

RECOMMENDED AMOUNT OF SLEEP FOR A HEALTHY ADULT

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

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The American Academy of Sleep Medicine and Sleep Research Society recently released a Consensus Statement regarding the recommended amount of sleep to promote optimal health in adults. This paper describes the methodology, background literature, voting process, and voting results for the consensus statement. In addition, we address important assumptions and challenges encountered during the consensus process. Finally, we outline future directions that will advance our understanding of sleep need and place sleep duration in the broader context of sleep health.

Keywords: sleep duration, consensus, recommendation, adult, health

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1.0 INTRODUCTION

Sleep is vital to human health, necessary for life,^{1,2} and it serves critical roles in brain functions including neurobehavioral, cognitive and safety-related performance,^{3–13} memory consolidation,^{14,15} mood regulation,^{16,17} nociception^{18,19} and clearance of brain metabolites.^{20,21} Sleep is also critically involved in systemic physiology, including metabolism,^{22–26} appetite regulation,^{27,28} immune and hormone function,^{29–33} and cardiovascular systems.^{34–37} Sleep duration is associated with mortality risk^{38–40} and with illnesses ranging from cardiovascular⁴¹ and cerebrovascular⁴² disease to obesity,⁴³ diabetes,⁴⁴ cancer,^{45,46} and depression.⁴⁷

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These observations raise a critical question: How much sleep is needed for optimal health?

Sleep duration shows substantial intra- and inter-individual variation. Twin studies show sleep duration heritability between 31% and 55%, suggesting substantial genetic influences on sleep need.^{23,48,49} Environmental factors, such as occupational duties and commute time, family responsibilities, and social and recreational opportunities, can lead to substantial discrepancies between the amount of sleep needed and the amount of sleep obtained.⁵⁰ A recent Centers for Disease Control and Prevention (CDC) analysis shows that between 1985 and 2012 mean sleep duration decreased and the percentage of adults sleeping \leq 6 hours in a 24-hour period increased. This trend represents a near doubling in the number of U.S. adults sleeping \leq 6 hours in a 24-hour period from 38.6 million to 70.1 million.⁵¹ The CDC presently considers this progressive decline in sleep duration a public health epidemic.⁵²

In 2013, the American Academy of Sleep Medicine and Sleep Research Society received a one year grant, renewable annually for up to five years, from the CDC entitled the “National Healthy Sleep Awareness Project.” This Project addresses the four sleep health objectives from Healthy People 2020,⁵³ a U.S. Department of Health and Human Services initiative to improve the nation’s health. Objective four is to “increase the proportion of adults who get sufficient sleep.” In the course of stakeholder discussions on this objective it became evident that the fields of sleep research and sleep medicine lack a clear recommendation regarding what constitutes “sufficient” sleep. The absence of such guidance has wide ranging implications for personal and public health. Sleep restriction is the most common cause of sleepiness in society, yet clinicians struggle to tell their adult patients how much sleep is necessary to improve alertness. Public policy initiatives addressing operator fatigue and transportation safety are likewise hindered by the absence of evidence-based guidance regarding healthy habitual sleep duration in adults. The sleep medicine and research community stresses the importance of sleep for health, but this message is likewise undermined by the lack of consensus regarding healthy sleep duration in adults. The absence of such a consensus ultimately weakens the message that sleep is essential for health. Thus, clinical, public policy, and public health activities would all benefit from a consensus recommendation addressing the amount of sleep necessary to support optimal health and functioning in an adult.

A panel of 15 experts in sleep medicine and sleep research used a modified RAND Appropriateness Method⁵⁴ to develop an evidence based recommendation statement regarding the sleep duration that promotes optimal health in adults aged 18 to 60 years.⁵⁵ Sleep duration is the subject of the recommendation statement, but other sleep measures also impact health. Sleep timing, self-reported sleep quality, day-to-day variability in sleep duration, napping, and sleep disorders all influence health outcomes in cross-sectional and/or longitudinal studies.^{56,57} At present, however, sleep duration is the most widely-studied, best-supported, and most straightforward sleep measure to address in relation to health. This supporting manuscript further describes the process, rationale, and discussion that resulted in this evidence-based sleep duration recommendation statement.

2.0 METHODS

The American Academy of Sleep Medicine (AASM)/Sleep Research Society (SRS) Sleep Duration Consensus Conference used a modified RAND Appropriateness Method (RAM)⁵⁴ to establish consensus for the amount of sleep needed to promote optimal health in adults.

2.1 Expert Panel Selection

In accordance with recommendations of the RAM, the Sleep Duration Consensus Conference panel comprised 15 members, including a moderator (who was also a member of both the Board of Directors of the American Academy of Sleep Medicine and the National Healthy Sleep Awareness Project Strategic Planning Group). All panel members are experts in sleep medicine and/or sleep science. The panel consisted of members

of the AASM and/or the SRS who were recommended by the Board of Directors of these respective organizations.

Panel members were sent a formal letter of invitation from the AASM and SRS, and were required to complete Conflict of Interest disclosures before being officially accepted. To avoid further conflicts, panel members were not permitted to participate in similar consensus activities by other organizations.

2.2 Modified RAND Appropriateness Method

The RAND Appropriateness Method uses a detailed search of the relevant scientific literature, followed by two rounds of anonymous voting, to determine consensus on the appropriateness of a recommendation. The first round of voting is completed without panel interaction to prevent panel members from influencing each other’s votes. The second round of voting occurs after a panel discussion of the available evidence and round 1 voting results.

In a modification to RAM, the Consensus Conference included a third round of voting, which considered all available evidence and the previous voting results, to establish a single recommendation for the amount of sleep needed to promote optimal health in adults. The third round also involved a discussion of the merits of recommending an optimal sleep duration *range* versus a simple *threshold* value. The final Consensus Recommendation Statement⁵⁵ resulted from the third round of voting.

The charge to the Consensus Conference panel was to determine a sleep duration recommendation for adults. Panel members voted on the appropriateness of one-hour increments ranging from 5 to 10 hours of sleep, and of < 5 and ≥ 10 hours of sleep. One hour increments were selected because these were the most commonly-reported units in epidemiologic and experimental studies. Substantial heterogeneity was present in sleep duration assessment instruments. For the sake of parsimony, the consensus recommendation focused on “nightly” sleep without specification of napping, as this conformed with the majority of assessments used in epidemiologic studies. The final recommendation was based on the one-hour values that were determined by the panel to be “appropriate” to promote optimal health in adults.

2.3 Detailed Literature Search and Review

The AASM and SRS charged the panel with developing a recommendation for sleep duration in adults. This charge coincides with the goals of the National Healthy Sleep Awareness Project (NHSAP) and with a Sleep Health Objective of Healthy People 2020 to “increase the proportion of adults who get sufficient sleep.”⁵³

After a preliminary review of the literature, the scope of the recommendation was limited to adults aged 18 to 60 years. The age cutoffs were based on a meta-analysis of sleep obtained by healthy individuals across the lifespan that showed children and adolescents have longer sleep times than adults, and older adults show no substantial age related declines in sleep duration after the age of 60.⁵⁸ Epidemiological studies of a very large representative sample of Americans also supported the conclusion that adults aged 18 to 60 years had shorter sleep durations than those younger and older.^{50,59} Older adults are also more likely to suffer from medical disorders that could

Table 1—Data extracted from Oxford Grade I, II, and III studies for evidence tables.

1. Study design
2. Number of study participants
3. Percent of female study participants
4. Method by which sleep duration was obtained
5. Age-range of “adult” participants
6. Major outcomes and conclusions
7. Gender differences

confound associations between sleep duration and health outcomes. Initially, the panel planned to evaluate the literature separately for those aged 18–45 and 46–60, but the substantial overlap of age ranges among published studies precluded such analyses.

The panel also initially planned to evaluate sleep duration separately for men and women. As detailed below, gender-specific voting was conducted during round 1 voting in all categories for which gender-specific evidence was available. After round 1 voting, however, the gender-specific votes were collapsed after voting results demonstrated the evidence did not meaningfully suggest different sleep duration recommendations between genders.

A preliminary search of the literature and specific National Library of Medicine Medical Subject Headings (MeSH) terms identified several health outcomes that were most commonly examined in relation to sleep duration. Based on this evidence, the panel decided to focus on the relationships between sleep duration and nine health categories: (1) general health; (2) cardiovascular health; (3) metabolic health; (4) mental health; (5) immunologic health; (6) human performance; (7) cancer; (8) pain; and (9) mortality.

After establishing the health categories, a detailed literature search was performed in PubMed on October 28, 2014. The search terms used for the literature search are detailed in Appendix A. The search was restricted to studies in human adults, published in English, with no publication date limit. Case reports, editorials, commentaries, letters, and news articles were excluded from the search results. The initial search produced 5,314 publications. The search results were reviewed based on title and excluded a priori for the following reasons: focusing on sleep quality or fatigue instead of sleep duration; assessing sleep duration in specific illnesses or sleep disorders; experimentation involving total sleep deprivation; inclusion of subjects sleeping outside normal day/night sleep schedules; assessing sleep deprivation as a treatment (e.g., depression); focusing on medication effects on sleep duration; and inclusion of participants outside the age range of 18 to 60 years. Application of these restrictions resulted in 1,266 publications.

The panel reviewed the abstracts of these remaining publications using the same criteria described above. Pearling was used to capture important publications that were not identified by the search. Accepted publications were graded for quality using Oxford criteria.⁶⁰ Each panel member assigned to a particular health category was asked to identify the five most informative studies based on study design and evidence quality. All accepted publications with an Oxford grade of I,

Table 2—Nine health categories and subcategories with indication if gender-specific recommendations were considered in round 1 voting.

Category	Sex-Specific
General Health	Yes
Cardiovascular Health a. Cardiovascular Disease b. Hypertension	Yes
Metabolic Health a. Diabetes b. Obesity	Yes
Mental Health a. Mood b. Psychiatric Health	No
Immunologic Health a. Immune Function b. Inflammation	No Yes
Human Performance a. Cognitive Performance b. Driving Performance c. Job Performance	No
Cancer a. Female Cancers (Breast, Ovarian) b. General Cancers c. Colorectal Cancer	No Yes Yes
Pain	No
Mortality	Yes

II, or III were reviewed in detail and the data listed in Table 1 were extracted. Based on the data extraction, accepted studies were subdivided into the categories and subcategories listed in Table 2. The extraction sheet and full text of all accepted publications were made available to the panel members for review. A second PubMed literature search was performed immediately prior to the conference (on January 22, 2015) to collect any additional relevant studies. The final list included 311 publications for consideration by the panel (Appendix B).

2.4 Round 1 Voting

Prior to the conference, panel members reviewed the accepted publications and extraction sheets. Based on their review of this material and their clinical and research expertise, members voted to indicate their agreement with the following statement: “Based on the available evidence, [X] hours of sleep is associated with optimal health within the [X] subcategory in the [X] category.” “Hours of Sleep” was categorized as < 5 hours, 5 to 6 hours, 6 to 7 hours, 7 to 8 hours, 8 to 9 hours, 9 to 10 hours, and ≥ 10 hours. The panel members voted using a 9-point Likert scale where 1 meant “strongly disagree”, 9 meant “strongly agree”, and 5 meant “neither agree nor disagree”. Panel median values were placed into three broader categories with the following interpretations; 1–3 indicated disagreement with the statement, 4–6 indicated uncertainty, 7–9 indicated agreement with the statement.

Panel members were instructed not to discuss the evidence or their votes with each other to ensure independence. Panel

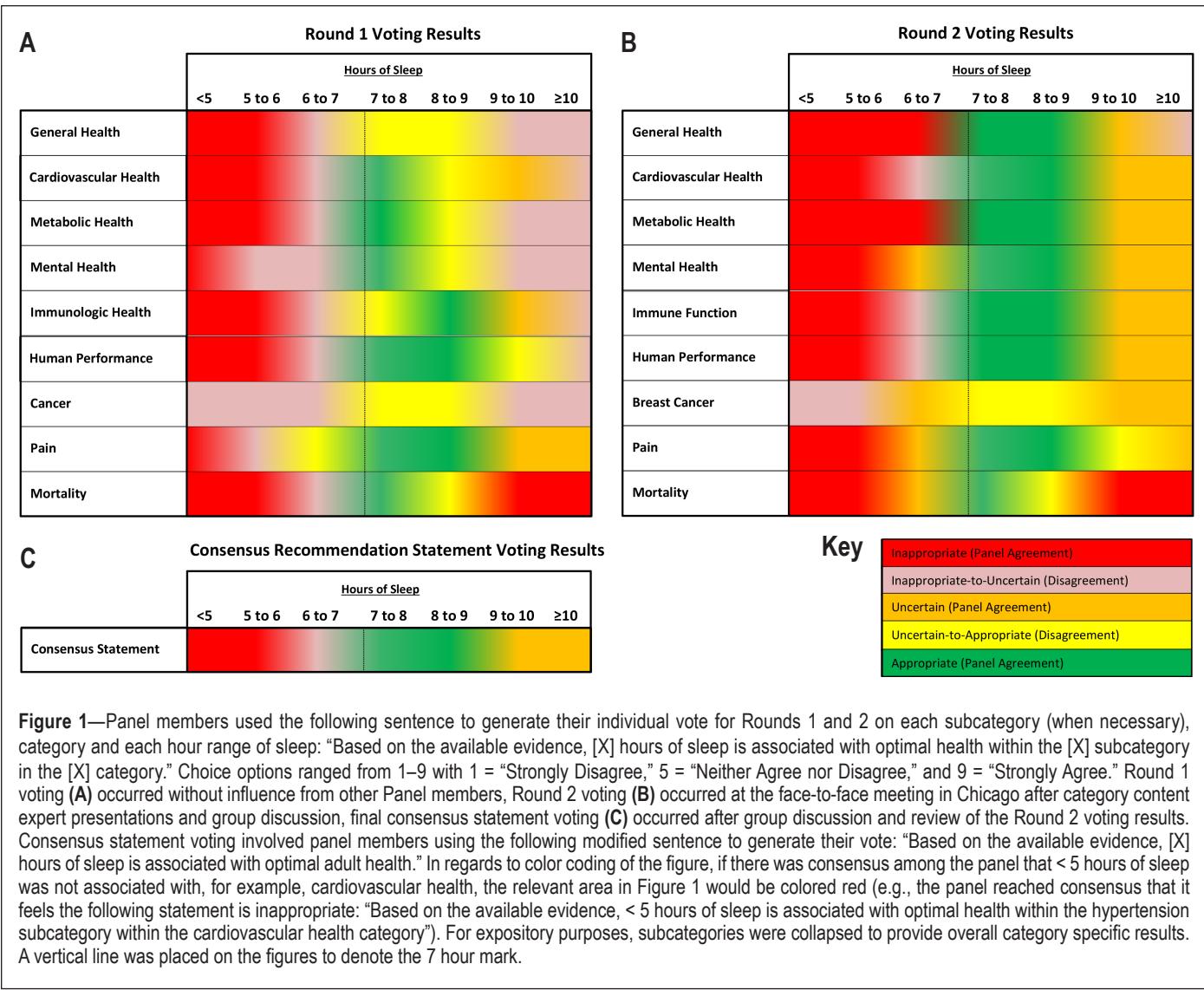


Figure 1—Panel members used the following sentence to generate their individual vote for Rounds 1 and 2 on each subcategory (when necessary), category and each hour range of sleep: “Based on the available evidence, [X] hours of sleep is associated with optimal health within the [X] subcategory in the [X] category.” Choice options ranged from 1–9 with 1 = “Strongly Disagree,” 5 = “Neither Agree nor Disagree,” and 9 = “Strongly Agree.” Round 1 voting (A) occurred without influence from other Panel members, Round 2 voting (B) occurred at the face-to-face meeting in Chicago after category content expert presentations and group discussion, final consensus statement voting (C) occurred after group discussion and review of the Round 2 voting results. Consensus statement voting involved panel members using the following modified sentence to generate their vote: “Based on the available evidence, [X] hours of sleep is associated with optimal adult health.” In regards to color coding of the figure, if there was consensus among the panel that < 5 hours of sleep was not associated with, for example, cardiovascular health, the relevant area in Figure 1 would be colored red (e.g., the panel reached consensus that it feels the following statement is inappropriate: “Based on the available evidence, < 5 hours of sleep is associated with optimal health within the hypertension subcategory within the cardiovascular health category”). For expository purposes, subcategories were collapsed to provide overall category specific results. A vertical line was placed on the figures to denote the 7 hour mark.

members’ votes were collected and compiled to determine the median and distribution of votes. Individual results tables were created and distributed to members at the consensus conference, displaying the distribution of votes (anonymized), the member’s vote, and the median vote. When relevant, subcategory results were collapsed to reveal overall category specific results (Figure 1A).

2.5 Conference Proceedings and Round 2 Voting

Prior to the conference, one panel member was selected to act as a category expert for each category. At the conference, members reviewed the results of Round 1 voting for a category and the category expert presented a review of the best available evidence for that category. Panel members then discussed the results of Round 1 voting, the accepted publications for the category, and any other relevant evidence. After discussions, panel members completed Round 2 voting for the category and subcategories (when relevant) following the same procedures from Round 1 voting. The conference proceeded in this manner for all categories.

Based on the results of Round 1 voting and the conference discussions, and with the agreement of all panel members,

some subcategories were collapsed or dropped for Round 2 voting. This decision was based on the availability and strength of evidence. This resulted in the following categories/subcategories for Round 2 voting: (1) general health, (2) cardiovascular health (subdivided into hypertension and cardiovascular disease), (3) metabolic health (subdivided into diabetes and obesity), (4) mental health (subdivided into mood and psychiatric health), (5) immunologic health, (6) human performance (subdivided into cognitive performance and driving performance), (7) breast cancer, (8) pain, and (9) mortality. As with Round 1, Round 2 voting results for subcategories were collapsed to reveal overall category specific results (Figure 1B).

2.6 Round 3 Voting and Development of Recommendation Statement

Panel members reviewed and discussed Round 2 voting results for all categories and the entire body of accepted publications in preparation for voting on a single recommendation statement. After discussions were concluded, panel members completed Round 3 voting for the single recommendation statement (Figure 1C), following the same procedures as Round 1 and Round 2 voting but using the following statement:

“Based on the available evidence, [X] hours of sleep is associated with optimal adult health.” Upon completion of Round 3 voting, the panel members reviewed the voting results and crafted the language of the recommendation statement. After all panel members approved the language of the final statement it was submitted to the AASM and SRS Boards of Directors for their endorsement.

3.0 SUMMARY OF LITERATURE

The following sections succinctly summarize the key evidence considered by the panel in developing the recommendation statement while acknowledging that a complete review of the evidence is beyond the scope of this document.

3.1 General Health

The majority of studies in this category were large-scale cross-sectional studies, although there were also prospective cohort and sleep restriction studies, with sample sizes ranging from 30 (prospective cohort study) to 75,718 (cross-sectional study) individuals. Some of the studies evaluated the relationship between sleep duration and general health using health-related quality-of-life (HRQOL) measures. The associations of sleep duration with HRQOL and sleep health disparities were examined in 2,391 young adults (20–39 years) using cross-sectional data from the National Health and Nutrition Examination Survey 2005–2008 (NHANES).⁶¹ Young adults who slept < 7 hours were more likely to report poor general health and low overall physical, and mental HRQOL than those sleeping ≥ 7 hours. Other studies focused on the risk or presence of one or more specific diseases. Many but not all of the studies indicated that < 7 hours is associated with poorer general health (typically assessed by HRQOL measures) and increased risk or presence of disease compared to 7–8 hours of sleep. There is less evidence for an association of longer sleep duration and adverse health status, with only a few studies demonstrating an association of poorer general health or increased risk/presence of disease with ≥ 9 hours of sleep.

3.2 Cardiovascular Health

The panel reviewed numerous studies addressing the association between sleep duration and broadly-defined cardiovascular disease. Many studies specifically targeted the relationship between sleep duration and hypertension. Most were cohort or cross-sectional studies of community based populations, although some utilized a case-control study design. The number of participants ranged from less than 100 in the case-control studies to over 200,000 in some of the cohort studies. For studies focused on overall cardiovascular disease, the most common outcomes were coronary heart disease, stroke or a combination of both, adjudicated through medical records or central registries. Hypertension was variously defined by self-report, blood pressure measurements and/or use of anti-hypertensive medications. Sleep duration in virtually every study was ascertained by self-report and presented in several different formats, making comparisons across studies challenging.

Most studies demonstrated a positive association between sleep durations of less than 6 hours and overall cardiovascular disease in comparison to sleep durations between 7 and 8

hours. The relationship was stronger for cross-sectional than prospective studies. In contrast, only a few studies demonstrated an association with cardiovascular disease for sleep durations between 6 and 7 hours. For sleep durations greater than 8 hours, the data were more heterogeneous. However, the majority of both cross-sectional and prospective studies found a positive association between sleep duration greater than 9 hours and cardiovascular disease, in comparison to sleep durations of 7–8 hours.

Fewer prospective studies were available for hypertension, but similar to overall cardiovascular disease, short sleep durations, especially less than 6 hours were associated with hypertension in comparison to 7–8 hours of sleep. For sleep durations greater than 8 hours, the evidence was less compelling with only a few studies demonstrating a relationship with hypertension.

Several meta-analyses that included most of the large cohort studies support these general conclusions. Both “short (≤ 5 –6 hours)” and “long (> 8 –9 hours)” sleep duration were associated with incident cardiovascular disease in one of these.⁶² In contrast, another meta-analysis found an association between both short and long sleep and hypertension in cross-sectional studies, but only for short sleep in longitudinal studies.⁶³

In summary, elevated risk for both overall cardiovascular disease and hypertension is associated with sleep durations less than 6 hours, and possibly for sleep durations of 6–7 hours compared to sleep durations of 7–8 hours. Evidence for increased risk of cardiovascular disease and hypertension is less compelling for sleep durations greater than 8 hours.

3.3 Metabolic Health

Experimental studies and population-based observational studies provide strong evidence for a link between short sleep duration and metabolic function. Experimental sleep restriction reduces cellular and whole body insulin sensitivity, lowers glucose tolerance, and raises afternoon and evening levels of cortisol, an insulin antagonist.^{64,65} If these effects are prolonged, the increased load on the pancreas can compromise β -cell function and lead to type 2 diabetes.⁶⁶ Experimental sleep restriction also promotes a positive energy balance by affecting levels of the hunger regulating hormones leptin and ghrelin;²⁷ increasing hunger and appetite,²⁷ with particular cravings for fat and sweet and salty snacks;^{27,28} increasing caloric intake;^{27,67} decreasing caloric expenditure through physical activity;⁶⁸ and increasing body weight.^{28,67,69} Over time these effects can lead to overweight and obesity which are risk factors for metabolic syndrome and diabetes. The primary limitations of experimental studies is that they examine a short duration of sleep restriction, have small sample sizes with limited generalizability, and restrict sleep to an extreme degree (typically 4 hours per night). The extent to which individuals adapt to the effects of short sleep duration over time is unknown. Conversely, small uncontrolled studies have reported beneficial effects of sleep extension on glucose metabolism and appetite ratings in individuals who habitually curtail their sleep.^{70,71}

Numerous cross-sectional and longitudinal population-based observational studies have assessed the relationships between sleep duration and diabetes, obesity, and the metabolic syndrome. Three meta-analyses of prospective studies on

sleep duration and diabetes were identified. All three found a significant association between short sleep duration and the incidence of type 2 diabetes.^{24,72,44} A meta-analysis of cross-sectional studies found a significant negative association between hours of sleep and body mass index; short sleep duration was significantly associated with obesity.⁷³ A meta-analysis of longitudinal studies showed that short sleep duration was associated with incident obesity.⁷⁴ Two meta-analyses of cross sectional studies found short sleep duration to be associated with the prevalence of the metabolic syndrome.^{73,74}

Some studies have also found significant associations between long sleep duration and metabolic outcomes, but the results of meta-analyses relating long sleep duration to metabolic outcomes are mixed. Two meta-analyses showed an association between long sleep duration and incidence of diabetes,^{24,44} and one meta-analysis showed no relationship.⁷² In a meta-analysis of longitudinal studies, no relationship was found between long sleep duration and obesity incidence.⁷⁴ One meta-analysis of cross sectional studies found a significant relationship between long sleep duration and the prevalence of the metabolic syndrome,⁷⁵ while another meta-analysis found no relationship.⁷⁶ Given the lack of experimental evidence for detrimental effects of long sleep duration, the observed associations between long sleep duration and metabolic outcomes are often interpreted to reflect residual confounding.

3.4 Mental Health

Relationships between sleep duration and psychiatric health have been addressed in numerous publications. These studies vary widely in design, including observational, experimental, and treatment intervention studies; cross-sectional and longitudinal designs; healthy, patient, and population samples; and outcomes including symptom severity or categorical diagnoses. Many studies addressing sleep and mental health focus on insomnia rather than sleep duration per se. Given the number and diversity of published studies and the consensus process aims, strongest consideration was given to cross-sectional and longitudinal epidemiologic studies of self-reported sleep duration in relation to dimensionally or categorically-defined depression.^{77–84} No published meta-analysis has specifically addressed the relationship between sleep duration and depression, anxiety or other psychiatric disorders.^{77,79,80,85}

Short self-reported sleep duration is associated with increased cross-sectional and longitudinal risk for depression, whether measured as symptoms or as a diagnosis.^{77,79–84,86} The threshold for short sleep varies across studies from 5–7 hours, with the majority using 6 hours. Some data also demonstrate increased risk associated with sleep duration longer than 8–9 hours.^{80,82} Few studies parsed the specific risk associated with one-hour increments of sleep duration. Sleep duration is also associated with important symptoms related to depression, such as suicidal ideation and psychological distress.^{77,87,88} Finally, the direction of sleep duration-mental health relationships is not entirely clear. Experimental^{14,89,90} and longitudinal observational studies^{88,91} suggest short sleep duration can lead to depression and other mental health symptoms. On the other hand, insomnia symptoms typically improve when depression is treated, even when the treatment does not specifically target sleep.⁹² Variable effects of depression treatment have been

observed on sleep duration per se.^{93,94} Experimental data are not available to suggest a causal role for long sleep duration in relation to mental health.

3.5 Immunologic Health

The effects of sleep duration on immunity have been examined from the cellular to the systemic level, and have included outcomes ranging from natural killer cell function and leukocyte activity to vaccine immune response and risk of infection following pathogen exposure. Sleep duration has been measured with sleep logs and actigraphy, although the definition of short sleep varies between studies. Studies with small numbers of subjects in both cross-sectional and experimental designs consistently demonstrate an association between short sleep duration and decreased natural killer cell function and mobilization. One observational study²⁹ and one controlled study³⁰ assessed the effect of sleep duration on immune response and vaccine clinical protection status. In both studies, shorter sleep was associated with decreased vaccine immune response.

Two studies assessed infection risk in relation to sleep duration. One observational study of 153 individuals found that subjects reporting less than 7 hours of sleep were at higher risk of developing an upper respiratory infection following rhinovirus exposure.³¹ A larger prospective observational study of over 56,000 people found that self-reported sleep of less than or equal to 5 hours and greater than or equal to 9 hours was associated with an increased risk of pneumonia.⁹⁵ The paucity and heterogeneity of literature regarding inflammation resulted in the panel dropping this subcategory from consideration in Round 2 voting.

3.6 Human Performance

This area focused on the relationship between sleep duration and various aspects of cognitive performance that have been scientifically validated to be sensitive to sleep loss, as well as daytime sleep propensity and drowsy driving. Job performance was originally included but not retained due to an inadequate number of studies measuring actual job performance. Several studies were identified as relevant to this area but the vast majority had multiple limitations that included lack of objective measurement of sleep duration, focus on a single sleep restriction (often < 6 hours), limited duration of exposure to the restriction (a factor considered essential to uncovering cumulative effects from sleep restriction, especially mild-to-moderate sleep restriction), and lack of comparison and control conditions. A number of randomized controlled trials (RCTs) met the criteria for Oxford Level of Evidence I or II for the effects of sleep duration dose on cognitive performance across days. Collectively these studies included more than 200 healthy women and men ages 21–62 years. Population-based studies on a total of more than 5,600 adults evaluated associations between self-reported sleep duration and daytime sleep propensity (measured by sleep latency) or self-reported drowsy driving.

Studies using cognitive performance as an outcome have focused especially on tasks that assess the stability of vigilant attention (e.g., psychomotor vigilance test), cognitive processing speed, and working memory. One study found that time in bed (TIB) of 9 hours for sleep yielded higher performance on some

cognitive domains than did 7 hours TIB. Fourteen studies found that 8–8.5 hours TIB resulted in cognitive performance superior to 6 hours or less TIB. A few studies found that 7 hours TIB yielded better performance than 5 hours TIB, while others found that 6 hours TIB was superior to 4–5 hours TIB. Sleep time of 4 hours yielded better cognitive performance than 3, 2, 1 or 0 hours for sleep.

Research findings show two consistent cognitive performance dynamics relative to 8 hours TIB for sleep: (1) The shorter the sleep duration, the greater the cognitive performance deficits; and (2) the longer the exposure to sleep restriction, the greater the cognitive deficits. Thus, the less sleep obtained, and the longer this continues, the more quickly cognitive deficits become evident.^{3,5} Self-reported sleepiness does not show the latter dynamic and therefore cannot be used to track increasing performance deficits. In addition, total sleep duration per 24 hours is the critical factor relative to performance, since split-sleep schedules also show the same sleep dose-response effects.⁹⁶ Finally, the adverse effects of limited sleep time are especially severe at circadian times when sleep propensity is high.^{96,97}

Scientific reports on sleep duration relative to daytime sleep propensity and drowsy driving revealed similar findings. Daytime sleep propensity as measured by the Multiple Sleep Latency Test (MSLT) was one of the earliest objective physiological measures of the cumulative daytime effects of sleep restricted to 5 hours a night for 1 week.⁹⁸ A more recent study showed that adults reporting sleep durations of 6.75 to 7.5 hours, and less than 6.75 hours, had a 27% and 73% increase, respectively, in the risk of sleep onset during the MSLT, compared to adults reporting > 7.5 hours of sleep.⁹⁹ Motor vehicle crash risk also increases when self-reported sleep duration is less than 6 hours. A recent cross-sectional survey of drivers found an association between self-reported sleep duration less than 7 hours and at least one self-reported incident of falling asleep while driving during the prior year.¹⁰⁰

In summary, Level I evidence demonstrates that cognitive performance involving vigilance attention, cognitive processing speed and working memory, as well as physiological sleep propensity and drowsy driving are all sensitive to sleep duration below 7 hours. These deficit vulnerabilities increase inversely with declining duration and increasing chronicity of sleep amount. There is no clear evidence that sleep duration greater than 8 hours has an impact on these domains, beyond what is found for sleep durations of 7–8 hours per night, although “extra” sleep may provide some prophylactic benefits for performance during subsequent sleep restriction.¹⁰¹

3.7 Cancer

The literature addressing sleep duration and cancer risk involved studies focused on “female” cancers (breast, ovarian), colorectal, and general cancer diagnoses. These were mostly large prospective cohort studies including 12,222–110,011 subjects, although some were smaller and utilized a case-control study design. Breast cancer, the most commonly investigated neoplasm, was examined in 10 studies, including five large prospective cohort studies involving a combined total of more than 250,000 women. Four studies showed no association between sleep duration and breast cancer, while one showed ≤ 6 hours

of sleep was associated with increased risk of breast cancer compared to 7 hours of sleep.⁴⁶ Case-control studies showed no association between sleep duration and breast cancer.

Three large prospective cohort studies assessed sleep duration and general cancer mortality, with none showing an association for either short or long sleep duration. Three studies addressed sleep duration and colorectal cancer, and each reached different conclusions. A case-control study¹⁰² found short sleep < 6 hours, but not long sleep, was associated with colorectal adenoma, while a large prospective cohort study showed both extreme short (≤ 5 h) and long (≥ 9 h) sleep durations were associated with increased risk of colorectal cancer.⁴⁵ A third study only found an association in those who were overweight or snored, which may signify the impact of sleep apnea and its attendant intermittent hypoxemia.¹⁰³ A number of large prospective cohort studies assessed sleep duration and general cancer mortality with none showing an association for either short or long sleep duration. One prospective cohort study assessed the association between sleep duration and ovarian cancer and found sleep > 7 hours was associated with reduced ovarian cancer risk.¹⁰⁴

Given the strengths of the studies addressing breast cancer, and the small size and limitations of the data assessing colorectal cancer, general cancer, and ovarian cancer, the panel decided to focus on breast cancer alone for Round 2 voting.

3.8 Pain

A number of papers related to sleep duration and pain were reviewed, including cross-sectional survey and experimental studies, and studies with self-report and objectively-measured sleep time. Sleep durations below 5 hours were associated with increased pain in all of these study types.^{18,19,105–110} Increased pain symptoms were associated with sleep duration of less than 6 hours in four studies (three self-report and one objective monitoring).^{18,19,105,106} Sleep durations of 7–8 or 8–9 hours were consistently associated with reduced pain symptoms.^{18,105–109} Results were less consistent for sleep durations of 6–7 hours and 9 or more hours, primarily due to the small number of studies examining sleep durations in these time ranges.

3.9 Mortality

This literature includes numerous studies, of which many were included in two independent meta-analyses.^{38,111} Both meta-analyses found increased mortality risk associated with short sleep and long sleep durations. “Short” and “long” sleep were defined differently across studies. Nevertheless, self-reported sleep duration of 7–8 hours was generally associated with the lowest mortality risk, and both short and long sleep duration were associated with increased risk. Given the heterogeneity of short and long sleep definitions, the most reliable comparisons examined these broad categories. However, examination of one hour sleep duration categories in large prospective studies suggests that the most extreme sleep durations are associated with the greater risk, especially in the case of long sleep. This U-shaped relationship has been demonstrated repeatedly (but not universally) and has been replicated using objective sleep measurement with actigraphy. The sleep duration-mortality risk relationship appears relatively stable across demographic groups, with one exception: Increased mortality

risk associated with long sleep may be partially explained by age.

The panel's recommendation statement focuses on adults up to age 60 years, but many of the deaths in the studies examining mortality likely took place after subjects were 60 years old, given the longitudinal study designs. One meta-analysis¹¹¹ did not find a significant difference in mortality risk by age. Further, the role of medical conditions that could lead to both mortality and either short or long sleep duration is unclear. Although many potential confounders can be entered into analyses of large data sets, it may be difficult to interpret mortality risk after accounting for many of the leading causes of death, a large number of which may also be related to sleep duration. For example, the only study to assess the relationship between sleep duration and mortality in healthy individuals showed no association;⁴⁰ an association was evident only in those who were in poor health at the start of the study. These findings suggest that sleep duration-mortality risk associations may be driven more by underlying diseases than by sleep per se. Finally, one of the reviewed studies¹¹² included a sample so disproportionately large that it may exert undue influence on the overall conclusion. However, another meta-analysis³⁸ found that similar overall effects remained even after excluding this study from analysis.

4.0 STRENGTHS AND WEAKNESSES OF THE LITERATURE

The panel recommendation statement⁵⁵ was based on a literature characterized by numerous strengths. Taken together, studies on sleep duration include data on millions of participants, studied across several continents, aggregated over several decades. The studies include cross-sectional and longitudinal epidemiologic designs, randomized controlled trials, meta-analyses, and a range of other designs. Studies in the human performance category may have the strongest evidence base, which included experimental laboratory studies, objective measure of sleep and outcomes, evidence of cumulative effects, and support from population-based cohort studies documenting "real life" outcomes (e.g., driving performance) associated with sleep duration. Studies in the cardiovascular, metabolic, and mental health categories also include both laboratory experiments and epidemiological cohort studies. Numerous, large cross-sectional and longitudinal population-based observational studies provide largely concordant findings linking short sleep duration to obesity, cardiovascular disease, diabetes, and depression. Meta-analyses further support the findings reported in individual studies. The immunologic health and pain categories are supported by fewer studies, but these also include both observational and laboratory designs. In particular, studies of immune function in relation to sleep duration examine possible mechanisms at the cellular level. The literature also includes a large number of studies spanning several decades in the general health, cancer, and mortality categories. Studies in the mortality category include large samples and demonstrate largely convergent results that are supported by multiple meta-analyses.

A number of important limitations in both epidemiologic and laboratory-based studies are also evident, as described in previous reviews.¹¹³ Epidemiologic studies maximize generalizability at the expense of measurement precision, whereas

experimental studies maximize measurement precision at the expense of generalizability. However, these limitations are mitigated by the general agreement in findings between laboratory-based and epidemiologic studies.

Epidemiologic studies pose several specific limitations. First, most of the studies reviewed were cross-sectional, precluding any statements regarding causation. Second, sleep duration is typically assessed for a limited time frame around the assessment, whereas most of the health conditions have been developing or present for years prior to assessment. While cross-sectional associations may be valid, "predicting" chronic health conditions from concurrent sleep duration presents a conceptual challenge. Third, many epidemiologic studies have limited ability to explore potential mediators and effect modifiers. Fourth, some studies may have insufficient adjustment for confounders. Conversely, excluding too many health conditions may make interpretation difficult (e.g. If likely causes of death are removed from the analysis, it is difficult to study mortality).

Specific methods of sleep assessment also present some limitations in epidemiologic studies. First, most of these studies rely on retrospective self-report of habitual sleep duration, which may be less accurate than averages from daily self-report (i.e., sleep diary). Self-reported sleep duration can over- or under-estimate sleep duration measured objectively with actigraphy or polysomnography. Second, studies have varied in how they assess self-reported sleep duration. For instance, different studies may ask participants to report "typical," "average," "weeknight," or "24-hour" sleep duration. Some epidemiologic studies capture napping, while others do not. Third, while the survey items addressing sleep duration may have good face validity, most have not been formally validated with psychometric analyses. Fourth, sleep duration is not consistently defined across studies. For example, short sleep may be categorized as < 5, 5, 6, or < 8 hours, and reference groups may have sleep durations of 7, 8, 7–8, 7–9, or 6–8 hours. Fifth, measures of sleep duration do not capture information about the regularity of sleep patterns, the timing of sleep, or the quality of sleep. Each of these facets of sleep may interact with sleep duration to affect health. Finally, many epidemiologic studies rely on self-reported health outcomes, such as height and weight, diabetes, and hypertension which may provide an additional source of measurement error.

Experimental designs have important limitations as well. First, few studies examined sleep manipulations for more than 7 days. The acute effects of sleep deprivation may be poor approximations of real-world effects that typically reflect accumulated sleep debt over weeks, months, or years. Similarly, the time course of habituation in the laboratory may not reflect habituation effects outside of the laboratory, or the degree to which self-directed changes in sleep (e.g., oversleeping on weekends) affects risk profiles. Second, few studies examined sleep duration in the range of 6 to < 7 hours. This likely reflects the aims of experimental studies, which often maximize differences in outcomes by contrasting extreme sleep duration groups. The absence of experimental groups in the 6–7 hour sleep range creates uncertainty in recommendations for the large portion of the population that report sleep durations of 6–7 hours. Third, many experimental studies lack generalizability

because they include small samples that do not represent the population in terms of age, sex, race/ethnicity, socioeconomic status, or health history. Fourth, while the focus on objective, physiological sleep is a strength of laboratory studies, these objective measures correlate weakly with self-reported sleep duration, which is the method most relevant to clinical, public health, and policy recommendations. Standard methods to model such discrepancies must be sought until accurate, scalable, objective measures of sleep duration are developed for utilization in large epidemiological studies.

5.0 VOTING SUMMARY

Voting results from all 3 rounds are presented in Figure 1. In general, there was consensus that 6 hours of sleep or less was inappropriate to support optimal health in adults. There was also consensus that 7–9 hours of sleep were appropriate to support optimal health in adults. There was consensus that the appropriateness of 9 or more hours of sleep on optimal adult health could not be ascertained with certainty. Consensus could not be reached regarding the appropriateness of sleep durations in the 6–7 hour range, but the median vote indicated this duration was in the inappropriate range.

The panel then discussed the merits of recommending a sleep duration threshold versus a sleep duration range to promote optimal health. Implicit to a range recommendation is the conclusion that sleep duration above a certain amount is detrimental to health. Although there was evidence of an association between long sleep and adverse health outcomes in some categories, Round 3 voting revealed uncertainty regarding the appropriateness of > 9 hours of sleep for adult health. Further, although some studies have suggested potential reasons why longer sleep durations may be harmful,¹¹⁴ the panel was unable to come to a consensus regarding biologically plausible pathways by which long sleep could explicitly cause poor health (acknowledging that biological plausibility depends on knowledge available at the time). With these considerations in mind, the panel decided to recommend a minimum threshold value rather than a range. The threshold was set at the lowest sleep duration the panel agreed was appropriate to support optimal health in adults: 7 hours.⁵⁵

6.0 DISCUSSION

Sleep is a biological imperative. Meeting our need for sleep duration, timing, regularity, and quality requires volitional behaviors partially dictated by genetic and physiologic factors. However, a large proportion of inter-individual variability in sleep is likely explained by psychological, behavioral, social, cultural, and environmental factors (Figure 2). Sleep disorders, which are frequently undiagnosed and/or untreated, further contribute to this variability.

For reasons stated above, the consensus panel focused solely on the dimension of sleep duration, while recognizing the importance of other dimensions such as timing, regularity, and quality. The recommendation statement⁵⁵, which focuses on the sleep amount that promotes *optimal* adult health, does not address these other dimensions. Although our literature search excluded studies focusing primarily on one of these other dimensions, we recognize that they may have contributed important unmeasured variance to the reviewed studies. We also

excluded research assessing the physiological impact of total sleep deprivation, since it can only be maintained for a few days at a time and cannot reflect habitual sleep, which was the focus of the panel.

When gauging the value and utility of the literature in addressing our question, the panel was keenly focused on the nine tenets of causality typically referred to as the Bradford Hill criteria,¹¹⁵ which include: (1) strength of association, (2) consistency of findings, (3) specificity and (4) temporal sequence of association, (5) biological gradient and (6) plausibility, (7) coherence of the data, (8) experimentation results, and (9) analogous scenarios. Although empirical data were not available to address each of these criteria for each health outcome, they served as a framework for discussion, voting, and recommendations.

The issue of biological plausibility is particularly salient to the associations between long sleep, health, and mortality. The panel struggled to identify plausible physiologic mechanisms by which longer sleep might *cause* poor health or increase mortality. The recommendation statement indicates a threshold value for the sleep duration necessary to support optimal health in adults. This threshold implies that more sleep is likely not damaging to health. By contrast, “optimal dose” conceptualization of sleep, inherent to a range recommendation, suggests health is compromised by obtaining too little or too much sleep (Figure 3). Since the panel could not reach consensus that longer sleep was physiologically harmful, and since there was a consensus that longer sleep is beneficial for some individuals (e.g., younger adults, those recovering from sleep loss), no upper limit of sleep duration was included in the recommendation statement. As more evidence is collected regarding long sleep, this recommendation may need to be revisited. More importantly, regardless of whether a threshold or range model is endorsed, both constructs support the notion that too little sleep is unhealthy.

Another important issue with regard to longer sleep durations is the dearth of studies assessing the physiological impact of sleep extension. Evidence in most categories regarding the association between long sleep and poor health was mixed, with the exception of mortality, where a U-shaped relationship between sleep duration and death was consistently observed (and where, indeed, relationships with long sleep may even be more robust than short sleep). Lacking convincing experimental evidence showing that sleep extension alters human physiology in unfavorable ways, and acknowledging that even the most carefully conducted epidemiological studies cannot control for all potentially relevant variables, the panel decided that the association between long sleep and increased mortality risk most likely represented the confounding effects of uncontrolled chronic illness. In other words, it seems plausible that illness associated inactivity likely increased both subjective reports of sleep duration and mortality risk. Interestingly, the only study that assessed the sleep duration/mortality question in healthy individuals failed to show an association.⁴⁰ The panel strongly encourages future experimental studies to examine the effects of sleep extension on health outcomes.

Our consensus recommendation statement presents sleep duration as static, as most epidemiological studies assessed sleep duration via a single question or measurement and

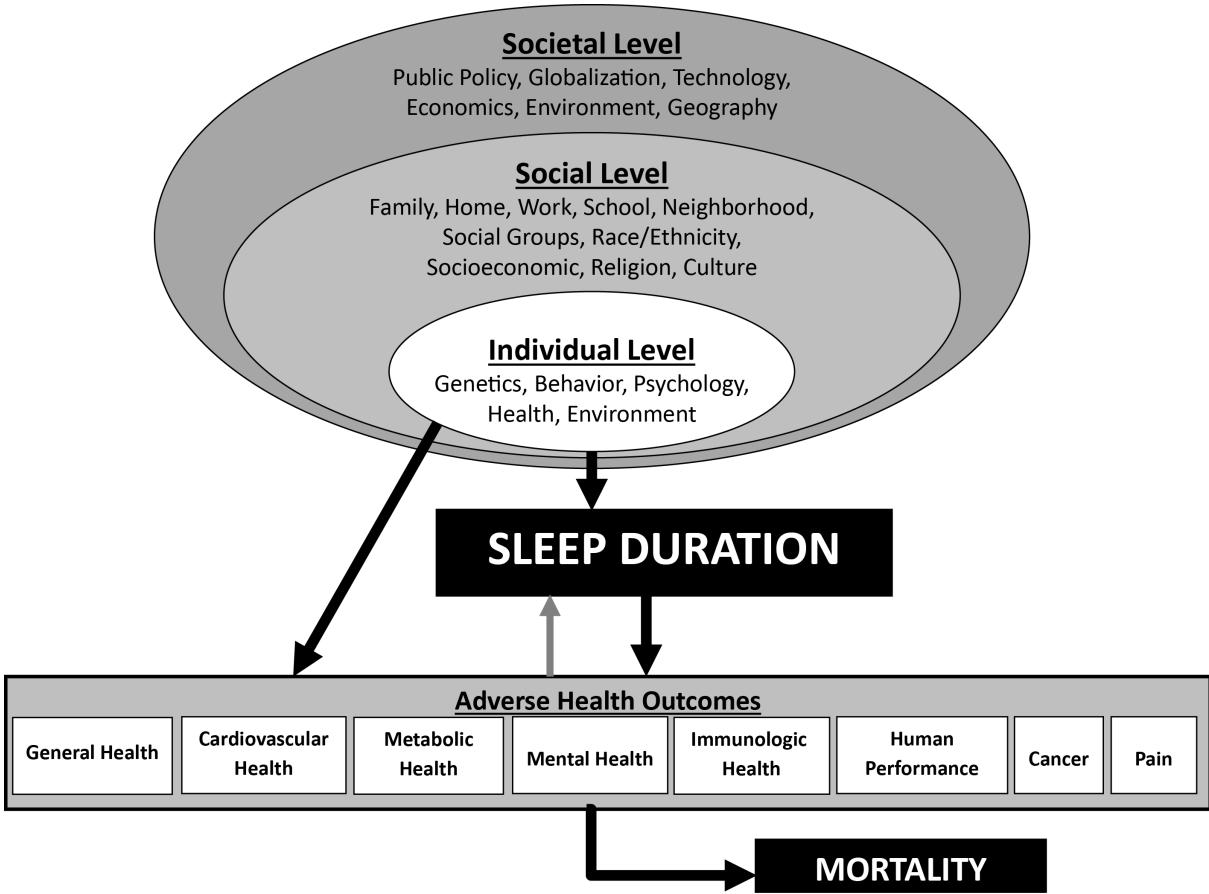


Figure 2—Biopsychosocial model of sleep duration drivers (adapted with permission from Grandner, Hale, Moore & Patel, 2010).

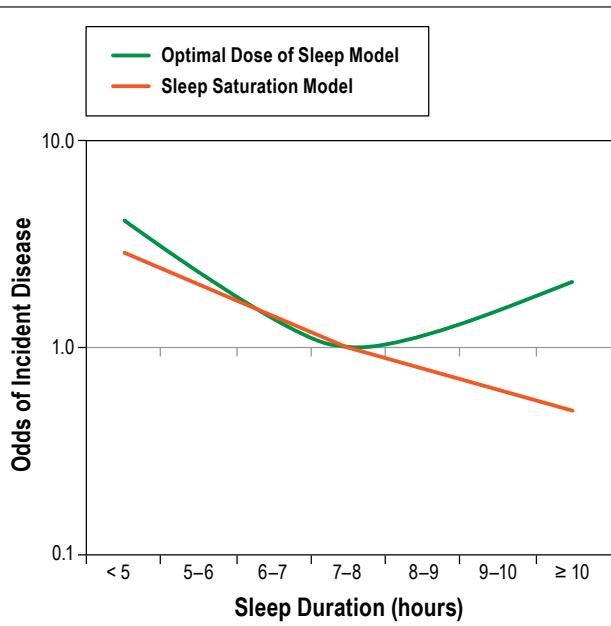


Figure 3—Two conceptualizations of sleep duration (adapted with permission from Marshall et al. *Sleep Med Rev* 2008;12:289–298). The green line represents an optimal dose of sleep where the odds of incident disease are lowest. The orange line represents a sleep saturation model, where longer sleep is not necessarily associated with poor health, and may be beneficial in some circumstances (e.g., recovery from sleep deprivation or illness).

experimental studies held sleep constant throughout the research protocol. However, the panel understood this is not the most ecologically valid construct for sleep duration. For instance, many individuals have a variable sleep lifestyle, curtailing sleep on weekdays and extending sleep on weekends—typically by staying up later at night and sleeping in later in the morning. This pattern can result in untoward circadian effects or “social jetlag,”¹¹⁶ where the body experiences circadian disruption equivalent to taking a 2–3 hour “flight” westward on Friday night (with later circadian bedtimes and wake times than usual) only to “fly” back on Sunday night—waking earlier than desired Monday morning. Ecological validity also touches upon the limitations of highly controlled, laboratory based studies of sleep deprivation. These studies are not able to ascertain compensatory physiological effects that are likely at play over time. Thus, sleep duration in the real world is a dynamic process; understanding this process requires research that considers the many factors that influence the natural impact of sleep curtailment on human health.

The panel faced many challenges in the process of generating the consensus recommendation. Perhaps the biggest issue was the heterogeneity of sleep duration measurement.¹¹⁷ Retrospective self-report, the most common method in epidemiologic studies and in clinical practice, is easy and has good face validity. However, sleep duration can vary substantially over time,^{118–120} and there is little information on how individuals account for such variation in their reports. Also, self-report

questions may have captured time in bed rather than time asleep. This distinction is particularly important among individuals with chronic illness who spend long periods of time in bed. It is also uncertain, in some studies, whether individuals include nap time in their reports of total sleep time. Self-reported sleep duration often differs considerably from objective measures of sleep duration, and may underestimate or overestimate sleep duration compared to these other methods.^{121–123}

Polysomnography (PSG) and actigraphy were utilized as objective measures in some studies. Actigraphy has better sensitivity (detecting sleep) than specificity (detecting wake).¹²⁴ As a result it often overestimates sleep duration relative to self-reports and to a lesser extent polysomnography, particularly in poor sleepers. PSG is the only common method that directly measures brain activity. However, PSG is more intrusive than self-report or actigraphy, and may interfere with the very thing it measures, as suggested by the “first-night effect.”¹²⁵ PSG is expensive and less well-suited for measuring sleep in large numbers of individuals, in participants’ home environments, and over multiple nights. Moving forward, the widespread availability and acceptance of consumer sleep technologies may create opportunities for accurate, reliable, scalable objective sleep duration assessment in large epidemiological studies.¹²⁶

7.0 FUTURE DIRECTIONS

Despite a large number of studies that have drawn connections between sleep duration and health, many critical questions remain open. The recommendations of the panel are intended to be a first step toward promoting adequate sleep duration for all adults, rather than a final destination. The panel achieved consensus based on the existing literature, but noted many knowledge gaps that need to be addressed in order to refine future recommendations. Based on this process, five specific areas for future research consideration are presented.

1. Improved sleep duration measures and study designs. Studies of sleep-health relationships should include objective measures of sleep when possible, well-validated self-report measures, and ecologically valid study designs. Epidemiological and longitudinal cohort studies would benefit from using home polysomnography, actigraphy, or other novel objective methods to measure sleep duration. The challenges of objective sleep measurement are to measure sleep without disturbing it, and to achieve this at reasonable cost. Self-report assessments should include psychometrically-validated questions and measures. When possible, measuring other dimensions of sleep health, such as timing, regularity, and quality, could lead to a more nuanced understanding of sleep-health relationships. These approaches should also be reflected in experimental studies. In addition, more laboratory studies are needed that systematically vary sleep opportunity in discrete steps between doses of 6 hours and 8 hours, using objective assessments of sleep physiology and cognitive performance. These studies should examine relevant time periods (e.g., 30 days), to develop more precise dose-response curves for sleep and recovery effects within the ranges most often reported by people in the population. Other laboratory studies could systematically mimic the more typical lifestyle of cycling through doses of shorter (restricted) and longer (recovery) sleep duration.

2. Investigate downstream mechanisms linking habitual sleep duration to health and functioning. Investigating mechanisms requires studies from epidemiologic and experimental perspectives, as well as research study designs that bridge these two approaches. For example, additional studies are needed that bring real-world short and long sleepers into the laboratory for in-depth assessment of the metabolic, cardiovascular, and neurocognitive correlates of habitual sleep duration. Intervention studies could also help to clarify whether modifying sleep improves health outcomes. Such studies could help to address whether sleep plays a causal role in health and functioning, or whether it serves as a marker of other processes.

3. Better delineate the upstream physiologic, behavioral, social, and environmental factors that may play a role in sleep duration and health outcomes. We need to better understand the genetic factors related to individual sleep need, resilience to sleep loss, and perception of sleep. In addition, the roles of race/ethnicity, socioeconomic factors, neighborhood, and other factors that may contribute to sleep and other adverse outcomes require further study. Better understanding the genetic, physiologic, and environmental factors that influence sleep duration can inform intervention strategies.

4. Develop intervention studies. Since we do not yet know whether habitual sleep duration *can* be modified in the real world, a systematic approach, moving from treatment development studies, to efficacy studies, to large-scale pragmatic trials, is warranted. Intervention studies can determine whether increasing habitual sleep duration among insufficient sleepers or extending sleep in normal sleepers results in improved outcomes, and how such changes can best be achieved. Such studies would not only assess the effects of sleep extension on human physiology, but also address the inconsistent epidemiological data showing long sleep is associated with poor health and increased mortality. Intervention studies may also help to understand how different health and functioning outcomes are related to each other. Additional studies could examine how such behavioral changes are best achieved. In short, how can we get people who cannot find time for sleep, or do not prioritize sleep, to increase their sleep duration? How do we convince a population where undiagnosed sleep disorders are more common than diagnosed sleep disorders to get proper screening, diagnosis, and treatment?

5. Identify biomarker(s) of sleep need or sleep deprivation. Inexpensive, reliable, feasible biomarkers could advance the goals of clinical care, public health, and public policy. For instance, biomarkers would allow clinicians to provide more accurate sleep schedule recommendations to patients, and policy makers to facilitate policy decisions (e.g., transportation safety, resident duty hours). Biomarkers would also catalyze research assessing the long term consequences of sleep curtailment, or the health ramifications of “social jetlag.”

8.0 CONCLUSION

The panel used a modified RAND appropriateness method to generate a consensus recommendation for the amount of sleep necessary to support optimal health in adults. Multiple rounds of evidence review, discussion, and voting were conducted to arrive at the final recommendation.⁵⁵ Additional research on the role of sleep in health will not only raise awareness of

sleep's importance, but also lead to improved health and well-being for the general population and contribute to broader economic and social benefits.

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APPENDIX A. LITERATURE SEARCH TERMS

Category	Search Term	
Sleep Duration	Short sleep	[All fields]
	Long sleep	[All fields]
	Sleep deprivation	[All fields]
	Insufficient sleep syndrome	[All fields]
	Excessive sleep	[All fields]
	Sleep curtailment	[All fields]
	Sleep length	[All fields]
	Sleep need	[All fields]
	Sleep duration	[All fields]
	Sleep deficiency	[All fields]
General Health	Epidemiology	[MeSH terms]
	Prevention medicine	[MeSH terms]
	Emergencies	[All fields]
	Endemic diseases	[All fields]
	Environmental medicine	[All fields]
	Environmental microbiology	[MeSH terms]
	Disease transmission, infection	[MeSH terms]
	Environmental pollution	[MeSH terms]
	Public health practice	[MeSH terms]
	Wellness	[All fields]
	Well-being	[All fields]
	Quality of life	[MeSH terms]
Cardiovascular Health	Cardiovascular diseases	[MeSH terms]
	Heart valves	[MeSH terms]
	Heart valve diseases	[MeSH terms]
Metabolic Health	Metabolism	[MeSH terms]
	Body weight	[MeSH terms]
	Metabolic disease	[MeSH terms]
	Insulin	[MeSH terms]
	Orexins	[MeSH terms]
	Ghrelin	[MeSH terms]
	Adipokines	[MeSH terms]
	Waist-hip ratio	[MeSH terms]
	Thyroid gland	[MeSH terms]
Mental Health	Mental health	[MeSH terms]
	Depression	[MeSH terms]
	Psychiatry	[MeSH terms]
	Anxiety disorders	[MeSH terms]
	Dementia	[MeSH terms]
	Mood disorders	[MeSH terms]
	Schizophrenia and disorders with psychotic features	[MeSH terms]
	Substance-related disorders	[MeSH terms]
Immunologic Health	Inflammation	[MeSH terms]
	Autoimmune disease	[MeSH terms]
	Cytokines	[MeSH terms]
	Leukocytes	[MeSH terms]
	Phagocytes	[MeSH terms]
	Immunoproteins	[MeSH terms]
	Vaccination	[MeSH terms]
Human Performance	Function	[All fields]
	Activities of daily living	[MeSH terms]
	Alertness	[All fields]
	Cognition	[MeSH terms]
	Patient safety	[All fields]
	Patient harms	[All fields]
	Accidental falls	[All fields]
	Accidents, aviation	[All fields]
	Accidents, home	[All fields]
	Accidents, occupational	[All fields]
	Accidents, traffic	[All fields]
	Fatigue	[MeSH terms]
	Vigilance	[All fields]
	Psychomotor performance	[MeSH terms]
Cancer	Reaction	[All fields]
	Learning	[MeSH terms]
	Comprehension	[MeSH terms]
	Confusion	[MeSH terms]
	Impairment	[All fields]
Pain	Sleep satisfaction	[All fields]
	Achievement	[MeSH terms]
	Neoplasms	[MeSH terms]
Mortality	Pain	[MeSH terms]
	Nociception	[MeSH terms]
	Rheumatic diseases	[MeSH terms]
	Aging	[MeSH terms]
	Death	[MeSH terms]
	Survival	[MeSH terms]
	Vital statistics	[MeSH terms]

APPENDIX B. REFERENCE LIST OF FINAL EVIDENCE

General Health

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