about sleep difficulties from their college or university, but 52% wished that their institution provided more information. In this same study, 20% reported that sleep difficulties have been “traumatic or very difficult to handle” in the past 12 months, 28% reported extreme difficulty falling asleep or early morning awakenings at least 3 times per week, 61% reported excessive tiredness at least 3 days per week, and 33% reported going to bed because they could not maintain wakefulness at least 3 times per week [7,8]. These data are supported by a meta-analysis across elite athlete populations reporting a prevalence of approximately 26% of sleep disturbances [9].

Regarding sleep disorders, prevalence estimates are not widely available. Insomnia disorder is present in about 10% of the general population [10], and indications are that this is comparable to rates seen in athletes. Sleep apnea is another common sleep disorder in the population [11], but since common risk factors include obesity, high blood pressure, and older age [12], rates are likely lower among athletes. Still, sleep apnea can occur in those with otherwise few risk factors. Some athlete populations, partially due to body size and/or neck circumference, may present with high risk for sleep apnea. For example, 73% of professional (American) football players screened as high risk for sleep apnea, with over half of those later testing positive for the disorder [13–15]. Other sleep disorders may be present in athletes as well, though it is not clear that rates are any different from those seen in the general population.

* This chapter is adapted from and includes sections from two previous works: Grandner, M. A. (2022). Sleep disorders and sleep concerns. In: Reardon, C. (Ed.). Mental Health Care for Elite Athletes. New York: Springer. Grandner, M. A., Mills, J., Clarke, M., and Athey, A. B. (2024). Sleep and circadian health promotion programs for athletes. In: Grandner, M. A. and Athey, A. B. (Eds.) Sleep and Sport. London: Academic Press.

Importance of sleep health in athletes

A complete overview of all of the ways that sleep is important for health and performance in athletes is beyond

the scope of this chapter. Several recent reviews have explored these issues in detail [4,5,16–18]. A summary of the relationship between sleep health and athletic performance is depicted in Fig. 45.1, which was adapted [5] from the review by Charest and Grandner.

Many previous studies have documented adverse effects of poor sleep on physical performance. Sleep restriction, in particular, has been associated with both cardiorespiratory and neurobehavioral effects both in the short term and over periods of days to weeks [5]. Mechanisms of this relationship are still being explored. For example, physical performance following sleep restriction may require greater physiologic output, leading to more rapid exhaustion [19]. This is supported by work showing that maximal power output is reduced following sleep restriction [20,21]. Other studies have shown that sleep restriction impairs tennis serving accuracy [22,23], treadmill running distance [24], sprint speed [25], isometric force [26], and testosterone levels [27,28]. Sleep restriction impairs muscle glycogen recovery [29] and contributes to overtraining.

Poor sleep is also a risk factor for injury among athletes. Elite athletes screened for subclinical sleep concerns were followed for 1 year. Those that reported daytime sleepiness or insomnia symptoms at baseline were more likely to experience a concussion in the subsequent year, and these predictors outperformed more standard concussion risk factors including gender, sport played, and prior concussion history [30,31]. This work is consistent with other research showing that athletes who reported shorter sleep were more likely to experience an injury [32].

Insomnia is a reliable predictor of depression and other mental health symptoms and disorders [33,34]. In particular, poor sleep is associated with a tripling of suicide risk [35–38]. This is especially alarming because suicide is among the leading causes of death among young adults, including athletes. In particular, being awake during the night, when the brain is predisposed to sleep, may lead to a neurophysiologic cascade that leads to unhealthy decision-making, including suicide [37,39,40]. Among collegiate student athletes, shorter sleep duration was associated with greater perceived stress and higher depression scores [41]. In this sample, worse overall sleep quality was also associated with more stress, depression, and anxiety, as were insomnia symptoms and fatigue. In addition, decreased social support was experienced by athletes who slept less and experienced worse sleep quality. Decreased social support was also reported by student athletes who reported a delayed sleep-wake phase, and this decreased social support partially explained relationships to depression [42]. Among a national sample of collegiate student athletes, sleep-related distress and insufficient sleep were associated with a greater likelihood of suicide ideation [43].

Guideline documents and consensus statements

Several organizations have published guideline documents that address the issue of sleep in sport. The NCAA Sport Science Institute (SSI) produced the “Interassociation Consensus Document: Best Practices for Understanding and Supporting Student-Athlete Mental

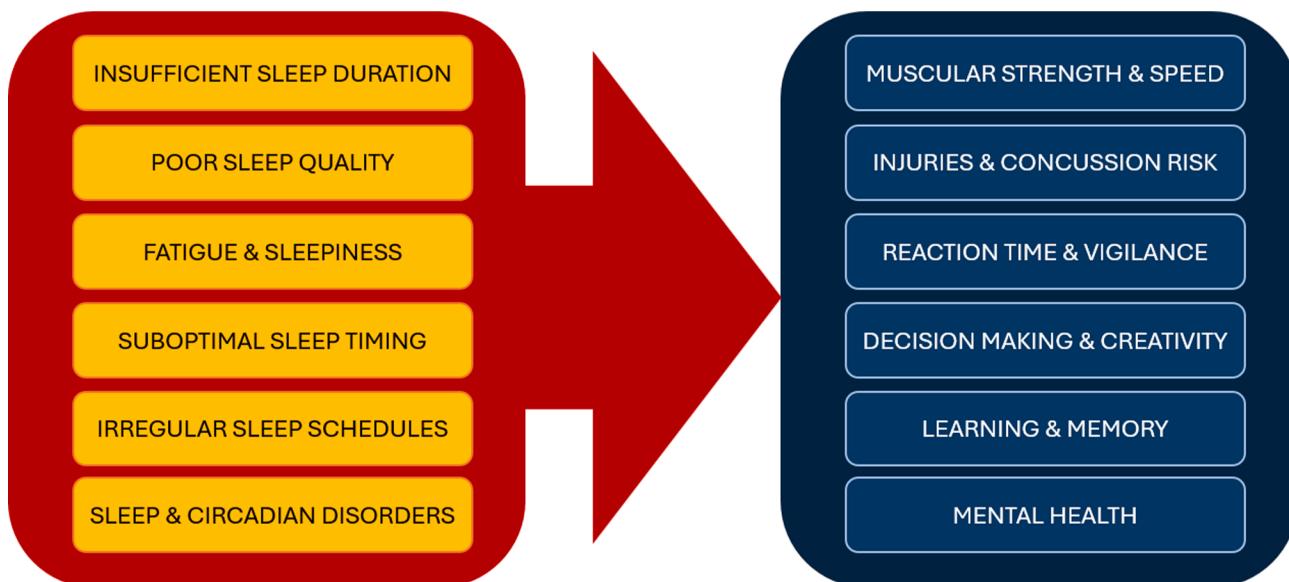


FIGURE 45.1 Associations between aspects of sleep and circadian health and aspects of athletic performance. Adapted from Charest J, Grandner MA. *Sleep and athletic performance: impacts on physical performance, mental performance, injury risk and recovery, and mental health: an update*. *Sleep Med Clin* 2022;17:263–82. <https://doi.org/10.1016/J.JSMC.2022.03.006>.

Wellness" outlining best practices of health-promoting environments that support mental well-being and resilience. This resource targets anyone that may have an influence on athletes such as athlete advisory committees, coaches, and faculty representatives. Topics discussing the sleep environment, sleep duration, and sleep timing are included in the document. Mental health best practices include providing clinical licensed practitioners for mental health care, identifying and referring student-athletes to professionals, preparticipation mental health screening, and fostering supportive environments. The document is currently in its second edition [44]. Subsequently, the International Olympic Committee (IOC) published its first consensus statement on mental health in elite athletes. This document contained a section on sleep and suggests that athletics programs should include screening for primary sleep disorders and provision of sleep improvement programs for those that present with sleep problems [45–47].

The Sleep and Wellness task force of the NCAA recommended that athletics programs should incorporate five key elements: (1) an annual time demands survey, (2) sleep screening to be included in pre-participation examinations, (3) sleep education programs for athletes, (4) sleep education programs for coaches/staff, and (5) efforts to ensure that any wearables and sleep tracking technology adheres to appropriate privacy standards [3].

This is supported by the international consensus for athlete sleep programs, which recommends that athletics programs engage in four types of activities to promote sleep health: (1) sleep education for athletes, (2) regular systematic screening for sleep problems and sleep concerns, (3) encouragement of naps to improve performance (i.e., brief naps in the middle of the day), and (4) banking sleep, defined as accumulating periods of optimal sleep to buffer against planned periods of poor sleep [18]. This document also provided a useful figure that depicts how both sport and nonsport factors may play a role in sleep health (depicted in Fig. 45.2).

The international consensus document also outlined recommendations for conceptualizing a screening and triage program [18]. These recommendations were reiterated and expanded [48] and depicted in Fig. 45.3.

Another international consensus document outlines relationships between circadian health and athletic performance [49]. This document provides a general overview of how circadian rhythms impact performance. For example, a useful image depicts how different activities may be optimized for different times of day (reprinted as Fig. 45.4), and how jet lag leads to sleep and circadian disruption (reprinted as Fig. 45.5).

Identification and management of sleep disorders

The core elements of a sleep health program aim to assist athletes regarding improving their sleep health and, ultimately, their performance. However, if athletes have an untreated sleep disorder, these strategies will have limited effectiveness. This is because sleep disorders preclude many sleep strategies from improving sleep quality and next-day functioning. For example, if an athlete has an undiagnosed and/or untreated case of sleep apnea, or narcolepsy or another similar condition, the other strategies used to improve performance will not be able to be effective. Therefore, any sleep program needs to prioritize the identification and management of sleep disorders or else any other efforts will be insufficient.

Psychophysiologic insomnia is especially common among athletes when they attempt to fall asleep despite excess mental and/or physical activation that is otherwise incompatible with sleep. This repeated pairing of sleep attempts and inability to sleep results in conditioned arousal that generalizes to other situations. The recommended first-line treatment for Insomnia Disorder is Cognitive Behavioral Therapy for Insomnia [50]. Additional evidence supports treatment with some medications. However, this is often suboptimal since the use of sedative hypnotics in athletes may carry risk of injuries, melatonin may improve sleep without these risks but often is ineffective, and other strategies have not been well-explored in athletes. Athletes with an Insomnia Disorder may find that recommendations for improving sleep health are ineffective and some recommendations (e.g., extending time in bed to obtain more sleep) may be contraindicated. For these reasons, treatment of insomnia disorder is recommended for athletes.

Circadian rhythm sleep-wake disorders represent dysregulation of 24-hour rhythms in ways that disrupt sleep schedules. The most common problem among athletes is a delayed circadian rhythm, such that the biological night is placed later in the 24-hour rhythm than desired. Individuals with Delayed Sleep-Wake Phase Disorder have difficulty going to sleep and waking up earlier and prefer to stay up late and wake up late. This is especially common in adolescents and young adults. Advanced Sleep-Wake Phase Disorder, on the contrary, involves falling asleep earlier and waking up earlier. These conditions may make it difficult to keep a schedule aligned with others in their athletic program. For example, an athlete with a delayed rhythm may have difficulty waking for early morning training exercises and also may have difficulty falling asleep early enough to obtain enough sleep to wake up early. Other circadian rhythm sleep-wake disorders that

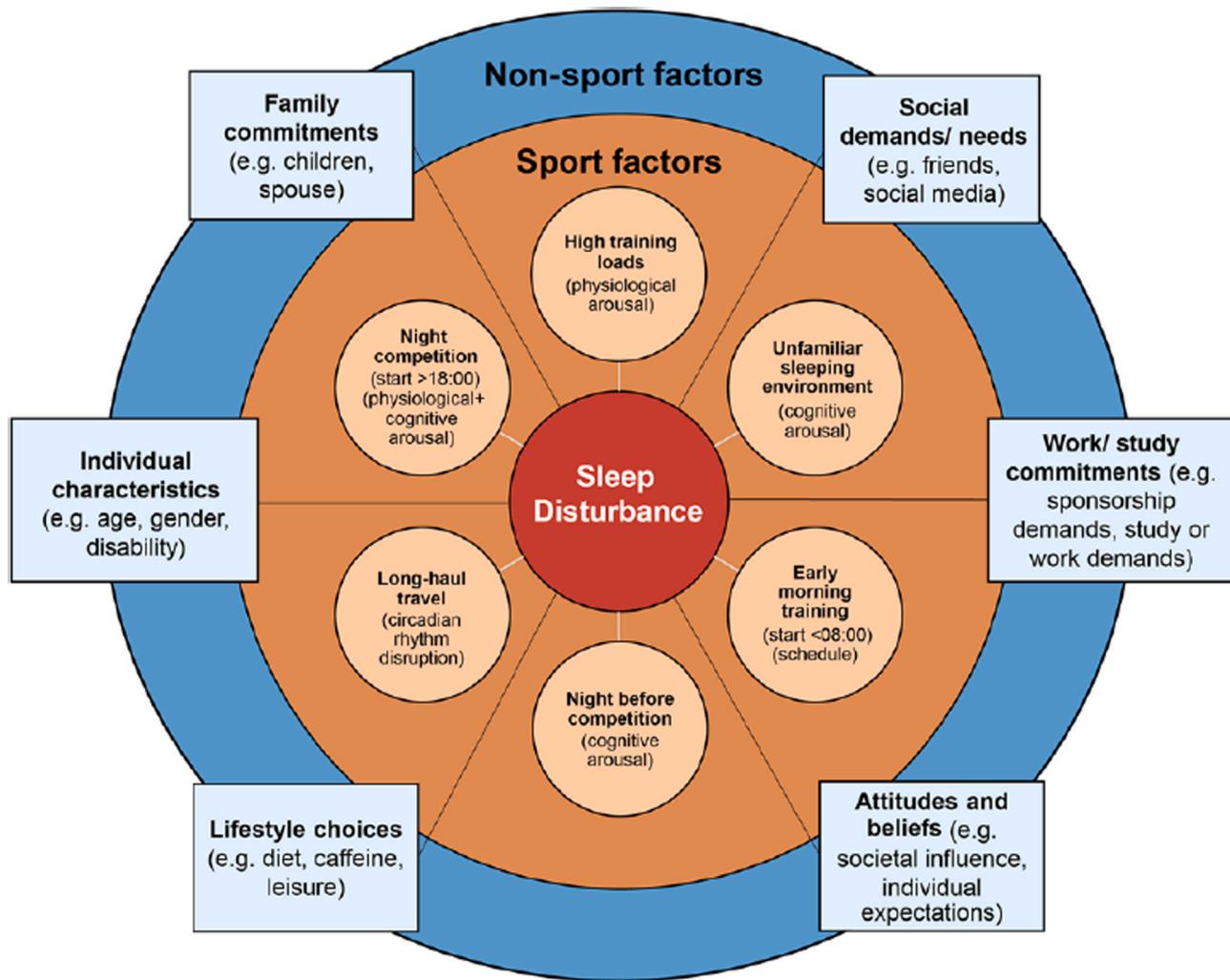


FIGURE 45.2 Factors contributing to sleep disturbance in athletes. Reprinted from Walsh NP, Halson SL, Sargent C, Roach GD, Nédélec M, Gupta L, et al. Sleep and the athlete: narrative review and 2021 expert consensus recommendations. *Br J Sports Med* 2020;55(7):356–68. <https://doi.org/10.1136/bjsports-2020-102025>

can occur in athletes include Shift Work Sleep Disorder, which can occur when regular schedules conflict with natural sleep schedules, and Irregular Sleep-Wake Phase Disorder, which can occur when there is no clear day-night rhythm. Treatments for circadian rhythm sleep-wake disorders usually involve chronobiotic medications (such as melatonin) and light and behavioral therapy.

Sleep-disordered breathing can include obstructive or central sleep apnea, as well as a range of other respiratory disorders can occur during sleep. Central sleep apnea may occur in otherwise healthy individuals who sleep at high altitude, which can occur in some athletes. This is especially the case for athletes training and/or competing in high-altitude environments. Obstructive sleep apnea is more common among athletes. In the general population, it is generally associated with older age, obesity, and cardiometabolic disease risk; though these risk factors are uncommon among athletes, these conditions are common

enough in the population that even those without these risk factors may have sleep apnea. This is especially the case for adolescents and young adults for whom one of the leading risk factors is enlarged tonsils or adenoids, which can occur irrespective of cardiometabolic risk. Also, athletes who typically have a large body size, especially a large neck circumference, may have elevated risk of obstructive sleep apnea. American football players are especially prone to this condition. The first-line treatment is Positive Airway Pressure therapy devices, though dental devices may also be effective, especially for more mild cases which may be more common among athletes.

Of note, many medications for hypersomnia disorders are problematic for athletes as they are often banned substances due to performance-enhancing effects for those without hypersomnia disorders. Behavioral therapies can often supplement medication, though medication is typically required.

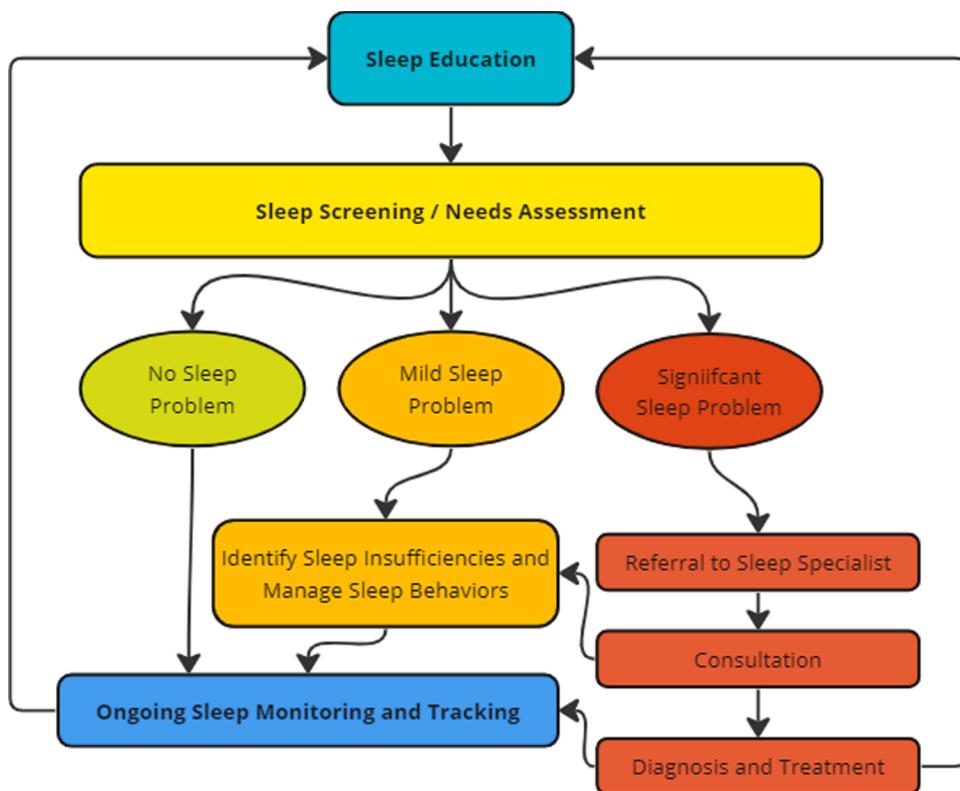


FIGURE 45.3 Strategy for assessment of sleep problems in athletes. Reprinted from Grandner MA, Mills J, Clarke M, Athey AB. Sleep and circadian health promotion programs for athletes. *Sleep Sport* 2024;313–26 and adapted from NP, Halson SL, Sargent C, Roach GD, Nédélec M, Gupta L, et al. Sleep and the athlete: narrative review and 2021 expert consensus recommendations. *Br J Sports Med* 2020;55(7):356–68. <https://doi.org/10.1136/bjsports-2020-102025>.

Screening for sleep disorders

Screening for sleep disorders can be accomplished using questionnaires. These include broad surveys like the SDSCL [51], or questionnaires targeted to insomnia (e.g., ISI [52]), sleep apnea (e.g., BQ [53]), and other conditions. Other strategies may also be used. For example, blood tests can identify people with low iron as an explanation for restless legs symptoms [54]. Screening for sleep apnea may require objective tests [55]. Although these are traditionally done in a sleep laboratory, many portable devices can be used to quickly screen for sleep-disordered breathing using the recording of a single night at home. These devices need to be read by a qualified physician, but athletics programs can screen multiple layers simultaneously using this strategy.

Developing a referral strategy for managing sleep disorders

Sleep disorders need to be diagnosed and treated by a clinician with specialized training in this field. There are different types of individuals who manage sleep disorders. Athletics programs should have a plan in place for referral and treatment of sleep disorders when that expertise does

not exist in the current program. For this reason, athletics programs should have plans for referring to a sleep physician and/or a behavioral sleep medicine specialist, as appropriate [56]. While athletes are under the care of sleep specialists, they can participate in all of the other sleep health promotion programs and may benefit from them. Of note, some sleep disorders (e.g., insomnia) may permanently resolve after a course of treatment, whereas others (e.g., sleep apnea, narcolepsy) may represent chronic health conditions that require ongoing management.

Education and culture

Any sleep health promotion program must address the issue of lack of knowledge about sleep and circadian rhythms. The NCAA's guidelines specifically state that programs should provide collegiate athletes with evidence-based sleep education that includes: (1) information on sleep best practices; (2) information about the role of sleep in optimizing athletic and academic performance and overall well-being; and (3) strategies for addressing sleep barriers. In addition, the guidelines suggest that programs should provide coaches with evidence-based sleep education that includes: (1) information on sleep best practices;

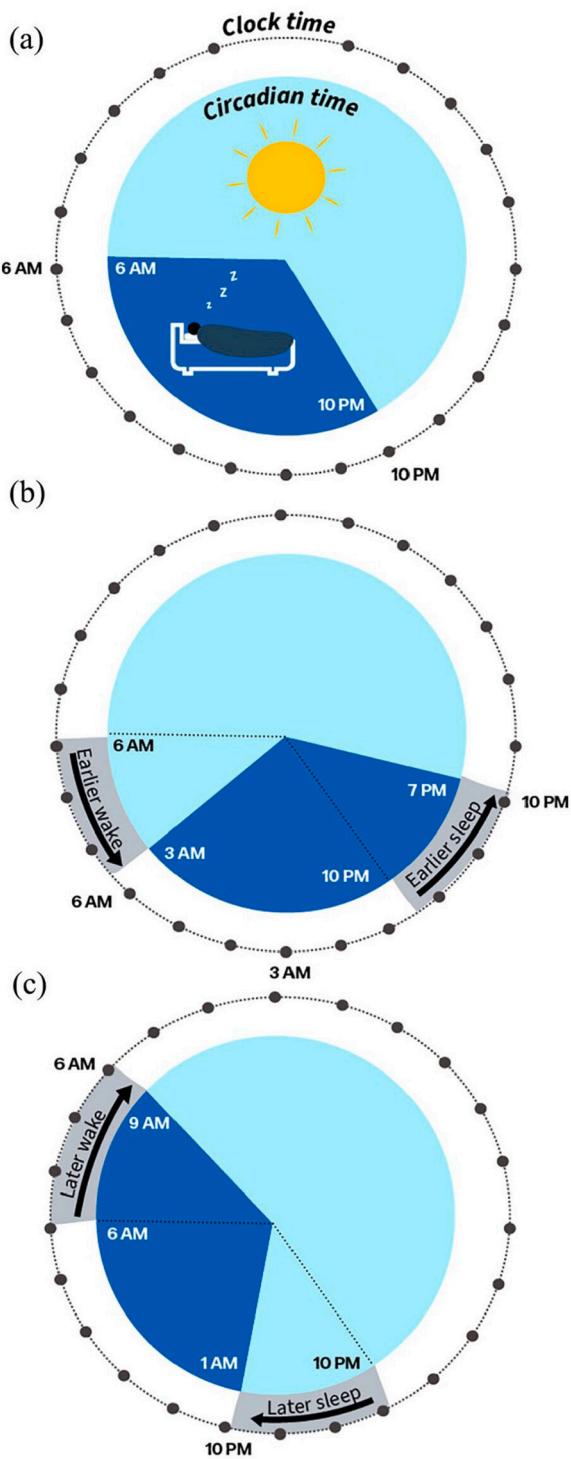


FIGURE 45.4 Disruptions of circadian rhythms caused by eastward and westward travel across 3 time zones. (A) The outer circle represents clock time. The inner circle represents circadian time. Before travel, these two cycles largely coincide. Small differences due to the fact that the period of the circadian rhythm is not exactly 24 h are corrected by the process of entrainment largely due to exposure to light in the morning and evening. Daily activities such as bedtime and waketime occur at specific times or phases of the circadian clock. (B) Traveling 3 time zones to the east puts the circadian clock 3 h behind local time, requiring the circadian clock to

(2) information about the role of sleep in optimizing athletic and academic performance and overall well-being; and (3) strategies to help optimize collegiate athlete sleep. In addition to education, many athletics programs require somewhat of a culture change when it comes to sleep health. In a culture of performance, sleep is often seen as a time commitment that competes with training and improvement. Yet, the evidence clearly suggests the contrary. Sleep health actually improves recovery and next-day performance. Sometimes, the cultural attitudes that devalue sleep are overt, but they may also be subtle.

Elements of an educational program

Several components are involved when building an educational program. The following elements could be included:

- *Overview of sleep and circadian science.* To be able to understand the subsequent information and make informed decisions about sleep and circadian health, athletes and staff should be informed of the basics of sleep-wake and circadian physiology. This includes information about sleep architecture, sleep continuity, and basic sleep and circadian physiology to the degree to which it is relevant. In addition, basic information should include models underlying sleep health, including the 3-P model, the 2-process model, and the social-ecological model. Additional information can include information about methods of sleep measurement and quantification (e.g., polysomnography, actigraphy, diaries, and questionnaires) and information about relationships between sleep and relevant domains of health (e.g., cardiovascular health, metabolic health, immune health, cognitive health, mental health, and behavioral health).
- *Sleep problems and sleep disorders.* Athletes and coaches should know the difference between normal and abnormal sleep. Education should include a basic overview of the signs and symptoms of common sleep disorders, as well as nonclinical sleep complaints. The multidimensional nature of sleep health should be

be moved ahead, or phase advanced by 3 h. This phase advance may take several days to once again synchronize circadian time to local time, and until that occurs the onset and termination of optimal sleep will be delayed. (C) Conversely, traveling 3 time zones to the west puts the circadian clock 3 h ahead of local time. Until the process of entrainment brings circadian time in synchrony with local time by a phase delay of the circadian clock, the onset and termination of optimal sleep will occur at earlier clock times than desired. *Figure and caption reprinted from Heller HC, Herzog E, Brager A, Poe G, Allada R, Scheer F, et al. The negative effects of travel on student athletes through sleep and circadian disruption. J Biol Rhythms 2024;39:5–19. <https://doi.org/10.1177/07487304231207330>*

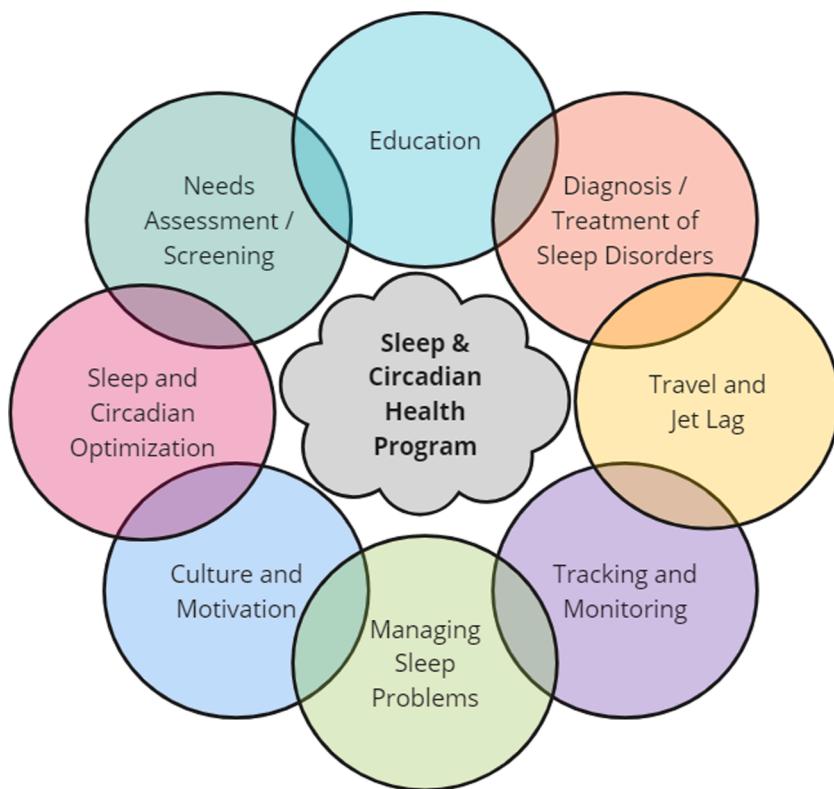


FIGURE 45.5 Components of a sleep and circadian health promotion program. Reprinted from Grandner MA, Mills J, Clarke M, Athey AB. Sleep and circadian health promotion programs for athletes. *Sleep Sport* 2024;313–26.

discussed, including duration, quality, timing, regularity, continuity, and daytime sleepiness/alertness. In addition, common sleep problems including insufficient sleep and poor sleep quality should be discussed, as well as advanced, delayed, and irregular circadian phase (and social jetlag), and daytime consequences of sleep problems, including increased sleep propensity, tiredness, and fatigue. Sleep disorders including insomnia, sleep apnea, sleep-related movement disorders, circadian rhythm sleep-wake disorders, parasomnias, and hypersomnia disorders. This material should also include information about how to seek help if it is needed.

- *Sleep and circadian impacts on athletes.* Educational programs should help link these discussions to their real-world outcomes for athletes. Previous studies linking aspects of sleep health to dimensions of athletic performance should be discussed. These include studies of sleep deprivation and extension, associations between sleep symptoms and outcomes in athletes, and system-level factors (e.g., travel schedules) on athlete and team performance.
- *Strategies for addressing sleep problems.* The majority of the educational content should focus on strategies for improving sleep, addressing sleep problems, and troubleshooting challenges. Potential topic areas include

maintaining healthy sleep habits (including sleep hygiene suggestions), discussing how stimulus control can prevent and fix sleep problems and increase a sense of control over sleep, strategies for how to fall asleep faster, strategies for how to get out of bed in the morning to maximize mood and energy and reduce sleep inertia, concepts around strategic napping, suggestions for managing electronic devices and their impact on sleep, suggestions for managing travel and jet lag, dealing with insomnia the night before competition (e.g., anticipatory insomnia), strategies for maximizing sleep efficiency, strategies for using caffeine effectively, information about when and how to use melatonin, the impacts of alcohol and sleep, information about nutritional and workout supplements and their relationship to sleep, and strategies to increase self-efficacy around sleep.

- *Tracking and optimization.* In addition to a focus on assessing and mitigating sleep-related problems, an educational program should also include strategies for optimizing already good sleep and implementing sleep-tracking programs. For example, this content can discuss wearables and other technology for tracking sleep, including best practices for choosing, using, and interpreting data from wearables. This content can also include strategies for optimizing sleep, using sleep data

to improve performance, and using techniques such as sleep banking to prevent performance impairments.

A graphical depiction of the components of a sleep and circadian health program are depicted in Fig. 45.4, which was previously published [48].

Optimization and competitive advantage

Improving healthy sleep

In addition to reducing the impact of sleep problems, many of these strategies can be used to improve already-healthy sleep. For example, athletes who are experiencing sufficient sleep duration may improve performance by increasing their amount of sleep (since younger adults tend to perform better with slightly more sleep, even above the minimum requirements). Also, stimulus control can be beneficial in general and help inoculate individuals against periodic sleep disturbances. Good circadian habits can also improve performance and reduce even minor sleep problems.

Ongoing monitoring programs

Many athletics programs may have ongoing monitoring programs, using wearables and/or periodic evaluations of sleep health. The value of these programs will be based on the degree to which the data obtained is monitored and used in a helpful way. For example, wearables can assess aspects of sleep prospectively, but missing data, inaccurate data, and nonvalidated metrics can interfere with the program's ability to make accurate predictions. Ideally, any sleep monitoring program is built around well-chosen assessment devices or other strategies, incorporates actionable feedback, and leverages the information for what it can accurately predict, ignoring metrics that may distract more than guide.

Managing travel and jetlag for performance

Issues surrounding travel and jetlag are variably relevant for athletics organizations. For example, some only compete locally and do not need to consider circadian adjustments to their performance (over and above the usual considerations of timing within the 24 h for training, practice, and competition). Many athletics programs travel regionally but stay within 1–2 time zones, rarely experiencing a significant circadian advance or delay. Many organizations (e.g., professional sports in the United States) routinely travel 2–3 time zones at a time, which can induce travel fatigue and circadian misalignment more

significantly. And some athletics programs are global (e.g., Olympic sports), often necessitating travel around the world and inducing profound circadian disruptions. These different types of programs may require different strategies for mitigating the adverse effects of circadian misalignment on health and performance.

Evaluation of schedules

One element of a program could be the evaluation of existing schedules. Often timing of competition is not negotiable, including the location of the competition. Furthermore, the timing can be uncertain and not known far in advance (e.g., postseason travel depends on competition results). It is important to consider when would be strategic to sleep prior to travel and when it might make more sense to travel first and sleep at the destination. Sleep while in transit is also a consideration, especially on long-haul flights. The degree to which these considerations are possible may depend on the mode of travel, degree of control over schedules, etc. A program can evaluate these options and propose strategies for optimizing performance in the context of travel.

Utilizing circadian technology

Circadian technologies may be beneficial to use. These include technologies meant to enhance a daytime signal when such a result is desirable or enhance a nighttime signal when a daytime signal is not desirable. For example, lenses, lights, and visors can be used to enhance short-wavelength light that stimulates a daytime signal. On the contrary, light-blocking strategies, including lenses and curtains and bulbs, can reduce the degree to which environmental factors are impinging on natural circadian rhythms. Another example of circadian technology includes algorithm-based decision tools to determine optimal timing for administration and/or avoidance of light and/or melatonin. These strategies can enhance the ability of a program to optimize circadian principles.

Conclusion

Sleep health is important for athletes. Sleep is fundamental to many physiologic processes, and healthy sleep in athletes can promote wellbeing, better cardiometabolic and immune health, improved cognition, reduced injury risk, faster and more efficient recovery, and improved mental health. Yet, sleep disorders and sleep concerns are highly prevalent in athletics populations. This may be due to risk factors associated with sport and being an athlete, and these may also be due to social and environmental constraints. For these reasons, sleep concerns should be prioritized by athletics programs. Promoting sleep health in

athletes includes four components: (1) screening and assessment to identify and triage problems, (2) referral and treatment to address sleep disorders, (3) education and culture change to empower athletes to strategically prioritize sleep, and (4) sleep training programs that can optimize sleep among athletes. To assist with these efforts, it is recommended that athletics programs refer to published statements and guidelines [3,18,45,49] to develop programs, reviews [4,5,9,16,17,57,58] to conceptualize the role of sleep in athletics, and qualified sleep specialists to assist in addressing sleep concerns.

Different types of activities and skills have different circadian rhythms in optimal performance under entrained conditions (i.e., normal training week). Game day travel (especially east-west travel) often misaligns these circadian rhythms of athletic performance making optimal performance more challenging to achieve. Figure and caption reprinted from Ref. [49].

References

- [1] Penn Schoen Berland. Student-athlete time demands. Penn Schoen Berland; 2015.
- [2] Carskadon MA. Sleep in adolescents: the perfect storm. *Pediatr Clin North Am* 2011;58:637–47. <https://doi.org/10.1016/j.pcl.2011.03.003>.
- [3] Kroshus E, Wagner J, Wyrrick D, Athey A, Bell L, Benjamin HJ, et al. Wake up call for collegiate athlete sleep: narrative review and consensus recommendations from the NCAA Interassociation Task Force on Sleep and Wellness. *Br J Sports Med* 2019;53:731–6. <https://doi.org/10.1136/bjsports-2019-100590>.
- [4] Charest J, Grandner MA. Sleep and athletic performance: impacts on physical performance, mental performance, injury risk and recovery, and mental health. *Sleep Med Clin* 2020;15:41–57. <https://doi.org/10.1016/j.jsmc.2019.11.005>.
- [5] Charest J, Grandner MA. Sleep and athletic performance: impacts on physical performance, mental performance, injury risk and recovery, and mental health: an update. *Sleep Med Clin* 2022;17:263–82. <https://doi.org/10.1016/J.JSMC.2022.03.006>.
- [6] Grandner MA. Sleep, health, and society. *Sleep Med Clin* 2022;17:117–39. <https://doi.org/10.1016/j.jsmc.2022.03.001>.
- [7] Athey A, Grandner MA. Student athletes' access to healthy sleep information on campus: how does it relate to other types of health information and to sleep difficulties? *Sleep* 2017;40:A451.
- [8] Turner RW, Vissa K, Hall C, Poling K, Athey A, Alfonso-Miller P, et al. Sleep problems are associated with academic performance in a national sample of collegiate athletes. *J Am Coll Health* 2021;69:74–81. <https://doi.org/10.1080/07448481.2019.1655027>.
- [9] Gouttebarge V, Castaldelli-Maia JM, Gorczynski P, Hainline B, Hitchcock ME, Kerkhoffs GM, et al. Occurrence of mental health symptoms and disorders in current and former elite athletes: a systematic review and meta-analysis. *Br J Sports Med* 2019;53:700–6. <https://doi.org/10.1136/bjsports-2019-100671>.
- [10] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6:97–111. <https://doi.org/10.1053/smrv.2002.0186>.
- [11] Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177:1006–14. <https://doi.org/10.1093/aje/kws342>.
- [12] Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *Br J Anaesth* 2012;108:768–75. <https://doi.org/10.1093/bja/aes022>.
- [13] George CF, Kab V, Kab P, Villa JJ, Levy AM. Sleep and breathing in professional football players. *Sleep Med* 2003;4:317–25. [https://doi.org/10.1016/s1389-9457\(03\)00113-8](https://doi.org/10.1016/s1389-9457(03)00113-8).
- [14] George CF, Kab V. Sleep-disordered breathing in the national football league is not a trivial matter. *Sleep* 2011;34:245.
- [15] George CF, Kab V, Levy AM. Increased prevalence of sleep-disordered breathing among professional football players. *N Engl J Med* 2003;348:367–8. <https://doi.org/10.1056/NEJM200301233480422>.
- [16] Brauer AA, Athey AB, Ross MJ, Grandner MA. Sleep and health among collegiate student athletes. *Chest* 2019;156:1234–45. <https://doi.org/10.1016/j.chest.2019.08.1921>.
- [17] Simpson NS, Gibbs EL, Matheson GO. Optimizing sleep to maximize performance: implications and recommendations for elite athletes. *Scand J Med Sci Sports* 2017;27:266–74. <https://doi.org/10.1111/sms.12703>.
- [18] Walsh NP, Halson SL, Sargent C, Roach GD, Nédélec M, Gupta L, et al. Sleep and the athlete: narrative review and 2021 expert consensus recommendations. *Br J Sports Med* 2020;55(7):356–68. <https://doi.org/10.1136/bjsports-2020-102025>.
- [19] Mougin F, Davenne D, Simon-Rigaud ML, Renaud A, Garnier A, Magnin P. Disturbance of sports performance after partial sleep deprivation. *C R Seances Soc Biol Fil* 1989;183:461–6.
- [20] Mougin F, Bourdin H, Simon-Rigaud ML, Didier JM, Toubin G, Kantelip JP. Effects of a selective sleep deprivation on subsequent anaerobic performance. *Int J Sports Med* 1996;17:115–9. <https://doi.org/10.1055/s-2007-972818>.
- [21] Mougin F, Simon-Rigaud ML, Davenne D, Renaud A, Garnier A, Kantelip JP, et al. Effects of sleep disturbances on subsequent physical performance. *Eur J Appl Physiol Occup Physiol* 1991;63:77–82. <https://doi.org/10.1007/BF00235173>.
- [22] Reyner LA, Horne JA. Sleep restriction and serving accuracy in performance tennis players, and effects of caffeine. *Physiol Behav* 2013;120:93–6. <https://doi.org/10.1016/j.physbeh.2013.07.002>.
- [23] Schwartz J, Simon J. RD. Sleep extension improves serving accuracy: a study with college varsity tennis players. *Physiol Behav* 2015;151:541–4. <https://doi.org/10.1016/j.physbeh.2015.08.035>.
- [24] Oliver SJ, Costa RJ, Laing SJ, Bilzon JL, Walsh NP. One night of sleep deprivation decreases treadmill endurance performance. *Eur J Appl Physiol* 2009;107:155–61. <https://doi.org/10.1007/s00421-009-1103-9>.
- [25] Skein M, Duffield R, Edge J, Short MJ, Mundel T. Intermittent-sprint performance and muscle glycogen after 30 h of sleep deprivation. *Med Sci Sports Exerc* 2011;43:1301–11. <https://doi.org/10.1249/MSS.0b013e31820abc5a>.
- [26] Ben Cheikh R, Latiri I, Dogui M, Ben Saad H. Effects of one-night sleep deprivation on selective attention and isometric force in adolescent karate athletes. *J Sports Med Phys Fit* 2017;57:752–9. <https://doi.org/10.23736/S0022-4707.16.06323-4>.
- [27] Cote KA, McCormick CM, Geniole SN, Renn RP, MacAulay SD. Sleep deprivation lowers reactive aggression and testosterone in

- men. *Biol Psychol* 2013;92:249–56. <https://doi.org/10.1016/j.biopsych.2012.09.011>.
- [28] Leproult R, Van Cauter E. Effect of 1 week of sleep restriction on testosterone levels in young healthy men. *JAMA* 2011;305:2173–4. <https://doi.org/10.1001/jama.2011.710>.
- [29] Costill DL, Flynn MG, Kirwan JP, Houmard JA, Mitchell JB, Thomas R, et al. Effects of repeated days of intensified training on muscle glycogen and swimming performance. *Med Sci Sports Exerc* 1988;20:249–54. <https://doi.org/10.1249/00005768-198806000-00006>.
- [30] Raikes AC, Athey A, Alfonso-Miller P, Killgore WDS, Grandner MA. Author response: concussion assessment tools – a possible measure of sleepiness? *Sleep Med* 2020;66:260–1. <https://doi.org/10.1016/j.sleep.2019.08.004>.
- [31] Raikes AC, Athey A, Alfonso-Miller P, Killgore WDS, Grandner MAA. Insomnia and daytime sleepiness: risk factors for sports-related concussion. *Sleep Med* 2019;58:66–74. <https://doi.org/10.1016/j.sleep.2019.03.008>.
- [32] Milewski MD, Skaggs DL, Bishop GA, Pace JL, Ibrahim DA, Wren TA, et al. Chronic lack of sleep is associated with increased sports injuries in adolescent athletes. *J Pediatr Orthop* 2014;34:129–33. <https://doi.org/10.1097/BPO.0000000000000151>.
- [33] Gupta R, Lahan V. Insomnia associated with depressive disorder: primary, secondary, or mixed? *Indian J Psychol Med* 2011;33:123–8. <https://doi.org/10.4103/0253-7176.92056>.
- [34] Spiegelhalder K, Regen W, Nanovska S, Baglioni C, Riemann D. Comorbid sleep disorders in neuropsychiatric disorders across the life cycle. *Curr Psychiatry Rep* 2013;15:364. <https://doi.org/10.1007/s11920-013-0364-5>.
- [35] Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry* 2012;73:e1160–7. <https://doi.org/10.4088/JCP.11r07586>.
- [36] Liu RT, Steele SJ, Hamilton JL, Do QBP, Furbish K, Burke TA, et al. Sleep and suicide: a systematic review and meta-analysis of longitudinal studies. *Clin Psychol Rev* 2020;81:101895. <https://doi.org/10.1016/j.cpr.2020.101895>.
- [37] Tubbs AS, Perlis ML, Grandner MA. Surviving the long night: the potential of sleep health for suicide prevention. *Sleep Med Rev* 2019;44:83–4. <https://doi.org/10.1016/j.smrv.2019.01.001>.
- [38] Perlis ML, Grandner MA, Chakravorty S, Bernert RA, Brown GK, Thase ME. Suicide and sleep: is it a bad thing to be awake when reason sleeps? *Sleep Med Rev* 2016;29:101–7. <https://doi.org/10.1016/j.smrv.2015.10.003>.
- [39] Perlis ML, Grandner MA, Basner M, Chakravorty S, Brown GK, Morales KH, et al. When accounting for wakefulness, completed suicides exhibit an increased likelihood during circadian night. *Sleep* 2014;37:A268–9.
- [40] Perlis ML, Grandner MA, Brown GK, Basner M, Chakravorty S, Morales KH, et al. Nocturnal wakefulness as a previously unrecognized risk factor for suicide. *J Clin Psychiatry* 2016;77:e726–33. <https://doi.org/10.4088/JCP.15m10131>.
- [41] Grandner MA, Hall C, Jaszevski A, Alfonso-Miller P, Gehrels J, Killgore WDS, et al. Mental health in student athletes: associations with sleep duration, sleep quality, insomnia, fatigue, and sleep apnea symptoms. *Athl Train Sports Health Care* 2021;13(4):e159–67.
- [42] Wills C, Ghani S, Tubbs A, Fernandez F-X, Athey A, Turner R, et al. Chronotype and social support among student athletes: impact on depressive symptoms. *Chronobiol Int* 2021;38:1–11. <https://doi.org/10.1080/07420528.2021.1927072>.
- [43] Khader WS, Tubbs AS, Haghghi A, Athey AB, Killgore WD, Hale L, et al. Onset insomnia and insufficient sleep duration are associated with suicide ideation in university students and athletes. *J Affect Disord* 2020;274:1161–4. <https://doi.org/10.1016/j.jad.2020.05.102>.
- [44] NCAA Sport Science Institute. Mental health best practices: understanding and supporting student-athlete mental health. 2nd ed. Indianapolis: NCAA; 2020.
- [45] Reardon CLL, Hainline B, Aron CMM, Baron D, Baum ALL, Bindra A, et al. Mental health in elite athletes: International Olympic Committee consensus statement. *Br J Sports Med* 2019;53:667–99. <https://doi.org/10.1136/bjsports-2019-100715>.
- [46] Reardon CL, Hainline B, Aron CM, Baron D, Baum AL, Bindra A, et al. Infographic. Sleep disorders in athletes. *Br J Sports Med* 2020;54(3):188–9. <https://doi.org/10.1136/bjsports-2019-101107>.
- [47] Reardon CL, Hainline B, Aron CM, Baron D, Baum AL, Bindra A, et al. Infographic: mental health in elite athletes. An IOC consensus statement. *Br J Sports Med* 2020;54:49–50. <https://doi.org/10.1136/bjsports-2019-101087>.
- [48] Grandner MA, Mills J, Clarke M, Athey AB. Sleep and circadian health promotion programs for athletes. In: *Sleep and sport*. Elsevier; 2024. p. 313–26.
- [49] Heller HC, Herzog E, Brager A, Poe G, Allada R, Scheer F, et al. The negative effects of travel on student athletes through sleep and circadian disruption. *J Biol Rhythms* 2024;39:5–19. <https://doi.org/10.1177/07487304231207330>.
- [50] Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Clinical guidelines committee of the American college of P. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American college of physicians. *Ann Intern Med* 2016;165(2):125–33.
- [51] Klingman KJ, Jungquist CR, Perlis ML. Introducing the sleep disorders symptom checklist-25: a primary care friendly and comprehensive screener for sleep disorders. *Sleep Med Res* 2017;8:17–25.
- [52] Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297–307. [https://doi.org/10.1016/s1389-9457\(00\)00065-4](https://doi.org/10.1016/s1389-9457(00)00065-4).
- [53] Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;131:485–91. <https://doi.org/10.7326/0003-4819-131-7-199910050-00002>.
- [54] Trott LM, Bhadriraju S, Becker LA. Iron for restless legs syndrome. *Cochrane Database Syst Rev* 2012;5:CD007834. <https://doi.org/10.1002/14651858.CD007834.pub2>.
- [55] Randerath WJ, Sanner BM, Somers VK. *Sleep apnea: current diagnosis and treatment*. Basel: Karger; 2006.
- [56] Grandner MA. Healthy sleep for student-athletes: a guide for athletics departments and coaches42. NCAA Sport Sciences Institute Newsletter; 2016.
- [57] Nedelec M, Halson S, Abaidia AE, Ahmaidi S, Dupont G. Stress, sleep and recovery in elite soccer: a critical review of the literature. *Sports Med* 2015;45:1387–400. <https://doi.org/10.1007/s40279-015-0358-z>.
- [58] Rice SM, Gwyther K, Santesteban-Echarri O, Baron D, Gorczynski P, Gouttebarge V, et al. Determinants of anxiety in elite athletes: a systematic review and meta-analysis. *Br J Sports Med* 2019;53:722–30. <https://doi.org/10.1136/bjsports-2019-100620>.

Chapter 46

Digital and telehealth sleep health interventions

Ruth K. Brombach and Jessica R. Dietch

Oregon State University, School of Psychological Science, Corvallis, OR, United States

Introduction

Cognitive behavioral therapy for insomnia (CBTI) is recommended as the first-line treatment for primary insomnia [1]. It has comparable short-term efficacy to pharmacotherapy and better long-term efficacy [2,3]. CBTI was originally developed and tested as a therapist-led, in-person intervention, and this method of delivery is generally considered the best option for treatment [4]. However, access to in-person therapist-led CBTI is limited due to barriers at multiple levels including a shortage of providers qualified to deliver this treatment [5] and an unequal distribution of providers across the US [6]. Digital sleep health interventions, including therapist-led telehealth and self-guided digital CBTI (dCBTI), offer one solution to address these barriers to accessibility [7]. One central benefit of digital health interventions is that they offer greater flexibility with regard to patient and provider location and schedule [8,9]. However, current digital sleep health solutions have their own limitations that may hinder their potential impact in the current healthcare landscape.

Digital health broadly refers to the use of digital technologies to accomplish several health-related goals (e.g., screening, prevention, assessment/monitoring, and intervention). This chapter will take a narrow focus on digital sleep health interventions, primarily dCBTI. We will describe the nature, structure, and evidence base of digital sleep health interventions, including both opportunities and challenges. Throughout, we will use dCBTI as a common example as it is the most widespread digital sleep health intervention.

Defining terms: Digital health, mHealth, eHealth, and telehealth

Digital health is a broad term that encompasses the use of digital technologies and platforms to improve health

outcomes, manage health-related data, and deliver care remotely. Digital health includes a range of applications that exist on web-based platforms, smartphones, wearables, nearables, and various other digital technologies [10]. In the context of sleep health, digital health interventions can include applications that track sleep patterns, wearable or nearable devices that monitor physiological signals during sleep, and smartphone- or web-based platforms that deliver behavioral therapeutic interventions [11,12]. The overarching term digital health can be divided into mobile health (mHealth) and electronic health (eHealth), and telehealth which can span across both mHealth and eHealth. See Table 46.1 for an overview of these terms.

mHealth refers to the use of mobile or wireless devices such as smartphones, tablets, nearables, wearables, or some combination of these tools to deliver healthcare services and manage patient information [13]. mHealth applications can range from simple SMS-based notifications to advanced mobile applications that monitor sleep, deliver health education, and provide platforms for tele-consultations. mHealth for sleep health could include, for example, apps that track sleep via diaries or sensors, guide users through relaxation techniques before bedtime, or send reminders to support treatment recommendations. mHealth interventions for sleep health can be either entirely self-guided or supported by a provider who offers some level of clinical support but not as much as would be provided in a therapist-led intervention. Concerningly, a review of self-guided mHealth apps for sleep health suggests that few apps met prespecified criteria for quality, content, and functionality [14]. Despite the rapid evolution of sleep self-management apps, the lack of validation studies is a significant concern that may limit the clinical value of these apps.

eHealth refers to health services and information delivered through the Internet and other information and communication technologies [13]. It includes a broader

TABLE 46.1 Overview of digital health, mHealth, eHealth and telehealth terms.

Term	Definition	Examples
Digital health	A broad term encompassing the use of digital technologies and platforms to improve health outcomes, manage health-related data, and deliver care remotely. Includes applications on web-based platforms, smartphones, wearables, and more.	Apps for tracking sleep, wearables monitoring physiological signals, web-based therapeutic interventions.
mHealth	Focuses on the use of mobile or wireless devices like smartphones, tablets, wearables, and nearables to deliver healthcare services and manage patient information.	Sleep tracking apps, mobile platforms for health education, teleconsultations, some dCBTI platforms.
eHealth	Pertains to health services and information delivered through the internet and other communication technologies. Broader than mHealth, encompassing electronic health records, e-prescribing, and online patient portals.	Web-based platforms for cognitive behavioral therapy, online support groups, patient portals, some dCBTI platforms.
Telehealth	A subset of digital health that utilizes electronic services to support remote patient care, education, and monitoring. Focuses on the delivery of health services via digital communication technologies to facilitate a provider's care from a distance, involving direct patient-provider connections.	Virtual consultations with sleep specialists, remote monitoring of sleep patterns via wearable devices, therapist-led telehealth CBTI.

range of systems and services than mHealth, such as electronic health records, e-prescribing, and online patient portals and aims to improve the quality of healthcare delivery, reduce medical errors, and enhance the efficiency of healthcare. eHealth provides the infrastructure for digital health and mHealth solutions [15]. eHealth solutions for sleep might include web-based platforms for dCBTI or sleep health information, online support groups for individuals with sleep disorders, or patient portals where users can access their sleep health information and communicate with healthcare providers.

Telehealth, a subset of digital health interventions, utilizes electronic services to support remote patient care, education, and monitoring. It specifically focuses on the delivery of health services and information via digital communication technologies to facilitate a provider's care from a distance. In contrast to eHealth and mHealth, which do not necessarily involve a direct patient-provider connection, telehealth facilitates remote interactions between the individual patient and their human provider via video appointments, remote monitoring, and teletherapy [16]. Telehealth relies on eHealth and/or mHealth technology to facilitate patient-provider interactions. Telehealth in the field of sleep health could include virtual consultations with sleep specialists, remote monitoring of sleep patterns via wearable devices, or teletherapy CBTI, allowing patients to access treatment without the need to travel to a healthcare provider. One trial of $N = 60$ individuals with insomnia disorder compared a sleep health intervention (CBTI) delivered by telehealth versus in-person and found telehealth-delivered treatment was not

inferior to in-person treatment on any measured outcome including insomnia symptoms [17].

An exemplar digital sleep health intervention: dCBTI

Therapist-led CBTI is the gold standard therapist-led intervention for insomnia, supported by numerous meta-analyses [18–21]. In brief, CBTI is a multicomponent intervention which typically includes, at a minimum, stimulus control therapy, sleep restriction therapy, and cognitive therapy, and may include relaxation therapy, sleep education, sleep hygiene, or other components as needed (see Table 46.2 for overview of standard components). Therapist-led interventions are guided by a trained clinician and can be delivered via several formats, most commonly in person, telehealth, or telephone. Therapist-led modalities can be supported or augmented by use of mHealth (e.g., a digital sleep diary) or eHealth (e.g., a web-based patient portal) technologies, but the primary intervention components are driven by synchronous contact between the patient and provider. dCBTI applies the principles of CBTI to a digital self-guided format.

Self-guided digital interventions are fully autonomous programs that users can navigate independently, without direct input from healthcare providers. Self-guided interventions can use eHealth or mHealth technologies, or be completely analog (e.g., a self-help workbook). Digital self-guided interventions rely on preprogrammed content, interactive components, and algorithms to deliver therapeutic content and adapt to user inputs (e.g., sleep diaries

TABLE 46.2 Overview of cognitive behavioral therapy for insomnia (CBTI) standard treatment components.

Component	Basic recommendations and methods	Aims and intended impact
Cognitive therapy	<ul style="list-style-type: none"> - Address cognitions that promote sleep interfering behaviors, maintain insomnia, and/or interfere with treatment adherence - Can use a variety of techniques including behavioral experiments, acceptance-based strategies, guided discovery/Socratic questioning, cognitive restructuring, cost-benefit analysis, downward arrow, motivational enhancement 	<ul style="list-style-type: none"> - Eliminate sleep-interfering behaviors - Reduce both sleep-related and general arousal - Improve adherence to other treatment components
Relaxation therapy; arousal reduction strategies	<ul style="list-style-type: none"> - Can include relaxation techniques such as progressive or passive muscle relaxation, meditation, guided imagery, diaphragmatic breathing - Can include problem-solving therapy or “scheduled worry time” - Develop a consistent presleep unwinding routine/buffer zone 	<ul style="list-style-type: none"> - Eases somatic and cognitive arousal throughout the day and before bedtime
Sleep education	<ul style="list-style-type: none"> - Dispelling myths and unhelpful beliefs about sleep - Providing information about normative sleep (e.g., sleep across the lifespan) - Providing rationale for behavioral recommendations 	<ul style="list-style-type: none"> - Provides context for treatment recommendations and promotes autonomy in decision-making around sleep - Promotes buy-in for behavioral changes
Sleep hygiene and environment	<ul style="list-style-type: none"> - Provide recommendations regarding use of caffeine, alcohol, nicotine, and other sleep-interfering substances, as well as eating and physical activity - Address sleep-interfering environmental factors as appropriate including light, noise, temperature, bedpartners, and feelings of safety. 	<ul style="list-style-type: none"> - Adjust, change, or accept certain behaviors, habits, or environmental factors that interfere with sleep - Educates users on conducive sleep practices and environment
Sleep restriction therapy	<ul style="list-style-type: none"> - Stabilize the sleep schedule, typically by keeping a consistent wake time every day - Limit time in bed, typically reduced to the baseline sleep duration (or baseline sleep duration + 30 min) - Gradually adjust time in bed based on sleep diary-reported sleep efficiency until sufficient sleep duration and satisfaction is achieved 	<ul style="list-style-type: none"> - Increase sleep efficiency - Build sleep drive - Strengthen circadian signaling
Stimulus control therapy	<ul style="list-style-type: none"> - Limit time awake in bed by getting out of bed if unable to sleep - Don't get into bed until feeling sleepy - Use the bed and bedroom for sleep and sex only - Limit daytime napping 	<ul style="list-style-type: none"> - Reduce conditioned arousal in bed and bedroom - Strengthen circadian signaling - Build sleep drive

and self-report measures). Self-guided interventions allow increased flexibility, as the patient can engage with the intervention content in the way that best suits their individual schedule and interests. This approach can significantly reduce costs and has the potential to reach underserved populations [12]. Digital self-guided interventions often include automated reminders or other methods for increasing engagement, but ultimately rely on the patient to choose to interact with the intervention. The lack of personalized support may impact patient engagement and adherence to treatment negatively, which can lead to reduced effectiveness for some individuals. A meta-analysis by Ref. [22] supports the efficacy of self-guided digital CBT for insomnia, showing significant improvements in sleep outcomes. However, the results also suggested interventions incorporating some level of therapist support might achieve higher effect sizes. dCBTI excels in comparison with therapist-led CBTI primarily in the domains of accessibility and cost [23]. Additional comparisons between therapist-led CBTI and dCBTI are shown in [Table 46.3](#).

Falling somewhere in between therapist-led and self-guided interventions are supported interventions. The format and structure of supported digital interventions can vary greatly. Support can be provided by people with a range of CBTI expertise and can include paraprofessionals (e.g., “coaches”), master’s level mental health clinicians, nurses, and psychologists, among others. Supporting providers can provide tailored reminders and encouragement, answer questions, check in on progress, provide feedback, and give additional recommendations. These contacts can occur by email, text message, phone call, telehealth, or in person. In some cases, supporting providers deliver one or more therapist-led intervention sessions during the course of treatment. The main advantage of therapist guidance is personal support and accountability, which can improve motivation and adherence to the intervention. In addition, therapist-led programs can be more easily adapted to the patient’s evolving needs, which can lead to better outcomes [24]. Some iterations of dCBTI have been tested in a supported manner and demonstrate generally improved performance compared with entirely self-guided dCBTI.

A proliferation of dCBTI platforms has occurred since the early 2010s [25]. Because the landscape of digital interventions is rapidly changing, it is fruitless to attempt to catalog every available platform for dCBTI. We instead direct the reader to other sources that collate information about existing options [26], including the American Academy of Sleep Medicine [27] and Sleep Review Mag [28] though no source appears comprehensive. dCBTI platforms range from completely free (e.g., Path to Better Sleep, eHealth platform) [29] to low cost (e.g., Go! To Sleep by Cleveland Clinic, eHealth platform, \$40 at time of writing) [30] to higher cost (e.g., Sleep Reset; mHealth

platform, approximately \$300 at time of writing) [31]. Some platforms are publicly available, whereas others are only accessible to limited populations. For example, Sleepio, one of the most well-studied dCBTI platforms, is only available to those served by the National Health Service of the United Kingdom or those whose employers sponsor coverage within the United States. Furthermore, the availability of dCBTI platforms can change rapidly; Somryst, the first dCBTI app to gain FDA approval, was taken off the market when parent company Pear Therapeutics filed for bankruptcy in 2023. The volume of dCBTI platforms and the lack of standard evaluation metrics make it challenging for potential users to have a clear picture of their options for dCBTI.

Delivery format may play a role in accessibility, engagement, and effectiveness of digital health interventions. Web-based platforms are accessible via Internet browsers and allow users to access intervention content from desktop computers, laptops, or other devices with a web browser. Web-based dCBTI programs are typically presented in a fixed structure, meaning that the order in which content is presented is the same across users. These programs typically use a modular structure that guides users through the main components of CBTI, commonly including psychoeducation, sleep restriction therapy, stimulus control therapy, relaxation therapy, cognitive therapy, and sleep hygiene instructions. The interactive nature of web platforms often includes features such as progress monitoring, personalized feedback, and multimedia components to enhance learning and engagement [12,26]. A key advantage of web-based formats is the ability for personalized feedback and limited customization of therapy content based on user input, such as sleep diaries or questionnaires. Most often this takes the form of using user-entered sleep diary data to adjust the time-in-bed recommendation component of sleep restriction therapy.

mHealth applications similarly use a fixed modular structure and can further extend the accessibility and convenience of dCBTI by allowing users to engage with therapeutic content on their smartphones. Per a 2021 Pew research study, smartphone ownership is currently estimated at 85% of the US population and this number continues to grow [32]. mHealth applications, in addition, include features such as notifications for completing intervention tasks and flexibility in ability to engage with the content in a variety of locations. In addition, mobile apps can use the sensors and data collection capabilities of smartphones to provide insights into sleep patterns and environmental factors that affect sleep which has the potential to increase therapy adherence and effectiveness [26]. However, thus far limited evidence exists that convincingly supports the utility of integrating wearable/nearable technology into sleep health interventions.

TABLE 46.3 Comparison between therapist-led CBTI and dCBTI.

Factor	Therapist-led CBTI	dCBTI
Accessibility	Low, depends on regionally limited availability of trained therapists; must coordinate between therapist and patients' schedules	Moderate to high, available to anyone with an appropriate device and internet access; can be accessed on the patient's schedule
Cost	Moderate to high, depending on insurance coverage and number sessions required	Low to moderate, often a one-time fee or subscription; insurance reimbursement is nonexistent or limited
Delivery method	Synchronous sessions with a trained therapist, delivered in person, via telehealth, or on the phone	Delivered via digital platforms (apps, websites) without direct therapist involvement
Dropout	Low to moderate (e.g., 0%–33%)	High (e.g., 50%–80%)
Duration of intervention content	Treatment sessions typically range from 15 to 60 min	Duration can vary as most modules are self-paced
Efficacy	High (often produces significant improvement in sleep outcomes, with lasting effects; effectiveness is well-documented in a variety of settings and populations)	Moderate (effective in improving sleep outcomes, though less effective than therapist-led interventions)
Length of treatment	Varies based on individual needs; most typically 4–8 sessions delivered weekly or biweekly	Typically fixed for all patients; most typically 5–6 modules with a new one available to review each week, for a total of a 6–8 week treatment period
Patient support	Direct, with active feedback and encouragement from the therapist	Indirect, via automated messages or community forums (if available); if supported, may be direct but briefer than therapist-led
Personalization of treatment	High, therapist can adjust the order and emphasis on treatment components and integrate additional treatment components as needed	Low, generally offers the same treatment components to each user; some platforms claim to offer adaptive algorithms
Sleep diary	Can be delivered in a variety of formats including paper-and-pencil, an app, a digital form, or a spreadsheet. Often requires calculation of sleep parameters by patient or therapist	A digital tool that automatically calculates sleep parameters
Symptom assessment	Typically gathered during intake assessment and throughout treatment using a mix of clinical interview and self-report measures, either paper-and-pencil or digital	Gathered at treatment outset and throughout; digital self-report measures

Most dCBTI programs include a standard duration of 6–10 weeks [33], which loosely mirrors the duration of therapist-led CBTI in research trials of 4–8 weekly or biweekly sessions [4]. New components of CBTI are introduced gradually so as not to overwhelm the user with information [34]. Digital platforms can offer flexibility in the timing of intervention delivery that allows users to progress at their own pace and consume content at a time that works best for them. In contrast, therapist-led interventions are subject to the limits of both the provider and patients' schedules. Some dCBTI programs include algorithms that adjust program progression based on user feedback and engagement metrics, potentially lengthening or shortening the standard duration to optimize outcomes [12,26]. This personalized pace can improve the user experience and lead to better treatment adherence and outcomes by accounting for individual differences in learning and adapting to changes in behavior. Studies that examined variations in treatment duration in therapist-led studies suggest relatively brief programs may be effective, particularly for individuals with mild to moderate insomnia symptoms [35,36].

Effectiveness of dCBTI

The majority of research on dCBTI has been conducted among general adult populations. Meta-analyses have demonstrated the efficacy of dCBTI compared with treatment as usual or other control conditions in reducing insomnia symptoms and improving sleep parameters, most notably sleep efficiency, sleep onset latency, and sleep quality, with mixed findings for wake after sleep onset and total sleep time [22,37–40]. Based on recent meta-analyses of insomnia severity, pooled effect sizes comparing dCBTI to various control conditions are typically small to medium, ranging from $d = 0.39$ [40] to 0.78 [39]. One meta-analysis of comparative effectiveness by CBTI format [39] found that both self-guided ($d = 0.78$) and supported ($d = 0.71$) dCBTI produced effect sizes of a smaller magnitude compared with therapist-led group ($d = 1.00$) and individual therapist-led face-to-face ($d = 1.27$) and telehealth ($d = 1.28$) CBTI.

Advantages and benefits of dCBTI

A central benefit of dCBTI is its accessibility, scalability, convenience, and relatively low resource burden. These factors significantly expand the potential that CBTI can reach patients in remote or underserved locations where qualified providers may not be as available [41]. Unlike therapist-led treatment, dCBTI offers the advantage of being accessible 24/7, accommodating those with irregular schedules or who cannot attend synchronous treatment sessions due to geographic or physical limitations [9,42].

dCBTI programs are generally considered more cost-effective than therapist-led CBTI [23]. Furthermore, the scalability of digital platforms allows for the treatment to be extended to a larger population without substantial increases in per-user cost [9]. dCBTI also offers consistency and standardization in the delivery of therapeutic content, minimizing the variability in treatment quality that can occur across therapists. Digital platforms can be continuously updated and refined based on user feedback and new research findings, ensuring that the therapeutic methods remain current and effective. In addition, these programs could be tailored to adjust the pace and focus based on individual user progress and specific needs, providing a more personalized treatment experience [42], although this remains largely a future direction.

Challenges and opportunities for dCBTI and other digital sleep health interventions

Personalization

Although dCBTI has the potential to increase accessibility and scalability of insomnia treatment, certain aspects of therapist-led CBTI have not thus far been replicated in a digital format. A recent qualitative study of patients' perceptions of dCBTI [43] indicated one of the major barriers to use of dCBTI was a desire for additional human support, lack of personalization for complex clinical presentations, and lack of support for adherence challenges. In some cases, dCBTI may not be an appropriate choice over therapist-led treatment, particularly among patients with complex clinical presentations or elevated safety concerns. Therapist-led CBTI can be tailored to the patient's unique clinical presentation, which includes specific factors such as current life circumstances, willingness to engage with the intervention, safety considerations, and cooccurring symptoms or disorders. This tailoring extends beyond adjusting sleep schedules which is the primary form of tailoring in current iterations of dCBTI interventions [44]. For example, a case conceptualization-based approach allows a therapist to choose the order and emphasis of treatment components to be optimally aligned with the patient's changing needs across treatment [45]. In contrast, personalization in dCBTI is derived from sleep diary entries or other static data collection tools that lack the context and dynamism of an interpersonal relationship between therapist and patient [26]. In addition, therapist-led CBTI often involves detailed cognitive therapy which can help address sleep-interfering cognitions and barriers to treatment adherence. Although some dCBTI programs offer limited cognitive restructuring components, they currently lack the depth of personalized feedback, dynamic interaction, and validation that a

therapist can provide [25,44]. It remains unknown whether these processes can be improved by using artificial intelligence (e.g., “chatbot”) technologies.

Therapeutic relationship

The therapeutic relationship between a patient and a therapist plays a significant role in the success of psychotherapies including CBTI and can be particularly important for supporting patients’ adherence to challenging treatment components like sleep restriction [35] and treatment completion. Entirely self-guided dCBTI has limited personal interaction and support that can be important for some patients, potentially impacting their willingness to initiate treatment, remain engaged, successfully implement treatment strategies, and persevere through challenges with the program. This lack of therapeutic relationship and accountability may be largely responsible for the high dropout rates seen in dCBTI (e.g., 50%–80%) [46,47] compared with therapist-led treatment (e.g., 0%–33%) [19]. In addition, engagement with dCBTI strategies is low, which may interfere with effectiveness of the intervention. Supported dCBTI offers some elements of the therapeutic relationship and may partially ameliorate these challenges.

Digital literacy

The format of both web-based and mHealth dCBTI programs can pose some potential challenges in comparison with traditional therapist-led interventions. Although digital solutions are proposed to overcome the gap of healthcare providers trained in CBTI and the demand of CBTI, disparities in digital access, also referred to as the digital divide, limit their reach [24]. This divide includes the availability of Internet connections and digital devices and varies across different demographics, including age, socioeconomic status, and urban versus rural residency, potentially exacerbating existing health inequalities. The digital divide can prevent equal access to digital sleep health interventions among those with low digital or technological literacy, thereby reinforcing health disparities rather than reducing health inequalities [5,16]. In addition, existing programs may have certain mechanical or visual limitations that impact or prohibit user experience and satisfaction [14]. Privacy concerns are another major challenge for digital sleep health interventions. The collection, storage, and analysis of personal health data via digital platforms can raise concerns about data security and privacy [16,24]. Robust data protection measures and transparent communication about how patient data are used and protected are critical to build trust and further promote the use of digital interventions.

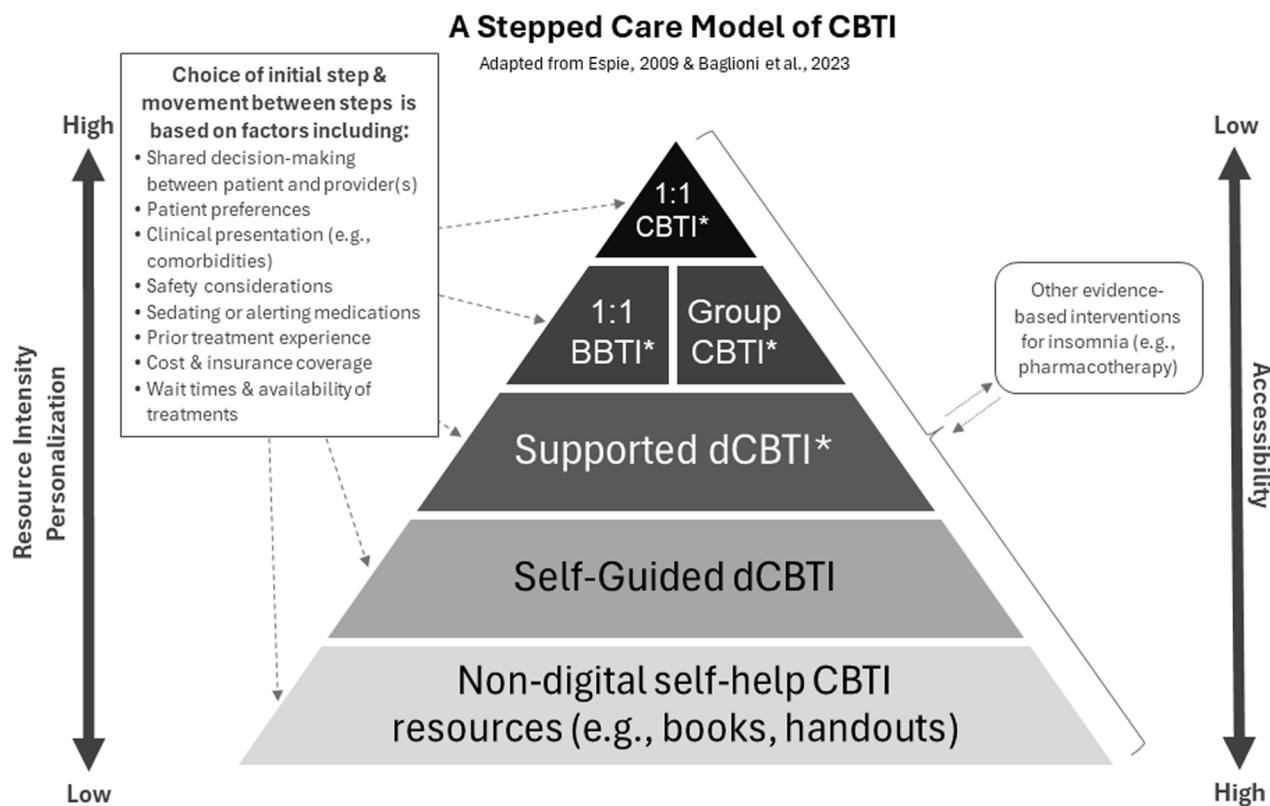
Digital sleep health interventions like dCBTI offer promising solutions for improving the accessibility and quality of care for individuals with sleep disorders.

However, challenges related to access, cost and insurance reimbursement, patient preferences, privacy, and the need for customization need to be addressed to fully realize their potential. Overcoming these challenges requires efforts from healthcare providers, insurers, developers of digital therapeutics, and policymakers to ensure that these innovative treatments can benefit a broad and diverse patient population.

dCBTI and other digital sleep health interventions belong in a stepped care model

Based on the current evidence, dCBTI is not poised to solve the problem of CBTI accessibility unless it is embedded within a stepped care framework. dCBTI is not currently sufficient to address the broad range of presentations, complexities, and preferences of patients with insomnia. However, a system which can appropriately step up the level of care for people for whom dCBTI is inappropriate or ineffective has the potential to widen the bottleneck of access to CBTI. One of the original dCBTI platforms [48] was developed as an answer to the CBTI accessibility problem. In this model, dCBTI would serve as the “base” of a stepped care model [44]. See Fig. 46.1 for an example adaptation of Espie’s original stepped care model [48] that explicitly incorporates dCBTI with and without provider support. Briefly, in the stepped care model, patients with insomnia are triaged to an appropriate, evidence-based intervention. Higher levels on the model indicate a gradually increasing intensity of care that simultaneously increases in resource intensity and decreases in accessibility.

We propose the choice of level in which people with insomnia would enter the model and their movement between levels would be best made via shared decision-making process between the patient and their provider(s). This process would necessarily consider factors such as cost, insurance coverage, wait times, availability of treatment, comorbidities and special circumstances, patient preferences, medication burden, prior experience with interventions, and insomnia symptom severity and complexity. Emerging research is beginning to test different models of assigning people with insomnia to an initial step of therapist-led or supported/self-guided digital CBTI [49,50], but more work is needed to refine and test allocation algorithms. If a patient is unsuccessful in achieving their desired treatment outcome at a lower level of care, they would move up to a higher “step.” Systems of care could implement a stepped care model using a subset of the proposed levels which are feasible given available resources, personnel, and patient population. Real-world implementation of stepped care models urgently needs to be tested and refined.



1:1 = individual; BBTI = brief behavioral therapy for insomnia; BSM = behavioral sleep medicine; CBTI = cognitive behavioral therapy for insomnia; dCBTI = digital CBTI

*Gradient of resource intensity, personalization, availability, and ability to handle complexity within each level depending on provider's training; ranging from specialty-trained peers/paraprofessionals to clinicians with some specialty training to behavioral sleep medicine expert clinicians. Additionally, each level could be conducted using in-person or telehealth modalities.

FIGURE 46.1 A stepped care model of CBTI. An adaptation of Espie's (2009) stepped care model of CBTI to explicitly include digital CBTI. Modified from Espie CA. "Stepped care": a health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. *Sleep* 2009;32(12):1549–1558. <https://doi.org/10.1093/sleep/32.12.1549>.

Conclusions and future directions

Evidence supporting dCBTI has grown immensely since its introduction and rise in popularity in the last 10–15 years. dCBTI offers benefits over “traditional” models of CBTI in the form of lower cost and greater accessibility. However, current iterations of dCBTI are not a panacea for the societal burden of insomnia; dCBTI is not currently and may never be acceptable to all patients or appropriate for certain presentations of insomnia (e.g., those with a high degree of complexity). Embedding dCBTI and eventually other digital sleep health interventions within a stepped model of care has the potential to alleviate these challenges and provide solutions for patients with insomnia and other sleep health problems. To accomplish this vision, additional questions must be answered. For example, which factors are most critical to a patient's success in digital sleep health interventions? How can we improve digital sleep health interventions to increase effectiveness and acceptability, particularly considering recent innovations in

artificial intelligence? How can we increase the uptake and availability of digital sleep health interventions worldwide? Finally, how can we ensure that digital sleep health interventions continue to evolve with changes in technology and the growing treatment evidence base? Each of these questions gives rise to exciting new challenges and solutions in the future of digital sleep health interventions.

References

- [1] Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Barry MJ, Boyd C, Chow RD, Fitterman N, Harris RP, Humphrey LL, Manaker S, McLean R, Mir TP, Schünemann HJ, Vijan S, Wilt T. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American college of physicians. *Ann Intern Med* 2016;165(2):125–33. <https://doi.org/10.7326/M15-2175>.
- [2] Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep Med Rev* 2009;13(3):205–14. <https://doi.org/10.1016/j.smrv.2008.06.001>.

- [3] van Straten A, van der Zweerde T, Kleiboer A, Cuijpers P, Morin CM, Lancee J. Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. *Sleep Med Rev* 2018;38:3–16. <https://doi.org/10.1016/j.smrv.2017.02.001>.
- [4] Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia MJ, Troxel WM, Zhou ES, Kazmi U, Heald JL, Martin JL. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med* 2021;17(2):263–98. <https://doi.org/10.5664/JCSM.8988>. <http://jcsm.aasm.org/doi/10.5664/jcsm.8988>.
- [5] Koffel E, Bramoweth AD, Ulmer CS. Increasing access to and utilization of cognitive behavioral therapy for insomnia (CBT-I): a narrative review. *J Gen Intern Med* 2018;33(6):955–62. <https://doi.org/10.1007/s11606-018-4390-1>.
- [6] Thomas A, Grandner M, Nowakowski S, Nesom G, Corbitt C, Perlis ML. Where are the behavioral sleep medicine providers and where are they needed? A geographic assessment. *Behav Sleep Med* 2016;14(6):687–98. <https://doi.org/10.1080/15402002.2016.1173551>.
- [7] Morin CM. Cognitive-behavioral approaches to the treatment of insomnia. *J Clin Psychiatr* 2004;65(16):33–40.
- [8] Ali EE, Chew L, Yap KYL. Evolution and current status of mhealth research: a systematic review. *BMJ Innov* 2016;2(1):33–40. <https://doi.org/10.1136/bmjinnov-2015-000096>.
- [9] Borrelli B, Ritterband LM. Special issue on eHealth and mHealth: challenges and future directions for assessment, treatment, and dissemination. *Health Psychol* 2015;34(Suppl. 1):1205–8. <https://doi.org/10.1037/he0000323>.
- [10] Fatehi F, Samadbeik M, Kazemi A. What is digital health? Review of definitions. *Stud Health Technol Inform* 2020;275:67–71. <https://doi.org/10.3233/SHTI200696>.
- [11] De Zambotti M, Cellini N, Goldstone A, Colrain IM, Baker FC. Wearable sleep technology in clinical and research settings. *Med Sci Sports Exerc* 2019;51(7):1538–57. <https://doi.org/10.1249/mss.0000000000001947>.
- [12] Luik AI, van der Zweerde T, van Straten A, Lancee J. Digital delivery of cognitive behavioral therapy for insomnia. *Curr Psychiatry Rep* 2019;21(7):50. <https://doi.org/10.1007/s11920-019-1041-0>.
- [13] Chan J. Exploring digital health care: eHealth, mHealth, and librarian opportunities. *J Med Libr Assoc* 2021;109(3). <https://doi.org/10.5195/jmla.2021.1180>.
- [14] Choi YK, Demiris G, Lin SY, Iribarren SJ, Landis CA, Thompson HJ, McCurry SM, Heitkemper MM, Ward TM. Smartphone applications to support sleep self-management: review and evaluation. *J Clin Sleep Med* 2018;14(10):1783–90. <https://doi.org/10.5664/jcsm.7396>.
- [15] Oh H, Rizo C, Murray E, Jadad A, Powell J, Pagliari C. What is eHealth (3): a systematic review of published definitions. *J Med Internet Res* 2005;7(1):e1. <https://doi.org/10.2196/jmir.7.1.e1>.
- [16] Schwamm LH. Telehealth: seven strategies to successfully implement disruptive technology and transform health care. *Health Aff* 2014;33(2):200–6. <https://doi.org/10.1377/hlthaff.2013.1021>.
- [17] Gehrman P, Gunter P, Findley J, Frasso R, Weljie AM, Kuna ST, Kayser MS. Randomized noninferiority trial of telehealth delivery of cognitive behavioral treatment of insomnia compared to in-person care. *J Clin Psychiatr* 2021;82(5). <https://doi.org/10.4088/JCP.20M13723>.
- [18] Hertenstein E, Trinca E, Wunderlin M, Schneider CL, Züst MA, Fehér KD, Su T, Straten Av, Berger T, Baglioni C, Johann A, Spiegelhalder K, Riemann D, Feige B, Nissen C. Cognitive behavioral therapy for insomnia in patients with mental disorders and comorbid insomnia: a systematic review and meta-analysis. *Sleep Med Rev* 2022;62:101597. <https://doi.org/10.1016/j.smrv.2022.101597>.
- [19] Okajima I, Komada Y, Inoue Y. A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. *Sleep Biol Rhythm* 2011;9(1):24–34. <https://doi.org/10.1111/j.1479-8425.2010.00481.x>.
- [20] Trauer JM, Qian MY, Doyle JS, Rajaratnam SMW, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. *Ann Intern Med* 2015;163(3):191–204. <https://doi.org/10.7326/M14-2841>.
- [21] van der Zweerde T, Bisdounis L, Kyle SD, Lancee J, van Straten A. Cognitive behavioral therapy for insomnia: a meta-analysis of long-term effects in controlled studies. *Sleep Med Rev* 2019;48:101208. <https://doi.org/10.1016/j.smrv.2019.08.002>.
- [22] Zachariae R, Lyby MS, Ritterband LM, O'Toole MS. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia - a systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev* 2016;30:1–10. <https://doi.org/10.1016/j.smrv.2015.10.004>.
- [23] Darden M, Espie CA, Carl JR, Henry AL, Kanady JC, Krystal AD, Miller CB. Cost-effectiveness of digital cognitive behavioral therapy (Sleepio) for insomnia: a Markov simulation model in the United States. *Sleep* 2021;44(4):zsaa223. <https://doi.org/10.1093/sleep/zsaa223>.
- [24] Lehtimaki S, Martic J, Wahl B, Foster KT, Schwalbe N. Evidence on digital mental health interventions for adolescents and young people: systematic overview. *JMIR Ment Health* 2021;8(4):e25847. <https://doi.org/10.2196/25847>.
- [25] Luik AI, Kyle SD, Espie CA. Digital cognitive behavioral therapy (dCBT) for insomnia: a state-of-the-science review. *Curr Sleep Med Rep* 2017;3(2):48–56. <https://doi.org/10.1007/s40675-017-0065-4>.
- [26] Erten Uyumaz B, Feijis L, Hu J. A review of digital cognitive behavioral therapy for insomnia (CBT-I apps): are they designed for engagement? *Int J Environ Res Public Health* 2021;18(6):2929. <https://doi.org/10.3390/ijerph18062929>.
- [27] Shah S, Schutte-Rodin S, Paruthi S, Chiang A, Cordoba, Gipson K, Jerkins E, Olson EJ. Digital cognitive behavioral therapy for insomnia. American Academy of Sleep Medicine; 2024.
- [28] Roy S. Digital cognitive behavioral therapy for insomnia comparison guide. *Sleep Review*; 2020.
- [29] Veteran training: path to better sleep. General Information; 2022.
- [30] Go! To sleep online program. Cleveland Clinic Wellness; 2024.
- [31] Pennicotte-Collier N. Sleep reset: The new tools of rest & recovery. Ebury Publishing; 2023.
- [32] Mobile technology and home broadband. Pew Research Center; 2021.
- [33] Espie CA, Luik AI, Cape J, Drake CL, Siriwardena AN, Ong JC, Gordon C, Bostock S, Hames P, Nisbet M, Sheaves B, Foster R, Freeman D, Costa-Font J, Emsley R, Kyle SD. Digital Cognitive Behavioural Therapy for Insomnia versus sleep hygiene education: the impact of improved sleep on functional health, quality of life and psychological well-being. *Study protocol for a randomised controlled trial. Trials* 2016;17(1):257. <https://doi.org/10.1186/s13063-016-1364-7>.

- [34] Pigeon WR. Treatment of adult insomnia with cognitive-behavioral therapy. *J Clin Psychol* 2010;66(11):1148–60. <https://doi.org/10.1002/jclp.20737>.
- [35] Edinger JD, Wohlgemuth WK, Radtke RA, Coffman CJ, Carney CE. Dose-response effects of cognitive-behavioral insomnia therapy: a randomized clinical trial. *Sleep* 2007;30(2):203–12. <https://doi.org/10.1093/sleep/30.2.203>.
- [36] Wagley JN, Rybarczyk B, Nay WT, Danish S, Lund HG. Effectiveness of abbreviated CBT for insomnia in psychiatric outpatients: sleep and depression outcomes. *J Clin Psychol* 2013;69(10):1043–55. <https://doi.org/10.1002/jclp.21927>.
- [37] Cheng SK, Dizon J. Computerised cognitive behavioural therapy for insomnia: a systematic review and meta-analysis. *Psychother Psychosom* 2012;81(4):206–16. <https://doi.org/10.1159/000335379>.
- [38] Gao Y, Ge L, Liu M, Niu M, Chen Y, Sun Y, Chen J, Yao L, Qi W, Li Z, Xu J, Li M, Hou L, Shi J, Yang K, Cai Y, Li L, Zhang J, Tian J. Comparative efficacy and acceptability of cognitive behavioral therapy delivery formats for insomnia in adults: a systematic review and network meta-analysis. *Sleep Med Rev* 2022;64:101648. <https://doi.org/10.1016/j.smrv.2022.101648>.
- [39] Simon L, Steinmetz L, Feige B, Benz F, Spiegelhalder K, Baumeister H. Comparative efficacy of onsite, digital, and other settings for cognitive behavioral therapy for insomnia: a systematic review and network meta-analysis. *Sci Rep* 2023;13(1). <https://doi.org/10.1038/s41598-023-28853-0>.
- [40] Soh HL, Ho RC, Ho CS, Tam WW. Efficacy of digital cognitive behavioural therapy for insomnia: a meta-analysis of randomised controlled trials. *Sleep Med* 2020;75:315–25. <https://doi.org/10.1016/j.sleep.2020.08.020>.
- [41] Espie CA, Kyle SD, Williams C, Ong JC, Douglas NJ, Hames P, Brown JSL. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep* 2012;35(6):769–81. <https://doi.org/10.5665/sleep.1872>.
- [42] Espie CA, Emsley R, Kyle SD, Gordon C, Drake CL, Siriwardena AN, Cape J, Ong JC, Sheaves B, Foster R, Freeman D, Costa-Font J, Marsden A, Luik AI. Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: a randomized clinical trial. *JAMA Psychiatry* 2019;01/01;76(1):21–30. <https://doi.org/10.1001/jamapsychiatry.2018.2745>.
- [43] Cheng P, Santarossa S, Kalmbach D, Sagong C, Hu K, Drake C. Patient perspectives on facilitators and barriers to equitable engagement with digital CBT-I. *Sleep Health* 2023;9(5):571–8. <https://doi.org/10.1016/j.sleh.2023.07.003>.
- [44] Baglioni C, Espie CA, Altena E, Gavriloff D, Jernelöv S, Holzinger B, Schlarb A, Riemann D. Cognitive behavioural therapy for insomnia disorder: extending the stepped care model. *J Sleep Res* 2023;32(6):e14016. <https://doi.org/10.1111/jsr.14016>.
- [45] Manber R, Carney CE. Treatment plans and interventions for insomnia: a case formulation approach. Guilford Publications; 2015.
- [46] Freeman D, Sheaves B, Goodwin GM, Yu LM, Nickless A, Harrison PJ, Emsley R, Luik AI, Foster RG, Wadekar V, Hinds C, Gumley A, Jones R, Lightman S, Jones S, Bentall R, Kinderman P, Rowse G, Brugha T, Blagrove M, Gregory AM, Fleming L, Walklet E, Glazebrook C, Davies EB, Hollis C, Haddock G, John B, Coulson M, Fowler D, Pugh K, Cape J, Moseley P, Brown G, Hughes C, Obonsawin M, Coker S, Watkins E, Schwannauer M, MacMahon K, Siriwardena AN, Espie CA. The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *Lancet Psychiatry* 2017;4(10):749–58. [https://doi.org/10.1016/S2215-0366\(17\)30328-0](https://doi.org/10.1016/S2215-0366(17)30328-0).
- [47] Xu Z, Anderson KN. Real-world evaluation of digital CBT for insomnia in the primary care setting – many should not log on to doze off. *The Cognitive Behaviour Therapist* 2019;12. <https://doi.org/10.1017/s1754470x19000242>.
- [48] Espie CA. “Stepped care”: a health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. *Sleep* 2009;32(12):1549–58. <https://doi.org/10.1093/sleep/32.12.1549>.
- [49] Forsell E, Jernelöv S, Blom K, Kraepelien M, Svanborg C, Andersson G, Lindefors N, Kaldo V. Proof of concept for an adaptive treatment strategy to prevent failures in internet-delivered CBT: a single-blind randomized clinical trial with insomnia patients. *Am J Psychiatr* 2019;176(4):315–23. <https://doi.org/10.1176/appi.ajp.2018.18060699>.
- [50] Manber R, Tully IA, Palaniappan L, Kim JP, Simpson N, Zulman DM, Goldhaber-Fiebert JD, Rangel E, Dietch JR, Rosas LG. RCT of the effectiveness of stepped-care sleep therapy in general practice: the RESTING study protocol. *Contemp Clin Trials* 2022;116:106749. <https://doi.org/10.1016/j.cct.2022.106749>.

Chapter 47

Sleep health in the primary care setting

Ivan Vargas^a, Jamie Walker^b, Mara Egeler^a, Abigail Vance^a, Julia T. Boyle^{c, d, e} and Alexandria Muench^f

^aDepartment of Psychology, University of Notre Dame, Notre Dame, IN, United States; ^bDepartment of Psychological Science, University of Arkansas, Fayetteville, AR, United States; ^cOffice of Research and Development, VA Boston Healthcare System, Boston, MA, United States; ^dNew England Geriatric Research Education and Clinical Center, VA Boston Healthcare System, Boston, MA, United States; ^eDepartment of Psychiatry, Harvard Medical School, Boston, MA, United States; ^fBehavioral Sleep Medicine Program, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, United States

Introduction

A textbook such as this one exists because the consequences of poor sleep are pervasive. Globally, between 6% and 10% of adults meet diagnostic criteria for chronic insomnia symptoms at any given time [1]. These numbers are even higher (27%–48%) when acute or subclinical insomnia is considered [2–4]. This is especially important considering that the chapters in this book provide ample evidence that insufficient and disrupted sleep affect nearly every human system (e.g., cardiometabolic, stress, and executive control) and behavior (e.g., physical activity, alcohol and substance use, and eating). The factors that impact poor sleep health do not discriminate, and affect people of all ages, vocations, cultures, and socioeconomic strata, albeit some groups are impacted more than others (e.g., racial and ethnic minorities) [5–8].

Moreover, securing adequate sleep or treating sleep disorders is often not considered a major public health priority. For example, cognitive behavioral therapy for insomnia (CBT-I), the first-line treatment for insomnia [9], is still mostly considered a “boutique” therapy that is only accessible to those with the resources or privilege to spend the time and money on treating their sleep (i.e., many insurance companies do not cover behavioral interventions for sleep) [10–12]. This is true for several reasons, but notably: (1) many western cultures, particularly the United States, minimize the importance of sleep and take a “grit” approach to sleep health (e.g., many wear their sleeplessness as a badge of honor or importance), (2) most health providers lack the training to diagnose, treat, or refer patients for sleep-related services, and (3) there are few behavioral sleep medicine providers available, most of which have long waitlists [13,14].

While there has been some progress in advancing public knowledge about the importance of good sleep health (e.g., the American Heart Association now includes healthy sleep in their list of “Life’s Essential 8”; most wearable technology includes sleep tracking) [15], there have been few efforts to identify strategies for how to meet this growing need and increase opportunities for sleep treatment. Considering that most patients express their sleep-related concerns to their primary care provider (PCP) a relevant question is, “what role does one’s primary care team have in improving sleep health?” [16–18]. The goal of this chapter is to review the relative importance of utilizing primary care to improve sleep health, especially as it relates to assessment and treatment options. We also discuss common barriers and potential future directions that will facilitate the integration of behavioral sleep health services into primary care.

Prevalence and risk

The prevalence of sleep problems among primary care patients is high, with over half of patients reporting at least one sleep complaint [18,19]. The most prevalent sleep issue is insomnia. Upwards of 50% of primary care patients report at least some insomnia symptoms and nearly 20% report chronic insomnia [20–23]. This has larger health implications considering that patients with insomnia are more likely to endorse greater functional impairment, disability, and healthcare utilization [24]. Fortunately, over half of primary care patients with sleep problems do report their symptoms to their PCP [25]. In fact, PCPs are the most consulted provider when it comes to sleep-related concerns. Specifically, of those patients who reported

insomnia to their provider, 83% consulted their PCP [16,17].

Symptoms of sleep-disordered breathing (SDB) and obstructive sleep apnea (OSA) are also highly prevalent in primary care patients. One study found that 32% of respondents (primarily from Europe and the United States) scored as at-risk for OSA, with some symptoms being reported in nearly half of the sample (i.e., 44% reported frequent snoring and breathing pauses) [26]. A related study found similar rates of OSA symptoms among primary care patients, and that these rates were higher among those patients with certain comorbid conditions (e.g., COPD) [27]. The prevalence of SDB among Veterans Affairs (VA) patients was estimated to be 22.2% in 2018 (up from 7.4% in 2012). This resulted in an increase in the number of annual sleep-related appointments from less than 250,000 in 2012 to over 720,000 in 2018 [28]. Another study found that nearly a quarter of patients attending a primary care clinic in a rural community reported OSA symptoms [29]. According to these studies, common risk factors for OSA symptoms included being a man, overweight, and older.

While the prevalence rates of other sleep disorders (e.g., narcolepsy, periodic limb movement disorder, and REM sleep behavior disorder) are appreciably lower when compared to rates of chronic insomnia and SDB, it is still the case that a growing number of patients are being diagnosed with and referred for diagnostic sleep testing [30]. This is a public health problem because sleep disorders are related to increased morbidity and impairment in overall functioning. *Among patients in the United States who meet criteria for a sleep disorder, healthcare utilization and expenditures are greater (i.e., increased healthcare office visits, emergency department visits, and prescriptions) compared to patients without a sleep disorder [31,32]*. This is especially true among patients with underlying medical conditions. For example, patients who are chronically ill (e.g., major depression, heart failure, and chronic pain) and have a comorbid sleep problem reported a reduced quality of life and greater healthcare utilization, compared with chronically ill patients without a comorbid sleep problem [33]. The prevalence and impact of sleep disturbance among primary care patients highlight the importance of incorporating sleep-focused assessment and treatment into routine care.

Assessment

To incorporate the assessment of sleep health into routine care, providers will need to be equipped with brief, yet reliable, screeners to efficiently evaluate the need for a sleep-based intervention. During the initial primary care visit, for example, screening forms, such as the Insomnia Severity Index (ISI) and the Sleep Disorders Symptom

Checklist (SDS-CL), can be used to screen for insomnia and other sleep-related concerns [34,35]. The ISI is a brief seven-item self-report instrument that measures insomnia symptom severity and is comprised of two components. The first three questions assess the severity of insomnia symptoms. The remaining four questions broadly assess the overall impact of insomnia (e.g., worries about sleep). The seven items are rated on a 5-point Likert scale (e.g., 0 = none and 4 = very severe), with scores ranging from 0 to 28. The ISI classifies insomnia into four categories: 0–7 = No clinically significant insomnia, 8–14 = subthreshold insomnia, 15–21 = clinical insomnia—moderate severity, and 22–28 = clinical insomnia—severe. Patients with a score of 15 or higher are considered good candidates for CBT-I [36], though in a primary care setting, a patient with an ISI of 8 or greater may also benefit from CBT-I (as an early intervention or prevention strategy). While using this lower ISI cutoff may ensure that patients with preclinical insomnia are not missed, some additional screening is recommended before proceeding with behavioral therapy. The SDS-CL is a self-report measure that is also considered a good tool for PCPs, as it can be used to quickly screen for six different categories of sleep disorders (i.e., insomnia, OSA, restless leg syndrome, circadian rhythm, narcolepsy, and parasomnias). The items are organized by clusters, and patients are asked to rate how frequently they experience various sleep-related symptoms. Cutoff scores for each cluster are provided to determine whether the patient positively screened for a sleep disorder and require further assessment [37].

In addition to these screeners, PCPs can utilize diagnostic interviewing to better characterize the patient's sleep problems. As Yamamoto and colleagues suggest, it is important to evaluate at least four aspects of the presenting problem: (1) the nature of the sleep problem (e.g., what symptoms is the patient experiencing?), (2) frequency and chronicity of the sleep problem (e.g., how many days per week? How long has this been going on for?), (3) sleep schedule (e.g., what time does the patient typically go to bed? Wake up?), and (4) sleep hygiene (e.g., how much morning light, exercise, caffeine is the patient getting?) [38]. These questions will allow the provider to gain a better understanding of the patient's sleep problem and proceed with a treatment recommendation. If necessary, additional assessment strategies are readily available, including daily sleep diaries (many electronic versions are now available), wearable devices (e.g., Fitbit and Garmin), and other screening measures. These assessment tools offer important information about a patient's sleep, though each come with their set of limitations (see “[Chapter 10](#)—Screening for sleep disorders” for a more detailed summary).

Treatment

There are several empirically supported treatments that behavioral sleep medicine (BSM) has to offer, including but not limited to CBT-I. CBT-I is a behavioral intervention that is highly efficacious [39,40] and has been named the first-line treatment for chronic insomnia [9,41]. It primarily targets the mechanisms believed to perpetuate chronic insomnia (i.e., decreased homeostatic sleep drive and a maladaptive conditioning pattern with one's bed) [42]. The treatment effects of CBT-I are durable [43] and have been tested in various patient populations [44–49] and settings, including primary care [50]. All this said, it is still not widely used or available. While there are several considerations and challenges to the widespread availability and use of CBT-I, two key barriers are (1) limited knowledge about sleep and its interventions, especially among health providers [51,52], and (2) that CBT-I is almost exclusively offered by BSM therapists in specialty clinics (i.e., there is an overall lack of therapists) [13].

One approach to increasing treatment access is via a primary care behavioral health (PCBH) model. Within the PCBH model, a behavioral health consultant (BHC) works alongside a patient's PCP and is available whenever behavioral health needs are identified [53]. The BHC can provide a high volume of services and is able to see a large percentage of the clinic's population. To accomplish this, visits are kept to no more than 30 min and are focused on improving specific symptoms. Follow-up visits are scheduled until the BHC and PCP begin to see improvement in sleep and daytime functioning [54]. Not all primary care clinics, however, follow a PCBH model. It is therefore important to consider how a similar model could be implemented within non-PCBH primary care clinics. One possible challenge is access to a BSM-trained clinician. Fortunately, research supports that CBT-I can be effectively delivered by providers other than psychologists and BHCs [55–57]. Efforts to train providers from adjacent disciplines (e.g., nurses and masters-level practitioners) may therefore help increase access to CBT-I more broadly.

Moreover, to allow CBT-I to fit into the high volume, quick turnaround model of primary care, other aspects of the treatment must be modified. It is important, for example, that sleep-related problems can be assessed, and a treatment plan can be determined efficiently. In the case of insomnia, the modules of CBT-I may need to be shortened to allow the material to be delivered in less than 30 min. Some aspects of the treatment may also need to be completed independently (i.e., without the clinician) as there may be a multiweek delay between sessions. Alternative forms of CBT-I have already been developed and tested. Multiple studies support that abbreviated (e.g., Brief Behavioral Therapy for insomnia [BBTI]; "Single-Shot") and digital CBT-I are effective interventions for treating

insomnia [58–60], and that these briefer modalities have been found to be useful within a primary care setting [61–63]. BBTI is often suggested to combat the paucity of CBT-I providers and was developed for patients who may not need a full eight-session protocol [64]. The "Single-Shot" and digital apps still require more testing within a primary care setting but have the potential to help meet the increasing demand for BSM services. **Please note: a standard course of CBT-I is the primary clinical recommendation for patients with chronic insomnia or insomnia disorder, patients with acute or subclinical insomnia can still benefit from these abbreviated versions [65–67].**

Another approach to increasing access to behavioral sleep interventions would be to utilize a stepped care model within primary care settings, by which patients are triaged to the appropriate level of care [68]. For example, patients who may benefit from briefer interventions may be better suited to primary care, while some patients may benefit from a higher level of care and referral to, especially when other psychiatric and/or medical comorbidities are present (e.g., when ruling out OSA) [69]. While these approaches may help increase access to behavioral sleep interventions within primary care, other barriers and challenges still require attention.

Barriers and challenges

Despite effective behavioral interventions for sleep and insomnia, the assessment and behavioral treatment of sleep remains elusive, especially within primary care settings. This is likely because sleep interventions are (1) mostly unknown to general practitioners, (2) unavailable to those who do seek them out, (3) not a priority compared with other psychological and medical conditions, and (4) too burdensome and/or expensive for most individuals.

Despite the prevalence of sleep problems in primary care, most general practitioners do not feel adequately equipped to treat or refer patients for insomnia treatment. One study, for example, surveyed a group of primary care providers within the Veterans Affairs (VA) Health Care System and found that the most commonly used treatment methods included standalone sleep hygiene (i.e., a suboptimal treatment) or pharmacotherapy [70]. This is consistent with prior reports suggesting that psychoactive medications were the most common treatment option for insomnia [71–73]. Part of the reason for this is that nearly 60% of providers had not heard of CBT-I or did not understand how it works. Nearly half of those providers also did not know where to refer patients for CBT-I or whether it was available in their clinic [70]. The results from this study are surprising, however, considering that the VA is responsible for the only large-scale efforts to incorporate CBT-I into primary care, including a national roll-out of

provider training for CBT-I [74] and the development of web-based programs for augmenting CBT-I (i.e., CBT-I Coach, Insomnia Coach, and Path to Better Sleep) [75–77]. These percentages are likely higher among non-VA providers. One study that aimed to highlight the referral practices and attitudes toward insomnia treatments found that physicians saw an average of 15.2 patients with insomnia complaints per month. However, only 1.5 of those patients were referred for CBT-I. Another study found that most BSM referrals within a large academic medical center came from Sleep Medicine (74% of referrals) [12]. That is, very few physicians working outside of sleep make referrals to BSM. One reason may be that only 9.2% of physicians believed that CBT-I was the most effective treatment approach [78]. When different medical providers were asked about their insomnia treatment practices, practitioners were more likely to recommend pharmacotherapy, sleep hygiene, and relaxation therapy [79]. Many believed that sleep hygiene is an effective stand-alone treatment despite little empirical support for its efficacy, and in some cases, evidence that it may lead to worse patient outcomes [80,81]. When PCPs were asked about their treatment methods for insomnia, many suggested that before they would consider using CBT-I, they would want to see positive evidence that it is beneficial to patients [82]. This suggests that many practitioners have not been informed about the utility of CBT-I and may hold inaccurate information about the treatment (e.g., that CBT-I is equivalent to sleep hygiene education) [83].

Understandably, if PCPs are unfamiliar with a particular treatment, it is not something they will recommend. This then leads one to ask, “what sleep education or training do PCPs receive?” A survey of medical schools found that, on average, only 2.5 h were spent on sleep education, with 27% of programs providing no education at all [84]. Along the same lines, residency programs spend an average of 4.7 h per year discussing sleep. While programs such as neurology, pulmonology, and critical care medicine retain 2–3 faculty members who specialize in sleep medicine, others like family medicine, psychiatry, and otolaryngology typically have none [85]. When sleep education is provided, it is usually in the form of lectures, journal clubs, or grand round speakers, and not full-semester courses. The result is that physicians report limited knowledge about the assessment and treatment of sleep disorders [86,87].

Even when PCPs refer patients to BSM, they may still be unable to access treatment as it is often too expensive. While there is no set cost for BSM services, individuals may expect to spend anywhere between \$200 and \$2500 depending on the clinician, location, and number of sessions. Many insurance companies will cover cognitive behavioral therapy; however, they do not uniformly reimburse for BSM [10]. Access is even more limited for those

who live in rural settings as insurances like Medicare will only reimburse a limited number of telehealth sessions. It can also be costly for sleep clinics as BSM services are typically billed as mental health and many sleep disorders centers do not have the credentials or administrative infrastructure to provide behavioral therapy. One suggestion is to broaden the provider base to include master’s level practitioners and nurses. Nurse practitioners and physician’s associates, for example, are well-positioned to offer sleep health services because of their training in medical assessments, taking a biopsychosocial approach to conceptualization, and primary care skills. Furthermore, their ability to bill under a medical rather than mental health coverage code means that they could be easily integrated into various primary care settings [10].

Future directions

There is room for improvement in the treatment of sleep health in primary care, specifically in the access to and implementation of CBT-I. Increasing the availability of BSM services in primary care is important because it can help relieve the burden and functional impairment caused by sleep disorders and other sleep-related problems. In addition, the sleep disorders treatment in primary care can function as a form of primary and secondary prevention for other mental and physical health disorders, given that sleep disturbance, especially insomnia, is a known risk factor for several conditions, such as depression and suicidality [88–91]. Because of the practical limitations associated with delivering clinical services in a primary care setting, abbreviated interventions may prove to be useful, especially for patients with acute (as opposed to chronic) sleep problems. Primary care and PCBH settings are an ideal opportunity to offer just-in-time interventions. These interventions typically include only a limited number of follow-ups that focus on improving patient day-to-day functioning related to a wide variety of mental and physical health concerns. Improving sleep in this setting is both possible and necessary.

References

- [1] Morin CM, Jarrin DC. Epidemiology of insomnia: prevalence, course, risk factors, and public health burden. *Sleep Med Clin* 2022;17(2):173–91.
- [2] Ellis J, Perlis ML, Neale LF, Espie CA, Bastien CH. The natural history of insomnia: focus on prevalence and incidence of acute insomnia. *J Psychiatr Res* 2012;46(10):1278–85. <https://doi.org/10.1016/j.jpsychires.2012.07.001>.
- [3] Perlis ML, Vargas I, Ellis JG, Grandner MA, Morales KH, Gencarelli A, et al. The natural history of Insomnia: the incidence of acute insomnia and subsequent progression to chronic insomnia or recovery in good sleeper subjects. *Sleep* 2020;43(6):1–8.

- [4] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6(2):97–111. <http://www.sciencedirect.com/science/article/pii/S1087079202901863>.
- [5] Kalmbach DA, Pillai V, Arnedt JT, Drake CL. DSM-5 insomnia and short sleep: comorbidity landscape and racial disparities. *Sleep* 2016;39(12):2101–11. <https://academic.oup.com/sleep/article/39/12/2101/2706340>.
- [6] Pigeon WR, Heffner K, Duberstein P, Fiscella K, Moynihan J, Chapman BP. Elevated sleep disturbance among blacks in an urban family medicine practice. *J Am Board Fam Med* 2011;24(2):161–8. <https://www.jabfm.org/content/24/2/161>.
- [7] Grandner MA, Ruiter Petrov ME, Rattanaumpawan P, Jackson N, Platt A, Patel NP. Sleep symptoms, race/ethnicity, and socioeconomic position. *J Clin Sleep Med* 2013;9(9):897–905. <https://jasm.aasm.org/doi/abs/10.5664/jcsm.2990>.
- [8] Grandner MA, Williams NJ, Knutson KL, Roberts D, Jean-Louis G. Sleep disparity, race/ethnicity, and socioeconomic position. *Sleep Med* 2016;18:7–18. <https://doi.org/10.1016/j.sleep.2015.01.020>.
- [9] Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Barry MJ, et al. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American college of physicians. *Ann Intern Med* 2016;165(2):125–33.
- [10] Perlis ML, Smith MT. How can we make CBT-I and other BSM services widely available? *J Clin Sleep Med* 2008;4(1):11–3.
- [11] Manber R, Simpson N, Gumpert NB. Perspectives on increasing the impact and reach of CBT-I. *Sleep* 2023;46(12):1–7. <https://doi.org/10.1093/sleep/zsad168>.
- [12] Chernyak Y, Ofner S, Williams MK, Bolarinwa C, Manchanda S, Otte JL. Patient accessibility and utilization of behavioral sleep medicine referrals in an academic center. *J Clin Sleep Med* 2024. <https://jasm.aasm.org/doi/10.5664/jcsm.11252>.
- [13] Thomas A, Grandner M, Nowakowski S, Nesom G, Corbitt C, Perlis ML. Where are the behavioral sleep medicine providers and where are they needed? A geographic assessment. *Behav Sleep Med* 2016;14(6):687–98. <https://www.tandfonline.com/doi/abs/10.1080/15402002.2016.1173551>.
- [14] Golden ME, Cosottile M, Meadows T, Parikh MR, O'Dell SM. Primary care providers' practices regarding patient sleep: impact of integrated behavioral health. *Fam Syst Health* 2023;41(2):192.
- [15] Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, et al. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation* 2022;146(5):E18–43. <https://www.ahajournals.org/doi/10.1161/CIR.0000000000001078>.
- [16] Morin CM, LeBlanc M, Daley M, Gregoire JP, Mérette C, Merette C, et al. Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Med* 2006;7(2):123–30. <http://linkinghub.elsevier.com/retrieve/pii/S1389945705001954>.
- [17] Torrens DI, Argüelles-Vázquez R, Lorente-Montalvo P, Torrens-Darder M, del M, Esteva M. Primary care is the frontline for help-seeking insomnia patients. *Eur J Gen Pract* 2021;27(1):286–93. <https://www.tandfonline.com/doi/abs/10.1080/13814788.2021.1960308>.
- [18] Alattar M, Harrington JJ, Mitchell CM, Sloane P. Sleep problems in primary care: a North Carolina family practice research network (NC-FP-RN) study. *J Am Board Fam Med* 2007;20(4):365–74. <https://www.jabfm.org/content/20/4/365>.
- [19] Vinson DC, Manning BK, Galliher JM, Dickinson LM, Pace WD, Turner BJ, et al. Alcohol and sleep problems in primary care patients: a report from the AAFP national research network. *Ann Fam Med* 2010;8(6):484–92. <https://www.annfammed.org/content/8/6/484>.
- [20] Shochat T, Umphress J, Israel A, Ancoli-Israel S. Insomnia in primary care patients. *Sleep* 1999;22(Suppl. 2):S359–65.
- [21] Maire M, Linder S, Dvorák C, Merlo C, Essig S, Tal K, et al. Prevalence and management of chronic insomnia in Swiss primary care: cross-sectional data from the "Sentinella" practice-based research network. *J Sleep Res* 2020;29(5).
- [22] Arroll B, Fernando A, Falloon K, Goodyear-Smith F, Samaranayake C, Warman G. Prevalence of causes of insomnia in primary care: a cross-sectional study. *Br J Gen Pract* 2012;62(595).
- [23] Simon GE, Vonkoff M. Prevalence, burden, and treatment of insomnia in primary care. *Am J Psychiatr* 1997;154(10):1417–23. <https://pubmed.ncbi.nlm.nih.gov/9326825/>.
- [24] Wickwire EM, Tom SE, Scharf SM, Vadlamani A, Bulatao IG, Albrecht JS. Untreated insomnia increases all-cause health care utilization and costs among Medicare beneficiaries. *Sleep* 2019;42(4). <https://pubmed.ncbi.nlm.nih.gov/30649500/>.
- [25] Aikens JE, Rouse ME. Help-seeking for insomnia among adult patients in primary care. *J Am Board Fam Pract* 2005;18(4):257–61.
- [26] Netzer NC, Hoegel JJ, Loube D, Netzer CM, Hay B, Alvarez-Sala R, et al. Prevalence of symptoms and risk of sleep apnea in primary care. *Chest* 2003;124(4):1406–14.
- [27] Karachaliou F, Kostikas K, Pastaka C, Bagiatis V, Gourgoulianis KI. Prevalence of sleep-related symptoms in a primary care population—their relation to asthma and COPD. *Prim Care Respir J* 2007;16(4):222–8. <https://www.nature.com/articles/pcrj200745>.
- [28] Folmer RL, Smith CJ, Boudreau EA, Hickok AW, Totten AM, Kaul B, et al. Prevalence and management of sleep disorders in the Veterans Health Administration. *Sleep Med Rev* 2020;54:101358.
- [29] Kushida CA, Nichols DA, Simon RD, Young T, Grauke JH, Britzmann JB, et al. Symptom-based prevalence of sleep disorders in an adult primary care population. *Sleep Breath* 2000;4(1):11–5. <https://link.springer.com/article/10.1007/s11325-000-0011-3>.
- [30] Acquavella J, Mehra R, Bron M, Suomi JMH, Hess GP. Prevalence of narcolepsy and other sleep disorders and frequency of diagnostic tests from 2013–2016 in insured patients actively seeking care. *J Clin Sleep Med* 2020;16(8):1255–63. <https://jasm.aasm.org/doi/10.5664/jcsm.8482>.
- [31] Huyett P, Bhattacharyya N. Incremental health care utilization and expenditures for sleep disorders in the United States. *J Clin Sleep Med* 2021;17(10):1981–6. <https://jasm.aasm.org/doi/10.5664/jcsm.9392>.
- [32] Novak M, Mucsi I, Shapiro CM, Rethelyi J, Kopp MS. Increased utilization of health services by insomniacs—an epidemiological perspective. *J Psychosom Res* 2004;56(5):527–36.
- [33] Manocchia M, Keller S, Ware JE. Sleep problems, health-related quality of life, work functioning and health care utilization among the chronically ill. *Qual Life Res* 2001;10(4):331–45. <https://link.springer.com/article/10.1023/A:1012299519637>.

- [34] Morin CM. Insomnia: psychological assessment and management. New York: Guilford Press; 1993. <http://www.guilford.com/books/Insomnia/Charles-Morin/9781572301207/reviews>.
- [35] Klingman KJ, Jungquist CR, Perlis ML. Questionnaires that screen for multiple sleep disorders. *Sleep Med Rev* 2017;32:37–44. <https://doi.org/10.1016/j.smrv.2016.02.004>.
- [36] Gagnon C, Bélanger L, Ivers H, Morin CM. Validation of the insomnia severity Index in primary care. *J Am Board Fam Med* 2013;26(6):701–10. <https://www.jabfm.org/content/26/6/701>.
- [37] Klingman K, Jungquist C, Perlis M, Klingman K J, Klingman C R, Perlis M L, et al. Introducing the sleep disorders symptom Checklist-25: a primary care friendly and comprehensive screener for sleep disorders. *Sleep Med Res* 2017;8(1):17–25. <http://www.sleepmedres.org/journal/view.php?doi=10.17241/smri.2017.00010>.
- [38] Yamamoto M, Lim CT, Huang H, Spottswood M, Huang H. Insomnia in primary care: considerations for screening, assessment, and management. *J Med Access* 2023;7. <https://journals.sagepub.com/doi/10.1177/27550834231156727>.
- [39] Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatr* 1994;151(8):1172–80.
- [40] Mitchell MD, Gehrmann P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Fam Pract* 2012;13.
- [41] Schutte-Rodin SL, Broch L, Buysee D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008;4(5):487–504. <https://jcsm.aasm.org/doi/10.5664/jcsm.27286>.
- [42] Bootzin RR. Stimulus control treatment for insomnia. The American Psychological Association: A Historical Perspective 1972;7:395–6.
- [43] Morin CM, Vallières A, Guay B, Ivers H, Savard J, Merette C, et al. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. *JAMA* 2009;301(19):2005–15.
- [44] Garland SN, Johnson JA, Savard J, Gehrmann P, Perlis M, Carlson L, et al. Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in cancer patients. *Neuropsychiatric Dis Treat* 2014;10:1113–23. <https://www.tandfonline.com/action/journalInformation?journalCode=ndnt20>.
- [45] Cunningham JEA, Shapiro CM. Cognitive Behavioural Therapy for Insomnia (CBT-I) to treat depression: a systematic review. *J Psychosom Res* 2018;106:1–12.
- [46] Selvanathan J, Pham C, Nagappa M, Peng PWH, Englesakis M, Espie CA, et al. Cognitive behavioral therapy for insomnia in patients with chronic pain – a systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev* 2021;60:101460.
- [47] Huang K, Li S, He R, Zhong T, Yang H, Chen L, et al. Efficacy of cognitive behavioral therapy for insomnia (CBT-I) in older adults with insomnia: a systematic review and meta-analysis. *Australas Psychiatry* 2022;30(5):592–7. <https://journals.sagepub.com/doi/10.1177/10398562221118516>.
- [48] Cheng P, Luik AI, Fellman-Couture C, Peterson E, Joseph CLM, Tallent G, et al. Efficacy of digital CBT for insomnia to reduce depression across demographic groups: a randomized trial. *Psychol Med* 2019;49(3):491–500. <https://www.cambridge.org/core/journals/psychological-medicine/article/abs/efficacy-of-digital-cbt-for-insomnia-to-reduce-depression-across-demographic-groups-a-randomized-trial/FF45FDFB5774AE60E1E4D3E1252676A4>.
- [49] Palermo TM, Beals-Erickson S, Bromberg M, Law E, Chen M. A single arm pilot trial of brief cognitive behavioral therapy for insomnia in adolescents with physical and psychiatric comorbidities. *J Clin Sleep Med* 2017;13(3):401–10. <https://jcsm.aasm.org/doi/10.5664/jcsm.6490>.
- [50] Davidson JR, Dickson C, Han H. Cognitive behavioural treatment for insomnia in primary care: a systematic review of sleep outcomes. *Br J Gen Pract* 2019;69(686):E657–64.
- [51] Grandner MA, Chakravorty S. Insomnia in primary care: misreported, mishandled, and just plain missed. *J Clin Sleep Med* 2017;13(8):937–9.
- [52] Koffel E, Bramoweth AD, Ulmer CS. Increasing access to and utilization of cognitive behavioral therapy for insomnia (CBT-I): a narrative review. *J Gen Intern Med* 2018;33(6):955–62.
- [53] Robinson PJ, Reiter JT. Behavioral consultation and primary care: the “why now?” and “how?”. In: Behavioral consultation and primary care; 2016. p. 3–22. https://link.springer.com/chapter/10.1007/978-3-319-13954-8_1.
- [54] Reiter JT, Dobmeyer AC, Hunter CL. The primary care behavioral health (PCBH) model: an overview and operational definition. *J Clin Psychol Med Settings* 2018;25(2):109–26. <https://link.springer.com/article/10.1007/s10880-017-9531-x>.
- [55] Armstrong S, Pattinson J, Siriwardena AN, Kyle SD, Bower P, Yu LM, et al. Nurse-delivered sleep restriction therapy in primary care for adults with insomnia disorder: a mixed-methods process evaluation. *Br J Gen Pract* 2024;74(738):e34–40. <https://bjgp.org/content/74/738/e34>.
- [56] van Straten A, van Trigt S, Lancee J. How to boost implementation for insomnia treatment in primary care? *Lancet* 2023;402(10406):940–1.
- [57] Espie CA, MacMahon KMA, Kelly HL, Broomfield NM, Douglas NJ, Engleman HM, et al. Randomized clinical effectiveness trial of nurse-administered small-group cognitive behavior therapy for persistent insomnia in general practice. *Sleep* 2007;30(5):574–84. <https://doi.org/10.1093/sleep/30.5.574>.
- [58] Troxel WM, Germain A, Buysse DJ. Clinical management of insomnia with brief behavioral treatment (BBTI). *Behav Sleep Med* 2012;10(4):266–79. <https://www.tandfonline.com/doi/abs/10.1080/15402002.2011.607200>.
- [59] Hasan F, Tu YK, Yang CM, James Gordon C, Wu D, Lee HC, et al. Comparative efficacy of digital cognitive behavioral therapy for insomnia: a systematic review and network meta-analysis. *Sleep Med Rev* 2022;61:101567. <https://doi.org/10.1016/j.smrv.2021.101567>.
- [60] Linardon J, Anderson C, McClure Z, Liu C, Messer M. The effectiveness of smartphone app-based interventions for insomnia and sleep disturbances: a meta-analysis of randomized controlled trials. *Sleep Med* 2024;122:237–44.
- [61] Edinger JD, Sampson WS. A primary care “friendly” cognitive behavioral insomnia therapy. *Sleep* 2003;26(2):177–82. <https://pubmed.ncbi.nlm.nih.gov/12683477/>.
- [62] Bramoweth AD, Lederer LG, Youk AO, Germain A, Chinman MJ. Brief behavioral treatment for insomnia vs. Cognitive behavioral therapy for insomnia: results of a randomized noninferiority clinical trial among Veterans. *Behav Ther* 2020;51(4):535–47. <https://pubmed.ncbi.nlm.nih.gov/32586428/>.

- [63] Buysse DJ, Germain A, Moul DE, Franzen PL, Brar LK, Fletcher ME, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med* 2011;171(10):887–95. <https://pubmed.ncbi.nlm.nih.gov/21263078/>.
- [64] Okun ML, Glidewell RN. Brief behavioral interventions for insomnia. *Curr Sleep Med Rep* 2024;1–8. <https://link.springer.com/article/10.1007/s40675-024-00309-5>.
- [65] Kwon M, Wang J, Wilding G, Dickerson SS, Dean GE. Brief behavioral treatment for insomnia: a meta-analysis. *Behav Sleep Med* 2021. <https://www.tandfonline.com/doi/abs/10.1080/15402002.2021.1982715>.
- [66] Ellis JG, Cushing T, Germain A. Treating acute insomnia: a randomized controlled trial of a “single-shot” of cognitive behavioral therapy for insomnia. *Sleep* 2015. <https://academic.oup.com/sleep/article-lookup/doi/10.5665/sleep.4752>.
- [67] Boullin P, Ellwood C, Ellis JG. Group vs. Individual treatment for acute insomnia: a pilot study evaluating a “One-Shot” treatment strategy. *Brain Sci* 2017;7(1):1–10. <http://www.ncbi.nlm.nih.gov/pubmed/28025539>.
- [68] Espie CA. “Stepped care”: a health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. *Sleep* 2009;32(12):1549–58.
- [69] Baglioni C, Espie CA, Altena E, Gavriloff D, Jernelöv S, Holzinger B, et al. Cognitive behavioural therapy for insomnia disorder: extending the stepped care model. *J Sleep Res* 2023;32(6). <https://pubmed.ncbi.nlm.nih.gov/37584390/>.
- [70] Ulmer CS, Bosworth HB, Beckham JC, Germain A, Jeffreys AS, Edelman D, et al. Veterans affairs primary care provider perceptions of insomnia Treatment. *J Clin Sleep Med* 2017;13(8):991–9.
- [71] Falloon K, Arroll B, Elley CR, Fernando A. The assessment and management of insomnia in primary care. *BMJ* 2011;342.
- [72] Moloney ME, Ciciurkaitė G, Brown RL. The medicalization of sleeplessness: results of U.S. office visit outcomes, 2008–2015. *SSM Popul Health* 2019;8:100388.
- [73] Germain A, Wolfson M, Klenczar B, Brock MS, Hearn H, O'Reilly B, et al. Survey of resources in behavioral sleep medicine across the department of defense, defense health agency. *Mil Med* 2024;189(5–6):e1089–97. <https://doi.org/10.1093/milmed/usad409>.
- [74] Manber R, Simpson N. Dissemination of CBT for insomnia. *Curr Sleep Med Rep* 2016;2(3):136–41. <https://link.springer.com/article/10.1007/s40675-016-0048-x>.
- [75] Kuhn E, Weiss BJ, Taylor KL, Hoffman JE, Ramsey KM, Manber R, et al. CBT-I coach: a description and clinician perceptions of a mobile app for cognitive behavioral therapy for insomnia. *J Clin Sleep Med* 2016;12(4):597–606.
- [76] Kuhn E, Miller KE, Puran D, Wielgosz J, YorkWilliams SL, Owen JE, et al. A pilot randomized controlled trial of the insomnia coach mobile app to assess its feasibility, acceptability, and potential efficacy. *Behav Ther* 2022;53(3):440–57.
- [77] Ulmer CS, Farrell-Carnahan L, Hughes JM, Manber R, Legget MK, Tatum J, et al. Improve your sleep: a self-guided approach for veterans with insomnia (self-help workbook). 2018.
- [78] Conroy D, Ebbin MR. Referral practices for cognitive behavioral therapy for insomnia: a survey study. *Behav Neurol* 2015. <https://www.hindawi.com/journals/bn/2015/819402/>.
- [79] Moss T, Lachowski A, Carney CE. What all treatment providers should know about sleep hygiene recommendations. *Behav Ther* 2013. <https://psycnet.apa.org/record/2013-12511-001>.
- [80] Chung KF, Lee CT, Yeung WF, Chan MS, Chung EWY, Lin WL. Sleep hygiene education as a treatment of insomnia: a systematic review and meta-analysis. *Fam Pract* 2018;35(4):365–75. <https://doi.org/10.1093/fampra/cmx122>.
- [81] Morgenthaler T, Kramer M, Alessi C, Friedman L, Boehlecke B, Brown T, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American academy of sleep medicine report. *Sleep* 2006;29(11):1415–9. <https://doi.org/10.1093/sleep/29.11.1415>.
- [82] Davy Z, Middlemass J, Siriwardena AN. Patients' and clinicians' experiences and perceptions of the primary care management of insomnia: qualitative study. *Health Expect* 2015;18(5):1371–83. <https://onlinelibrary.wiley.com/doi/full/10.1111/hex.12119>.
- [83] Koffel E, Amundson E, Polusny G, Wisdom JP. “You're missing out on something great”: patient and provider perspectives on increasing the use of cognitive behavioral therapy for insomnia. *Behav Sleep Med* 2020;18(3):358–71.
- [84] Mindell J, Bartle A, Wahab NA, medicine YAS. Sleep education in medical school curriculum: a glimpse across countries. Elsevier; 2011. <https://www.sciencedirect.com/science/article/pii/S1389945711002218>.
- [85] Sullivan SS, Cao MT. Sleep medicine exposure offered by United States residency training programs. *J Clin Sleep Med* 2021;17(4):825–32. <https://jcsmaasm.org/doi/abs/10.5664/jcsm.9062>.
- [86] Khawaja IS, Dickmann PJ, Hurwitz TD, Thuras PD, Feinstein RE, Douglass AB, et al. The state of sleep medicine education in North American psychiatry residency training programs in 2013: chief resident's perspective. *Prim Care Companion CNS Disord* 2017;19(4). <https://www.psychiatrist.com/pcc/assessment/education/sleep-medicine-education-in-north-american-psychiatry-residency-training>.
- [87] Pediatrics JO. The practice of pediatric sleep medicine: results of a community survey. 2001. <https://publications.aap.org/pediatrics/article-abstract/108/3/e51/66662>.
- [88] Simmons Z, Burlingame G, Korbanke J, Eastman K, Thomas D, Christensen J, et al. Insomnia symptom severity is associated with increased suicidality and death by suicide in a sample of patients with psychiatric disorders. *Sleep* 2021;44(7). <https://doi.org/10.1093/sleep/zsab032>.
- [89] Tubbs AS, Fernandez FX, Grandner MA, Perlis ML, Klerman EB. The mind after midnight: nocturnal wakefulness, behavioral dysregulation, and psychopathology. *Frontiers in Network Physiology* 2022;1:830338. www.frontiersin.org.
- [90] Tubbs AS, Gallagher R, Perlis ML, Hale L, Branas C, Barrett M, et al. Relationship between insomnia and depression in a community sample depends on habitual sleep duration. *Sleep Biol Rhythm* 2020;18(2):143.
- [91] Vargas I, Perlis ML. Insomnia and depression: clinical associations and possible mechanistic links. In: Current opinion in psychology, 34. Elsevier B.V.; 2020. p. 95–9.

This page intentionally left blank

Chapter 48

Sleep health as an issue of public safety

Alexander P. Wolkow^a, Laura K. Barger^{b, c} and Matthew D. Weaver^{b, c}

^aSchool of Psychological Sciences, Monash University, Clayton, VIC, Australia; ^bDivision of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA, United States; ^cDivision of Sleep Medicine, Harvard Medical School, Boston, MA, United States

Introduction

The public safety net is comprised of three principal components: Police (law enforcement), Fire (rescue services), and Emergency Medical Services (medical services). Highly reliable 24-7 operations are critical to protect the health and safety of the public and effectively assist them in their time of need. The occupation is uniquely challenging. The work environment is uncontrolled, high-stress, and unpredictable. Rapid, risk-averse decision-making is critical. Tasks are often physically demanding. Public safety professionals also must operate motor vehicles in an unconventional manner, using lights and sirens on crowded roadways.

As is common in many occupations, work schedules are often based on tradition rather than sleep or circadian principles. Rapid backward rotation of shifts persists [1]. Police officers often work extended weekly work hours which are compounded by court appearances and special details outside of their scheduled work shifts. Extended-duration shifts (≥ 24 h) are the most commonly scheduled shift among firefighters, and 12 or 24 h shifts are most common in the Emergency Medical Services (EMS) setting [2–5]. Seniority drives competition for planned overtime shifts, and unplanned overtime is a regular occurrence. Opportunities for rest are largely unpredictable. Secondary employment is also routine [5,6]. Furthermore, the prevalence of sleep disorders in this population approaches 40% [7,8].

One can imagine the myriad of ways that sleep health can impact this occupational group. Sleep disorders drive up the risk of crashes, injuries, and chronic health conditions [7,8]. Emerging research is beginning to yield even more insights about the pervasive impact of fatigue. Police officers who slept less prior to a test were more likely to exhibit implicit racial bias by associating Black Americans with weapons, and were more likely to make errors in

shoot/do not shoot situations [9,10]. Fatigue impairs balance and increases gait variability, which are critical to prevent firefighters from falling in active fire situations [11]. EMS providers who are fatigued are more likely to report occupational injuries, medical errors, and actions which compromise the safety of themselves and their patients [3]. Less than optimal health, safety, and performance of police officers, firefighters and EMS providers may negatively impact public safety through crashes, errors, and other mishandling of situations, ultimately compromising the integrity of the public safety net.

The purpose of this chapter is to outline our current understanding of sleep health in the public safety setting. We discuss work hours and scheduling characteristics of public safety personnel, the consequences of work hours on sleep, including the physiological sleep factors that determine alertness and performance, sleep disorders in public safety personnel, and finally, the potential of fatigue risk management programs to improve the health and safety of these first responders.

Demographics

Organizational structure

Police are most often employed by the local or city government, and their coverage area is arranged by precincts. It is common practice for police to actively patrol their service area throughout their work shifts. Fire and EMS services are less consistent in their organization and structure. Fire departments service a clearly defined geographic area. They tend to maintain operations at the fire station and respond to calls as they are received. Fire personnel are often volunteers, and as such, would respond to the station from their current location in the event of a call, staff the emergency response vehicle, and then respond to the scene of the emergency. Approximately

40% of fire departments also employ cross-trained EMS personnel [12]. These departments deliver both rescue and medical services. However in many communities, EMS and fire are separate entities. EMS agencies may be government, private, or hospital-based, and can include individuals with varied training and responsibilities. The most common roles include emergency medical technicians (EMT) and paramedics, with emergency medical responders, advanced EMTs, and prehospital nurses operating in some locations. EMS agencies are increasingly adopting system status management practices, which involves positioning ambulances throughout the service area to minimize emergency response times and/or preemptively allocate resources to areas of expected need [13]. These industry practices are relevant when considering the opportunity for and applicability of various fatigue risk management strategies.

Individuals

There are approximately 650,000 police officers, 1.2 million firefighters, and 825,000 EMS providers in the United States (Table 48.1). Approximately 90% of police officers are male, as are 95% of firefighters, while 1 in 4 EMS providers are female [14]. Racial and ethnic minorities are often underrepresented in these occupational groups [14]. EMS professionals tend to be younger than police or firefighters. The vast majority of public safety personnel are overweight or obese [15,16].

Many firefighters serve as volunteers (70%), and scheduling practices often provide 48 or 96 h off between shifts. Likewise, 70% of EMS providers are either volunteers or part-time employees. Consequently, it is common for public safety professionals to work more than one job.

Approximately 40% of EMS providers work for more than one EMS agency [17], logging an average of 25 h per month at the second job [18], while one in three firefighters holds multiple jobs [19].

Work hours and scheduling characteristics

Public safety professionals must be available for duty 24-7. This requires employment outside of regular daylight hours to fulfill workforce needs. Although federal regulations strictly limit the number of consecutive hours that truck drivers can drive and that pilots can fly, there are no standardized regulations which limit work hours among public safety personnel.

The optimal timing and duration of work hours is an interesting and multifaceted problem. Shorter shifts may permit employees to maintain high levels of vigilance throughout the duration of the shift and thus may be safer. In industry, short shifts have been associated with greater individual productivity and job satisfaction [20]. However, these schedules require more workers to be hired and trained to fulfill workforce needs. Longer shifts in general allow for a smaller overall workforce, thus lowering overhead benefit costs [21]. However, longer shifts may introduce a greater risk of fatigue-related performance deficiency [22]. Extended shifts likely require more preparation on the part of the worker to arrive capable of working for an extended period. Extended shifts also require a comparatively longer duration of downtime after the shift for recovery purposes, particularly if the shift involves nighttime work [23].

TABLE 48.1 Demographic characteristics of public safety personnel.

	Police	Fire	EMS
Workforce size ^a	657,690	1,160,450	826,000
Age (mean years)	39	38	35
Gender			
Male	88%	95%	72%
Female	12%	5%	28%
Racial or ethnic minority	33%	21%	22%
Overweight or obese	80%	80%	71%
Most common shift	8 h	24 h	12 or 24 h
2016 nonfatal occupational injury rate (per 100 FTE) ^a	10.2	9.5	7.8

^aEMS, Emergency medical services; FTE, full-time equivalent.
U.S. Bureau of Labor Statistics, U.S. Department of Labor.

Shift duration

Police tend to work shifts of less than 12 h duration [24], while extended-duration (≥ 24 h) shifts are often utilized by fire and EMS services. The most commonly scheduled shift duration is 24 or 48 h in US fire departments [2]. Particularly in the western US, the 48/96 schedule has become increasingly popular [25]. Firefighters working these very long shifts often commute extended distances. The most common shift lengths in EMS are 12 or 24 h in duration. In a national study of 511 EMS workers, approximately 50% (48.5%) of respondents reported working 24-hour shifts, while 38.4% reported working 12-hour shifts [3]. It is commonly believed that rural agencies are more likely to schedule shifts of 24 h or longer duration. An increased prevalence of extended shifts in rural areas may be necessary to provide 24-hour coverage with smaller workforces.

Weekly work hours

There are few reliable estimates of work hours among police. There are multiple examples of police officers averaging more than 80 weekly work hours over the course of a year [26]. Many of these hours are accumulated through overtime. We found police officers in North America averaged 21 h per month of overtime, which comprised both mandatory (8 h per month) and voluntary overtime (13 h per month) [27]. Similarly, Vila et al. found that police in large, urban departments average between 15 and 40 h of overtime per month, though some officers exceeded 80 h of overtime monthly [28]. In our survey of nearly 7000 firefighters employed by 66 departments nationally, respondents reported working an average of 64 h per week after accounting for overtime and secondary employment [7].

The Longitudinal EMT Attribute Demographic Study (LEADS) is a 10-year, longitudinal survey of nationally registered EMS providers. The LEADS survey found that EMS personnel were available for response approximately 50 h per week [6]. The high prevalence of part-time work may lead to a subset of providers covering the majority of shifts. One national effort found that 1/3 of all shifts are worked by EMS providers who have already worked at least 48 h in the 7 days preceding the shift, and 10% of shifts are staffed by providers who have already exceeded 60 h of work in that week [29]. Recovery between shifts, measured by the Occupational Fatigue Exhaustion Recovery (OFER) scale, is highest for EMS providers who work extended-duration shifts, and lowest for providers who work 12 h shifts, likely as a result of schedule compression [30].

The association between work schedules and health and safety outcomes

The bulk of evidence to inform the association between work schedules and health and safety outcomes among police was generated through the Buffalo Cardio-Metabolic Occupational Police Stress (BCOPS) study. BCOPS was a cross-sectional study of Buffalo police which enrolled 65% of the urban police force between 2004 and 2009. BCOPS found that night shift work was associated with poor sleep quality [31], as well as extended absence for sick leave [32] and injury risk, conferring a 72% increased risk of injury [33]. When combined with short sleep duration or overtime hours, the officers who worked night shifts were also more likely to meet criteria for metabolic syndrome [34]. Furthermore, in our study of more than 3000 police officers from across North America, short sleep (<6 h), mandatory overtime, irregular work schedules, and night shifts were all associated with an increased risk of burnout [27].

Similarly, temporal patterns of work-related injury among firefighters are closely aligned with the circadian rhythm of alertness, with the highest risk of injury for calls occurring at 0200 h [35]. The work schedules of firefighters have also been associated with health outcomes, though not in a consistent manner. Firefighters who worked 48 h shifts were significantly more likely to have excessive daytime sleepiness relative to firefighters on 24-hour or 10/14-hour schedules, and those with excessive daytime sleepiness were twice as likely to report depressive symptoms [36], as well as burnout-emotional exhaustion and -depersonalization [37]. In addition, cardiovascular disease is the leading cause of on-duty death among firefighters, and 24-hour shifts may increase the risk of elevated diastolic blood pressure in this group [38,39].

Evaluations of shift schedules in EMS have focused on safety and clinical outcomes. Allen et al. compared the endotracheal intubation success rates of Air Medical providers for 12-hour and 24-hour shifts after an organization wide change in shift length [40]. They concluded that since success rates were not different before and after the change, the psychomotor agility of providers was not affected by increasing shift length from 12 to 24 h. Similar studies found no difference in cognitive performance for 12- versus 18-hour shifts in a population of 10 flight nurses [41], 12- versus 24-hour shifts in a population of helicopter EMS providers [42], or <24- versus 24-hour shifts [43] in sample of air-medical EMS workers. Despite these nonsignificant findings for shift length, air-medical EMS personnel had a higher number of lapses and false starts during night shifts compared with day shifts, highlighting the performance impairment associated with this aspect of the shift schedule [43].

LEADS data have also been utilized to evaluate the prevalence of sleep problems in EMS workers nationally [44]. Among respondents to this survey, sleep maintenance disorder was more common in providers working 24-hour shifts, those working more than 40-hours in a week, and those working in rural areas. These findings are aligned with those from 30 EMS agencies nationally who administered the Pittsburgh Sleep Quality Index (PSQI) and Chalder Fatigue Questionnaire (CFQ) to determine the prevalence of poor sleep quality and severe fatigue in their workforces [3]. Nearly 60% of respondents reported poor sleep quality ($PSQI > 5$), and 55% were found to have severe mental or physical fatigue. The prevalence of fatigue was highest among those who worked 24-hour shifts. Fatigue was associated with nearly twice the odds of injury, 2.2 times the odds of medical error, and more than threefold increased odds of safety-compromising behaviors.

The demand for medical emergencies far exceeds that of fire or rescue services [45]. As such, opportunities for sleep on-shift may be less common for EMS providers compared with firefighters. While firefighters have adopted increasingly longer shift durations with little evidence of adverse safety outcomes, these schedules are hazardous in the EMS setting. An observational study of nearly 1 million shifts over a 3-year period determined that the risk of occupational injury or illness in EMS personnel was increased for shifts ≥ 10 h duration [4]. Relative to 8-hour shifts, 12-hour shifts were associated with a 43% increased risk and 16-hour shifts an 82% increased risk, while 24-hour shifts more than doubled the risk of an occupational injury or illness. The National Highway Traffic Safety Administration subsequently supported The Fatigue in EMS Research Project—a series of systematic reviews and meta-analyses designed to develop evidence-based guidelines for Fatigue Risk Management in EMS [46]. While the overall evidence base was considered to be low quality, the expert panel recommended that EMS shift duration should be less than 24 h [13].

Implementation of schedules based on sleep and circadian principles

There have been few efforts to optimize work schedules based on sleep and circadian principles, though experimental evidence has demonstrated that matching shifts with chronotype (with early chronotypes working morning shifts, and evening chronotypes on evening or night shifts) improves sleep duration, sleep quality, and measures of well-being [47]. In one of the few investigations of chronotype and scheduling in public safety, police officers reporting an evening chronotype actually had lower sleep quality and shorter sleep duration on night shift schedules compared with morning types [1]. However, this design

may have been compromised by the rapid, counterclockwise rotation of shifts worked by the police officers under study. There is an opportunity for vast improvements over the current scheduling paradigms. Future efforts should seek to identify and evaluate work schedules that optimize alertness and promote utilization of these schedules among public safety personnel.

Physiological determinants of alertness

There are four major physiological determinants of fatigue, alertness, and performance: (1) circadian phase (biological time of day); (2) number of hours awake; (3) nightly sleep duration; and (4) sleep inertia (impaired performance upon waking). Circadian misalignment [48–51], acute sleep deprivation [52–56], chronic sleep deficiency [57–62], and abrupt awakening [63–65], often inherent to police, firefighter, and EMS schedules have each been independently associated with decrements in performance, and an increased risk of errors and accidents.

Physiological determinants of fatigue in public safety

The detrimental effects of each of these four factors are exacerbated by the long work hours, night and rotating shifts, extended-duration shifts, and quick turn-around inherent in public safety schedules that are required to cover 24 h per day, 365 days per year (Fig. 48.1).

Alertness and performance vary rhythmically with a period of roughly 24 h [66,67] driven by an endogenous circadian pacemaker located in the suprachiasmatic nucleus of the hypothalamus [68]. The largest performance decrements are seen when participants are awake during the biological night, with the worst performance several hours before normal wake time (e.g., ~3:00–6:00 a.m.) [48–51]. Further, not only is the ability to stay alert dependent on the time of day, but the quality and quantity of sleep also varies with circadian phase such that sleep during the day is shorter and of poorer quality than sleep during the night [69–71]. Thus, night shift workers are commonly unable to sleep during daytime hours and are fatigued at night [72–74]. Not surprisingly, there is an increased rate of industrial and driving accidents during the night as compared to the day [75]. Public safety personnel regularly work during the biological night when the endogenous drive for alertness is lowest. As mentioned previously, firefighters and police have increased rates of occupational injury on the night shift [2,33,35].

Extended-duration shifts are common among public safety personnel, requiring long continuous episodes of wakefulness that induce fatigue. Acute sleep deprivation causes decrements in human alertness and performance, independent of the circadian system [52–56]. Every hour

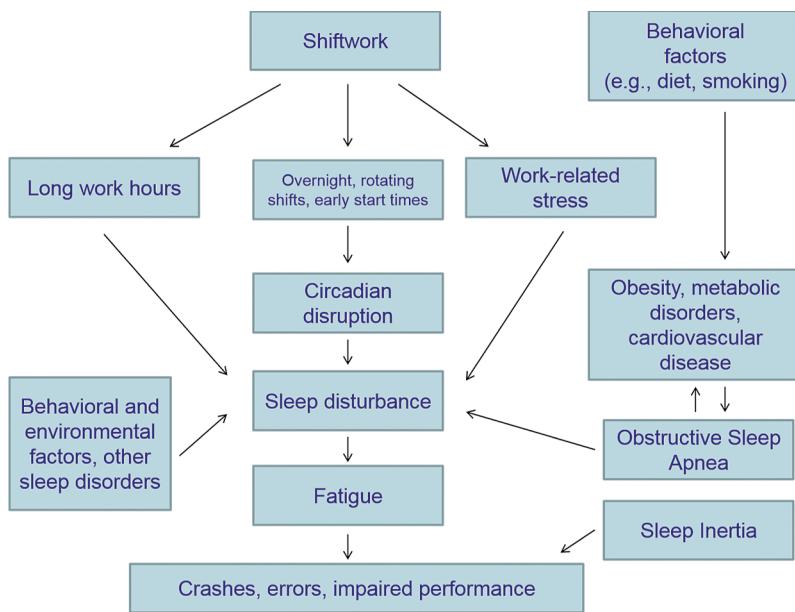


FIGURE 48.1 Factors which interact to impact safety and performance in public safety.

that one is awake, the homeostatic drive to sleep increases resulting in deteriorating performance. This deterioration results in an increase in the risk of fatigue-related fatal truck crashes with increased hours driving and awake [76]. Compared with the first hour, there is more than a 15-fold increase in the risk of a fatigue-related fatal crash after 13 h of driving. Long transports are common for fire and EMS in rural areas or in areas where specialized care is not available locally. In one national study, 4% of EMS providers reported tiredness-related difficulties operating the ambulance for short distances in the past month; while more than twice as many (10%) reported such difficulties operating the ambulance for long distances [44].

Fatigue-related impairments associated with extended shifts can also manifest in increased injury risk. In a review of newly implemented 48-hour shifts, it was reported that firefighters had significantly more injuries in the second day as compared to the first day of the shift [2]. In a cross-sectional study of 511 EMS providers nationally, the proportion of providers considered to be fatigued was highest among those working 24 h shifts [3].

Public safety personnel are regularly exposed to chronic partial sleep deprivation when they fail to obtain adequate recovery sleep after working long shifts or shifts scheduled too close together. The history of nightly sleep duration has also been demonstrated to affect performance. Sleep loss on a nightly basis, chronic sleep deficiency, results in a sleep “debt.” The consequences of the sleep debt are cumulative and affect health and performance [57–61]. Participants restricted to approximately 5 h of sleep per night for 7 nights exhibit significantly more

lapses on a vigilance task [62]. Loss of even 2 h of nightly sleep for 5–7 consecutive nights causes decrements in performance comparable to those seen after 24 h of continuous sleep deprivation. After 12–14 consecutive nights at this level of sleep restriction, lapses of attention on the task were comparable to those observed after 48 h of total sleep deprivation [62]. Opportunity for recovery between work shifts is often limited, a problem that is amplified among those who work multiple jobs [30]. Nearly 60% of EMS providers report poor sleep quality [3], and more than 1/3 have excessive daytime sleepiness [44]. Nearly 30% of police officers [8] and just over 40% of firefighters also have excessive daytime sleepiness [77].

Public safety personnel who routinely obtain inadequate nightly sleep and also work extended-duration shifts experience even worse decrements in performance as there is synergy between acute and chronic sleep loss. The rate of deterioration in performance during extended (>16 h) wakefulness is greatly increased, particularly during the circadian night, when accompanied by the chronic sleep deficiency that often builds up when working 24 h shifts [78]. When acute sleep deprivation occurs on a background of chronic sleep deficiency, performance is markedly degraded. As an example, laboratory experiments have revealed that performance during 28 h of wakefulness was 10-fold worse following 3 weeks of chronic sleep restriction, even when participants were tested after 10 h of recovery sleep [78].

Despite unpredictable calls for services and extended-duration shifts, local policies and/or norms may discourage sleep while at work or restrict sleep to the

nighttime hours. Public safety personnel who do manage to sleep on-shift are often asked to perform emergent actions immediately upon awakening (e.g., firefighters driving immediately after being awakened by an alarm). In fact, the time it takes to leave the station following a call for service is a quality measure, with “chute time” expected to be 1 min or less. This can be dangerous as alertness and performance are markedly impaired immediately following awakening. For instance, in EMT and paramedic personnel working a simulated night shift, cognitive performance assessed after an intra-shift nap was worse compared with the prenap assessment [79]. This impairment, known as sleep inertia, is more profound when workers are sleep deprived or have been awakened at an adverse circadian phase (e.g., during the night shift) [64]. Chronic sleep deficiency, which increases the depth of subsequent sleep, also worsens the adverse effects of sleep inertia. The effects of sleep inertia dissipate over time in an asymptotic manner [64]. The consequences of its impact upon awakening are particularly relevant to first responders and present an additional challenge for fatigue risk management programs [80]. Sensory activations which accompany calls for service (such as alarms, lights, and sirens) may promote wakefulness during this period of vulnerability, but their effects remain understudied.

Sleep deficiency and health

Sleep deficiency is an underlying cause of many short- and long-term health problems. Sleep deficiency and working during an adverse circadian phase have been linked with increased risks of weight gain, obesity, cardiovascular disease, stroke, myocardial infarction, depression, and cancer [81]. Workers who routinely work extended hours and night shifts are at particularly high risk of suffering these adverse health consequences. Nearly half (45%) of the deaths that occur among US firefighters while at work are attributed to heart disease [2]. Police officers also have an increased risk of cardiovascular disease [82].

In addition to the other common risk factors (e.g., stress and burnout) that first responders face in their jobs, sleep deficiency can exacerbate their risk of poor health. Increased stress experienced by first responders may exacerbate sleep disruption and consequently sleepiness. Sleep deficiency, sleep disorders, and shift work interact with the processes controlling appetite and metabolism, increasing the risk of weight gain, which is a risk factor for sleep apnea, and over the long term, increases the risk of cardiovascular disease and diabetes [81]. The vast majority of public safety personnel are overweight or obese (Table 48.1). Public safety personnel in less than optimal health are at risk for adverse events at work. In this setting, adverse events can have far-reaching implications for the safety of the public. Safety-conscious scheduling, along

with sleep health interventions, may help to reduce these risks. Importantly, sleep health interventions must address undiagnosed and untreated sleep disorders.

Sleep disorders

An Institute of Medicine report declared sleep deficiency and untreated sleep disorders an unmet public health problem, estimating 50–70 million people in the US are living with a sleep disorder [83]. In addition to the degradation in an individual’s health, alertness, performance, safety, and quality of life, untreated sleep disorders are responsible for substantial costs to employers and society. Sleep-deficient individuals and those who have a sleep disorder have up to a 20% increased utilization of the healthcare system [84]. In the year before diagnosis with obstructive sleep apnea (OSA), a common sleep disorder characterized by repetitive pharyngeal collapse during sleep [85], individuals’ medical costs were almost twice as much as those without OSA [86]. Costs to employers and society are systemic, and are revealed through increased rates of absenteeism, disability day usage, reduced productivity (presenteeism), injuries, accidents, and even increased alcohol consumption [87]. These indirect costs have been estimated in the hundreds of billions of dollars [88]. In the case of public safety personnel, untreated sleep disorders are not only a threat to personal health, but may also endanger the public in their role as a public safety workforce. Furthermore, costs associated with sleep disorders are avoidable, but are often borne by taxpayer support.

In a cross-sectional survey of 4957 police officers, 40.4% screened positive for at least one sleep disorder [8] (Fig. 48.2). The most common sleep disorder was OSA (33.6%), followed by shift work disorder (14.5%), and insomnia (6.5%). Similarly, in a nationwide survey of 6933 firefighters, 37.2% of firefighters screened positive for a sleep disorder [7]. Again, the most common sleep disorder was OSA (28.4%), followed by shift work disorder (9.1%), and insomnia (6.0). In the subset of firefighters who reported their primary responsibility as medical care (fire-based EMS), 45% screened positive for at least one common sleep disorder, with 33.9% screening positive for OSA, 10.1% for shift work disorder, and 7.5% for insomnia [89]. Across these survey studies, more than 80% of those who screened positive for a sleep disorder were previously undiagnosed and untreated. A high rate of sleep disorders has also been found in first responders outside North America. For instance, in France, 18.8% of firefighters screened at risk of moderate to severe insomnia [90], while in a large sample of South Korean firefighters ($n = 3810$), 9.1% of these personnel screened at risk of insomnia [91].

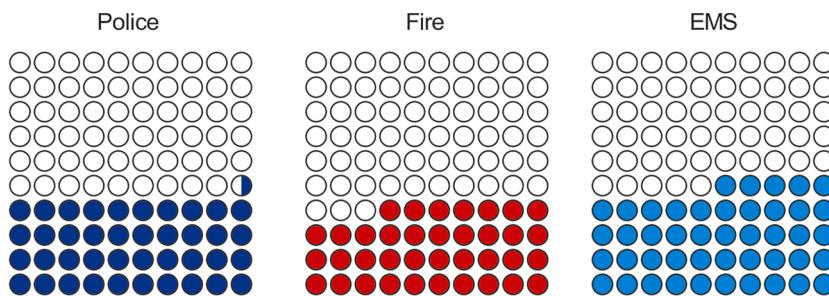


FIGURE 48.2 The prevalence of positive sleep disorder screening across branches of public safety, including police, fire, and emergency medical services (EMS).

In a widespread cross-sectional survey of police officers ($n = 4957$) from the US and Canada, positive sleep disorder screening was associated with adverse health and safety outcomes [8]. Compared with those officers who did not screen positive for a sleep disorder, positive screening was associated with more than twice the prevalence of reported depression and burnout-emotional exhaustion and three times the risk of anxiety; as well as approximately twice the risk of diabetes and cardiovascular disease.

In a 2-year follow-up period, 3545 police officers completed 15,735 online monthly surveys (6587 person-months with positive screens and 9148 with negative screens for sleep disorders) to capture performance and safety outcomes [8]. Each officer completed approximately four monthly surveys. Compared with those officers who did not screen positive for a sleep disorder, officers who were prospectively identified as screening positive for a sleep disorder had higher risk of reporting a serious administrative error, falling asleep while driving, an error or safety violation attributed to fatigue, occupational injury, and other adverse work-related performance measures, including uncontrolled anger toward a suspect, absenteeism, and falling asleep during meetings (Fig. 48.3).

Similarly, in a nationwide survey of firefighters, those who screened positive for OSA were twice as likely to report a motor vehicle crash (MVC) and falling asleep while driving; 85% of MVCs were documented with police reports or detailed descriptions and 48% occurred at work or during commutes [7]. Additional safety outcomes of near miss crashes and injuries were also elevated in those screening positive for OSA (Fig. 48.3).

Positive screening for OSA was also associated with adverse health outcomes. Firefighters who screened positive for a sleep disorder were 106% more likely to report having cardiovascular disease, 84% more likely to report diabetes, 195% more likely to report depression, and 163% more likely to report anxiety and to report poorer health status ($P < .0001$), compared with those who did not screen positive [7]. Further analysis of this data revealed firefighters who screened positive for insomnia, OSA, or

shift work disorder were at increased risk of each of the burnout dimensions, with the highest risk found for burnout-emotional exhaustion [37]. Safety outcomes were similarly significantly increased in those firefighters who screened positive for any sleep disorder compared with those who did not screen positive, including among fire-based EMS personnel [89] (Fig. 48.3).

529 firefighters reported a current diagnosis of depression and/or anxiety (9% depression and/or anxiety; 6% depression; 4% anxiety) [7]. Although these rates are similar to those in the general population [92], our data revealed an almost 3-fold increase in the odds of the diagnosis for those who screened positive for OSA. The BCOPS study also reported on the association between sleep (sleep quality in this case) and depression among police officers. The investigators found that depression severity scores increased as sleep quality scores increased [93]. Sleep quality was independently associated with depressive symptoms. Sleep disorders and mood disorders are closely intertwined. Sleep disturbance and fatigue are two of the diagnostic criteria for depression in the Diagnostic and Statistical Manual of Mental Disorders [94],

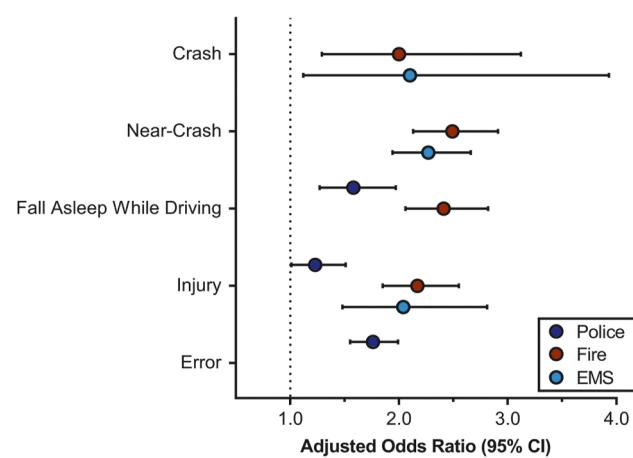


FIGURE 48.3 Adjusted associations between sleep disorders and safety outcomes in branches of public safety, including police, fire, and emergency medical services (EMS).

with emerging research in police showing sleep difficulties and fatigue pretrauma predict the later development of depression symptoms [95]. Treatment for sleep disorders has been shown to reduce symptoms of depression and anxiety [96], and likewise, treatment for depression can reduce symptoms of insomnia [97]. Soldiers with insomnia reported more difficulty with social functioning, lower morale, perceived less support, and reported being less able to cope with stress following deployment [98]. Depression leads to reduced productivity at work and adversely impacts social relationships [88], and may impact the on-demand productivity in the work of public safety personnel and the occupational culture of living as a group in the fire department, EMS base, and police barracks.

Sleep disorders are endemic in police and firefighters. Given the similarities in demographic characteristics and occupational demands, it is likely that there is a similar prevalence of sleep disorders among EMS providers. However, there has been little research in this area. One national survey found that the odds of involvement in an ambulance crash are significantly higher for EMS providers with sleep problems [99]. A separate national survey determined that 70% of actively working EMS providers had a sleep problem [44]. This effort found that 10% of respondents self-reported snoring and pauses in breathing, while 5% self-reported snoring, pauses in breathing, and excessive daytime sleepiness, suggestive of sleep apnea. This approach likely results in underreporting, as respondents would often be unaware of these events happening during their sleep periods. Building on this earlier work, recent research using validated sleep disorder screening measures reports that paramedic personnel have higher rates of OSA (41.5%) and insomnia (30%) compared with the general population [100]. Shift work disorder is also found to be highly prevalent in paramedic personnel [100], including among those in their early career (i.e., the first 6-month) [101]. Furthermore, among the subset of firefighters in our nationwide survey [7] who were cross-trained as EMS providers and reported their primary responsibility as medical care, the prevalence of positive sleep disorder screening was 45%, higher than what we observed among police or fire-only personnel (Fig. 48.2). Sleep disorders were also associated with adverse outcomes in this group. After controlling for age, gender, body mass index, exercise frequency, years of experience, shift schedule, work at multiple jobs, and call volume; positive sleep disorder screening was independently associated with more than twice the odds of an occupational injury, MVC, and near-crash [89]. Furthermore, similar to what has been found in police [95], research in recruit paramedics has shown higher insomnia symptoms prework predict increased depression symptoms after 6-months of emergency work, highlighting poor sleep as a possible early risk factor for mental health in this

occupation [102]. Additional research is now needed to evaluate the prevalence of sleep disorders and their impact on other health and safety outcomes among the third component of the public safety net, EMS clinicians.

Sleep disorders are highly treatable and treatment can reduce associated health and safety risks. For example, in the case of OSA, patients adherent to continuous positive airway pressure (CPAP) therapy have better cardiovascular health outcomes compared with those who are nonadherent [103]. Successful treatment of OSA with CPAP therapy has resulted in a significant decrease in MVC rates [104–106] and reverses the trend in increased health care costs seen prior to treatment [107,108]. Treatment for insomnia involves cognitive behavioral therapy (CBT-I), medication, or a combination of the two [109]. CBT-I is effective at improving sleep and reducing fatigue [110]. Recent efforts have even shown that the use of fully automated web-based CBT-I is as effective as in-person therapy sessions [111].

Fatigue risk management

In an effort to improve health and safety, industries such as aviation, railroad, and trucking are mandated or encouraged to institute fatigue risk management programs [112,113]. To address sleep deficiency and sleep disorders, police, fire departments and EMS agencies should consider programs to address sleep health and fatigue risk management. The key components of a comprehensive fatigue risk management program should ideally include: a sleep health education program, recurrent and with certification testing; work schedule policies that are grounded in sleep and circadian science with monitoring of compliance and enforcement; and mandatory screening for sleep disorders with follow-up on effectiveness and compliance with any treatment [114].

The Royal Canadian Mounted Police (RCMP) implemented and evaluated a fatigue management program in a pilot study using a before-after design [115]. Following a train-the-trainer approach, the approximately 4-hour program, emphasizing the science of sleep, sleep apnea, and other sleep disorders and fatigue countermeasures, was presented to 61 RCMP members. On surveys completed 4 weeks following the training, members reported an increased satisfaction with sleep, reduced symptoms of insomnia, and reduced incidence of headaches. The authors stressed that this training program should continue to be tested in larger police organizations to confirm the sleep health benefits for police officers.

A station-randomized trial of a sleep health education and sleep disorders screening program was conducted in a large municipal fire department. Of 1211 active firefighters identified at study onset, 604 were assigned to the intervention group and 607 to the control group. In an intention-

to-treat analysis, firefighters assigned to intervention stations which participated in education sessions and had the opportunity to complete sleep disorders screening reported half the number of disability days on average than those assigned to control stations, as recorded by payroll records. In post hoc analysis accounting for exposure to the intervention, firefighters who attended education sessions were 24% less likely to file at least one official injury report during the study duration than those firefighters who did not attend regardless of randomization [116].

More recently, the National Highway Traffic Safety Administration commissioned a systematic review of published evidence to mitigate fatigue in emergency service personnel [46]. A diverse team of experts in sleep medicine, fatigue science, risk management, and emergency medicine reviewed more than 38,000 pieces of literature involving EMS personnel or similar shift workers. The systematic review leads to five recommendations: the use of reliable and/or valid fatigue survey tools to diagnose fatigue in the workplace [117]; shifts <24 h in duration [13]; the use of caffeine as a fatigue countermeasure [118]; napping [119]; and sleep health education and training [120].

The EMS systematic review revealed that sleep health education and training improved patient safety, personal safety, and ratings of acute fatigue and reduced stress and burnout. Further, a meta-analysis of the literature showed improvement in sleep quality following fatigue training in shift workers; however, the quality of literature was low due mainly to a lack of randomized control trials [120]. To begin to address this limitation, Patterson et al. conducted a cluster-randomized waitlist control trial of a sleep health education program comprising 10 modules focusing on different aspects of sleep health and fatigue that were tailored to EMS [5]. A total of 54 EMS agencies completed the study. Although the intention-to-treat analyses revealed the intervention had no significant impact on sleep or fatigue at the 3-month follow-up, further analyses showed personnel who completed more modules had greater improvements in fatigue and sleep quality [5].

Additional research is necessary to further dissemination of successful fatigue risk management programs in public safety personnel. Different branches of public safety and different departments and organizations within the same branch have different resources and needs. With sleep health education and sleep disorders screening programs, it has been shown that several forms of implementation (i.e., expert-led, train-the-trainer, and online) can be successful in improving sleep health in firefighters [121]. The most pertinent information to include in an education program, the length of the program, and the durability of the benefits remains to be determined [120].

Conclusion

The sleep health of public safety personnel is a major concern. Rapid backward shift rotation, prolonged weekly work hours, and extended-duration shifts contribute to sleep deficiency and circadian misalignment. Poor sleep quality and fatigue increase the risk of adverse safety outcomes and contribute to chronic health problems. Furthermore, there is an epidemic of sleep disorders among police, firefighters, and EMS providers. Fatigue risk management programs are effective, but remain underutilized. Future research should seek to develop and test schedules which align with sleep and circadian principles. Advocacy efforts should promote increased adoption of sleep health education, sleep disorder screening, and fatigue risk management programs. As a society, we rely on the public safety net to act swiftly and appropriately in emergencies. Efforts to improve sleep have the potential to vastly improve the safety, health, and performance of this vulnerable occupational group, benefiting not only them, but the public that they serve.

References

- [1] Martin JS, Laberge L, Saserville A, Bérubé M, Alain S, Houle J, Hébert M. Day and night shift schedules are associated with lower sleep quality in evening-types. *Chronobiol Int* 2015;32(5):627–36. <https://doi.org/10.3109/07420528.2015.1033425>.
- [2] Elliot DL, Kuehl KS. Effects of sleep deprivation on fire fighters and EMS responders. 2007.
- [3] Patterson PD, Weaver MD, Frank RC, Warner CW, Martin-Gill C, Guyette FX, Fairbanks RJ, Hubble MW, Songer TJ, Callaway CW, Kelsey SF, Hostler D. Association between poor sleep, fatigue, and safety outcomes in emergency medical services providers. *Prehosp Emerg Care* 2012;16(1):86–97. <https://doi.org/10.3109/10903127.2011.616261>.
- [4] Weaver MD, Patterson PD, Fabio A, Moore CG, Freiberg MS, Songer TJ. An observational study of shift length, crew familiarity, and occupational injury and illness in emergency medical services workers. *Occup Environ Med* 2015;72(11):798–804. <https://doi.org/10.1136/oemed-2015-102966>.
- [5] Patterson PD, Martin SE, Brassil BN, Hsiao WH, Weaver MD, Okerman TS, Seitz SN, Patterson CG, Robinson K. The emergency medical services sleep health study: a cluster-randomized trial. *Sleep Health* 2023;9(1):64–76. <https://doi.org/10.1016/j.slehd.2022.09.013>.
- [6] Brown WE, Dickison PD, Misselbeck WJA, Levine R. Longitudinal emergency medical technician attribute and demographic study (LEADS): an interim report. *Prehosp Emerg Care* 2002;6(4):433–9. <https://doi.org/10.1080/10903120290938085>.
- [7] Barger LK, Rajaratnam SMW, Wang W, O'Brien CS, Sullivan JP, Qadri S, Lockley SW, Czeisler CA. Common sleep disorders increase risk of motor vehicle crashes and adverse health outcomes in firefighters. *J Clin Sleep Med* 2015;11(3):233–40. <https://doi.org/10.5664/jcsm.4534>.
- [8] Rajaratnam SMW, Barger LK, Lockley SW, Shea SA, Wang W, Landrigan CP, O'Brien CS, Qadri S, Sullivan JP, Cade BE,

- Epstein LJ, White DP, Czeisler CA. Sleep disorders, health, and safety in police officers. *JAMA* 2011;306(23):2567–78. <https://doi.org/10.1001/jama.2011.1851>.
- [9] James L. The stability of implicit racial bias in police officers. *Police Quart* 2018;21:30–52.
- [10] Blake D, Cumella EJ. Factoring fatigue into police deadly force encounters: decision making and reaction time. *Law Enforc Exec Forum* 2015;15(1):44–65. <https://doi.org/10.19151/LEEF.2015.1501d>.
- [11] Kong PW, Beauchamp G, Suyama J, Hostler D. Effect of fatigue and hypohydration on gait characteristics during treadmill exercise in the heat while wearing firefighter thermal protective clothing. *Gait Posture* 2010;31(2):284–8. <https://doi.org/10.1016/j.gaitpost.2009.11.006>.
- [12] Calams S. Private vs. public ambulance services: what's the difference? *EMS News*; 2017.
- [13] Patterson PD, Runyon MS, Higgins JS, Weaver MD, Teasley EM, Kroemer AJ, Matthews ME, Curtis BR, Flickinger KL, Xun X, Bizhanova Z, Weiss PM, Condle JP, Renn ML, Sequeira DJ, Coppler PJ, Lang ES, Martin-Gill C. Shorter versus longer shift durations to mitigate fatigue and fatigue-related risks in emergency medical services personnel and related shift workers: a systematic review. *Prehosp Emerg Care* 2018;22:28–36. <https://doi.org/10.1080/10903127.2017.1376135>.
- [14] Schafer K, Sutter S. Gibbons, characteristics of individuals and employment among first responders. 2015.
- [15] Patterson PD, Weaver MD, Hostler D, Guyette FX, Callaway CW, Yealy DM. The shift length, fatigue, and safety conundrum in EMS. *Prehosp Emerg Care* 2012;16(4):572–6. <https://doi.org/10.3109/10903127.2012.704491>.
- [16] Luckhaupt SE, Cohen MA, Li J, Calvert GM. Prevalence of obesity among U.S. workers and associations with occupational factors. *Am J Prev Med* 2014;46(3):237–48. <https://doi.org/10.1016/j.amepre.2013.11.002>.
- [17] Bentley MA, Shoben A, Levine R, Crowe RP. The demographics and education of Emergency Medical Services (EMS) professionals: a national longitudinal investigation. *Prehospital Disaster Med* 2016;31(1):s18. <https://doi.org/10.1017/S1049023X16001060>.
- [18] Beaton RD, Murphy SA. Sources of occupational stress among firefighter/EMTs and firefighter/paramedics and correlations with job-related outcomes. *Prehospital Disaster Med* 1993;8(2):140–50. <https://doi.org/10.1017/s1049023x00040218>.
- [19] Hippel SF. Multiple jobholding during the 2000s. *Mon Labor Rev* 2010;133(7):33–4.
- [20] Spiegel U, Gonon LD, Weber M. Duration and optimal number of shifts in the labour market. *Appl Econ Lett* 2014;21(6):429–32. <https://doi.org/10.1080/13504851.2013.864027>.
- [21] Dembe AE. Ethical issues relating to the health effects of long working hours. *J Bus Ethics* 2009;84(2):195–208. <https://doi.org/10.1007/s10551-008-9700-9>.
- [22] Rosenbluth G, Landrigan CP. Sleep science, schedules, and safety in hospitals. Challenges and solutions for pediatric providers. *Pediatr Clin* 2012;59(6):1317–28. <https://doi.org/10.1016/j.pcl.2012.09.001>.
- [23] Radstaak M, Geurts SAE, Beckers DGJ, Brosschot JF, Kompier MAJ. Recovery and well-being among helicopter emergency medical service (HEMS) pilots. *Appl Ergon* 2014;45(4):986–93. <https://doi.org/10.1016/j.apergo.2013.12.002>.
- [24] Amendola KL, Weisburd D, Hamilton E. The shift length experiment: what we know about 8-, 10-, and 12-hour shifts in policing. In: Police foundation advancing policing through innovation and science; 2011.
- [25] Poole TL. The 48/96 work schedule: a viable alternative? *Fire Eng* 2012;165:85–9.
- [26] Vila B. Police executive research forum tired cops: the importance of managing police fatigue. 2000.
- [27] Peterson SA, Wolkow AP, Lockley SW, O'Brien CS, Qadri S, Sullivan JP, Czeisler CA, Rajaratnam SMW, Barger LK. Associations between shift work characteristics, shift work schedules, sleep and burnout in North American police officers: a cross-sectional study. *BMJ Open* 2019;9(11). <https://doi.org/10.1136/bmjopen-2019-030302>.
- [28] Vila B, Morrison GB, Kenney DJ. Improving shift schedule and work-hour policies and practices to increase police officer performance, health, and safety. *Police Q* 2002;5(1):4–24. <https://doi.org/10.1177/109861102129197995>.
- [29] Weaver MD, Patterson PD, Fabio A, Moore CG, Freiberg MS, Songer TJ. The association between weekly work hours, crew familiarity, and occupational injury and illness in emergency medical services workers. *Am J Ind Med* 2015;58(12):1270–7. <https://doi.org/10.1002/ajim.22510>.
- [30] Patterson PD, Buysse DJ, Weaver MD, Callaway CW, Yealy DM. Recovery between work shifts among emergency medical services clinicians. *Prehosp Emerg Care* 2015;19(3):365–75. <https://doi.org/10.3109/10903127.2014.995847>.
- [31] Fekedulegn D, Burchfiel CM, Charles LE, Hartley TA, Andrew ME, Violanti JM. Shift work and sleep quality among urban police officers. *J Occup Environ Med* 2016;58(3):e66. <https://doi.org/10.1097/JOM.0000000000000620>.
- [32] Fekedulegn D, Burchfiel CM, Hartley TA, Andrew ME, Charles LE, Tinney-Zara CA, Violanti JM. Shiftwork and sickness absence among police officers: the BCOPS study. *Chronobiol Int* 2013;30(7):930–41. <https://doi.org/10.3109/07420528.2013.790043>.
- [33] Violanti JM, Fekedulegn D, Andrew ME, Charles LE, Hartley TA, Vila B, Burchfiel CM. Shift work and the incidence of injury among police officers. *Am J Ind Med* 2012;55(3):217–27. <https://doi.org/10.1002/ajim.22007>.
- [34] Violanti JM, Burchfiel CM, Hartley TA, Mnatsakanova A, Fekedulegn D, Andrew ME, Charles LE, Vila BJ. Atypical work hours and metabolic syndrome among police officers. *Arch Environ Occup Health* 2009;64(3):194–201. <https://doi.org/10.1080/19338240903241259>.
- [35] Riedel M, Berrez S, Pelisse D, Brousse E, Forget C, Marlot M, Smolensky MH, Touitou Y, Reinberg A. 24-hour pattern of work-related injury risk of French firemen: nocturnal peak time. *Chronobiol Int* 2011;28(8):697–705. <https://doi.org/10.3109/07420528.2011.603170>.
- [36] Haddock CK, Poston WSC, Jitnarin N, Jahnke SA. Excessive daytime sleepiness in firefighters in the central United States. *J Occup Environ Med* 2013;55(4):416–23. <https://doi.org/10.1097/JOM.0b013e31827cbb0b>.
- [37] Wolkow AP, Barger LK, O'Brien CS, Sullivan JP, Qadri S, Lockley SW, Czeisler CA, Rajaratnam SMW. Associations

- between sleep disturbances, mental health outcomes and burnout in firefighters, and the mediating role of sleep during overnight work: a cross-sectional study. *J Sleep Res* 2019;28(6). <https://doi.org/10.1111/jsr.12869>.
- [38] Choi BK, Schnall P, Dobson M. Twenty-four-hour work shifts, increased job demands, and elevated blood pressure in professional firefighters. *Int Arch Occup Environ Health* 2016;89(7):1111–25. <https://doi.org/10.1007/s00420-016-1151-5>.
- [39] Soteriades ES, Smith DL, Tsismenakis AJ, Baur DM, Kales SN. Cardiovascular disease in US firefighters: a systematic review. *Cardiol Rev* 2011;19(4):202–15. <https://doi.org/10.1097/CRD.0b013e318215c105>.
- [40] Allen TL, Delbridge TR, Stevens MH, Dederia N. Intubation success rates by air ambulance personnel during 12- versus 24-hour shifts: does fatigue make a difference? *Prehosp Emerg Care* 2001;5(4):340–3. <https://doi.org/10.1080/10903120190939481>.
- [41] Thomas F, Hopkins RO, Handrahan DL, Walker J, Carpenter J. Sleep and cognitive performance of flight nurses after 12-hour evening versus 18-hour shifts. *Air Med J* 2006;25(5):216–25. <https://doi.org/10.1016/j.amj.2006.06.005>.
- [42] Guyette FX, Morley JL, Weaver MD, Patterson PD, Hostler D. The effect of shift length on fatigue and cognitive performance in air medical providers. *Prehosp Emerg Care* 2013;17(1):23–8. <https://doi.org/10.3109/10903127.2012.710719>.
- [43] Patterson PD, Weaver MD, Markosyan MA, Moore CG, Guyette FX, Doman JM, Sequeira DJ, Werman HA, Swanson D, Hostler D, Lynch J, Templin MA, Rozario NL, Russo L, Hines L, Swecker K, Runyon MS, Buysse DJ. Impact of shift duration on alertness among air-medical emergency care clinician shift workers. *Am J Ind Med* 2019;62(4):325–36. <https://doi.org/10.1002/ajim.22956>.
- [44] Pirrallo RG, Loomis CC, Levine R, Woodson T. The prevalence of sleep problems in emergency medical technicians. *Sleep Breath* 2012;16(1):149–62. <https://doi.org/10.1007/s11325-010-0467-8>.
- [45] FEMA. Fire department overall run profile as reported to the national fire incident reporting system. 2014.
- [46] Patterson PD, Higgins JS, Van Dongen HPA, Buysse DJ, Thackery RW, Kupas DF, Becker DS, Dean BE, Lindbeck GH, Guyette FX, Penner JH, Violanti JM, Lang ES, Martin-Gill C. Evidence-based guidelines for fatigue risk management in emergency medical services. *Prehosp Emerg Care* 2018;22:89–101. <https://doi.org/10.1080/10903127.2017.1376137>.
- [47] Vetter C, Fischer D, Matera JL, Roenneberg T. Aligning work and circadian time in shift workers improves sleep and reduces circadian disruption. *Germany Curr Biol* 2015;25(7):907–11. <https://doi.org/10.1016/j.cub.2015.01.064>.
- [48] Dijk D, Duffy JF, Czeisler CA. Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *J Sleep Res* 1992;1(2):112–7. <https://doi.org/10.1111/j.1365-2869.1992.tb00021.x>.
- [49] Johnson MP, Duffy JF, Dijk DJ, Ronda JM, Dyal CM, Czeisler CA. Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. *J Sleep Res* 1992;1(1):24–9. <https://doi.org/10.1111/j.1365-2869.1992.tb0004.x>.
- [50] Dijk DJ, Shanahan TL, Duffy JF, Ronda JM, Czeisler CA. Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *J Physiol* 1997;505(3):851–8. <https://doi.org/10.1111/j.1469-7793.1997.851ba.x>.
- [51] Czeisler CA, Dijk D-J, Duffy JF. Entrained phase of the circadian pacemaker serves to stabilize alertness and performance throughout the habitual waking day. *American Psychological Association (APA)*; 1994. p. 89–110. <https://doi.org/10.1037/10166-006>.
- [52] Dinges DF. The nature of sleepiness: causes, contexts, and consequences. Informa UK Limited; 2020. p. 147–79. <https://doi.org/10.1201/9780203771570-10>.
- [53] Carskadon MA, Dement WC. Multiple sleep latency tests during the constant routine. *Sleep* 1992;15(5):396–9. <https://doi.org/10.1093/sleep/15.5.396>.
- [54] Pilcher JJ, Huffcutt AI. Effects of sleep deprivation on performance: a meta-analysis. *Sleep* 1996;19(4):318–26. <https://doi.org/10.1093/sleep/19.4.318>.
- [55] Koslowsky M, Babkoff H. Meta-analysis of the relationship between total sleep deprivation and performance. *Chronobiol Int* 1992;9(2):132–6. <https://doi.org/10.3109/07420529209064524>.
- [56] Fröberg JE, Karlsson CG, Levi L, Lidberg L. Circadian rhythms of catecholamine excretion, shooting range performance and self-ratings of fatigue during sleep deprivation. *Biol Psychol* 1975;2(3):175–88. [https://doi.org/10.1016/0301-0511\(75\)90018-6](https://doi.org/10.1016/0301-0511(75)90018-6).
- [57] Carskadon MA, Dement WC. Cumulative effects of sleep restriction on daytime sleepiness. *Psychophysiology* 1981;18(2):107–13. <https://doi.org/10.1111/j.1469-8986.1981.tb02921.x>.
- [58] Carskadon MA. Sleep restriction. John Wiley & Sons Ltd; 1991. p. 155–67.
- [59] Gillberg M, Åkerstedt T. Sleep restriction and SWS-suppression: effects on daytime alertness and night-time recovery. *J Sleep Res* 1994;3(3):144–51. <https://doi.org/10.1111/j.1365-2869.1994.tb00121.x>.
- [60] Blagrove M, Alexander C, Horne JA. The effects of chronic sleep reduction on the performance of cognitive tasks sensitive to sleep deprivation. *Appl Cogn Psychol* 1995;9(1):21–40. <https://doi.org/10.1002/acp.2350090103>.
- [61] Brunner DP, Dijk D-J, Borbély AA. Repeated partial sleep deprivation progressively changes the EEG during sleep and wakefulness. *Sleep* 1993;16(2):100–13. <https://doi.org/10.1093/sleep/16.2.100>.
- [62] Van Dongen HPA, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26(2):117–26. <https://doi.org/10.1093/sleep/26.2.117>.
- [63] Achermann P, Werth E, Dijk DJ, Borbély AA. Time course of sleep inertia after nighttime and daytime sleep episodes. *Arch Ital Biol* 1995;134(1):109–19.
- [64] Jewett ME, Wyatt JK, de Cecco AR, Khalsa SB, Dijk DJ, Czeisler CA. Time course of sleep inertia dissipation in human performance and alertness. *J Sleep Res* 1999;8(1):1–8. <https://doi.org/10.1111/j.1365-2869.1999.00128.x>.
- [65] Dinges DF. Sleep, inertia, encyclopedia of sleep and dreaming. Macmillan Publishing Company; 1993. p. 553–4.
- [66] Richardson GS, Carskadon MA, Orav EJ, Dement WC. Circadian variation of sleep tendency in elderly and young adult subjects. *Sleep* 1982;5(2):S82. <https://doi.org/10.1093/sleep/5.s2.s82>.

- [67] Wyatt JK, Ritz-De Cecco A, Czeisler CA, Dijk DJ. Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. *Am J Physiol* 1999;277(4):R1152. <https://doi.org/10.1152/ajpregu.1999.277.4.r1152>.
- [68] Klein DC, Moore RY, Repert SM. Suprachiasmatic nucleus: the mind's clock. Oxford University Press; 1991.
- [69] Czeisler CA, Weitzman ED, Moore-Ede MC, Zimmerman JC, Knauer RS. Human sleep: its duration and organization depend on its circadian phase. *Science* 1980;210(4475):1264–7. <https://doi.org/10.1126/science.7434029>.
- [70] Strogatz SH, Kronauer RE, Czeisler CA. Circadian regulation dominates homeostatic control of sleep length and prior wake length in humans. *Sleep* 1986;9(2):353–64. <https://doi.org/10.1093/sleep/9.2.353>.
- [71] Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci* 1995;15(5):3526–38. <https://doi.org/10.1523/jneurosci.15-05-03526.1995>.
- [72] Colquhoun WP. Experimental studies of shiftwork. Westdeutscher Verlag; 1975.
- [73] Åkerstedt T, Torsvall L, Gillberg M. Sleep-wake disturbances in shift work: implications of sleep loss and circadian rhythms. *Sleep Res* 1983;12.
- [74] Vidaček S, Kalitera L, Radošević-Vidaček B, Folkard S. Productivity on a weekly rotating shift system: circadian adjustment and sleep deprivation effects? *Ergonomics* 1986;29(12):1583–90. <https://doi.org/10.1080/00140138608967271>.
- [75] Folkard S, Tucker P. Shift work, safety and productivity. *Occup Med* 2003;53(2):95–101. <https://doi.org/10.1093/occmed/kqg047>.
- [76] Barger LK, Lockley SW, Rajaratnam SMW, Landrigan CP. Neurobehavioral, health, and safety consequences associated with shift work in safety-sensitive professions. *Curr Neurol Neurosci Rep* 2009;9(2):155–64. <https://doi.org/10.1007/s11910-009-0024-7>.
- [77] Shi Y, Bender B, McGovern P, Mi Jung E, DeMoulin D, Jacobs S, Roxanne Prichard J, Kim H. Daytime sleepiness among Midwestern firefighters. *Arch Environ Occup Health* 2021;76(7):433–40. <https://doi.org/10.1080/19338244.2020.1841718>.
- [78] Cohen DA, Wang W, Wyatt JK, Kronauer RE, Dijk DJ, Czeisler CA, Klerman EB. Uncovering residual effects of chronic sleep loss on human performance. *Sci Transl Med* 2010;2(14):14. <https://doi.org/10.1126/scitranslmed.3000458>.
- [79] Patterson PD, Okerman TS, Roach DGL, Hilditch CJ, Weaver MD, Patterson CG, Sheffield MA, Di Salvatore JS, Bernstein H, Georges G, Andreozzi A, Willson CM, Jain D, Martin SE, Weiss LS. Are short duration naps better than long duration naps for mitigating sleep inertia? Brief report of a randomized crossover trial of simulated night shift work. *Prehosp Emerg Care* 2023;27(6):807–14. <https://doi.org/10.1080/10903127.2023.2227696>.
- [80] Dawson D, Ferguson SA, Vincent GE. Safety implications of fatigue and sleep inertia for emergency services personnel. *Sleep Med Rev* 2021;55:101386. <https://doi.org/10.1016/j.smrv.2020.101386>.
- [81] Kecklund G, Axelsson J. Health consequences of shift work and insufficient sleep. *BMJ* 2016;355:i5210. <https://doi.org/10.1136/bmj.i5210>.
- [82] Zimmerman FH. Cardiovascular disease and risk factors in law enforcement personnel: a comprehensive review. *Cardiol Rev* 2012;20(4):159–66. <https://doi.org/10.1097/CRD.0b013e318248d631>.
- [83] Colten HR, Altevogt, Committee on Sleep Medicine and Research. Sleep disorders and sleep deprivation : an unmet public health problem. National Academies Press; 2006.
- [84] Kapur VK, Redline S, Nieto FJ, Young TB, Newman AB, Henderson JA. The relationship between chronically disrupted sleep and healthcare use. *Sleep* 2002;25(3):289–96.
- [85] Malhotra A, White DP. Obstructive sleep apnoea. *Lancet* 2002;9328:237–45. [https://doi.org/10.1016/S0140-6736\(02\)09464-3](https://doi.org/10.1016/S0140-6736(02)09464-3).
- [86] Kapur V, Blough DK, Sandblom RE, Hert R, De Maine JB, Sullivan SD, Psaty BM. The medical cost of undiagnosed sleep apnea. *Sleep* 1999;22(6):749–55. <https://doi.org/10.1093/sleep/22.6.749>.
- [87] Hossain JL, Shapiro CM. The prevalence, cost implications, and management of sleep disorders: an overview. *Sleep Breath* 2002;6(2):85–102. <https://doi.org/10.1007/s11325-002-0085-1>.
- [88] Kessler RC, Berglund PA, Coulouvrat C, Hajak G, Roth T, Shahly V, Shillington AC, Stephenson JJ, Walsh JK. Insomnia and the performance of US workers: results from the America insomnia survey. *Sleep* 2011;34(9):1161–71. <https://doi.org/10.5665/SLEEP.1230>.
- [89] Weaver MD, Sullivan JP, Qadri S, Czeisler CA, Barger LK. Sleep disorders are common risk factors for occupational injury. *Prehosp Emerg Care* 2018;21.
- [90] Savall A, Marcoux P, Charles R, Trombert B, Roche F, Berger M. Sleep quality and sleep disturbances among volunteer and professional French firefighters: FIRELEEP study. *Sleep Med* 2021;80:228–35. <https://doi.org/10.1016/j.sleep.2021.01.041>.
- [91] Jang TW, Jeong KS, Ahn YS, Choi KS. The relationship between the pattern of shift work and sleep disturbances in Korean firefighters. *Int Arch Occup Environ Health* 2020;93(3):391–8. <https://doi.org/10.1007/s00420-019-01496-3>.
- [92] Kessler RC, Wai TC, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* 2005;62(6):617–27. <https://doi.org/10.1001/archpsyc.62.6.617>.
- [93] Slaven JE, Mnatsakanova A, Burchfiel CM, Smith LM, Charles LE, Andrew ME, Gu JK, Ma C, Fekedulegn D, Violanti JM. Association of sleep quality with depression in Police Officers. *Int J Emerg Ment Health* 2011;13(4):267–77.
- [94] American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. American Psychiatric Association; 2013.
- [95] Wolkow AP, Kaldewaij R, Klumpers F, Koch SBJ, Smit A, Drummond SPA, Roelofs K. Pre-trauma sleep difficulties and fatigue predict trauma-induced changes in mental health symptoms in recruit police officers. *Psychiatry Res* 2024;337:115920. <https://doi.org/10.1016/j.psychres.2024.115920>.
- [96] Edwards C, Mukherjee S, Simpson L, Palmer LJ, Almeida OP, Hillman DR. Depressive symptoms before and after treatment of obstructive sleep apnea in men and women. *J Clin Sleep Med* 2015;11(9):1029–38. <https://doi.org/10.5664/jcsm.5020>.
- [97] Yon A, Scogin F, Dinapoli EA, McPherron J, Arean PA, Bowman D, Jamison CS, Karpe JA, Latour D, Reynolds CF, Rohren N, Pardini JEL, Thompson LW. Do manualized treatments

- for depression reduce insomnia symptoms? *J Clin Psychol* 2014;70(7):616–30. <https://doi.org/10.1002/jclp.22062>.
- [98] Klingaman EA, Brownlow JA, Boland EM, Mosti C, Gehrman PR. Prevalence, predictors and correlates of insomnia in US army soldiers. *J Sleep Res* 2018;27(3). <https://doi.org/10.1111/jsr.12612>.
- [99] Studnek JR, Fernandez AR. Characteristics of emergency medical technicians involved in ambulance crashes. *Prehospital Disaster Med* 2008;23(5):432–7. <https://doi.org/10.1017/S1049023X00006166>.
- [100] Khan WAA, Conduit R, Kennedy GA, Jackson ML. The relationship between shift-work, sleep, and mental health among paramedics in Australia. *Sleep Health* 2020;6(3):330–7. <https://doi.org/10.1016/j.slehd.2019.12.002>.
- [101] Harris R, Drummond SPA, Meadley B, Rajaratnam SMW, Williams B, Smith K, Bowles KA, Nguyen E, Dobbie ML, Wolkow AP. Mental health risk factors for shift work disorder in paramedics: a longitudinal study. *Sleep Health* 2023;9(1):49–55. <https://doi.org/10.1016/j.slehd.2022.09.009>.
- [102] Nguyen E, Meadley B, Harris R, Rajaratnam SMW, Williams B, Smith K, Bowles K-A, Dobbie ML, Drummond SPA, Wolkow AP. Sleep and mental health in recruit paramedics: a 6-month longitudinal study. *Sleep* 2023;46(8). <https://doi.org/10.1093/sleep/zsad050>.
- [103] Butt M, Dwivedi G, Shantsila A, Khair OA, Lip GYH. Left ventricular systolic and diastolic function in obstructive sleep apnea: impact of continuous positive airway pressure therapy. *Circulation: Heart Fail* 2012;5(2):226–33. <https://doi.org/10.1161/CIRCHEARTFAILURE.111.964106>.
- [104] Engleman HM, Asgari-Jirhandeh N, McLeod AL, Ramsay CF, Deary IJ, Douglas NJ. Self-reported use of CPAP and benefits of CPAP therapy: a patient survey. *Chest* 1996;109(6):1470–6. <https://doi.org/10.1378/chest.109.6.1470>.
- [105] Cassel W, Ploch T, Becker C, Dugnus D, Peter JH, von Wichert P. Risk of traffic accidents in patients with sleep-disordered breathing: reduction with nasal CPAP. *Eur Respir J* 1996;9(12):2606–11. <https://doi.org/10.1183/09031936.96.09122606>.
- [106] Krieger J, Meslier N, Lebrun T, Levy P, Phillip-Joet F, Sailly JC, Racineux JL. Accidents in obstructive sleep apnea patients treated with nasal continuous positive airway pressure: a prospective study. *Chest* 1997;112(6):1561–6. <https://doi.org/10.1378/chest.112.6.1561>.
- [107] Albarak M, Banno K, Sabbagh AA, Delaive K, Walld R, Manfreda J, Kryger MH. Utilization of healthcare resources in obstructive sleep apnea syndrome: a 5-year follow-up study in men using CPAP. *Sleep* 2005;28(10):1306–11. <https://doi.org/10.1093/sleep/28.10.1306>.
- [108] Bahammam A, Delaive K, Ronald J, Manfreda J, Roos L, Kryger MH. Health care utilization in males with obstructive sleep apnea syndrome two years after diagnosis and treatment. *Sleep* 1999;22(6):740–7. <https://doi.org/10.1093/sleep/22.6.740>.
- [109] Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008;04(05):487–504. <https://doi.org/10.5664/jcsm.27286>.
- [110] Wu JQ, Appleman ER, Salazar RD, Ong JC. Cognitive behavioral therapy for insomnia comorbid with psychiatric and medical conditions a meta-analysis. *JAMA Intern Med* 2015;175(9):1461–72. <https://doi.org/10.1001/jamainternmed.2015.3006>.
- [111] Ritterband LM, Thorndike FP, Ingersoll KS, Lord HR, Gonder-Frederick L, Frederick C, Quigg MS, Cohn WF, Morin CM. Effect of a web-based cognitive behavior therapy for insomnia intervention with 1-year follow-up: a randomized clinical trial. *JAMA Psychiatry* 2017;74(1):68–75. <https://doi.org/10.1001/jamapsychiatry.2016.3249>.
- [112] Flightcrew member duty and rest requirements: 14 CFR Part 117, 119, and 121. 2012.
- [113] Quan S, Barger L. Brief review: sleep health and safety for transportation workers. *Southwest J Pulm Crit Care* 2015;10(3):130–9. <https://doi.org/10.13175/swjpc036-15>.
- [114] Czeisler CA. 86th Annual Meeting Japan Society for Occupational Health Role of sleep medicine and chronobiology for optimizing productivity, safety and health in the workplace. 2013.
- [115] James L, Samuels CH, Vincent F. Evaluating the effectiveness of fatigue management training to improve police sleep health and wellness: a pilot study. *J Occup Environ Med* 2018;60(1):77–82. <https://doi.org/10.1097/JOM.0000000000001174>.
- [116] Sullivan JP, O'Brien CS, Barger LK, Rajaratnam SMW, Czeisler CA, Lockley SW. Randomized, prospective study of the impact of a sleep health program on firefighter injury and disability. *Sleep* 2017;40(1). <https://doi.org/10.1093/sleep/zsw001>.
- [117] Patterson PD, Weaver MD, Fabio A, Teasley EM, Renn ML, Curtis BR, Matthews ME, Kroemer AJ, Xun X, Bishanov Z, Weiss PM, Sequeira DJ, Coppler PJ, Lang ES, Higgins JS. Reliability and validity of survey instruments to measure work-related fatigue in the emergency medical services setting: a systematic review. *Prehosp Emerg Care* 2018;22:17–27. <https://doi.org/10.1080/10903127.2017.1376134>.
- [118] Temple JL, Hostler D, Martin-Gill C, Moore C, Weiss PM, Sequeira DJ, Condle JP, Lang ES, Higgins JS, Patterson PD. Systematic review and meta-analysis of the effects of caffeine in fatigued shift workers: implications for emergency medical services personnel. *Prehosp Emerg Care* 2018;22:37–46. <https://doi.org/10.1080/10903127.2017.1382624>.
- [119] Martin-Gill C, Barger LK, Moore CG, Higgins JS, Teasley EM, Weiss PM, Condle JP, Flickinger KL, Coppler PJ, Sequeira DJ, Divecha AA, Matthews ME, Lang ES, Patterson PD. Effects of napping during shift work on sleepiness and performance in emergency medical services personnel and similar shift workers: a systematic review and meta-analysis. *Prehosp Emerg Care* 2018;22:47–57. <https://doi.org/10.1080/10903127.2017.1376136>.
- [120] Barger LK, Runyon MS, Renn ML, Moore CG, Weiss PM, Condle JP, Flickinger KL, Divecha AA, Coppler PJ, Sequeira DJ, Lang ES, Higgins JS, Patterson PD. Effect of fatigue training on safety, fatigue, and sleep in emergency medical services personnel and other shift workers: a systematic review and meta-analysis. *Prehosp Emerg Care* 2018;22:58–68. <https://doi.org/10.1080/10903127.2017.1362087>.
- [121] Barger LK, O'Brien CS, Rajaratnam SMW, Qadri S, Sullivan JP, Wang W, Czeisler CA, Lockley SW. Implementing a sleep health education and sleep disorders screening program in fire departments. *J Occup Environ Med* 2016;58(6):601–9. <https://doi.org/10.1097/JOM.0000000000000709>.

This page intentionally left blank

Chapter 49

The rise of patient advocacy in the sleep field

Julie Flygare

Project Sleep, Los Angeles, CA, United States

One must cease to regard all patients as replicas, and honor each one with individual reactions and propensities; and, in this way, with the patient as one's equal, one's co-explorer, not one's puppet, one may find therapeutic ways which are better than other ways, tactics which can be modified as occasion requires.

Sacks O. Awakenings. Vintage Books: [1]

Introduction: The long road ahead

As sleep science and medicine advances rapidly, huge gaps remain between what scientists know about sleep and how our society views sleep. Sleep is often seen as a blank space, something to skimp on, a luxury, or worse, a sign of laziness or weakness. Sayings like “We’ll sleep when we’re dead” remain culturally relevant, perpetuating misperceptions that sleep is expendable in pursuit of more life [2]. Further, an estimated one in five Americans lives with a chronic sleep disorder, yet the majority is undiagnosed, without treatment options and community support. Further, we are far from achieving a state of sleep equity in which everyone has an equal opportunity, based on their need, to obtain the amount and quality of sleep that promotes their physical and mental well-being.

Reaching a brighter future will require people working collaboratively and advocating from various perspectives, including those with expertise in science, clinical care, public health, and first-hand lived experiences. In order to improve the sleep of all Americans, partnering with patient advocacy communities is critical to advance meaningful and sustainable progress.

This chapter introduces patient advocacy groups (PAGs) as a key player in health care and the sleep space and outlines how scientific and medical professionals might increase partnership with PAGs to advance patient-centered outcomes and shared goals of improving people’s lives by improving their sleep.

The power of patient advocacy

Across the broader healthcare landscape, patient advocacy communities have played significant roles in advancing science and medicine. In the 1980s, people with HIV/AIDS and allies demanded important policy changes in how governments and societies responded to the AIDS epidemic [3]. In the early 2000s, the Cystic Fibrosis Foundation and Institute for Healthcare Improvement worked with researchers to expose the huge discrepancies in life expectancy for people with cystic fibrosis depending on the medical center where they received treatment. This led to important collaborative efforts to improve these outcomes across various medical centers [4].

Nonprofit patient advocacy groups (PAGs) address unmet societal needs in health care in a variety of ways (Fig. 49.1), including:

- **Awareness**—Increasing education and awareness of medical conditions to improve understanding, reduce stigma, and reduce delays to diagnosis.
- **Research**—Inspiring, stimulating, and partnering on scientific and clinical research
- **Policy**—Educating policymakers on unmet needs and priorities of patient communities, such as research, treatment options, and access to care.
- **Support**—Providing patients and families with practical advice, navigational support, and invaluable community connection.
- **Advocacy**—Advocating for patients by providing expertise and information to schools, workplaces, insurance companies, or healthcare providers.
- **Empowerment**—Educating patients and loved ones and training patient advocates into community leaders to serve as ambassadors, speakers, mentors, and media representatives.

THE ROLE OF PATIENT ADVOCACY GROUPS



FIGURE 49.1 Patient Advocacy Groups support the scientific and healthcare fields in a variety of ways, advancing awareness, research, policy, patient support, advocacy, and empowerment.

Some PAGs focus on specific health conditions while others represent a broader umbrella group of conditions (such as rare diseases, sleep disorders, or chronic conditions). PAGs may focus their efforts on helping people locally, regionally, nationally, or internationally.

How each group chooses to advance progress depends on a variety of factors, including the most pressing unmet needs of their communities, the organization's mission, leadership, resources, and capacity. PAGs address challenges with programs targeting different levels of the Social Ecological Model, including individual, community, and systems-level approaches. Addressing various levels is all important and interact with each other.

Advancing patient-centered research and care in the sleep field

The sleep field has increasingly recognized the importance of patient-centered research and care models [5,6]. Partnering with patient advocacy groups (PAGs) is a key strategy to accelerate patient-centered models and improve outcomes in the sleep space. Initial efforts to include PAGs and patient advocates in sleep research are underway, yet there remains room for more systematic collaboration between researchers, clinicians, and patient communities. To further the sleep community's path in this direction, key opportunities include:

1. Becoming familiar with the sleep-related PAGs and letting patients know about PAGs' resources
2. Elevating patient voices to effectively raise awareness about sleep and sleep disorders
3. Advancing community-based participatory research (CBPR) in the sleep space by involving PAGs and patient perspectives in every stage of the research process, including the brainstorming phase.

4. Systematically including PAGs and patient advocates in all spaces where scientific and clinical care discussions take place such as scientific conferences and advisory boards.

Sleep-related patient advocacy groups

Sleep-related PAGs offer programs specifically designed to help people living with sleep disorders and their families, yet many patients are unaware of these resources. People with sleep disorders often find PAGs after many years of living with a diagnosis, discovering PAGs on the internet or social media, and report wishing they'd found the organizations sooner. Ideally, healthcare providers would inform patients and family members about PAGs at any and every stage of their journey. It's never too early to start connecting with educational resources and a broader support system, even before any specific diagnosis.

Sleep-related PAGs are growing in sophistication and programmatic offerings, so anyone working in the research, health care, social work, or public health field should gain familiarity with the leading PAGs and let patients know about them. In addition, there are often opportunities for healthcare providers and scientists to get involved with PAGs to lend their perspective and expertise to support the organization's goals.

Sleep Umbrella Organizations:

- **National Sleep Foundation** is an independent nonprofit, dedicated to improving overall health and well-being by advancing sleep health. (Website: thensf.org)
- **Project Sleep** is a 501(c) (3) nonprofit organization dedicated to raising awareness about sleep health, sleep equity, and sleep disorders (Website: project-sleep.com)

Circadian Rhythm Sleep-Wake Disorders:

- **Circadian Sleep Disorders Network** is an independent nonprofit organization dedicated to improving the lives of people with chronic circadian rhythm disorders. (Website: circadiansleepdisorders.org)

Kleine-Levin Syndrome (KLS):

- **KLS Foundation** provides information and support to those diagnosed with KLS and their families. (Website: klsfoundation.org)

Narcolepsy and Idiopathic Hypersomnia:

- **Families and Children Experiencing Symptoms (FACES) of Narcolepsy** is a 501(c) (3) nonprofit organization providing children and young adults with narcolepsy and their families an avenue for connection, information, and guidance. (Website: facesofnarcolepsy.org)
- **Hypersomnia Foundation** engages, informs, and champions our global community to improve the lives of people with idiopathic hypersomnia and related sleep disorders. (Website: hypersomniafoundation.org)
- **Narcolepsy Network** is a national patient support organization founded in 1986 for people with narcolepsy and their families. (Website: narcolepsynetwork.org)
- **Pwn4Pwn** is a patient nonprofit organization for the support of people with narcolepsy and their caregivers. Bringing PWNs together to share experiences and best practices dealing with this invisible disorder. (Website: pwn4pwn.org)
- **Sleep Consortium** is a 501(c) (3) nonprofit organization created to accelerate next-generation research, disease understanding, and therapy development for those living with Central Disorders of Hypersomnolence (CDoH) and related diseases. (Website: sleepconsortium.org)
- **Wake Up Narcolepsy** is a 501(c) (3) not-for-profit organization dedicated to driving narcolepsy awareness, education, and research toward improved treatments and a cure. (Website: wakeupnarcolepsy.org)

Restless legs syndrome (RLS):

- **The Restless Legs Syndrome Foundation** is a nonprofit 501(c) (3) agency that is dedicated to improving the lives of men, women, and children who live with this often-devastating disease. (Website: rls.org)

Sleep Apnea:

- **Alliance of Sleep Apnea Partners** educates patients, caregivers, healthcare providers, and the public about sleep apnea causes, symptoms, therapies, and risks. (Website: apneapartners.org)

- **American Sleep Apnea Association** is a nonprofit organization that works to improve the lives of those affected by sleep apnea and leads the search for the elimination of this syndrome in future generations (Website: sleephealth.org).

At this time, there are no PAGs in the United States dedicated to supporting people with insomnia or REM Sleep Behavior Disorder (RBD). While not representing a specific group of patients, there are several organizations dedicated to advancing specific sleep policy priorities, including:

- **Start School Later, Inc./Healthy Hours** is a registered 501(c) (3) nonprofit organization dedicated to increasing public awareness about the relationship between sleep and school hours and to ensuring school start times compatible with health, safety, education, and equity (Website: <https://www.startschoollater.net/>).
- **Save Standard Time** is a 501(c) (4) nonprofit, nonpartisan, donor-funded, volunteer-supported effort to preserve and extend the observation of longitudinally correct Standard Time (Website: <https:////savestandardtime.com/>).

Increasing sleep awareness by elevating patient voices

In thinking about educating the public about sleep, it may be tempting to think that the public simply does not know enough about sleep, and that it is sleep professionals' role to educate the lay public. One could assume that the public will be grateful to learn from the scientific and healthcare experts and change their attitudes and behaviors about sleep based on this new information. This one-way flow of information from expert to layperson is known as the Knowledge Deficit Model, a persistent yet flawed way of thinking about science and health communications [7,8].

Research shows that the public does not change their opinions or behaviors about health or illness solely based on scientific information. Additional factors such as culture, beliefs, and personal experiences, play important roles. Communications experts advocate for more dialog models that no longer see the public as passive receivers of knowledge, but as engaged equals in a bidirectional dialog [9].

Further, communications research has shown that audiences are more likely to understand and remember health information when it is delivered by someone with lived experience as opposed to hearing a didactic presentation of facts and statistics [10]. For example, In Our Own Voices (IOOV) is a public education program delivered by the National Alliance on Mental Illness (NAMI), which trains individuals living with mental illness to deliver public presentations of their stories of illness and recovery.

Studies have found that presentations by IOOV trainees are incredibly effective in increasing knowledge and attitudes about mental illness and decreasing stigma among the general public, college students, and graduate-level Masters of Social Work (MSW) students [11–13].

In the sleep field, Rising Voices is a training program created by Project Sleep to train individuals living with sleep disorders on how to share their story effectively via presentations. Modeled after other story-sharing training programs with effectiveness metrics including NAMI's IOOV program, Rising Voices combines best practices of storytelling and health communications. The 1-month intensive Rising Voices training takes place online each summer with weekly assignments and individualized feedback to help the patient advocates build a powerful presentation.

Upon completing the training, Rising Voices speakers are prepared to deliver a 30-minute presentation based on their personal story weaving in basic facts about sleep disorders. To date, Project Sleep has trained over 160 speakers living with sleep disorders in 20 countries around the world. Rising Voices speakers are diagnosed with a variety of sleep conditions such as narcolepsy, idiopathic hypersomnia, sleep apnea, and REM sleep behavior disorder.

Despite research indicating that personal stories of illness are an effective model for education, there is limited inclusion of patient voices in public health campaigns, education activities, or at scientific or medical conferences.

Health professionals can leverage opportunities to learn from patient voices by coordinating engagements for Rising Voices speakers with organizations, groups, schools, and societies within their network or community. Further, a health professional could invite a Rising Voices speaker to share their story and then afterward, deliver a more didactic presentation building off the patient's story and broadening the discussion. By working together, patient advocates and healthcare professionals can foster more impactful sleep education and awareness initiatives and campaigns.

Partnership in research process

The sleep community is well-positioned to adopt a framework called community-based participatory research (CBPR) which includes community members, organizational representatives, and researchers as equal partners in the research process, working collaboratively and acknowledging the value of each other's perspectives [14]. Utilized in public health, sociology, and nursing, the goal of CBPR is to create change that is impactful and sustainable by working together with, for, and in communities [15].

In the Western traditional scientific process, researchers generate ideas and design interventions and generally

approach patient communities when looking for research participants. Moving away from this traditional approach toward a participatory framework requires acknowledging that researchers are not the gatekeepers of knowledge, and that members of the community have equally important perspectives and input which complement the scientific evidence-based approach in developing research questions and interventions [15].

Engaging PAGs and patient advocates

Both patient advocacy groups and individual patient advocates serve as important partners in implementing CBPR, but these two groups' contributions are not interchangeable, both should be involved. Individual patient advocates provide invaluable insight from living with a sleep disorder or having a loved one with a sleep disorder. These first-hand accounts about what they've experienced in their medical journeys help to illustrate the challenges, unmet needs, and goals of individuals and families.

Yet, there is often a wide variety of experiences and perspectives across any health condition community. PAGs can help to identify and amplify a diverse set of voices to inform research priorities. PAGs can also speak to trends and shifts in community needs and goals over time, and can serve as powerful partners in developing and implementing research and interventions to ensure their success and sustainability.

While researchers should seek patient advocates' perspectives outside of a clinical setting, inherent power imbalances between patients and scientific and medical professionals remain at play and should be acknowledged and accommodated for as best as possible [16,17]. The power dynamics between PAGs and researchers will be different, potentially allowing for important constructive feedback that individual patient advocates may not feel comfortable sharing.

Furthermore, PAGs build trust with their community and constituents by delivering programming over many years. Their ability to reach a large group of patients and families is a powerful resource. When researchers authentically partner with a PAG on a research project, the PAG will be more likely to support the project and educate their community about any opportunities for participation. Especially for those looking to develop psychosocial or self-management interventions, working with a PAG on design and implementation will ensure these interventions are not healthcare professional-centered, reach more patients and families, and are sustainable [17].

Progress in action: PCORI

The Patient-Centered Outcomes Research Institute (PCORI) has played a powerful role in moving healthcare researchers toward utilizing CBPR. PCORI is a

government-sponsored organization funding comparative effectiveness research aiming to help patients and caregivers make informed decisions about treatment and care options. Since its authorization by Congress in 2010, PCORI has promoted patient inclusion in several ways, including requiring research applicants to provide a plan for how they will work with patients and other stakeholders throughout their project.

PCORI also includes patients, family members, caregivers, and representatives of PAGs to serve on PCORI Advisory Panels or Merit Review Panels [18]. In 2024, two of Project Sleep's Rising Voices trained patient advocates took on roles on PCORI Merit Review Panels.

From 2016 to 2018, PCORI funded an Engagement Award Conference project called "Strategically Leverage Engage and Empower PCOR in Sleep (SLEEP-2)" led by Sairam Parthasarathy, MD at the University of Arizona. The project aimed to "engage patients, scientists, and other stakeholders across the entire span of sleep research, from developing ideas, conducting research, to spreading the information and making changes to healthcare delivery that are patient-centered." [19] The project included the Sleep Research Network along with Project Sleep serving as the patient advocacy partner organization. Together, the team conducted four in-person conferences over 2 years.

Believing in the power of multidisciplinary collaboration, Project Sleep invited a public health expert, Rebecca Fuoco, MPH to present at a SLEEP-2 conference on utilizing people-centered language in sleep research communications. This led to two publications in SLEEP, the journal of the Sleep Research Society on people-centered language choice [20,21]. Further, both the SLEEP journal and the Journal of Clinical Sleep Medicine changed their author guidelines to require people-centered language in their publications [22,23].

PCORI's focus on patient engagement throughout the research process systematically encourages CBPR. While other funders may not yet require the same level of partnership, researchers should still approach PAGs about potential research collaborations early in the brainstorming phase to increase accessibility, sustainability, and impact.

Patient inclusion at conferences

Since scientific and medical conferences and educational events serve as important venues to disseminate the latest research findings, exchange ideas, and discuss potential collaborations, including patients and PAGs at sleep-related conferences is one way to foster patient-centered sleep research and care models [24].

Further, one study suggests that when included in healthcare conferences, patient advocates play a powerful role in increasing the flow of scientific information via social media and generating more online discussion

compared with physicians [25]. Given the wide gap between scientific and public understanding of sleep, including patient communities at healthcare conferences is an important approach to help disseminate important research findings to the public [26].

Initiatives aiming to promote patient engagement at healthcare conferences include Patients Included inspired by healthcare innovator, Lucien Engelen and Everyone Included developed by Stanford Medicine X in 2016 [27,28]. For Lucien Engelen, his "aha" moment came as a keynote speaker at a major medical conference in Dubai where mHealth (mobile health) was all the buzz. Engelen describes, "When it was my turn to deliver my keynote, I asked the audience 'How many patients are present here?' Not one, it appeared. That there should be so much talk about what patients need and want without them being present prompted me to take action. I decided to no longer present nor visit conferences without patients being present on the stage, or as members of the organizing committee, or offering patients bursaries to attend and waiving the entrance fee" [27].

There are a number of ways to systematically encourage patient advocates and PAG inclusion in healthcare conferences. Approaches include:

- Speaking opportunities for patient advocates and PAG representatives, especially as keynote speakers and on multidisciplinary panels on a particular topic
- Active participation from patient advocates and PAGs in the design and planning of the event, including the selection of themes, topics, and speakers
- Travel reimbursement or scholarships for a certain number of patient advocates to attend the event for free or for a discounted rate
- Booth space for PAGs to showcase their programming and offerings to event attendees, provided for free or a discounted rate
- Highlighting PAGs in event materials (printed or digital) for free or a discounted rate
- Accommodating disability requirements for participants. For example at a large scientific or medical conference, having a designated quiet space or wellness room available on site when feasible
- Virtual participation opportunities for patient advocates via free live streaming or video recordings, when feasible

Individual sleep researchers and clinicians can help to uphold similar patient inclusion values. Upon receiving an invitation to speak at a meeting, a sleep professional can ask if a patient advocate or PAG will also be a speaker in the program agenda. If not, the professional can facilitate an introduction between the event organizer and a relevant PAG to help identify opportunities to include patient perspectives.

Progress in action: APSS SLEEP meeting

The annual SLEEP meeting is one of the premier clinical and scientific meetings in the sleep field, hosted by the Associated Professional Sleep Societies (APSS), a collaboration of the American Academy of Sleep Medicine (AASM) and the Sleep Research Society (SRS). Historically, patient advocates were unable to register to attend the SLEEP meeting, unless falsely checking a box pretending to be a healthcare professional and paying a professional registration rate. PAGs could obtain an exhibitor booth in the SLEEP meeting exhibit hall for a fee, but many small nonprofits found the rate cost-prohibitive.

In 2018, Project Sleep's leadership facilitated a meeting between APSS leadership and American Society of Clinical Oncology (ASCO) staff to learn about ASCO's programs and opportunities for PAGs and patient advocates to attend and participate in their annual meeting [29].

Subsequently, SLEEP 2019 was the first year patient advocates could attend the full SLEEP meeting for a reduced registration rate. When filling out the registration form, patient advocates must indicate which patient advocacy organization they are affiliated with in order to access the discounted rate.

For the first time, the SLEEP 2022 meeting exhibition hall featured an Advocacy Pavilion as a designated area highlighting PAGs. APSS offered a 10×10 booth space to PAGs for free and conducted special giveaways to encourage attendees to visit all the PAG booths.

Further, the 2024 SLEEP Session Proposal Submission Guide was updated to actively encourage clinicians and researchers applying for conference sessions to include patient input, stating "The APSS also encourages session proposals to include the perspectives of patients ... including inviting a patient to be a speaker, showing video testimonials from patients, or sharing results from a survey of patients." [30] This led to greater interest in including patient advocates in conference proposals, and at least five accepted 2024 SLEEP sessions included patient voices [31].

The APSS SLEEP meeting's increased commitment to patient advocacy inclusion is a leading model for other major sleep meetings and state sleep societies to follow. Providing similar opportunities to PAGs and patient advocates to share their perspectives and programs adds extra value to attendees.

Patient inclusion on advisory boards

Advisory boards and panels in the healthcare space often provide expertise on the unmet needs of patient populations and guidance on scientific projects [32]. Including PAG representatives and patient advocates on advisory boards alongside clinicians and researchers is an important way to break down silos and bring authentic representation from individuals directly impacted by the topics discussed.

This representation will help ensure the group's discussion is well-informed by patient-centered priorities and real-world unmet needs.

Progress in action: The National Center on Sleep Disorders Research

In 1993, Congress established the National Center on Sleep Disorders Research (NCSDR) at NIH to "conduct and support biomedical and related research and research training, the dissemination of health information, and the conduct of other programs with respect to various sleep disorders, the basic understanding of sleep, biological and circadian rhythm research, chronobiology and other sleep related research" (U.S. Congress, Senate, 1993). The original NCSDR authorizing legislation established an advisory board to the NCSDR, composed of 12 members of the public—eight scientific members and four public members who either are advocates for or have a particular sleep disorder [33].

The inclusion of four sleep disorder patient advocates on the NCSDR advisory board was particularly ahead of its time in the sleep space and may have been modeled after other NIH advisory boards where public members served alongside scientific members. To this day, this is a unique opportunity for PAG representatives and patient advocates to sit as equals alongside clinical and scientific experts in the sleep space.

Progress in action: Project Sleep's Expert Advisory Board

More recently, in 2022, Project Sleep started thinking about creating a "Scientific and Medical Advisory Board," and a separate "Patient Advisory Board" in keeping with what we saw other PAGs do. Yet, something didn't seem right about this, as Project Sleep is a strong advocate for patient inclusion and bringing expertise together into one space. So, Project Sleep created an "Expert Advisory Board" to break down silos by bringing a powerful group of clinicians, researchers, patients, and advocates all together onto one panel [34,35]. The word "expert" was chosen because Project Sleep believes that real-life lived experience offers a different form of expertise than clinicians and scientists.

Conclusion: Looking toward a brighter future

Addressing the complex challenges surrounding sleep health, sleep equity, and sleep disorders requires more than scientific and medical advancement; it calls for incorporating the lived experiences and priorities of those most affected. By forming strong partnerships with PAGs, scientific and medical professionals will be better equipped to develop patient-centered research and care that can positively impact more people's lives. Integrating PAGs and

patient advocates into every stage of the research and healthcare improvement process will break down silos, reduce stigma, and help build a culture which values sleep as a cornerstone of health and well-being. The path to improving people's lives by improving their sleep includes recognizing PAGs and patient advocates as co-explorers, honoring individual experiences, and elevating community perspectives in all facets of the sleep field.

References

- [1] Sacks O. *Awakenings*. Vintage Books; 1999.
- [2] The White House. Remarks by vice president Harris and Governor Tim Walz at a Campaign event in Las Vegas, NV on August 10, 2024. 2024. <https://www.whitehouse.gov/briefing-room/speeches-remarks/2024/08/10/remarks-by-vice-president-harris-and-governor-tim-walz-at-a-campaign-event-in-las-vegas-nv/>. [Accessed 15 November 2024].
- [3] Wright J. Only your calamity: the beginnings of activism by and for people with AIDS. *Am J Public Health* 2013;103(10):1788–98. <https://doi.org/10.2105/AJPH.2013.301381>.
- [4] Gawande A. The health care bell curve. *The New Yorker*; 2004. www.newyorker.com.
- [5] Zee PC, Badr MS, Kushida C, et al. Strategic opportunities in sleep and circadian research: report of the joint task force of the sleep research society and American academy of sleep medicine. *Sleep* 2014;37(2):219–227.2.
- [6] Redline S, Baker-Goodwin S, Bakker JP, et al. Sleep apnea patient-centered outcomes network. Patient partnerships transforming sleep medicine research and clinical care: perspectives from the sleep apnea patient-centered outcomes network. *J Clin Sleep Med* 2016;12(7):1053–8.
- [7] Grant W. The knowledge deficit model and science communication. Oxford Research Encyclopedia of Communication; 2023. <https://oxfordre.com/communication/view/10.1093/acrefore/9780190228613.001.0001/acrefore-9780190228613-e-1396>.
- [8] Nisbet MC, Scheufele DA. What's next for science communication? Promising directions and lingering distractions. *Am J Bot* 2009;96(10):1767–78. <https://doi.org/10.3732/ajb.0900041>.
- [9] Reincke CM, Bredenoord AL, van Mil MH. From deficit to dialogue in science communication: the dialogue communication model requires additional roles from scientists. *EMBO Rep* 2020;21(9):e51278. <https://doi.org/10.15252/embr.202051278>.
- [10] Corrigan PW, Rafacz JD, Hautamaki J, Walton J, Rüsch N, Rao D, et al. Changing stigmatizing perceptions and recollections about mental illness: the effects of NAMI's in our own voice. *Community Mental Health J* 2010;46(5):517–22.
- [11] Brennan M, McGrew JH. Evaluating the effects of NAMI's consumer presentation program, in our own voice. *Psychiatr Rehabil J* 2013;36(2):72–9.
- [12] Wood AL, Wahl OF. Evaluating the effectiveness of a consumer-provided mental health recovery education presentation. *Psychiatr Rehabil J* 2006;30(1):46–53.
- [13] Pittman JOE, Noh S, Coleman D. Evaluating the effectiveness of a consumer delivered anti-stigma program: replication with graduate-level helping professionals. *Psychiatr Rehabil J* 2010;33(3):236–8.
- [14] Wallerstein N, Duran B, Oetzel J, Minkler M. Community-based participatory research for health. In: 3rd. San Franciso. Jossey Bass; 2017.
- [15] Collins SE, Clifasefi SL, Stanton J, Board The Leap Advisory, Straits KJE, Gil-Kashiwabara E, Rodriguez Espinosa P, Nicasio AV, Andrasik MP, Hawes SM, Miller KA, Nelson LA, Orfaly VE, Duran BM, Wallerstein N. Community-based participatory research (CBPR): towards equitable involvement of community in psychology research. *Am Psychol* 2018;73(7):884–98. <https://doi.org/10.1037/amp0000167>.
- [16] Coulter A. Paternalism or partnership? Patients have grown up—and there's no going back. *BMJ* 1999;319:719. <https://doi.org/10.1136/bmj.319.7212.719>.
- [17] Wilson J. Acknowledging the expertise of patients and their organisations. *BMJ* 1999;319(7212):771–4. <https://doi.org/10.1136/bmj.319.7212.771>.
- [18] PCORI stakeholders. 2024. <https://www.pcori.org/about/about-pcori/our-programs/engagement/public-and-patient-engagement/pcoris-stakeholders#:%~:text=These%20individuals%20are%20included%20on,experienced%20across%20the%20healthcare%20continuum>. [Accessed 15 November 2024].
- [19] PCORI. <https://www.pcori.org/sites/default/files/EA-Parthasarathy004-Final-Summary-Report.pdf>. [Accessed 15 November 2024].
- [20] Fuoco RE. People-centered language recommendations for sleep research communication. *Sleep* 2017;40(4). <https://doi.org/10.1093/sleep/zsx039>.
- [21] Buysse DJ, Parthasarathy S, Flygare J. Introducing people-centered language to SLEEP. *Sleep* 2017;40(4):zsx038. <https://doi.org/10.1093/sleep/zsx038>.
- [22] PCORI. <https://www.pcori.org/engagement-research/influencing-culture-research>. [Accessed 15 November 2024].
- [23] JCSM manuscript submission guidelines. <https://jcsmaasm.org/submit/submitting-guidelines>. [Accessed 15 November 2024].
- [24] Hauss K. What are the social and scientific benefits of participating at academic conferences? Insights from a survey among doctoral students and postdocs in Germany. *Res Eval* 2020;27:rva018. <https://doi.org/10.1093/reseval/rva018>.
- [25] Utengen A, Rouholiman D, Gamble JG, Grajales III FJ, Pradhan N, Staley AC, Bernstein L, Young SD, Clauson KA, Chu LF. Patient participation at health care conferences: engaged patients increase information flow, expand propagation, and Deepen engagement in the conversation of Tweets compared to physicians or researchers. *J Med Internet Res* 2017;19(8):e280. <https://doi.org/10.2196/jmir.8049>.
- [26] Newman B, Bowden J, Jessup R, Christie LJ, Livingstone A, Sarkies M, Killedar A, Vleeskens C, Sarwar M, Tieu T, Chamberlain S, Harrison R, Pearce A. Engaging with health consumers in scientific conferences-as partners not bystanders. *Health Expect* 2024;27(4):e14147. <https://doi.org/10.1111/hex.14147>.
- [27] Patients included. <https://patientsincluded.org/>. [Accessed 15 November 2024].
- [28] Everyone included. <https://everyoneincluded.org/>. [Accessed 15 November 2024].
- [29] Patient advocate lounge. American Society of Clinical Oncology (ASCO); n.d. <https://conferences.asco.org/am/patient-advocate-lounge>. [Accessed 15 November 2024].
- [30] SLEEP 2024 call for sessions. https://www.sleepmeeting.org/wp-content/uploads/2023/10/SLEEP24_CallForSessions.pdf. [Accessed 15 November 2024].

- [31] Project sleep. <https://project-sleep.com/project-sleep-at-apss-sleep-meeting-2024/>. [Accessed 15 November 2024].
- [32] Tip sheet for medical advisory board recruitment and management. <https://rarediseases.org/wp-content/uploads/2022/10/Tip-Sheet-for-Medical-Advisory-Board.pdf>. [Accessed 15 November 2024].
- [33] Institute of Medicine (US). Committee on sleep medicine and research; Colten HR, Altevogt BM, editors. Sleep disorders and sleep deprivation: an unmet public health problem. Washington (DC): National Academies Press (US); 2006. p. 8. Bolstering Somnology and Sleep Disorders Research Programs, <https://www.ncbi.nlm.nih.gov/books/NBK19950/>.
- [34] Flygare J. Expert advisory boards: a new model for co-exploration. Society for Participatory Medicine; 2023. <https://participatorymedicine.org/epatients/2023/01/expert-advisory-boards-a-new-model-for-co-exploration.html>. [Accessed 15 November 2024].
- [35] Expert advisory board. Project Sleep; n.d. <https://project-sleep.com/expert-advisory-board/>. [Accessed 15 November 2024].

Index

'Note: Page numbers followed by "f" indicate figures and "t" indicate tables.'

A

- Academic achievement, 586–588
- Accelerometer, 196
- Acculturation, 89
- Acetaldehyde, 333
- Acetate, 333
- Acetylcholine, 8
- Acquired immune system, 387–388
- Actigraphy (ACT), 9, 23, 38, 254–255, 455–456, 490–491, 540, 574, 606
 - activity level changes, 202
 - commercially available sleep trackers, 203–204
 - device types, 197–198
 - dynamic range, 202
 - frequency response, 202
 - high and low frequency limit, 202
 - identifying sleep stages with, 199–201
 - limitations, 198–199
 - movement recording, 202
 - noise, 202
 - off-wrist time, 202
 - output deviation, 202
 - vs. polysomnography, 195, 196t
 - recording modes, 202
 - scientific guidelines, 202–203
 - scoring algorithms, 195–197
 - temperature sensitivity and range, 202
- Actillume, 197
- Activator protein 1 (AP-1), 391
- Actiwatch spectrum, 197
- Adaptive servoventilation, 513
- Adenosine, 322
 - receptors, 375
 - in sleep-wake cycle, 375
- Adenosine A_{2A} receptor (ADORA2A) gene, 375–376, 417
- Adenosine deaminase (ADA), 376, 417
- Adolescence
 - characteristics, 585
 - circadian biological clock, 585
 - delaying high school start time
 - academic achievement, 586–588
 - bedtime stability, 586
 - self-reported sleep duration, 586, 587f
 - students' letter grades, 587
 - early school start times, 585–586
 - mental health and sleep improvements, 578–580, 588–589
 - clinicians, 579–580

- families, 578
- policymakers, 580
- schools, 578–579
- recommended sleep duration for, 565t
- risky behavior, 588–589
- short sleep duration epidemic, 585
- sleep, 24–26
- sleep/wake homeostasis, 585
- social and environmental factors, 585
- unintentional injury, 589
- Adrenocorticotrophic hormone (ACTH), 500–501
- Adult sleep, 96–98
- Advanced sleep-wake phase disorder, athlete, 641–642
- Aerobic capacity, 442
- Aggressive/punitive responses, 428
- Aging immune system, 388
- Air quality, impact on sleep, 112–113
- Alameda 7 study, 557
- Alcohol, 333
 - dehydrogenase, 333
 - metabolism, 333
 - sleep hygiene, 187
- Alcohol dependence
 - active, 336
 - in acute withdrawal, 336
 - behavioral treatments for insomnia and, 337
 - circadian disruption, 337–338
 - early recovery, 336
 - insomnia in, 336–337
 - obstructive sleep apnea, 340
 - pharmacologic treatments for insomnia in, 337
 - sustained recovery, 337
- Alcohol use
 - breathing related sleep disorders and, 340
 - circadian rhythms and, 337–338
 - insomnia and, 333–337
 - napping, 341
 - neurobiology, 333
 - parasomnias and, 341
 - during pregnancy, 341
 - sleep duration abnormalities and, 338–339
 - sleep-related movement disorders and, 340–341
- Alcohol use disorder (AUD), 334, 481
- Aldehyde dehydrogenase, 333
- Alertness, 404–405, 670–672
- Alliance of Sleep Apnea Partners, 683
- Allostatic Load Model, 596

- Alternate payment models (APMs), 633, 633f
- Alzheimer's disease (AD), 461
 - definition, 462
 - neuroimaging biomarkers, 462
- Ambulatory Monitoring, Inc. (AMI), 197
- American Academy of Sleep Medicine (AASM), 172, 189, 541–542, 558–559, 565, 565t, 596, 622
- American College of Physicians (ACP), 502
- American Psychiatric Association (APA), 474
- American Sleep Apnea Association, 683
- American Time Use Survey (ATUS), 15, 157, 438, 597–598
- Anterior cingulate cortex (ACC), 240, 421
- Antigen presenting cells (APCs), 387–388
- Anti-retroviral therapy (ART), 357–358
- Anxiety, 573
 - cancer, 538
 - exercise, 322
- Anxiety disorders, 133, 479–480
- Anxious children, 576
- Apnea, 339, 509
 - Apnea-hypopnea index (AHI), 168, 323–324, 490–491
- Apnea Positive Pressure Long-term Efficacy Study (APPLES), 514
- Arachidonoylglycerol (2-AG), 307
- Arcuate nucleus (ARC), 292
- Armodafinil, 542
- Arrhythmia, 513
- Artificial light at night (ALAN), 107–109
- Associated Professional Sleep Societies (APSS), 686
- Athletes
 - circadian health promotion program, 645f
 - guideline documents and consensus statements, 640–641, 640f
 - monitoring programs, 646
 - optimization and competitive advantage, 646
 - sleep and circadian health, 640f
 - sleep concerns, 639
 - sleep disturbance, 642f
 - sleep education program
 - culture change, 643–644
 - elements, 644–646
 - evidence-based, 643–644
 - sleep health, 639–640
 - sleep problems

Athletes (*Continued*)
 assessment, 643f
 circadian rhythms disruptions, 644f
 identification and management, 641–643
 referral strategy, 643
 screening, 643
 travel and jetlag management, 646
 Atrial fibrillation, 513
 Attachment, 118
 Attention, 439–440
 Attention-deficit/hyperactivity disorder (ADHD), 480
 Attitude, 222–223
 Autism spectrum disorder (ASD), 481
 Autonomic nervous system (ANS), 9, 289–290, 394
 Awake after sleep onset (WASO), 127

B

Balloon Analog Risk Task (BART), 427
 B cells, 387–388
 Bedroom environment, 187–188
 Bedtime procrastination, 438
 Behavioral beliefs, 222–223
 Behavioral economics, 228–229
 Behavioral health consultant (BHC), 661
 Behavioral interventions, family sleep dynamics, 147–148
 Behavioral model, 476
 Behavioral rhythms, 288–289
 Behavioral Risk Factor Surveillance System (BRFSS), 14, 84, 351, 611
 Behavioral sleep medicine (BSM) services, 661–662
 Behavior change theory
 appropriate scales, 230–231
 behavioral economics, 228–229
 causation in, 218–220
 cognitive behavioral therapy (CBT), 225–226
 community level theories, 227–229
 confounding variables, 219
 continuum theories, 220
 draft instrument, 231
 foundation of theory for, 217–218
 instrument purpose, 229
 instrument reliability and validity, 232
 interpersonal theories, 226–227
 interventions and program, 217–218
 intrapersonal theories, 221–226
 items development, 231
 limitations, 232
 models, 217
 motivational interviewing (MI), 225
 objects of interest, 229–230
 constitutively define, 229–230
 identify, 229
 operationally define, 230
 original instrument, 230
 panel of experts, 231
 pilot test, 232
 previously developed instruments, 230
 readability test, 231
 socio-ecological model, 220, 221f

theoretical frameworks, 229
 utility of, 218
 Benzodiazepines, 359, 464, 530, 541–542
 Berlin questionnaire, 172, 173f
 Beta cell dysfunction, 265–266
 Bi-directional regulation, 292
 Binge-watching television, 160
 Biological clocks, 284, 558
 Biological rhythms, 289–292
 Biomarkers, 416
 Bipolar disorder (BPD), 479
 Blood alcohol level, 333
 Blood pressure (BP), 255–257, 491–497
 Body mass index (BMI), 24, 555–556, 623–624
 Body temperature, 322
 Brain derived neurotrophic factor (BDNF) gene, 422
 Brain health, 463f
 Brain oxygenation level-dependent (BOLD) activity, 441
 Brainstem, 8
 Breathing related sleep disorders, 340
 Brief Behavioral Therapy for insomnia (BBTI), 661
 Brief Index of Sleep Control (BrISC), 164
 Bright light therapy, 544, 579
 Bronfenbrenner's ecological systems theory, 578–580
 Buffalo CardioMetabolic Occupational Police Stress (BCOPS) study, 669
 Bupropion, 356
 B vitamins, 310
 2 B Web Alert tool, 379

C

Caffeine, 425
 adverse effects, 376
 alcohol use, 377
 beverages and contents, 371t
 chronotype/intake time, 376
 circadian misalignment, 378
 comorbid burden of disease, 377
 concurrent use of, 379
 environmental factors and response, 376–377
 epidemiology of sleep in, 370–372
 genetic factors and response, 374–377
 health implications of, 377–378
 insomnia, 374
 intake of, 369
 intoxication, 370
 nonspecific sleep disturbances, 378
 physiology, in sleep-wake cycle, 374–377
 recovery sleep, 374
 short sleep duration, 377–378
 sleep deprivation, 374
 sleep hygiene, 186
 sleepiness, 370–371, 374
 sociodemographic pattern, 377
 withdrawal, 376
 Caffeine-induced anxiety disorder, 370
 Caffeine-induced sleep disorder, 370
 Caffeine-insomnia, 369–370

Caffeine related disorder, 370
 Caloric consumption, 307
 Caloric intake, 237–238, 243
 Canadian National Health Population Survey, 450
 Cancer
 fatigue. *See* Cancer-related fatigue (CRF)
 sleep-wake disturbance
 bright light therapy, 544
 clinical interview, 539–540
 cognitive behavioral therapy for insomnia (CBT-I), 543
 exercise, 541
 fatigue only measures, 540
 mindful movement interventions, 543–544
 mindfulness-based interventions, 542–543
 perpetuating factors, 538–539
 pharmacotherapy, 541–542
 precipitating factors, 537–538
 predisposing factors, 536–537
 screening, 539
 sleep and wake measures, 540
 sleep only measures, 540
 Cancer-related fatigue (CRF)
 bright light therapy, 544
 cancer treatment, 537–538
 clinical interview, 539–540
 cognitive behavioral therapy for insomnia (CBT-I), 543
 exercise, 541
 lifestyle changes and financial stress, 538
 mechanisms, 536
 mindful movement interventions, 543–544
 mindfulness-based interventions, 542–543
 mood disturbances, 538
 pain, 538
 perpetuating factors
 diet, 538–539
 dysfunctional thoughts, 538
 napping and extending time, 538
 pharmacotherapy, 541–542
 precipitating factors
 cytokine dysregulation, 537
 HPA axis dysregulation, 537
 serotonin (5-HT) dysregulation, 537
 tumorigenesis, 537
 predisposing factors, 536–537, 536f
 biological sex, 537
 genetics, 536–537
 prevalence, 535
 screening, 539
 sleep and wake measures, 540
 sleep only measures, 540
 symptoms, 535
 Candidate Gene Association Resource (CARe), 277
 CANPAP trial, 513
 Carbohydrates, 308–309
 Cardiometabolic health
 behavioral rhythms, 288–289
 biological rhythms and, 289–292
 circadian disruption, 285–286

- environmental rhythms and, 288
- Cardiometabolic syndrome**, 283–284
- Cardiovascular disease**, 511–513
- arrhythmia, 513
 - coronary artery disease, 512
 - heart failure, 513
 - hypertension, 511–512
 - insufficient sleep
 - and blood pressure, 255–257
 - and coronary heart disease, 257–259
 - and heart failure, 259
 - and stroke, 259–260
 - pathological hypoxia, 514
- Cardiovascular functioning**, 286
- Cardiovascular health, older adults**
- insomnia, 40
 - sleep-disordered breathing, 40
 - sleep duration, 40
- Catecholamine**, 500
- Cellular senescence**, 388
- Centers for Disease Control and Prevention (CDC)**, 14, 555–556, 561–562, 611
- Central nervous system (CNS)**, 23–24
- Central sleep apnea (CSA)**, 323, 339, 509, 510f, 642
- Cerebrovascular disease**, 512–513
- Cerebrum**, 8
- Chalder Fatigue Questionnaire (CFQ)**, 670
- Cheyne-Stokes respiration (CSR)**, 259
- Childhood obesity**
- causes, 556
 - consequences, 556–557
 - energy homeostasis, 559–560
 - epidemic, reduction, 557
 - sleep and health, 557
 - sleep duration, 557–558
 - sleep parameters, 558–559
- Childhood sleep**, 24
- Children**
- diabetes and, 562–563
 - mental health and sleep improvements, 578–580
 - clinicians, 579–580
 - families, 578
 - policymakers, 580
 - schools, 578–579
 - obesity in, 555–556, 556f
 - overweight, 555–556, 556f
 - recommended sleep duration for, 565t
 - sleep and, 565
- Chronic insomnia**, 253–254
- Chronic insufficient sleep**, 168
- Chronic pain**, 159–160
- Chronic partial sleep deprivation**, 13
- Chronic sleep restriction**, 374
- Chronotypes**, 242, 337–338, 439, 670
- Cigarette smoking**
- epidemiology of, 347–348
 - smokers vs. nonsmokers
 - daytime sleepiness, 351–352
 - objective and subjective sleep metrics, 349t–350t
 - sleep architecture, 348
 - sleep continuity, 348, 351
- sleep fragmentation, 351
- Circadian biological clock, adolescence**, 585
- Circadian control, cardiometabolic system**, 286–287
- Circadian disruption**, 437
- and cardiometabolic health, 285–286
 - neurocognitive processes, 440f
 - screen use, 211
 - and social jetlag, 285
- Circadian health promotion program**, 645f
- Circadian misalignment**, 278, 378, 588–589, 601
- Circadian principles**, 670
- Circadian process**, 208, 412, 412f, 415f
- Circadian rhythm**, 284–285, 558
- alcohol use
 - alcohol dependent individuals, 338
 - chronopharmacokinetic studies, 338
 - clinical findings on shiftwork, 338
 - and diabetes, 271
 - disorders screening, 176
 - endogenous, 277
 - exogenous, 277
 - older adults, 35
 - sleep and, 6–8
- Circadian rhythm sleep-wake disorders (CRSWDs)**, 146, 641–642, 682
- Circadian Sleep Disorders Network**, 682
- Circadian technologies**, 646
- Clockwatching**, 188
- Clonazepam**, 341
- Cognitive Activation Theory of Stress**, 596
- Cognitive behavioral therapy (CBT)**, 225–226
- Cognitive behavioral therapy for insomnia (CBT-I)**, 147–148, 185, 226, 337, 359, 391, 443, 464, 502, 659, 661–662, 674
- cancer-related fatigue (CRF)**, 543
- comorbid insomnia and sleep apnea (COMISA)**
- four-session therapist-delivered CBT-I program, 528–529
 - randomized controlled trial, 529
 - respiratory arousal threshold, 528–529
 - sedative and hypnotic medicines, 530
 - suboptimal access, 529
- components**, 527t
- for primary insomnia, 649
 - psychiatric disorders, 482–483
 - sleep restriction, 482
 - standard treatment components, 651t
 - stimulus control, 482
 - therapist-led, 650, 654
- Cognitive behavioral therapy for insomnia for patients with bipolar disorder (CBTI-BP)**, 482–483
- Cognitive control**
- cognitive interference, 422–423
 - flexible attentional control, 423
 - multi-tasking and task-switching, 422
 - task-switching, 422
- Cognitive flexibility**, 421
- Cognitive framing**, 425–426
- Cognitive function, older adults**
- daytime napping, 38–39
 - excessive daytime sleepiness, 39
 - insomnia, 39
 - objectively measured sleep disturbances, 38
 - self-reported sleep complaints, 38
 - sleep disordered breathing, 39
 - sleep duration, 37–38
- Cognitive interference**, 422–423
- Cognitive model**, 476–477
- Cognitive stability**, 421
- Commercially available sleep trackers**, 203–204
- Commercial motor vehicle (CMV) operators**
- drowsy driving, 621
 - obstructive sleep apnea (OSA)**
 - current regulation, 622
 - daytime sleepiness, 621
 - diagnosis, 621, 624–625
 - education, 625
 - federally funded research and regulatory activity, 622
 - initial evaluation, 624
 - positive airway pressure (PAP) therapy, 625
 - prevalence, 621–622
 - screening criteria, 622–624, 624t
 - treatment, 625
- Community-based participatory research (CBPR)**, 684
- Community level theories**, 227–229
- Comorbid insomnia and sleep apnea (COMISA)**
- bidirectional associations, 525–526, 525f
 - characteristics, 522–523
 - distressing difficulties, 522–523
 - insomnia, 522
 - obstructive sleep apnea (OSA), 522
 - sleep onset and maintenance difficulties, 523f
 - consequences, 524–525
 - history, 521–522
 - prevalence, 523–524
 - treatment, 526–530
- Computer-adaptive tests (CAT)**, 176
- Concepts**, 217
- Concurrent validity**, 232
- Concussion**
- acute neuropathological changes, 454
 - cellular homeostasis disruption, 453–454
 - glutamate dynamics alterations, 453–454
 - glymphatic dysfunction, 453–454
 - neurochemical disruptions, 453–454
 - neuropsychiatric morbidity, 454
 - polysomnography, 455–456
 - prevalence, 450–451
 - risk factors, 449, 454
 - sleep disturbances, 454–455
 - neuropathological changes, 454
 - sex differences, 455
 - sleep-related symptoms, 454–455
 - sleep duration, 455
 - sport-related concussion (SRC), 449–450
 - symptoms, 449

Confounding variables, behavior change theory, 219
 Consensus Sleep Diary, 540
 Constructs, 217
 Construct validity, 232
 Consumer sleep technologies, 179–180
 Continuous positive airway pressure (CPAP) therapy, 243, 443, 510, 674 devices, 510
 OSA treatment, 526–527
 sleep-disordered breathing, 37
 Continuum theory, 220 behavioral economics, 228–229 social cognitive theory (SCT), 226 social network theory (SNT), 227
 Convergent thinking, 424
 Coronary artery disease, 512
 Coronary Artery Risk Development in Young Adults (CARDIA) study, 78, 255–256
 Coronary heart disease (CHD), 257–259, 499
 Cortisol, 284, 288, 291, 394–395, 500–501
 Cost-effectiveness analyses (CEAs), 630
 C-reactive protein (CRP), 255, 388, 500–501
 CYP1A2 gene polymorphism, 376
 Cytokine dysregulation, 537
 Cytokines, 387–388

D

Daytime function, comorbid insomnia and sleep apnea (COMISA), 524
 Daytime napping, 38–39
 Daytime sleepiness, 514 excessive, 274 in smokers vs. nonsmokers, 351–352
 Default mode network, 413
 Delay discounting, 440
 Delayed sleep-wake phase disorder, 176, 641–642
 Delaying school start time, 586
 Dementia, 461 diagnostic criteria, 462 disturbed sleep, 461 sleep disturbances, 462–464 sleep interventions, 464–465
 Depression, 573 cancer, 538 exercise, 322 insomnia, 477 smoking, 358
 Dextroamphetamine, 373, 426–427, 427f
 Diabetes, 562–563 circadian misalignment and, 278 circadian rhythm and, 271 endogenous circadian rhythm and, 277 epidemiological evidence, 276 exogenous circadian rhythm and, 277 and healthy sleep, 278–279 indirect effects of sleep on, 270–271 insomnia, 275–276 longer sleep and duration, 272

indirect relationship between, 273 negative associations, 272 protective effects of, 272 mechanistic studies, 276 mortality, 278 objective parameters, 267–273 obstructive sleep apnea (OSA), 274–275 physiological and biological mechanisms, 265–267, 274 population-level studies, 276 qualitative sleep parameters, 273–274 quality of life, 278 and sleep disorders, 274–276 sleep duration, 268–273 social and demographic factors, 271–272 sleep quality, 273 subjective parameters, 267–273
 Diabetic retinopathy (DR), 278
 Diet induced thermogenesis, 289 sleep disturbances and fatigue, 538–539
 Diffusion tensor imaging (DTI), 416–417
 Diffusion theory, 227–228
 Digital cognitive behavioral therapy for insomnia (dCBT), 649 advantages and benefits, 654 vs. cognitive behavioral therapy for insomnia (CBTI), 654 delivery format, 652 digital literacy, 655 effectiveness, 654 mHealth applications, 652 personalization, 654–655 platforms, 652 self-guided interventions, 650–652 stepped care model, 655, 656f therapeutic relationship, 655 vs. therapist-led CBT, 653t, 654 web-based, 652
 Digital health, 649, 650t
 Digital literacy, 655
 Dim-light melatonin onset (DLMO), 337, 480
 Disparities, 614–615
 Disturbed sleep, 461
 Divergent thinking, 424–425
 Dopamine, 8
 Dopamine D₂ receptor (DRD2), 423
 Dopamine transporter (DAT1) gene, 417
 Drowsy driving, 621
 Dual-energy-X-ray absorptiometry (DEXA), 559
 Duke Structured Interview for Sleep Disorders, 133
 Dysfunctional family dynamics, 141
 Dysfunctional thoughts, 538

E

Eating behavior, 437–438
 Ecological momentary assessment (EMA), 600
 Edmonton Symptom Assessment Scale, 539
 Effective Daylight Illuminance (EDI), 107
 Effort discounting, 440

Effort-Recovery Model, 596
 Electroencephalography (EEG), 4, 497
 Electronic book-readers (e-readers), 209
 Electronic health (eHealth), 649–650, 650t
 Electronics, removal of, 188
 Emotional well-being, family interactions, 143
 Emotion dysregulation, 358
 Emotion regulation, 574–575
 Endogenous circadian rhythm, 277
 Endothelial dysfunction, 278
 Energy drinks supplements, 369, 372–373
 Energy expenditure, 559–560
 Energy homeostasis, 559–560
 Energy metabolism, 287
 Enteric nervous system, 394
 Environmental exposures physical environment air quality, 112–113 light, 106–109 noise, 110–111 risk, protective, and resiliency factors, 106f seasonality and latitude/longitude, 113–114 temperature, 109–110 vibrations, 111 weather pattern changes, 105 pollution definitions and thresholds, 119t social environment interpersonal relationships, 116–118 neighborhood environment, 115–116 psychosocial stress, 114 racism, 114–115 socioeconomic status (SES), 114–115 work environment, 116
 Environmental rhythms, 288
 Epidemiologic Catchment Area study (ECA), 334
 Epworth Sleepiness Scale (ESS), 173–174, 274
 European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study, 259–260
 Excess adiposity, 556–557
 Excessive daytime sleepiness, 39, 454–455
 Excessive sleepiness, 168
 Executive dysfunction, 63–64
 Executive functions, 418–425, 440 cognitive control, 421–423 cognitive performance, 418–419 cognitive process, 418 inhibitory control, 420–421 problem solving, 423–425 working memory, 419–420
 Exercise, 319 acute, 320–321 chronic training, 321 experimental research, 320–321 observational research, 319–320 physical activity, 324 potential mechanisms adenosine, 322 anxiolytic and antidepressant effects, 322

body temperature effects, 322
circadian phase-shifting effects, 322
sedentary behavior, 321–322
sleep disorders
 insomnia, 322–323
 periodic limb movements during sleep (PLMS), 324
 restless legs syndrome (RLS), 324
 sleep-disordered breathing (SDB), 323–324
 sleep disturbances and cancer fatigue, 541
 sleep hygiene, 185–186
Exogenous circadian rhythm, 277

F

Families and Children Experiencing Symptoms (FACES) of Narcolepsy, 682

Family sleep dynamics
 behavioral factors, 145
 behavioral interventions, 147–148
 circadian rhythm sleep–wake disorders (CRSWDs), 146
 dysfunctional, 141
 educational programs, 148
 environmental factors, 145
 environmental modification, 148
 family systems theory, 141
 health promotion, 141–142
 hypersomnia disorders, 147
 insomnia disorder, 146
 intergenerational transmission, 141
 medical treatments, 148
 parasomnias, 147
 positive, 141
 psychological and emotional factors, 145
 psychological development, 141
 restless legs syndrome (RLS), 146–147
 sleep apnea, 146
 sleep health, 142
 benefits, 142
 and emotional well-being, 143
 poor, 142–143
 sleep patterns and needs
 adolescents, 144
 elderly family members, 144–145
 infants and toddlers, 143
 parents, 144
 school-aged children, 143–144
 socioeconomic and cultural influences, 145–146

Family systems theory, 141

Fat, 309–310

Fatigue, 667. *See also* Cancer-related fatigue (CRF)
 neurobiology, 412
 risk management, 674–675

Federal Motor Carrier Safety Administration (FMCSA), 621–622

Federal Road Administration (FRA), 622

Fee-for-service (FFS) model, 633

Fitbit, 179–180

Fitbit Charge 2, 198f

Flexible attentional control, 423

Food and Drug Administration (FDA), 376–377

Food intake
 alternative medicine, 311
 caloric consumption, 307
 carbohydrates, 308–309
 fat, 309–310
 homeostatic mechanisms, 305
 nocturnal wakefulness, 65
 nonhomeostatic mechanisms, 305–307
 protein, 307–308
 relation between sleep and, 305–307
 sleep duration and quality, 307–311
 sleep hygiene, 187
 sleep loss and, 304
 vitamins and supplements, 310

Food labeling practices, 379

Ford Insomnia Response to Stress Test (FIRST), 191

Fruits, 310–311

Functional outcomes of sleep questionnaire (FOSQ-30), 174

G

Gabapentin, 340–341

Gastroesophageal reflux disease (GERD), 127–128

Genetic polymorphisms, 417

Ghrelin, 274, 291–292, 560

Global Burden of Disease (GBD), 562

Glucagon like peptide-1 (GLP-1), 288, 290–291, 305

Glucagon-like peptide-1 (GLP-1) receptor, 465

Glucose metabolism, 287, 418

Glutamate dynamics alterations, 453–454

Glymphatic dysfunction, 453–454

Granulocytes, 388

Great sleep recession, 585

Growth hormone, 291

Gut microbiome, 289

H

Habitual sleep duration, 13

Health behaviors, 218, 500–501
 circadian disruption, 437, 443
 defined, 437
 exposure, 439
 influences on sleep and, 437–438
 neurocognitive factors, 439–440
 neuroimaging, 441
 short sleep duration, 438
 sleep loss, 437, 439, 441–442
 sleep related changes in neurocognitive function, 440–441

Health belief model (HBM), 160–161, 221–222, 222f

Healthcare resource utilization (HCRU), 629

Health-damaging behavior, 612

Health, definition, 218

Health differences, 612–615

Health disparities
 distal factors, 615

history and definition, 74

intermediate factors, 615

life expectancy, 615

minority Americans, 89, 90f

proximal factors, 614–615

Health economics
 insomnia treatment, 631, 632t
 OSA treatment, 631–633

Health equity, 612

Health literacy, 231

Health promotion, 141–142, 580–581

Health-related quality of life (HRQoL), 556–557, 630

Healthy sleep, 278–279, 563

Heart disease, 499–500

Heart failure
 and insufficient sleep, 259
 obstructive sleep apnea, 513

Heart-rate variability (HRV), 62, 497

Hedonic eating, 437–438

Hepatitis B vaccination, 390

High heat capacity mattress (HHCM), 109–110

Hill's Criteria of causation
 coherence, 219
 confounding variables, 219
 consistency, 219
 dose-response relationship, 219
 experimental evidence, 219
 generalizable theory, 220
 measurability, 220
 mediating variable, 219
 moderating variable, 219
 practical theory, 220
 predictability, 220
 specificity, 219
 strength of association, 219
 temporality, 219

Histamine, 8

HIV-associated neurocognitive disorder (HAND), 357–358

Homeostasis, 305, 412, 412f, 415f

Home sleep apnea testing (HSAT), 168, 624–625

Home sleep testing (HST), 339

Homicide, 64

Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ), 176–178

Hyperarousal, 477

Hyperarousal theory of insomnia, 542

Hypercapnia, 509

Hypersomnia disorder, 147, 642

Hypersomnia Foundation, 682

Hypersomnolence, 172–173

Hypertension (HTN), 255–256, 491–497, 511–512

Hypnogram, 6f

Hypocretin, 243

Hypopneas, 339

Hypothalamic-pituitary-adrenal (HPA) axis, 306–307, 394, 500

Hypothalamus, 8

Hypoxemia, 540

Hypoxia, 509

I

Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) battery, 455
 Immune system, 500–501
 acquired, 387–388
 aging, 388
 innate, 388
 stress–sleep connection, 395
 Immunological aging, 391–392
 Impedance cardiograph, 500
 Impulsive behavior, 427–428
 Impulsivity, 440
 Incremental cost-effectiveness ratio (ICER), 630
 Infant sleep, 23–24
 Infectious disease, 388–390
 Inflammaging, 388
 Inflammation, 274
 Inflammatory cytokines, 391
 Inflammatory disease, 390–391
 Inflammatory response, 391
 Information technology (IT), poor sleep health, 596–597, 597f
 Inhibitory control, 420–421
 Innate immune system, 388
 Innovative thinking, 424–425
 In Our Own Voices (IOOV) program, 683–684
 Insomnia
 acute, 190
 in alcoholics, 336–337
 alcohol use
 adult sleep problems and, 334
 behavioral treatments, 337
 childhood sleep problems, 333–334
 clinical findings, 335–336
 epidemiology, 333
 genetic studies, 335
 overnight polysomnographic sleep studies, 335
 pharmacologic treatments, 337
 spectral PSG studies, 341
 behavioral model, 476
 behavioral treatment, 482–483
 caffeine, 374
 and cardiometabolic disease risk
 blood pressure, 491–497
 health behaviors, 500–501
 heart disease, 499–500
 hypertension, 491–497
 immunity, 500–501
 insulin resistance, 497–498
 meta-analyses, 493t
 objective sleep measures, 494t–496t
 outcomes, 492t
 public health and clinical implications, 501–503
 stress, 500–501
 stroke, 499–500
 type 2 diabetes, 497–498
 cardiometabolic risk factors (CMR), 489
 chronic, 190–191, 473–474
 assessment, 660

prevalence and risk, 659–660
 treatments, 661
 cognitive behavioral therapy for insomnia (CBT-I), 482–483
 cognitive model, 476–477
 definition, 473–474, 490t
 and diabetes, 275
 diagnosis, 490–491
 DSM-5 criteria, 474
 etiological models, 190, 190f
 etiology, 474–476
 exercise, 322–323
 incidence, 474
 neighborhood factors, 97
 neurocognitive model, 476
 older adults, 36
 and painful diabetic neuropathy (PDN), 275–276
 parallel process, 475f, 477
 perinatal period
 assessment, 133
 treatment, 133–134
 predisposing, precipitating, and perpetuating factors, 536f
 pregnancy and postpartum
 anxiety disorders, 133
 depressive disorders, 132–133
 mental health problems, 132
 parent and child, 132
 prevalence, 131, 131f
 risk and protective factors, 131
 prevalence, 27, 474
 and psychiatric morbidity, 477–482
 alcohol use disorder (AUD), 481
 anxiety disorders, 479–480
 attention-deficit/hyperactivity disorder (ADHD), 480
 autism spectrum disorder (ASD), 481
 bipolar disorder, 479
 depressive disorders, 477–478
 posttraumatic stress disorder (PTSD), 480
 schizophrenia, 481–482
 suicide, 478–479
 psychobiological inhibition model, 476–477
 racial/ethnic groups, 83–84, 85t–86t
 sleep hygiene, 188–189
 and sleep quality, 174–175
 socioeconomic status (SES) groups, 84–87
 stimulus control model, 475–476
 suvorexant for, 360
 symptoms, 489–490
 treatment, economic aspects, 632t
 Insomnia disorder, 146, 535, 639
 Insomnia severity index (ISI), 175, 501, 660
 Insufficient sleep, 51, 411
 adolescence risk behavior, 588–589
 age, 15–16, 15f
 and blood pressure, 255–257
 and coronary heart disease, 257–259
 definition, 13–14, 254–255
 and diabetes, 268–271
 epidemiologic studies, 253
 by geography, 17–18, 17f–18f

and heart failure, 259
 and obesity
 group differences, 240–241
 individual differences, 241–242
 obesogenic behaviors, 237–239
 physiological mechanisms, 239–240
 sleep disorders, 243–244
 sleep duration, 237–242
 sleep timing, 242–243
 slow-wave sleep (SWS), 244
 weight-loss interventions, 244–245
 objective measurements, 253, 254f
 pathophysiologic mechanisms, 255
 poor sleep quality, 18–19
 in population, 14–15
 population estimates, 18
 prevalence of, 14
 by race/ethnicity, 16
 by sex, 16
 sleep complaints, 19–20, 20f
 sleep disorders, 19
 by socioeconomic status, 16–17
 and stroke, 259–260
 subjective measurements, 253, 254f
 Insulin, 287, 290, 564
 Insulin resistance (IR), 265–266, 274, 497–498, 559
 Integrated behavioral model (IBM), 161–162, 223
 Interleukin-6 (IL-6), 388, 391, 500–501, 536–537
 International Classification of Sleep Disorders (ICSD), 189
 International Dark Sky Association, 108
 International Restless Legs Syndrome Scale (IRLS), 179
 Interpersonal relationships, 116–118
 Intrapersonal theories, 226–227
 Intrapersonal theories, 221–226
 Intrinsically photosensitive retinal ganglion cells (ipRGC), 208
 Iowa Gambling Task (IGT), 426, 427f
 Irregular sleep–wake times, 285
 Isoflavones, 310
 Item Response Theory (IRT), 176

J

Job Demand Control (JD-C) model, 596, 598
 Job Demand-Resources (JD-R) model, 596, 598

K

Kantar World Panel, 372
 Karolinska Sleepiness Scale (KSS), 174, 175f
 Kava, 311
 Kleine-Levin Syndrome (KLS) Foundation, 682
 Knowledge Deficit Model, 683

L

- Large neutral amino acids (LNAA), 308f
 Leptin, 239, 274, 288, 291–292, 560
 Light, impact on sleep, 106–109
 Lipid metabolism, 287
 Lipopolysaccharide (LPS), 391
 Locomotor Inactivity During Sleep (LIDS), 199, 201f
 Logical deduction, 424
 Logic models, 217
 Longitudinal EMT Attribute Demographic Study (LEADS), 669
 Long sleep duration, 13
 Low heat capacity mattress (LHCM), 109–110
 Lymphocytes, 387–388

M

- Macronutrient intake, 238
 Macrophages, 388
 Magnesium, 310, 340–341
 Maintenance of wakefulness test (MWT), 172–173
 Major depressive disorder (MDD), 132–133, 477–478
 Major depressive episode (MDE), 477–478
 Meal timing, 238–239
 Mediterranean diet, 311
 Melatonin, 25, 208, 288, 291, 310, 337
 nicotine withdrawal, 358
 REM sleep behavior disorder, 341
 Melatonin receptor 1B (MTNR1B), 291
 Mental health, 588–589
 comorbid insomnia and sleep apnea (COMISA), 524
 sleep duration, 574–576
 and sleep improvements, children and adolescents
 clinicians, 579–580
 families, 578
 policymakers, 580
 schools, 578–579
 sleep quality, 576–578
 Mental illness, 573
 Metabolically relevant hormones, 290–292
 Metabolic disease, 561–562
 Metabolic syndrome (MetS)
 pathophysiologic mechanism, 283
 prevalence, 283–284
 Metabolic system, 286–287
 Methylphenidate, 542
 Middle-aged sleep, 26–27
 Mild cognitive impairment (MCI), 462
 Mild traumatic brain injury (mTBI), 449
 Mind After Midnight hypothesis, 61–64, 65f
 Mindful movement interventions, 543–544
 Mindfulness-based approaches, 134, 542–543
 Mindfulness based cognitive therapy for perinatal depression (MBCT-PD), 134

N

- Mindfulness based stress reduction (MBSR), 542
 Mini-Mitter Inc, 197
 Mobile health (mHealth), 649, 650t, 652
 Modafinil, 373, 426–427, 542
 Model of goal-directed behavior (MGDB), 223–224
 Moderate to vigorous physical activity (MVPA), 271
 Monoaminergic systems disruptions, 453–454
 Mood disturbance, cancer-related fatigue (CRF), 538
 Moral judgment, 428
 Morningness-eveningness questionnaire (MEQ), 176–178, 177f
 Motionlogger, 197
 Motivation, 442–443
 Motivational interviewing (MI), 225
 Movement behaviors, 324–325
 Multiple sclerosis (MS), 541
 Multiple sleep latency test (MSLT), 172–173, 497, 622–623
 Multi-tasking, 422
 Munich Chronotype Questionnaire (MCTQ), 179
 Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), 537
 Myocardial infarction (MI), 499, 512

O

- Neighborhood environment, impact on sleep, 115–116
 Neighborhood factors
 adult sleep, 96–98
 causal methods, 98
 interventions and policies, 99
 limitations, 98
 long-term trajectories, 98
 natural experiments, 98
 pediatric sleep, 96
 physical activity, 96
 technological advances, 98
 theoretical justification, 95–96
 violence and safety concerns, 96
 Neighborhood socioeconomic status (NSEs), 96
 Neurobehavioral consequences, 403
 Neurobiology, 412
 Neurocognitive factors, 439–440
 Neurocognitive model, 476
 Neuromodulators, 8
 Nicotine, sleep hygiene, 187
 Nicotine replacement therapy (NRT), 348, 356
 Nicotine withdrawal, 352
 cognitive-deficits, 357
 melatonin, 358
 Nightmares, 576
 Nocturnal hypoglossal nerve stimulation, 509–510
 Nocturnal wakefulness
 altered reward anticipation and receipt, 63
 behavioral dysregulation, 64–65
 central neurophysiology, 61–62
 executive dysfunction, 63–64
 food intake, 65
 homicide, 64
 impaired mood and affect, 63
 Mind After Midnight hypothesis, 64–65, 65f
 peripheral neurophysiology, 62
 substance use, 64
 suicide, 64
 Noise, impact on sleep, 110–111
 Nonhomeostatic mechanisms, 305–307
 Non-rapid eye movement (NREM) sleep, 4–5, 61–62, 348, 455–456
 acute exercise, 320–321
 parasomnias, 341
 stage dissection, 5
 Non-sport-related concussion, 451
 Non-verbal social cues, 595–596
 Norepinephrine, 8, 500
 Normal/normative sleep duration, 13
 Normative beliefs, 222–223
 Notice of Proposed Rulemaking (NPRM), 622
 Nuclear factor κB (NF-κB), 391

P

- Obesity, 270–271, 283, 303
 in children, 555–556, 556f
 insufficient sleep

- Obesity (Continued)**
- group differences, 240–241
 - individual differences, 241–242
 - obesogenic behaviors, 237–239
 - physiological mechanisms, 239–240
 - sleep disorders, 243–244
 - sleep duration, 237–242
 - sleep timing, 242–243
 - slow-wave sleep (SWS), 244
 - weight-loss interventions, 244–245
- relationship between sleep and diabetes, 270–271
- Obesogenic behaviors**, 237–239, 238f
- Objective reported sleep duration**, 78
- Obstructive sleep apnea (OSA)**, 243, 340, 392, 443, 455, 563–564
- anatomical/physiological predisposition, 509
 - apneic events, 514
 - arrhythmia, 513
 - athletes, 642
 - Berlin questionnaire, 172
 - vs. central sleep apnea, 509
 - in commercial motor vehicle (CMV) operators
 - current regulation, 622
 - daytime sleepiness, 621
 - diagnosis, 621, 624–625
 - education, 625
 - federally funded research and regulatory activity, 622
 - initial evaluation, 624
 - positive airway pressure (PAP) therapy, 625
 - prevalence, 621–622
 - screening criteria, 622–624, 624t
 - treatment, 625
- coronary artery disease, 512
- daytime sleepiness, 621
- and diabetes, 274–275
- diagnosis of, 339–340
- exercise, 323
- family sleep dynamics, 146
- health economics, 631–633
- heart failure, 513
- hypersomnolence, 172–173
- hypertension, 511–512
- neighborhood factors, 97–98
- overweight and obese status, 511
- pathological hypoxia, 514
- pathophysiological mechanisms and consequences, 509, 511f
- pregnancy, 511
- prevalence, 168
- public safety, 672–674
- screening, 168–172
- sedentary behavior, 321–322
- sleep fragmentation, 514
- STOP and STOP-BANG questionnaires, 172
- sympathetic tone, 514
- symptoms, 168, 660
- treatment, 509–510, 514–515, 526–527
- upper airways, 509
- Occupational Fatigue Exhaustion Recovery (OFER) scale**, 669
- Older adults**
- cardiovascular health, 39–40
 - circadian rhythm, 35
 - cognitive function, 37–39
 - health outcomes, 43t
 - insomnia, 36
 - pain, 41–42
 - poor sleep, 42, 42t
 - psychiatric illness, 40–41
 - sex differences, 27–28
 - sleep-disordered breathing, 36–37
 - sleep homeostasis, 35
 - sleep parameters, 35
- On-demand culture, 160
- Operationalized constructs**, 217
- Orbitofrontal cortex (OFC)**, 421
- Orexin**, 8, 360
- Orexin deficiency**, 243
- Overweight**, in children, 555–556, 556f
- Oxidative stress**, 266
- P**
- Paid employment**, 580
- Pain**, 538
- older adults, 41–42
 - prevalence, 41–42
 - psychiatric illness, 42
- Painful diabetic neuropathy (PDN)**, 275–276
- epidemiological and population-level studies, 276
 - mechanistic studies, 276
- Parallel process (transtheoretical) model**, 477
- Parasomnias**, 341
- and alcohol use, 341
 - defined, 341
 - family sleep dynamics, 147
- Parasympathetic nervous system (PNS)**, 394
- Paroxetine**, 542
- Paroxysmal nocturnal dyspnea**, 259
- Partial sleep deprivation (PSD)**, 13, 404
- Pathological hypoxia**, 514
- Patient advocacy groups (PAGs)**
- patient-centered research, 682–686
 - advisory boards, 686
 - healthcare conferences, 685–686
 - and individual patient advocates, 684–685
 - research process partnership, 684
 - sleep awareness, 683–684
 - role of, 683f
 - sleep-related, 682–683
 - Social Ecological Model, 682
 - societal needs, 681–682
- Patient-Centered Outcomes Research Institute (PCORI)**, 685
- Patient-Reported Outcomes Measurement Information System (PROMIS)**, 133, 176
- Pediatric sleep**, 96
- People living with HIV (PLWH)**, 357–358
- Peptide YY**, 305
- Perceived severity, health belief model**, 221–222
- Perceived susceptibility, health belief model**, 221–222
- Perinatal Understanding of Mindful Awareness for Sleep (PUMAS) intervention**, 134
- Periodic leg movement disorder (PLMD)**
- and alcohol use, 340–341
 - magnesium, 340–341
- Periodic limb movements during sleep (PLMS)**, 87–88, 324
- PERIOD3 (PER3)**, 419
- Peripheral blood mononuclear cells (PBMCs)**, 392
- Personality Assessment Inventory clinical scales**, 441–442
- Physical activity**, 96, 442
- Physical health, comorbid insomnia and sleep apnea (COMISA)**, 524–525
- Pittsburgh Sleep Quality Index (PSQI)**, 127, 133, 175–176, 392, 670
- Pollution, definition**, 119t
- Polysomnography (PSG)**, 9, 23, 195, 254–255, 339–340, 348, 474, 490–491, 573–574, 621–622
- vs. actigraphy, 195
 - concussion, 455–456
 - pregnancy, 127
 - screening, 168
 - sleep-disordered breathing, 36–37
- Poor decision-making**, 426
- Poor sleep**
- health, 611
 - screening, 168
- Population density**, 96
- Positional therapy**, 509–510
- Positive airway pressure (PAP) therapy**, 625, 642
- benefits, 625
 - monitoring, 625
- Positive family dynamics**, 141
- Positive predictive value (PPV)**, 168–172
- Postconcussion syndrome (PCS)**, 451
- Post-hoc analysis**, 674–675
- Post-traumatic stress disorder (PTSD)**, 477, 480
- Pramipexole**, 340–341
- Predictive validity**, 232
- Prefrontal cortex (PFC)**, 418, 421
- Pregnancy**
- hormonal fluctuations, 127–128
 - insomnia, 131–133
 - perinatal period, 133–134
 - pregnancy and postpartum period, 131–133
- physiological changes, 127–128, 128f
- psychosocial considerations, 128
- psychosocial factors, 128f
- restless leg syndrome (RLS), 128
- sleep changes, 127–128
- perinatal period, 129–130, 130f

- postpartum, 128–129
sleep-disordered breathing (SDB), 128
Prepotent response, cognitive interference, 422
Primary care behavioral health (PCBH) model, 661
Primary care setting
 chronic insomnia
 assessment, 660
 prevalence and risk, 659–660
 treatments, 661
 sleep education, 662
Veterans Affairs (VA) Health Care System, 661–662
Programme for International Student Assessment (PISA), 579
Progressive muscle relaxation (PMR), 337
Proinflammatory cytokines, 388
Project Sleep, 682
Project Sleep's Expert Advisory Board, 686
Prophylactic vaccination, 389–390
Proportional integral mode (PIM), 202
Protein, 307–308
Psychiatric illness
 adults, 588
 older adults
 anxiety and depression, 40–41
 insomnia, 41
 sleep-disordered breathing, 41
 sleep duration, 41
Psychiatric morbidity
 alcohol use disorder (AUD), 481
 anxiety disorders, 479–480
 attention-deficit/hyperactivity disorder (ADHD), 480
 autism spectrum disorder (ASD), 481
 bipolar disorder, 479
 depressive disorders, 477–478
 posttraumatic stress disorder (PTSD), 480
 schizophrenia, 481–482
 suicide, 478–479
Psychiatry illness, 573
Psychobiological inhibition model, 476–477
Psychoeducation, 579
Psychological stress, 393–394, 394f
Psychomotor vigilance test (PVT), 412–414
 attentional lapses, 413
 homeostatic and circadian process, 414, 415f
 mean response speed, 414f
 sleep deprivation, 412–413
 sleep loss, 404–405
 duration, 405–406
 outcome metric, 406
 software and hardware, 405
 sustained attention, 412–413
 time course, 413f
 time-on-task effect, 414
Psychophysiological insomnia, athletes, 641
Psychosocial stress, impact on sleep, 114
Psychostimulants, 373
Public health, 611–612
Public safety
 components, 667
demographic characteristics, 667–668, 668t
 firefighters, 668
 organizational structure, 667–668
extended-duration shifts, 667
fatigue, 667
physiological determinants
 fatigue, 670–672
 sleep deficiency, 672
sleep disorders, 672–674
work hours and scheduling characteristics
 extended shifts, 668
 health and safety outcomes, 669–670
 implementation, 670
 shift duration, 669
 short shifts, 668
 weekly work hours, 669
work schedules, 667
Pwn4Pwn, 682
- Q**
Quality-adjusted life year (QALY), 630
Quality of life, comorbid insomnia and sleep apnea (COMISA), 525
Quetiapine, 337
- R**
Racial ethnic disparities, 602–605, 612–615
 acculturation and cultural factors, 604
 Asian and White individuals, 604–605
 discrimination/harassment, 605
 employed immigrants, 605
 minoritized groups, 602–604
 occupational segregation, 602
 short sleepers, 604
 socially disadvantaged groups, 602
 underresourced groups, 602
Racial/ethnic groups
 circadian rhythms, 88–89
 insomnia, 83–84, 85t–86t
 minority Americans
 acculturation, 89
 health disparities, 89, 90f
 perceived discrimination, 89–90
 sleep opportunity, 90
 worry and risk perception, 90
 narcolepsy, 88
 objective reported sleep duration, 78
 periodic limb movements during sleep (PLMS), 87–88
 restless leg syndrome (RLS), 87–88
 self-reported sleep duration, 74–78, 75t–77t
 sleep architecture and continuity, 79–81
 sleep disordered breathing (SDB), 81
 diagnosis, 82–83
 symptoms and risk factors, 81–82
 sleep duration, 78–79
Racism, impact on sleep, 114–115
Randomized controlled trials (RCTs), 559–560
Rapid-eye movement (REM) sleep, 5–6, 109, 244, 348, 455–456, 588
parasomnia, 341
Reactive oxygen species (ROS), 514
Readability metrics, 231
Reasons for Geographic And Racial Differences in Stroke (REGARDS) study, 259–260
Recovery sleep, 374
REM behavioral disorder (RBD), 341
Restless Legs Syndrome Foundation, 683
Restless legs syndrome (RLS)
 and alcohol use, 340
 exercise, 324
 family sleep dynamics, 146–147
 pregnancy, 128
 racial/ethnic groups, 87–88
 screening, 179
Reversal learning paradigms, 423
Reward-based learning, 426–427
Rhinovirus, 389
RICCADSA trials, 512
Rising Voices program, 684
Risky behavior, adolescence, 588–589
Risky decision-making, 425–429
 aggressive/punitive responses, 428
 altered expectations of reward, 426
 cognitive framing, 425–426
 impulsive behavior, 427–428
 moral judgment, 428
 reward-based learning, 426–427
Ropinirole, 340–341
- S**
Save Standard Time, 683
SAVE trials, 512
Schizophrenia, 481–482
Screening
 Berlin questionnaire, 172
 circadian rhythm disorders, 176
 consumer sleep technologies, 179–180
 Epworth Sleepiness Scale (ESS), 173–174
 Fitbit, 179–180
 Functional outcomes of sleep questionnaire (FOSQ-30), 174
 Horne-Ostberg Morningness-Eveningness Questionnaire, 176–178
 hypersomnolence, 172–173
 Insomnia severity index (ISI), 175
 instruments, 168
 Karolinska Sleepiness Scale (KSS), 174
 Munich Chronotype Questionnaire (MCTQ), 179
patient-reported outcomes measurement information system (PROMIS), 176
Pittsburgh sleep quality index (PSQI), 175–176
questionnaires, 168, 169t–171t
restless legs syndrome (RLS), 179
sleep-disordered breathing, 168–172
SleepScore max, 179–180
Stanford Sleepiness Scale (SSS), 174
STOP and STOP-BANG questionnaires, 172
using data, 180–181

Screen usage
 artificial light exposure, 210
 circadian disruption, 211
 contextual factors, 209
 epiphenomenon of insomnia, 212
 mechanisms, 209–211, 210f
 modern, 209
 psychological stimulation and stress, 210
 and sleep behavior, 208–209
 sleep disorders, 212
 sleep fragmentation, 211
 sleep restriction, 211
 time displacement, 210
 Seasonal changes, impact on sleep, 113–114
 Sedentary behavior, 321–322
 Self-rated risk propensity, 425
 Self-reported sleep duration, 74–78, 75t–77t
 Senescence associated secretory phenotype (SASP), 388
 Sequence-type working memory task, 420
 Serotonin, 8, 307–308
 SERVE-HF trial, 513
 Sex differences
 in adolescent sleep, 24–26
 biologically based, 23
 in childhood sleep, 24
 infant sleep, 23–24
 in middle-aged sleep, 26–27
 in older adult sleep, 27–28
 in young adult sleep, 26
 Shift duration, 669
 Shift work, 242–243, 599, 615
 Short sleep, 13, 237
 Sleep
 and aging, 461–462
 architecture, 474
 across racial/ethnic groups, 81
 smokers vs. nonsmokers, 348
 and socioeconomic status, 81
 autonomic nervous system, 9
 brainstem, 8
 cerebrum, 8
 and circadian rhythm, 6–8
 and circadian rhythms, 207
 definition, 3
 and demographic differences, 455
 for health, 207
 health and mortality, 53f
 as health behavior, 3–4, 53–54
 hypothalamus, 8
 and immunological aging, 391–392
 neuromodulators, 8
 neurophysiological progressions, 452
 objective measure, 9–10
 opportunity, 3–4
 physiological process, 207
 as physiological process, 4–6
 physiology, 8–9
 at population level, 13
 and psychological stress, 393–394
 quantifying, 9–10
 questionnaires, 10t

stage N1, 452
 stage N2, 452
 stage N3, 452
 stages, 6
 staging, 452
 subjective measure, 9
 thalamus, 8
 two process model, 7f, 208
 Sleep ability, 3
 Sleep apnea, 27, 278, 639
 family sleep dynamics, 146
 Sleep changes, normal aging, 35
 Sleep Consortium, 682–683
 Sleep continuity, 348, 351
 Sleep deficiency, 253, 600, 672
 Sleep deprivation (SD), 13, 404, 563
 adolescence, 588
 caffeine, 370
 family process, 142–143
 glucose metabolism, 418
 psychomotor vigilance test (PVT), 412–413
 regional cerebral glucose metabolism, 419f
 self-rated risk propensity, 425
 Wisconsin Card Sorting Test, 424
 Sleep diary, 9, 573–574
 Sleep-disordered breathing (SDB), 489–490, 497
 athletes, 642
 diagnosis, 82–83
 exercise, 323–324
 first-line therapy, 37
 older adults, 36–37
 cardiovascular health, 40
 cognitive function, 39
 psychiatric illness, 41
 pregnancy, 128
 prevalence, 660
 racial/ethnic groups, 81
 screening, 168–172
 socioeconomic status (SES) groups, 83
 symptoms and risk factors, 81–82
 Sleep disorders, 243–244
 and diabetes, 274–276
 exercise, 322–324
 public safety, 672–674
 screen use, 212
 Sleep Disorders Symptom Checklist (SDS-CL), 660
 Sleep disruptive events, 348
 Sleep disturbance, 474
 athletes, 641, 642f
 caffeine, 378
 comorbid insomnia and sleep apnea (COMISA), 524
 concussion, 454–455
 older adults, 36–37
 Sleep Disturbance (SD) scale, 176
 Sleep-dose-response experiments, 403
 Sleep duration, 13–15, 237–242
 alcohol consumption
 adolescents and young adults, 339
 long sleep duration and, 339
 short sleep duration and, 339
 childhood obesity, 557–558
 cognitive function, older adults, 37–38
 concussion, 455
 defined, 338
 inadequate, 97
 mental health, children and adolescents
 anxiety and depression, 574
 ecological validity, 575
 emotional lability, 574
 emotion regulation, 574
 home-based studies, 574–575
 internalizing symptoms, 574
 mood symptoms, 574
 nightly sleep and daily mood, 575–576
 sleep loss, 575
 older adults, psychiatric illness, 41
 racial/ethnic groups, 78–79
 self-reported sleep duration, 78
 social cognitive factors, 438
 virus exposure, 388–390
 Sleep education program, athletes
 sleep and circadian health, 644
 sleep and circadian impacts, 645
 sleep problems and disorders, 644–645
 tracking and optimization, 645–646
 Sleep efficiency (SE), 320
 Sleep extension interventions, 245, 443, 476
 Sleep fragmentation, 514
 screen use, 211
 in smokers *versus* nonsmokers, 351
 Sleep gap, 612–615
 Sleep health, 358
 athletes, 639–640
 and brain health, 463f
 definition, 612, 615
 dimensions, 612
 economics
 cost-shifting approach, 633f
 direct costs, 629
 health-related quality of life (HrQOL), 630
 indirect costs, 629
 recommendations, 633
 sleep disorder treatments, 631–633
 sleep medicine, 630–631, 631t
 value-based care, 633
 epidemiology, 13–22
 family dynamics, 142
 health belief model (HBM), 160–161, 161f
 integrated behavioral model, 161–162
 perceived barriers, 163
 perceived benefits, 163
 readiness, 164–165
 real-world barriers
 chronic pain, 159–160
 distractions, 160
 health conditions, 159–160
 lack of time, 157
 on-demand culture, 160
 physical environment, 158–159
 social norms and beliefs, 158, 159f
 substance use, 160
 self-efficacy and control, 164
 social determinants, 612, 613t
 social norms, 164

- transtheoretical stages-of-change model, 162–163, 163f
- Sleep Heart Health Study (SHHS), 491–496, 499, 513
- Sleep homeostasis, 63
- Sleep hygiene
- alcohol, 187
 - bedroom environment, 187–188
 - caffeine, 186
 - clockwatching, 188
 - definition, 185, 186t
 - exercise, 185–186
 - food and liquid intake, 187
 - insomnia, 188–189
 - measuring, 188
 - nicotine, 187
 - practices, 379
 - recommendations, 186t
 - removal of electronics, 188
- Sleep inertia, 374
- Sleepiness assessments, 172–173
- Sleep loss, 13, 414–416, 437, 441–442, 575
- differential vulnerability, 403
 - food intake, 304
 - individual differences, 416–417
 - neurobehavioral consequences of acute and chronic, 403
 - neurocognitive processes, 440f
 - psychomotor vigilance test (PVT), 404–405
 - duration, 405–406
 - outcome metric, 406
 - software and hardware, 405
 - on vigilant attention, 403–404
- Sleep medicine, 189, 630–631, 631t
- Sleep need, 3
- Sleep onset latency (SOL), 320, 351
- Sleep opportunity, 3–4, 90
- Sleep paralysis, 341
- Sleep quality
- mental health
 - adolescent depression, 577–578
 - anxiety, 576
 - behavioral/emotional problems, 576–577
 - longitudinal studies, 576–577, 580
 - objective measures, 577
 - poor sleep quality, 576–577
 - sleep efficiency, 576
 - older adults, psychiatric illness, 41
- Sleep reactivity, 393
- Sleep regulation, process model, 412, 412f
- Sleep-related bruxism, 341
- Sleep-related eating disorder, 341
- Sleep-Related Impairment (SRI) scale, 176
- Sleep-related movement disorders, 340–341
- Sleep-related workplace initiatives, 602
- Sleep Research Society (SRS), 596
- Sleep restriction, 13, 482, 559–560
- adolescence, 588
 - on inflammation, 390–391
 - screen use, 211
 - therapy, 359
- SleepScore max, 179–180
- SleepScore MAX device, 197
- Sleep timing, 242–243
- delayed, 97
- Sleep trackers, 203–204
- Sleep Umbrella Organizations, 682
- Sleep-wake cycle
- adenosine and caffeine in, 374–377
 - environmental factors and response to caffeine, 376–377
 - genetic factors and response to caffeine, 374–377
 - orexin, 360
- Sleep-wake disturbance, 535
- in cancer. *See* Cancer
 - mechanisms, 536
 - prevalence, 535
- Sleep–wake homeostatic process, 208
- Sleep–wake rhythms, 285
- Sleep–wake times, 285
- Sleepwalking, 341
- Slow waves, 4
- Slow-wave sleep (SWS), 4, 244, 320, 564
- Smokers vs. nonsmokers
- daytime sleepiness, 351–352
 - objective and subjective sleep metrics, 349t–350t
 - sleep architecture, 348
 - sleep continuity, 348, 351
 - sleep fragmentation, 351
- Smoking cessation
- behavioral treatments, 359
 - changes in sleep, 352–353
 - outcomes, 353
 - poor sleep, 357–358
 - sleep metrics and, 354t–355t
- pharmacotherapy
- bupropion, 356
 - nicotine replacement therapy, 356
 - varenicline, 356–357
 - sleep deficits, 352
- Snoring, 339
- Social cognitive factors, sleep duration, 438
- Social cognitive theory (SCT), 226
- Social ecological model, 52–53, 52f, 682
- applications, 57–58
 - conceptualizing sleep, 52
 - downstream consequences, 56–57
 - exosystem, 52
 - individual level, 54–55
 - macrosystem, 52
 - mesosystem, 52
 - microsystem, 52
 - social level, 55, 55f
 - societal-level factors, 55–56
 - upstream influences, 56–57
- Social jetlag, 242, 274, 285, 558–559
- Social network theory (SNT), 227
- Social norms and beliefs, sleep health, 158, 164
- Society of Behavioral Sleep Medicine (SBSM), 202–203
- Socio-ecological model, 220, 221f
- Socioeconomic status (SES) groups
- impact on sleep, 114–115
 - insomnia complaints, 84–87
- sleep architecture and continuity, 81
- sleep disordered breathing (SDB), 83
- sleep duration, 79
- Spielman's 3P model, 476, 536
- Sport-related concussion (SRC), 449–450
- Stage theory, 224–225
- Stanford Sleepiness Scale (SSS), 174, 174f
- Start School Later, Inc./Healthy Hours organization, 683
- Stimulus control model, 475–476
- STOP and STOP-BANG questionnaires, 172
- Strategically Leverage Engage and Empower PCOR in Sleep (SLEEP-2), 685
- Stress, 500–501
- hormones, 567
 - influence immunity, 392–393
 - psychological, 393–394
- Stroke, 259–260, 499–500
- Stroop task, 422
- Study of Women's Health Across the Nation (SWAN) sleep, 78
- Subjective norms, 161
- Subjective sleep quality, 253
- Subjective socioeconomic status (SES), 395
- Suboptimal sleep, 454
- Substance use, 64, 160
- Sudden infant death syndrome (SIDS), 23–24
- Suicide, 64, 478–479
- Suprachiasmatic nucleus (SCN), 7, 208, 284, 337, 412, 558
- Sustained attention, 412–413
- Suvorexant, 360
- Sympathetic nervous system (SNS), 394

T

- Tai Chi Chih (TCC), 391, 543–544
- Target, action, context, and time (TACT), 218
- Task impurity problem, 418–419
- Task-switching, 422
- T cells, 387–388
- Telehealth, 650, 650t
- Telomeres, 388
- Temperature, impact on sleep, 109–110
- Thalamus, 8
- Theory of planned behavior (TPB), 223
- Theory of reasoned action (TRA), 222–223
- Time above threshold (TAT), 202
- Time in bed (TIB), 604–605
- Time management behavior (TMB) model, 224
- Time-on-task effect, 414
- Total dietary approaches, 311
- Total sleep deprivation (TSD), 13, 305, 404, 422
- Total sleep time (TST), 13, 78, 320
- Train-the-trainer approach, 675
- Transportation Safety Awareness Task Force (TSATF), 623
- Transtheoretical model (TTM), 224–225
- application, 225
 - decisional balance, 224–225

Transtheoretical model (TTM) (*Continued*)

- process of change, 224
- stages of change, 224
- Transtheoretical stages-of-change model, 163f
- Trazodone, 337, 502–503, 541–542
- Tricarboxylic acid (TCA) cycle, 333
- Tryptophan, 307–308, 308f
- Tumorigenesis, 537
- Tumor necrosis factor alpha (TNF α) gene, 417
- Two process model of sleep, 6–7, 7f, 208
- Type 1 diabetes (T1D), 562
- Type 2 diabetes (T2D), 265–266, 497–498, 562–565

U

- UK Prospective Diabetes Mellitus Study (UKPDS), 562
- Unhealthy behavior, 439
- Unintentional injury, 589
- Upper respiratory infection (URI), 389
- Urbanicity, and population density, 96
- Uvulopalatopharyngoplasty (UPPP), 509–510

V

- Valerian, 311
- Value-based care, 633
- Varenicline, 356–357
- Venlafaxine, 542
- Vibrations, impact on sleep, 111
- Vigilance decrement, 404

- Vigilant attention, sleep loss on, 403–404
- Visceral adiposity, 270–271
- Visual working memory (VWM), 420

W

- Wake-after-sleep-onset (WASO), 116–117, 200f, 320, 348, 558, 596–597
- Wakefulness, 4, 414–416
- Wake state instability, 414–416
- Wake Up Narcolepsy, 683
- WatchPAT, 199–200
- Web-based digital cognitive behavioral therapy for insomnia, 652
- Weight-loss interventions, 244–245
- Willingness to pay (WTP), 630
- Willis-Ekbom disease, 179. *See also* Restless legs syndrome (RLS)
- Wisconsin Card Sorting Test (WCST), 424
- Women's Health Initiative study, 259–260

Work

- demands, 599
- environment, 116
- epidemiology, 596–598
- factors impacts nighttime sleep, 595
- function and productivity, 595–596
- hours, 669
- interpersonal stressors at, 599
- schedules
 - health and safety outcomes, 669–670
 - sleep and circadian principles, 670
 - shift duration, 599, 669
 - stress, 598–599
 - stressors, 599

- micro-longitudinal (daily level) effects, 599–600
- work-family conflict, 599

Workers

- future health risks, 600
- interpersonal stressors, 599
- with multiple jobs, 599
- night shift, 670
- poorer sleep health, 600
- self-employed, 599
- Work-Home Resources (W-HR) model, 598
- Working memory, 419–420
- Work-Nonwork-Sleep framework, 598
- Workplace intervention, 603t
 - business case for sleep, 600–601
 - worksites programs, 602
 - worksites wellness, 601–602
- Work-related injury, 669
- Worksite programs, 602
- Worksite wellness, 601–602
- World Health Organization (WHO), 555–556

Y

- Yoga, 543–544
- Young adult sleep, 26
- Youth Risk Behavior Surveillance System, 611

Z

- Zero-crossing mode (ZCM), 202
- Zolpidem, 23, 502–503

SLEEP AND HEALTH

SECOND EDITION

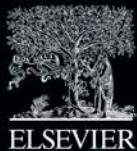
Edited by
Michael A. Grandner

Sleep and Health, Second Edition, provides an accessible yet comprehensive overview of the relationship between sleep and health at the individual, community, and population levels and a discussion of the implications for public health, public policy, and interventions.

Based on a firm foundation in many areas of sleep–health research, this text further provides introductions to each subarea of the field and a summary of the current research for each area. This book serves as a resource for those interested in learning about the growing field of sleep–health research, including sections on social determinants, cardiovascular disease, cognitive functioning, health behavior theory, smoking, and more.

Key features

- Highlights the important role of sleep across a wide range of topic areas
- Addresses important topics such as sleep disparities, sleep and cardiometabolic disease risk, the real-world effects of sleep deprivation, and the public policy implications of poor sleep
- Contains accessible reviews that point to all the relevant literature in these often-overlooked areas; it can serve as a “one-stop shop” for all the relevant information on this broad topic area, especially for people not directly working in this field but with an interest in this area



ACADEMIC PRESS

An imprint of Elsevier
elsevier.com/books-and-journals

ISBN 978-0-443-13954-3

A standard linear barcode representing the ISBN number 978-0-443-13954-3.

9 780443 139543