Sleep and Breathing (2022) 26:1479–1501
https://doi.org/10.1007/s11325-021-02458-1

METHODS • REVIEW

Sleep duration and health outcomes: an umbrella review

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Received: 6 May 2021 / Revised: 18 July 2021 / Accepted: 28 July 2021 / Published online: 26 August 2021

Abstract

Purpose To collect existing evidence on the relationship between sleep duration and health outcomes.

Methods A thorough search was conducted in PubMed, Web of Science, Embase, and the Cochrane Database of Systematic Reviews from inception to January, 2021. Meta-analyses of observational and interventional studies were eligible if they examined the associations between sleep duration and human health.

Results In total, this umbrella review identified 69 meta-analyses with 11 outcomes for cancers and 30 outcomes for non-cancer conditions. Inappropriate sleep durations may significantly elevate the risk for cardiovascular disease (CVD), cognitive decline, coronary heart disease (CHD), depression, falls, frailty, lung cancer, metabolic syndrome (MS), and stroke. Dose–response analysis revealed that a 1-h reduction per 24 hours is associated with an increased risk by 3–11% of all-cause mortality, CHD, osteoporosis, stroke, and T2DM among short sleepers. Conversely, a 1-h increment in long sleepers is associated with a 7–17% higher risk of stroke mortality, CHD, stroke, and T2DM in adults.

Conclusion Inappropriate sleep duration is a risk factor for developing non-cancer conditions. Decreasing and increasing sleep hours towards extreme sleep durations are associated with poor health outcomes.

Keywords Short sleep duration · Long sleep duration · Reference sleep duration · Appropriate sleep duration · Meta-analysis

Abbreviations

AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
FLD	Fatty liver disease
GDM	Gestational diabetes mellitus
HDL	High density lipoprotein
HR	Hazard ratio
LDL	Low density lipoprotein
LGA	Large for gestational age
MCI	Mild cognitive impairment
MS	Metabolic syndrome
NA	Not available
NFLD	Nonalcoholic fatty liver disease
OR	Odds ratio
RCTs	Random control trials
RR	Relative risk
SGA	Small for gestational age
T2DM	Type 2 diabetes mellitus

Introduction

While sleep takes up a huge proportion of the lifespan, its mechanisms and effects upon health are not fully understood. Healthy sleep, including appropriate sleep duration is crucial for the regulation of body metabolism and physiological functions. A recommended appropriate sleep duration or known as referent sleep duration has been published annually by the National Sleep Foundation (NSF) panel [1, 2]. In recent years there has been a trend world-wide towards fewer sleep hours each night [3], while an increased prevalence of longer sleep length in some parts of Australia, Finland, Sweden, the U.K., and the USA from 1970 to 2010s has been

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reported [4]. A complex alteration of sleep patterns has also been observed among individuals due to shift-work and 24–7 occupational requirements, resulting disorders of sleep. Therefore, great importance has been attached to the relationship between sleep duration and health outcomes. Short sleep time has been significantly linked with an increased risk for obesity [5], type 2 diabetes mellitus (T2DM) [5, 6], cardiovascular diseases (CVD) [7–9], coronary heart diseases (CHD) [8], hypertension [5, 10], and all-cause mortality [5, 11–13] in generally healthy populations. Other epidemiologic studies have shown an association between long sleep duration and increased risk for mortality [12], CVD [9, 14], obesity [15], incident diabetes mellitus [9, 16], and stroke [9, 17]. However, the strength and validity of associations between short and prolonged sleep duration remain weak and incomplete. Furthermore, there is a growing interest in investigating the connection between sleep and cancers. A potential role of sleep duration as a modifier of tumorigenesis and progression of cancers remains controversial [18, 19].

Numerous epidemiological studies and clinical trials have been conducted to assess the effects of sleep duration [5–22]. While these studies were conducted in various different populations, they did not provide a comprehensive view of diverse health outcomes [5, 8]. Furthermore, dose–response analyses on the relationship between sleep duration and health outcomes have yielded inconclusive results [12, 14, 22]. Therefore, a comprehensive evaluation is required to evaluate existing evidence from qualified meta-analyses with or without systematic reviews on multiple health outcomes [23, 24]. We therefore conducted an umbrella review to synthesize the data on sleep duration and its effects on health outcomes.

Experimental section

Umbrella review and literature search

Compared to a single meta-analysis, an umbrella review is a review of systematic reviews and meta-analyses characterizing the most comprehensive critical appraisals of previous published data. An umbrella review is one of the highest levels of evidence synthesis and is gaining traction in multidisciplinary areas [23, 24]. As sleep duration could be measured by hours in the meta-analyses, any systematic reviews without meta-analyses were excluded in this study. Four electronic databases were systematically searched through January, 2021 for articles that investigated the correlation between sleep duration and health outcomes: Embase, PubMed, Web of Science, and the Cochrane Database of Systematic Reviews. The following search terms were used: (sleep or sleep duration or sleep length or sleep time or sleep deprivation) AND (systematic review* OR meta-analys*), using truncated terminology following the SIGN guidance [25]. In addition, the reference lists of eligible articles were also screened for inclusion. Any discrepancies were resolved through discussion with a third reviewer.

Eligibility criteria

Articles with meta-analyses were deemed eligible if interventions were the length of sleep and outcomes were the diverse outcomes related to human beings. No restrictions were imposed on the age of populations, regions, races, or study categories, be they case–control studies, cohort studies, cross sectional studies, or randomized controlled studies. Articles were excluded if they (1) only included a systematic review, (2) were laboratory studies done in animals, (3) were published in languages other than English, (4) used undefined methodology. Investigations on sleep disruptions [14, 26] such as nocturnal urination, restless legs syndrome, apnea syndromes, were also excluded because researchers only focused on the length of sleep. If an article included more than one health outcome, these health outcomes were assessed separately. When two or more meta-analyses reported data for the same studies, we excluded the duplicate articles and selected the one with the largest sample size and the latest date of publication. When subgroup analyses in a study reported summary estimate effects of cohort and case–control studies separately, the cohort studies were included in this review because they were generally less susceptible to selection and recall biases.

Data extraction

The following information returned from the search were independently extracted by two authors (JL and DHC): (1) cancer outcomes and non-cancer outcomes, (2) first-author last name and publication year, (3) population, (4) meta-analysis metrics (the shortest vs. middle category, the longest vs. middle category, short vs. reference category, long vs. reference category, 1-h increment or 1-h decrement per day or night), (5) estimated effect (relative risk (RR), odds ratio (OR), hazard ratio (HR)), with the 95% confidence intervals (CIs), (6) number of cohorts/studies, (7) number of cases/total participants, (8) study design (cohort, case-control, cross-sectional, randomized controlled trial (RCT)), (9) type of effects model (random or fixed), (10) statistical p value, (11) I^2 metric, (12) Cochran's Q test value, and (13) publication bias.

Definition of sleep duration

Reference or appropriate sleep duration is conceptualized as a time point or a time period with a cutoff dividing the

sleep duration into short and long sleep duration. However, the exact reference sleep time from different source papers lacks definitional consensus. In our review, the duration of reference sleep in adults was defined based on each source paper. For papers investigating children or adolescents less than 18 years old, reference sleep duration was adopted according to the SHF criteria [1, 20]. In view of the fact that non-adults (< 18 years old) of different ages require differing sleep durations , the reference sleep time of the largest population in the specific study was selected as the representative standard by that source paper. Most articles embodied short and long sleep duration in comparison to reference time, while some papers also contained the longest or shortest sleep duration versus reference sleep duration in addition to the two typical pairs, which were also included in our study. When more than one sleep category more or less than the reference sleep duration were found simultaneously in a study, all qualified time categories that met the requirements were combined to be conceptualized as the short or long sleep duration category. Furthermore, when a study reported sleep durations both per night and per 24 h, the former was selected.

For dose–response analysis, two types of the comparisons were in line with the records. One was characterized as 1-h reduction in those who sleep less than reference duration and the other was 1-h increment in people with longer sleep duration.

Quality assessment and evidence grading

The methodological quality and risk of biases of included meta-analyses were assessed by the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2) [27], which featured an overall rating based on weaknesses in critical domains than the original AMSTAR. We assessed the quality of evidence for unique outcome through the grading of recommendations, assessment, development, and evaluation (GRADE) [28] working group classification system.

Data analysis

The most-adjusted summary estimates and 95% confidence interval (CI) calculated through fixed or random effects methods were selected from each meta-analysis in the review. Publication bias and the heterogeneity were respectively assessed by Egger's test, I^2 metric, together with Cochran's Q test when available. For heterogeneity and publication bias as well as other applicable tests, $P < 0.05$ was deemed as significance.

Results

Overall, 414 articles from databases were identified, out of which 198 articles were excluded after duplicates and 109 excluded after screening titles and abstracts. The remaining 216 articles yielded 69 meta-analyses after full-text screening (Fig. 1). The included articles covered 11 outcomes for cancers and mortality as well as 30 outcomes for non-cancer conditions (Fig. 2). The cancer and mortality outcomes are summarized in Tables 1 and 2. Tables 3, 4, and 5 show the associations between sleep duration and non-cancer problems in different populations. Full versions of the total summary data with regard to cancer and non-cancer outcomes (including the definition of sleep duration) are available in the Table S1 to Table S5, Supplementary data. AMSTAR2 scores and GRADE classifications are shown in Tables 6 and 7. The complete rating of AMSTAR2 scores and GRADE classifications relating to health outcomes are presented from Table S6 to Table S9, Supplementary data, respectively.

Furthermore, we illustrated the nonlinear dose–response relationship between sleep duration and some specific outcomes (Fig. 3).

Cancer and mortality outcomes

Long and short sleep were not associated with cancers, including ovarian cancer [29], prostate cancer [19], colorectal cancer [29], and breast cancer [30]. The same outcomes applied to the dose–response analysis on sleep duration and risk of cancers (Fig. 3a) [31]. Lung cancer was the only cancer found to be significantly associated with an elevated risk of mortality in short (1.21, 1.10–1.33) [29] and long duration sleepers (1.65, 1.36–2.00) [29].

Long sleep duration was significantly linked with an increased risk of all-cause mortality (1.39, 1.31–1.47) [8] and cancer-related mortality (1.05, 1.02–1.08) [12], while neither were influenced by short sleep. Extreme sleep durations both predicted the substantial increase in all-cause mortality, with the shortest duration sleepers having a 13% increase (1.13, 1.10–1.17) and the longest having a 35% increase (1.35, 1.29–1.41) [14]. Regarding the dose–response analysis in short sleep duration, 1-h increment more than reference time and 1-h decrement less than reference time per day or night were statistically significant parameters on all-cause mortality (Fig. 3b, c) [32].

Mortality in some specific diseases was also explored in part in this review. An hour increment per day significantly increased the stroke mortality by 17% (1.17, 1.13–1.20; Fig. 3d) in the general population [33]. Otherwise, no associations were found between sleep duration and the risk of

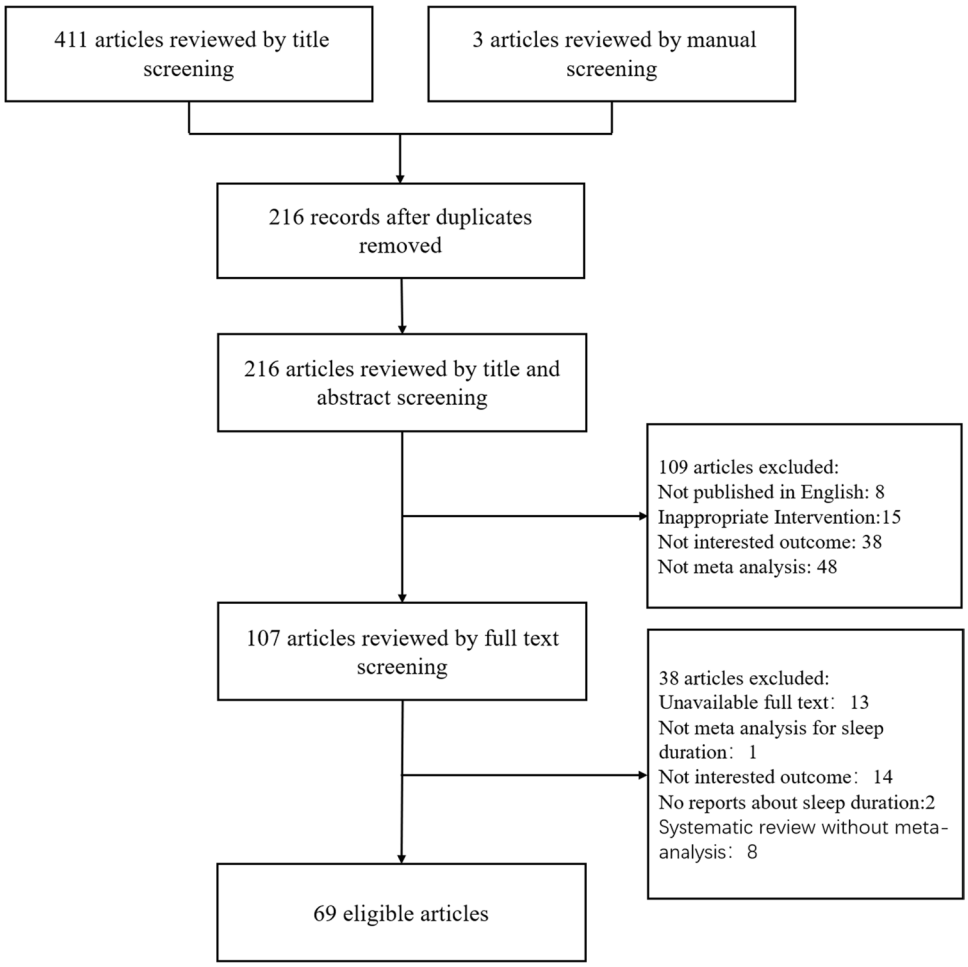

Fig. 1 Flowchart of the selection process

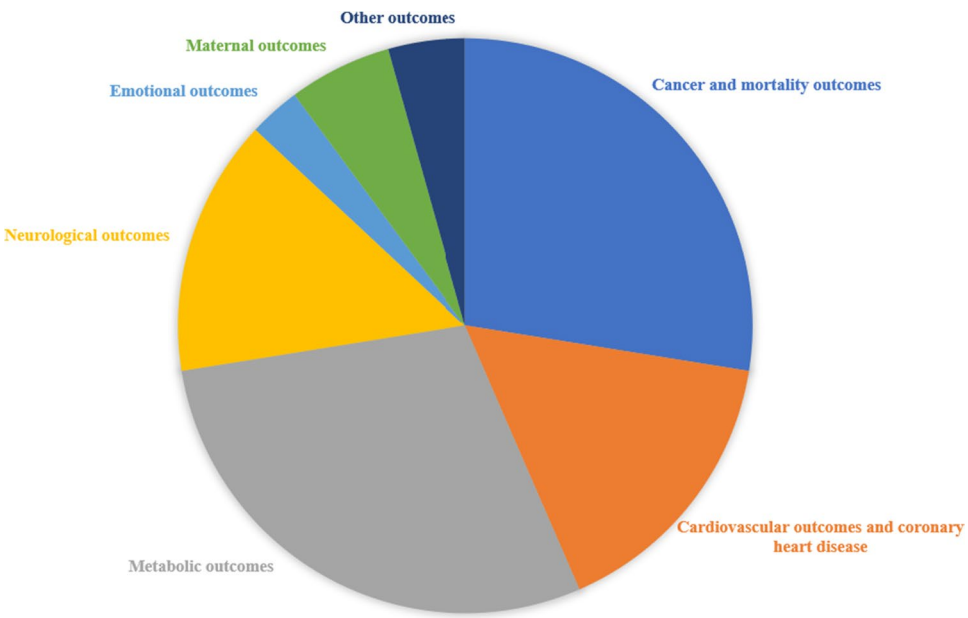

Fig. 2 Map of outcomes related to sleep durations

Table 1 Association between sleep duration and the risk cancers and mortality in adults

Outcome	Author-year	Metrics	Estimates	95% CI	No of studies	No of cases/total	Cohort	Case control	Cross sectional	RCTs	Effects model	*P* value	I^2	*Q* test	Egger test *p* value
Significant associations															
All-cause mortality	Jike 2018	RR[a]	1.39	1.31–1.47	36	NA/834,999	36	0	0	0	Random	<0.01	83%	<0.01	NA
All-cause mortality	Yin 2017	RR[d]	1.13	1.10–1.17	57	NA/2,246,116	57	0	0	0	Random	NA	37.5%	<0.01	NA
All-cause mortality	Yin 2017	RR[c]	1.35	1.29–1.41	57	NA/2,246,116	57	0	0	0	Random	NA	76.2%	<0.01	0.01
All-cause mortality	Liu 2017	RR[g]	1.07	1.03–1.11	28	NA/1,004,619	28	0	0	0	Random	<0.01	NA	NA	NA
All-cause mortality	Liu 2017	RR[e]	1.12	1.09–1.15	28	NA/1,004,619	28	0	0	0	Random	<0.01	NA	NA	NA
All-cause mortality	Itani 2017	RR[b]	1.12	1.08–1.16	36	NA/1,301,419	36	0	0	0	Random	<0.01	25%	NA	0.273
All-cause mortality	Liu 2017	RR[h]	1.07	1.02–1.14	14	NA/1,209,730	14	0	0	0	Random	<0.01	NA	NA	NA
All-cause mortality	Liu 2017	RR[f]	1.11	1.06–1.16	14	NA/1,209,730	14	0	0	0	Random	<0.01	NA	NA	NA
Cancer-related mortality	Li 2019	RR[a]	1.05	1.02–1.08	14	NA/ 866,877	14	0	0	0	Fixed	NA	0%	0.67	>0.05
Lung cancer	Stone 2019	HR[b]	1.21	1.10–1.33	4	NA/42,422	4	0	0	0	Random	NA	58.4%	NA	NA
Lung cancer	Stone 2019	HR[a]	1.65	1.36–2.00	4	NA/42,422	4	0	0	0	Random	NA	84.5%	NA	NA
Insignificant associations															
Breast cancer	Wong 2020	RR[b]	0.99	0.98–1.01	14	60,039/1,476,606	14	0	0	0	Random	NA	NA	0.4	NA
Breast cancer	Wong 2020	RR[a]	1.01	0.98–1.04	14	47,267/1,476,606	14	0	0	0	Random	NA	NA	0.3	NA
Cancer-related mortality	Li 2019	RR[b]	1.02	0.99–1.05	14	NA/ 866,877	14	0	0	0	Fixed	NA	0%	0.97	>0.05
Cancers	Chen 2018	OR[b]	1.01	0.97–1.05	65	NA/1,550,524	61	0	4	0	Random	NA	29.8%	0.02	0.05
Cancers	Chen 2018	OR[a]	1.02	0.97–1.07	65	NA/1,550,524	61	0	4	0	Random	NA	31.3%	0.01	0.94
Cancers	Chen 2018	OR[h]	1.02	0.98–1.07	65	NA/1,550,524	61	0	4	0	Random	NA	NA	NA	NA
Cancers	Chen 2018	OR[f]	1.00	0.97–1.03	65	NA/1,550,524	61	0	4	0	Random	NA	NA	NA	NA

Table 1 (continued)

Outcome	Author-year	Metrics	Estimates	95% CI	No of studies	No of cases/total	Cohort	Case control	Cross sectional	RCTs	Effects model	*P* value	I^2	*Q* test	Egger test *p* value
Cancer-specific mortality	Stone 2019	HR[b]	1.03	1.00–1.06	18	NA/1,128,283	18	0	0	0	Random	NA	0.8%	NA	0.14
Cancer-specific mortality	Stone 2019	HR[a]	1.09	1.04–1.13	20	NA/1,138,118	20	0	0	0	Random	NA	5.4%	NA	0.05
Colorectal cancer	Stone 2019	HR[b]	1.03	0.86–1.22	4	NA/6,245	4	0	0	0	Random	NA	28.0%	NA	NA
Colorectal cancer	Stone 2019	HR[a]	1.12	0.91–1.37	4	NA/6,245	4	0	0	0	Random	NA	30.4%`	NA	NA
Ovarian cancer	Stone 2019	HR[b]	1.01	0.73–1.40	1	NA/161,004	1	0	0	0	Random	NA	NA	NA	NA
Ovarian cancer	Stone 2019	HR[a]	1.08	0.82–1.42	1	NA/161,004	1	0	0	0	Random	NA	NA	NA	NA
Prostate cancer	Liu 2020	HR[b]	0.99	0.91–1.07	6	892/546,516	6	0	0	0	Random	0.74	0%	0.53	0.46
Prostate cancer	Liu 2020	RR[a]	0.88	0.75–1.04	6	678/546,516	6	0	0	0	Random	0.15	56.2%	0.04	0.13

CI, confidence interval; *OR*, odds ratio; *RR*, relative risk; *HR* hazard ratio; *NA*, not available; *RCTs*, random control trials; *CHD*, coronary heart disease

[a]Long vs. middle category; [b]Short vs. middle category; [c]The longest vs. middle category; [d]The shortest vs. middle category; [e]1-h increment/day; [f]1-h increment/night; [g]1-h reduction/day; [h]1-h reduction/night

Table 2 Association between sleep duration and the risk cancers and mortality in general population

Outcome	Author-year	Metrics	Estimates	95% CI	No of studies	No of cases/total	Cohort	Case control	Cross sectional	RCTs	Effects model	*P* value	I^2	*Q* test	Egger test *p* value
Significant associations															
Stroke mortality	Li 2016	RR[e]	1.17	1.13–1.20	6	6443/386,053	6	0	0	0	Fixed	NA	1.5%	0.43	> 0.05
Insignificant associations															
CHD mortality	Yang 2015	RR[b]	1.25	1.06–1.47	8	NA/212,749	8	0	0	0	Random	NA	40.9%	0.11	NA
CHD mortality	Yang 2015	RR[a]	1.26	1.11–1.42	8	NA/212,749	8	0	0	0	Random	NA	38.2%	0.13	NA
Stroke mortality	Li 2016	RR[g]	1.05	0.99–1.11	4	4667/308,901	4	0	0	0	Fixed	NA	0%	0.67	> 0.05

CI, confidence interval; *RR*, relative risk; *NA*, not available; *RCTs*, random control trials; *CHD*, coronary heart disease

[a]Long vs. middle category; [b]Short vs. middle category; [c]The longest vs. middle category; [d]The shortest vs. middle category; [e]1-h increment/day; [f]1-h increment/night; [g]1-h reduction/day; [h]1-h reduction/night

CHD mortality in general population [34] or cancer-specific mortality in adults [29].

Neurological outcomes

Inappropriate sleep durations were significantly associated with cognitive decline among adults [35]. Risk of dementia and Alzheimer's disease (AD) were increased by long sleep duration, both reaching significant statistics, representing (1.77, 1.32–2.37) and (1.63, 1.24–2.31) respectively [36], while short sleep did not affect incident disease rates. Longest and shortest sleep durations had a statistical effect on the risk of dementia and AD. The longest sleep duration doubled the risk of suffering from AD (2.19, 1.08–4.46) compared to the reference sleep time [37]. In children, short sleepers were at higher risk of attention deficit hyperactivity disorder (ADHD) (1.28, 1.16–1.41) [38]. From another perspective, the cerebral vascular disease, also known as stroke, was affected by inappropriate sleep durations. Short sleep in adults showed an increase of 32% of incident stroke (1.32, 1.18–1.47) [9], and long sleepers were at even higher risks than those with short sleep (1.48, 1.31–1.68) [9]. In addition, dose–response analysis corroborated the previous conclusion. General populations with long sleep duration met an increased risk of 17% (1.17, 1.14–1.20) of incident stroke with every 1-h increment while short sleepers increased 7% (1.07, 1.02–1.12) per hour decrement per night (Fig. 3e) [33].

Metabolic outcomes

Short and long duration were not significant indicators for dyslipidemia, including increases of triglycerides, total cholesterol, low density lipoprotein (LDL) cholesterol, or the decrease of high density lipoprotein (HDL) cholesterol [39], and the occurrence of fatty liver disease [40]. However, long sleep was associated with an increased risk of metabolic syndrome (MS) (1.25, 1.09–1.43) [9] in adults and osteoporosis among middle-aged and elderly women (1.22, 1.06–1.38) [41] compared with referent sleep hours. In one study there was a protective effect from obesity (0.99, 0.89–1.11) [42]. Sleep durations less than 7 to 8 h and 7 h per day were linked with 19% higher risk of nonalcoholic fatty liver disease (NFLD) (1.19, 1.04–1.36) [43], 41% higher risk of obesity and overweight (1.41, 1.18–1.69) [42], 34% higher risk of T2DM (1.34, 1.24–1.46) [9], and 19% higher risk of metabolic syndrome (1.19, 1.05–1.36) [9] in adults. A meta-analysis including 214,773 subjects reported that long sleep time was associated with 7% risk of gaining weight in adults but this finding did not achieve statistical significance (1.07, 0.98–1.17) [15]. In children and adolescents less than

Table 3 Association between sleep duration and non-cancer outcomes in general population

Outcomes	Author-year	Metrics	Estimates	95% CI	No. of studies	No of cases/total	Cohort	Case control	Cross sectional	RCTs	Effects model	*P* value	I^2	*Q* test	Egger test *p* value
Significant outcomes															
All-cause dementia	Fan 2019	RR[a]	1.77	1.32–2.37	7	NA/41,097	7	0	0	0	Random	< 0.01	68.3%	< 0.01	0.21
AD	Wu 2018	RR[d]	1.64	1.05–2.54	2	NA/3286	2	0	0	0	Random	0.03	0%	0.42	NA
AD	Wu 2018	RR[c]	2.19	1.08–4.46	2	NA/3286	2	0	0	0	Random	0.03	0%	0.6	NA
AD	Fan 2019	RR[a]	1.63	1.24–2.31	6	NA/40,018	6	0	0	0	Random	< 0.01	45.1%	0.11	0.76
ADHD	Lee 2019	OR[b]/RR[b]	1.28	1.16–1.41	8	NA/1,381,324	5	3	0	0	Random	NA	94.2%	NA	< 0.01
CVD	Kritanawong 2019	RR[b]	1.19	1.13–1.26	15	NA/1,381,324	11	0	4	0	Random	< 0.01	30.7%	0.03	NA
CVD	Kritanawong 2019	RR[a]	1.37	1.23–1.52	15	NA/1,381,324	12	0	3	0	Random	< 0.01	79.8%	< 0.01	NA
Cognitive decline	Wu 2018	RR[d]	1.37	1.18–1.60	3	NA/3286	3	0	0	0	Random	< 0.01	0	0.45	NA
Cognitive decline	Wu 2018	RR[c]	1.17	0.97–1.41	3	NA/3286	3	0	0	0	Random	0.1	0	0.88	NA
Cognitive disorders	Wu 2018	RR[d]	1.34	1.15–1.56	9	NA/3286	9	0	0	0	Random	0.01	29%	0.16	NA
Cognitive disorders	Wu 2018	RR[c]	1.21	1.06–1.39	9	NA/3286	9	0	0	0	Random	0.01	7%	0.38	NA
CHD	Kritanawong 2019	RR[b]	1.46	1.27–1.69	18	NA/816,995	18	0	0	0	Random	< 0.01	76.6%	< 0.01	NA
CHD	Kritanawong 2019	RR[a]	1.12	1.01–1.24	18	NA/816,995	18	0	0	0	Random	0.03	42.1%	0.03	NA
CHD	Wang 2016	RR[h]	1.11	1.05–1.16	17	NA/517,440	17	0	0	0	Random	NA	58.9%	< 0.01	NA
CHD	Wang 2016	RR[f]	1.07	1.00–1.15	17	NA/517,440	17	0	0	0	Random	NA	70.5%	< 0.01	NA
CHD	Yin 2017	RR[d]	1.22	1.13–1.31	27	NA	27	0	0	0	Random	NA	39.6%	0.02	NA
CHD	Yin 2017	RR[c]	1.21	1.12–1.30	27	NA	27	0	0	0	Random	NA	37.4%	0.03	NA
MS	Kritanawong 2019	RR[b]	1.19	1.05–1.36	15	NA/152,111	15	0	0	0	Random	< 0.01	80.8%	< 0.01	NA
MS	Kritanawong 2019	RR[a]	1.25	1.09–1.43	15	NA/152,111	15	0	0	0	Random	< 0.01	68.2%	< 0.01	NA
NFLD	Wijarnpreecha 2016	RR[b]	1,19	1.04–1.36	6	NA/59,094	1	5	0	0	Random	< 0.01	0%	NA	0.44

Table 3 (continued)

Outcomes	Author-year	Metrics	Estimates	95% CI	No. of studies	No of cases/total	Cohort	Case control	Cross sectional	RCTs	Effects model	*P* value	I^2	*Q* test	Egger test *p* value
Stroke	Krittanawong 2019	RR[b]	1.32	1.18–1.47	18	NA/612,860	18	0	0	0	Random	< 0.01	73.9%	< 0.01	NA
Stroke	Krittanawong 2019	RR[a]	1.48	1.31–1.68	18	NA/612,860	18	0	0	0	Random	< 0.01	73.9%	< 0.01	NA
Stroke	Li 2016	RR[f]	1.17	1.14–1.20	9	8,350/508,556	9	0	0	0	Fixed	NA	0%	0.52	> 0.05
Stroke	Li 2016	RR[h]	1.07	1.02–1.12	7	5,458/340,511	77	0	0	0	Fixed	NA	33.8%	0.13	> 0.05
T2DM	Krittanawong 2019	RR[b]	1.34	1.24–1.46	11	NA/301,882	11	0	0	0	Random	< 0.01	6.8%	0.37	NA
T2DM	Shan 2015	RR[d]	1.37	1.18–1.59	9	NA/475,741	9	0	0	0	Random	NA	57.1%	0.02	> 0.05
T2DM	Shan 2015	RR[g]	1.09	1.04–1.15	9	NA/475,741	9	0	0	0	Random	NA	63.5%	< 0.01	> 0.05
T2DM	Shan 2015	RR[c]	1.40	1.08–1.80	7	6,210/244,507	7	0	0	0	Random	NA	75.8%	< 0.01	> 0.05
T2DM	Shan 2015	RR[e]	1.14	1.03–1.26	6	5,980/237,998	6	0	0	0	Random	NA	79.1%	< 0.01	> 0.05
Insignificant outcomes															
All-cause dementia	Fan 2019	RR[b]	1.20	0.91–1.59	7	NA/41,097	7	0	0	0	Random	0.2	62.2%	> 0.01	0.21
AD	Fan 2019	RR[b]	1.18	0.91–1.54	6	NA/40,018	6	0	0	0	Random	0.22	57.8%	0.04	NA
ADHD	Lee 2019	OR[a]/RR[a]	1.02	0.88–1.19	4	NA/51,584	1	3	0	0	Random	NA	91.6%	NA	NA
Cognitive decline	Liang 2019	RR[f]	0.99	0.97–1.01	4	5,596/42,791	4	0	0	0	Random	NA	62.4%	0.02	NA
Dyslipidemia	Kruisbrink 2017	RR[b]	1.01	0.93–1.10	6	NA/30,033	6	0	0	0	Random	NA	56%	< 0.01	0.035
Dyslipidemia	Kruisbrink 2017	RR[a]	0.98	0.87–1.10	6	NA/30,033	6	0	0	0	Random	NA	63%	< 0.01	0.248
FLD	Shen 2016	OR[b]	1.17	0.98–1.38	8	NA/97,371	7	0	1	0	Random	NA	66.3%	< 0.01	0.87
FLD	Shen 2016	OR[a]	1.01	0.72–1.41	2	NA/10,329	2	0	0	0	Random	NA	54.7%	0.11	0.189
High LDL cholesterol	Kruisbrink 2017	RR[b]	0.97	0.78–1.21	1	90/7173	1	0	0	0	Random	0.79	NA	NA	NA
High LDL cholesterol	Kruisbrink 2017	RR[a]	1.08	0.83–1.40	1	150/7173	1	0	0	0	Random	0.56	NA	NA	NA
High total cholesterol	Kruisbrink 2017	RR[b]	1.10	0.99–1.22	2	NA/21,453	2	0	0	0	Random	0.07	29%	0.24	NA
High total cholesterol	Kruisbrink 2017	RR[a]	0.91	0.81–1.01	2	NA/21,453	2	0	0	0	Random	0.09	31%	0.23	NA

Table 3 (continued)

Outcomes	Author-year	Metrics	Estimates	95% CI	No. of studies	No of cases/total	Cohort	Case control	Cross sectional	RCTs	Effects model	*P* value	I^2	*Q* test	Egger test *p* value
High triglycerides	Kruisbrink 2017	RR[b]	1.07	0.90–1.28	4	NA/21,230	4	0	0	0	Random	0.44	57%	0.05	NA
High triglycerides	Kruisbrink 2017	RR[a]	1.08	0.77–1.53	4	NA/21,230	4	0	0	0	Random	0.64	73%	<0.01	NA
Low HDL cholesterol	Kruisbrink 2017	RR[b]	0.93	0.73–1.17	3	NA/21,884	3	0	0	0	Random	0.53	74%	<0.01	NA
Low HDL cholesterol	Kruisbrink 2017	RR[a]	0.82	0.58–1.16	3	NA/21,884	3	0	0	0	Random	0.27	69%	0.02	NA
MCI/dementia	Wu 2018	RR[d]	1.30	0.98–1.71	7	NA/3286	7	0	0	0	Random	0.07	47%	0.08	NA
MCI/dementia	Wu 2018	RR[c]	1.22	0.97–1.54	7	NA/3286	7	0	0	0	Random	0.08	29%	0.21	NA
MCI/dementia	Liang 2019	RR[f]	0.98	0.97–1.00	6	2718/39,575	1	0	5	0	Random	NA	0%	0.42	NA
T2DM	Krittanawong 2019	RR[a]	1.12	0.99–1.27	11	NA/301,882	11	0	0	0	Random	0.06	51.4%	0.03	NA

NA, not available; *AD*, Alzheimer's disease; *ADHD*, attention deficit hyperactivity disorder; *CHD*, coronary heart disease; *CVD*, cardiovascular disease; *FLD*, fatty liver disease; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein; *MCI*, mild cognitive impairment; *MS*, metabolic syndrome; *NFLD*, nonalcoholic fatty liver disease; *T2DM*, type 2 diabetes mellitus

[a]Long vs. middle category; [b]Short vs. middle category; [c]The longest vs. middle category; [d]The shortest vs. middle category; [e]1-h increment/day; [f]1-h increment/night; [g]1-h reduction/day; [h]1-h reduction/night

Table 4 Association between sleep duration and non-cancer outcomes in adults

Outcomes	Author-year	Metrics	Estimates	95% CI	No. of studies	No of cases/total	Cohort	Case control	Cross sectional	RCTs	Effects model	*P* value	I^2	*Q* test	Egger test *p* value
Significant outcomes															
CVD	Yin 2017	RR[d]	1.14	1.09–1.20	37	NA/1,160,531	37	0	0	0	Random	NA	31.1%	0.04	NA
CVD	Yin 2017	RR[c]	1.36	1.26–1.48	37	NA/1,160,531	37	0	0	0	Random	NA	71.2%	< 0.01	NA
Cognitive decline	Lo 2016	OR[b]	1.40	1.27–1.56	18	NA/97,624	7	0	11	0	Random	NA	39.1%	0.01	0.71
Cognitive decline	Lo 2016	OR[a]	1.58	1.43–1.74	17	NA/97,558	6	0	11	0	Random	NA	48.1%	< 0.01	0.18
Depression	Zhai 2015	RR[b]	1.31	1.04–1.64	6	NA/25,271	6	0	0	0	Random	NA	0%	0.57	0.95
Depression	Zhai 2015	RR[a]	1.42	1.04–1.92	5	NA/23,663	5	0	0	0	Random	NA	0%	0.59	0.53
Falls	Wu 2017	OR[b]	1.32	1.21–1.46	7	NA/212,829	1	0	6	0	Random	< 0.01	45%	0.06	0.83
Falls	Wu 2017	OR[a]	1.35	1.17–1.56	7	NA/212,829	1	0	6	0	Random	< 0.01	53%	0.02	0.95
Frailty	Ali 2020	OR[b]	1.13	1.08–1.18	7	NA/36,684	1	0	6	0	Random	NA	48.9%	0.40	0.59
Frailty	Ali 2020	OR[a]	1.21	1.10–1.30	6	NA/34,179	0	0	6	0	Random	NA	76.5%	< 0.01	0.33
GDM	Zhang 2020	RR[a]	1.19	1.04–1.35	4	NA/20,443	4	0	0	0	Random	NA	0%	0.44	NA
Hypertension	Wang 2020	RR[b]	1.16	1.06–1.27	10	NA/85,838	10	0	0	0	Random	NA	91.0%	< 0.01	0.21
Osteoporosis	Moradi 2017	OR[a]	1.22	1.06–1.38	6	NA/31,626	0	0	6	0	Random	NA	86.3%	< 0.01	NA
Osteoporosis	Wang 2018	OR[h]	1.03	1.01–1.06	2	2,667/11,378	0	0	2	0	Random	NA	0%	0.60	> 0.05
Overweight/obesity	Bacaro 2020	OR[b]	1.41	1.18–1.69	12	NA/154,936	12	0	0	0	Random	< 0.01	80.5%	< 0.01	0.81
Proteinuria	Cheungpasitporn 2017	RR[b]	1.47	1.26–1.72	3	NA/37,197	1	0	2	0	Random	< 0.01	0%	0.38	NA
Stroke	He 2017	RR[c]	1.37	1.23–1.54	12	NA/528,653	12	0	0	0	Random	NA	55.7%	< 0.01	0.62
Insignificant outcomes															
CKD	Cheungpasitporn 2017	RR[b]	1.51	0.90–2.55	6	NA/252,075	1	0	5	0	Random	0.12	91%	< 0.01	NA
GDM	Zhang 2020	RR[a]	1.24	0.91–1.68	4	NA/20,443	4	0	0	0	Random	NA	49.2%	0.1	0.004
Hypertension	Wang 2020	RR[a]	1.06	0.95–1.18	9	NA/85,838	9	0	0	0	Random	NA	84.8%	0	0.466
LGA	Warland 2018	OR[b]	1.50	0.70–2.80	2	NA/1090	1	0	1	0	Random	NA	44.6%	0.18	NA
Osteoporosis	Moradi 2017	OR[b]	0.98	0.90–1.05	6	NA/31,625	0	0	6	0	Random	NA	27.3%	0.23	NA
Osteoporosis	Wang 2018	OR[f]	1.01	1.00–1.02	4	9,393/51,784	0	0	4	0	Random	NA	70.2%	< 0.01	> 0.05

Table 4 (continued)

Outcomes	Author-year	Metrics	Estimates	95% CI	No. of studies	No of cases/total	Cohort	Case control	Cross sectional	RCTs	Effects model	*P* value	I^2	*Q* test	Egger test *p* value
Overweight/obesity	Bacaro 2020	OR[a]	1.00	0.89–1.11	8	NA/152,192	8	0	0	0	Random	0.94	0%	0.75	0.20
SGA	Warland 2018	OR[b]	1.3	0.90–2.00	7	NA/6720	7	0	0	0	Random	NA	57.4%	0.03	NA
Stroke	He 2017	RR[d]	1.10	0.97–1.24	12	NA/528,653	12	0	0	0	Random	NA	49.2%	> 0.01	0.48
Weight gain	Liu 2019	RR[a]	1.07	0.98–1.17	8	NA/214,773	8	0	0	0	Random	0.14	51.1%	0.05	0.047

NA, not available; *CKD*, chronic kidney disease; *CVD*, cardiovascular disease; *GDM*, gestational diabetes mellitus; *LGA*, large for gestational age; *SGA*, small for gestational age; *T2DM*, type 2 diabetes mellitus

[a]Long vs. middle category; [b]Short vs. middle category; [c]TShe longest vs. middle category; [d]The shortest vs. middle category; [e]1-h increment/day; [f]1-h increment/night; [g]1-h reduction/day; [h] 1-h reduction/night

Table 5 Association between sleep duration and non-cancer outcomes in children and adolescents < 18 years

Outcomes	Author-year	Metrics	Estimates	95% CI	No. of studies	No of cases/total	Cohort	Case control	Cross sectional	RCTs	Effects model	*P* value	I^2	*Q* test	Egger test *p* value
Significant outcomes															
Mood deficits	Short 2020	OR[b]	1.55	1.44–1.67	71	NA/361,505	19	0	42	0	Random	< 0.01	97.9%	< 0.01	NA
Overweight/obesity	Miller 2018	RR[b]	1.58	1.35–1.85	20	NA/75,499	20	0	0	0	Random	< 0.01	92%	< 0.01	0.005
Insignificant outcomes															
Overweight/obesity	Ruan 2015	OR[f]	0.92	0.81–1.05	9	3760/29,863	9	0	0	0	Random	NA	81.2%	< 0.01	0.01

NA, not available

[a] long vs. middle category; [b] short vs. middle category; [c] the longest vs. middle category; [d] the shortest vs. middle category; [e] 1 h increment/day; [f] 1 h increment/night; [g] 1 h reduction/day; [h] 1 h reduction/night

Table 6 Assessments of AMSTAR scores and GRADE classification in cancer and mortality outcomes

Outcome	Category	Author	Year	AMSTAR2	Quality
All-cause mortality	The long vs. middle category	Jike	2018	Low	Very low
All-cause mortality	The shortest vs. middle category	Yin	2017	Moderate	Low
All-cause mortality	The longest vs. middle category	Yin	2017	Moderate	Low
All-cause mortality	1-h reduction/day	Yin	2017	Moderate	Low
All-cause mortality	1-h increment/day	Liu	2017	Critically low	Very low
All-cause mortality	1-h reduction/night	Liu	2017	Critically low	Very low
All-cause mortality	The short vs. middle category	Itani	2017	Moderate	Low
All-cause mortality	1-h increment/night	Liu	2017	Critically low	Very low
All-cause mortality	The long vs. middle category	Liu	2017	Critically low	Very low
Breast cancer	1-h increment/day	Wong	2020	Critically low	Very low
Breast cancer	The short vs. middle category	Wong	2020	Critically low	Very low
Cancer-related mortality	The short vs. middle category	Li	2019	Critically low	Low
Cancer-related mortality	The long vs. middle category	Li	2019	Critically low	Low
Cancers	The short vs. middle category	Chen	2018	Low	Low
Cancers	The short vs. middle category	Chen	2018	Low	Very low
Cancers	The long vs. middle category	Chen	2018	Low	Very low
Cancers	1-h reduction/night	Chen	2018	Low	Very low
Cancer-specific mortality	1-h increment/night	Stone	2019	Critically low	Low
Cancer-specific mortality	The short vs. middle category	Stone	2019	Critically low	Low
Colorectal cancer	The long vs. middle category	Stone	2019	Critically low	Very low
Colorectal cancer	The short vs. middle category	Stone	2019	Critically low	Very low
CHD mortality	The long vs. middle category	Yang	2015	Critically low	Very low
CHD mortality	The short vs. middle category	Yang	2015	Critically low	Very low
Lung cancer	The long vs. middle category	Stone	2019	Critically low	Very low
Lung cancer	The short vs. middle category	Stone	2019	Critically low	Very low
Ovarian cancer	The long vs. middle category	Stone	2019	Critically low	Very low
Ovarian cancer	The short vs. middle category	Stone	2019	Critically low	Very low
Prostate cancer	The long vs. middle category	Liu	2020	Critically low	Very low
Prostate cancer	The short vs. middle category	Liu	2020	Critically low	Very low
Stroke mortality	The long vs. middle category	Li	2016	Critically low	Moderate
Stroke mortality	1-h reduction/day	Li	2016	Critically low	Low

CHD, coronary heart disease

18 years old, short sleep duration increased the risk of obesity by 58% (1.58, 1.35–1.85) [44].

Dose–response analyses showed that a 1-h reduction of sleep per day was linearly related to a 3% higher risk of osteoporosis (1.03, 1.01–1.06; Fig. 3f) [45] in adults and a 9% higher risk of T2DM (1.09, 1.04–1.15) in general populations (Fig. 3g) [16]. Furthermore, every 1-h increment was linearly associated with an increased risk of T2DM by 14% (1.14, 1.03–1.26) in general populations [16].

Cardiovascular outcomes and coronary heart disease

Compared to referent 7–8 sleeping hours per day, short sleep duration was positively associated with an increased risk of CVD (1.19, 1.13–1.26) [9], CHD (1.46, 1.27–1.69) [9], and hypertension (1.16, 1.06–1.27) [46]. In adults, similar higher risk of CVD and CHD outcomes were associated with longer sleep duration [9] and extreme sleep durations (including shortest and longest) [14]. Linear dose–response analysis showed that CHD risk was increased by a 1-h increment (1.07, 1.00–1.15) or decrement (1.11, 1.05–1.16) per night (Fig. 3h) [47].

Emotional outcomes

Proper sleep duration may be important for positive emotions. Evidence showed that short and long sleep duration were tightly associated with depression, increasing the risk by 31% (1.31, 1.04–1.64) and 42% (1.42, 1.04–1.92) in adults, respectively [48]. Adolescents with short sleep duration had an associated risk of mood deficits of 55% (1.55, 1.44–1.67) compared with normal sleep duration [49].

Table 7 Assessments of AMSTAR scores and GRADE classification in non-cancer outcomes

Outcome	Category	Author	Year	AMSTAR2	Quality
All-cause dementia	The long vs. middle category	Fan	2019	Critically low	Very low
All-cause dementia	The shortest vs. middle category	Fan	2019	Critically low	Very low
AD	The longest vs. middle category	Wu	2018	Critically low	Very low
AD	The long vs. middle category	Wu	2018	Critically low	Very low
AD	The short vs. middle category	Fan	2019	Critically low	Very low
AD	The short vs. middle category	Fan	2019	Critically low	Very low
ADHD	The long vs. middle category	Lee	2019	Low	Very low
ADHD	The shortest vs. middle category	Lee	2019	Low	Very low
CVD	The shortest vs. middle category	Krittanawong	2019	Critically low	Very low
CVD	The shortest vs. middle category	Krittanawong	2019	Critically low	Very low
CVD	The longest vs. middle category	Yin	2017	Low	Very low
CVD	The short vs. middle category	Yin	2017	Low	Very low
CKD	The long vs. middle category	Cheungpasitporn	2017	Critically low	Very low
Cognitive decline	The shortest vs. middle category	Wu	2018	Critically low	Very low
Cognitive decline	The longest vs. middle category	Wu	2018	Critically low	Very low
Cognitive decline	The short vs. middle category	Liang	2019	Low	Very low
Cognitive decline	The long vs. middle category	Lo	2016	Low	Low
Cognitive decline	The shortest vs. middle category	Lo	2016	Low	Low
Cognitive disorders	The longest vs. middle category	Wu	2018	Critically low	Low
Cognitive disorders	The short vs. middle category	Wu	2018	Critically low	Low
CHD	The long vs. middle category	Krittanawong	2019	Critically low	Very low
CHD	The short vs. middle category	Krittanawong	2019	Critically low	Very low
CHD	The long vs. middle category	Yin	2017	Moderate	Moderate
CHD	The short vs. middle category	Yin	2017	Low	Moderate
CHD	The long vs. middle category	Wang	2016	Critically low	Very low
CHD	The long vs. middle category	Wang	2016	Critically low	Very low
Depression	The short vs. middle category	Zhai	2015	Critically low	Very low
Depression	The short vs. middle category	Zhai	2015	Critically low	Very low
Dyslipidemia	The long vs. middle category	Kruisbrink	2017	Critically low	Very low
Dyslipidemia	The short vs. middle category	Kruisbrink	2017	Critically low	Very low
Falls	The short vs. middle category	Wu	2017	Low	Moderate
Falls	The long vs. middle category	Wu	2017	Low	Low
FLD	1-h reduction/night	Shen	2016	Critically low	Very low
FLD	Shortest vs. longest	Shen	2016	Critically low	Very low
Frailty	1-h increment/night	Ali	2020	Critically low	Very low
Frailty	The short vs. middle category	Ali	2020	Critically low	Very low
GDM	The short vs. middle category	Zhang	2020	Low	Very low
GDM	The short vs. middle category	Zhang	2020	Low	Low
High LDL cholesterol	The short vs. middle category	Kruisbrink	2017	Critically low	Very low
High LDL cholesterol	The long vs. middle category	Kruisbrink	2017	Critically low	Very low
High total cholesterol	1-h increment/night	Kruisbrink	2017	Critically low	Very low
High total cholesterol	1-h reduction/night	Kruisbrink	2017	Critically low	Very low
High triglycerides	The longest vs. middle category	Kruisbrink	2017	Critically low	Very low
High triglycerides	The short vs. middle category	Kruisbrink	2017	Critically low	Very low
Hypertension	The shortest vs. middle category	Wang	2020	Critically low	Very low
Hypertension	1-h reduction/night	Wang	2020	Critically low	Very low
LGA	The longest vs. middle category	Warland	2018	Critically low	Very low
Low HDL cholesterol	1-h increment/day	Kruisbrink	2017	Critically low	Very low
Low HDL cholesterol	The short vs. middle category	Kruisbrink	2017	Critically low	Very low
MS	The short vs. middle category	Krittanawong	2019	Critically low	Very low

Table 7 (continued)

Outcome	Category	Author	Year	AMSTAR2	Quality
MS	The long vs. middle category	Krittanawong	2019	Critically low	Very low
MCI/dementia	The short vs. middle category	Wu	2018	Critically low	Very low
MCI/dementia	1-h increment/night	Wu	2018	Critically low	Very low
MCI/dementia	1-h reduction/night	Liang	2019	Low	Very low
Mood deficits	1-h increment/night	Short	2020	Low	Very low
NFLD	The short vs. middle category	Wijarnpreecha	2016	Critically low	Low
Osteoporosis	The long vs. middle category	Moradi	2017	Critically low	Very low
Osteoporosis	The short vs. middle category	Moradi	2017	Critically low	Very low
Osteoporosis	The long vs. middle category	Wang	2018	Critically low	Low
Osteoporosis	The short vs. middle category	Wang	2018	Critically low	Very low
Overweight/obesity	The short vs. middle category	Ruan	2015	Critically low	Very low
Overweight/obesity	The long vs. middle category	Ruan	2015	Low	Very low
Overweight/obesity	The short vs. middle category	Miller	2018	Low	Very low
Overweight/obesity	The long vs. middle category	Bacaro	2020	Low	Very low
Overweight/obesity	The short vs. middle category	Bacaro	2020	Critically low	Very low
Preterm birth	The long vs. middle category	Wang	2020	Critically low	Very low
Proteinuria	The long vs. middle category	Cheungpasitporn	2017	Critically low	Very low
SGA	The short vs. middle category	Warland	2018	Critically low	Very low
Stroke	The short vs. middle category	Krittanawong	2019	Critically low	Very low
Stroke	The long vs. middle category	Krittanawong	2019	Critically low	Very low
Stroke	The shortest vs. middle category	Li	2016	Critically low	Low
Stroke	The longest vs. middle category	Li	2016	Critically low	Moderate
Stroke	1-h increment/night	He	2017	Critically low	Low
Stroke	The short vs. middle category	He	2017	Critically low	Low
T2DM	1-h increment/night	Krittanawong	2019	Critically low	Very low
T2DM	The long vs. middle category	Krittanawong	2019	Critically low	Very low
T2DM	Shortest vs. longest	Shan	2015	Critically low	Low
T2DM	The short vs. middle category	Shan	2015	Critically low	Low
T2DM	The shortest vs. middle category	Shan	2015	Critically low	Very low
T2DM	The long vs. middle category	Shan	2015	Critically low	Very low
Weight gain	The long vs. middle category	Liu	2019	Critically low	Very low

AD, Alzheimer's disease; *ADHD*, attention deficit hyperactivity disorder; *CHD*, coronary heart disease; *CKD*, chronic kidney disease; *CVD*, cardiovascular disease; *FLD*, fatty liver disease; *GDM*, gestational diabetes mellitus; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein; *LGA*, large for gestational age; *MCI*, mild cognitive impairment; *MS*, metabolic syndrome; *NFLD*, nonalcoholic fatty liver disease; *SGA*, small for gestational age; *T2DM*, type 2 diabetes mellitus

Maternal outcomes

Short sleep duration was not significantly linked to large for gestational age (1.5, 0.7–2.8) or small for gestational age (1.3, 0.9–2.0) in pregnant women [2]. There was evidence that short sleep was not related to gestational diabetes mellitus (GDM) (1.24, 0.91–1.68) [50]. Conversely, adults with longer sleep time were significantly at higher risk of GDM (1.19, 1.04–1.35) [50].

Other outcomes

There is some evidence that sleeping less or more than reference duration significantly elevated the risk of falls in adults and frailty in elderly adults [51, 52]. Otherwise, no relationship was observed between short sleep duration and chronic kidney disease (CKD) [53], but there was a 47% increased risk (1.47, 1.26–1.72) of proteinuria in adults associated with suboptimal sleep duration [53].

Heterogeneity

Of all the studies, 9 studies presented a high degree of heterogeneity with $I^2 > 75\%$; 44 meta-analyses presented moderate level of heterogeneity, with I^2 ranging from 25 to 75%; 10 meta-analyses had a low heterogeneity with $I^2 < 25\%$. However, 6 meta-analyses did not report the heterogeneity.

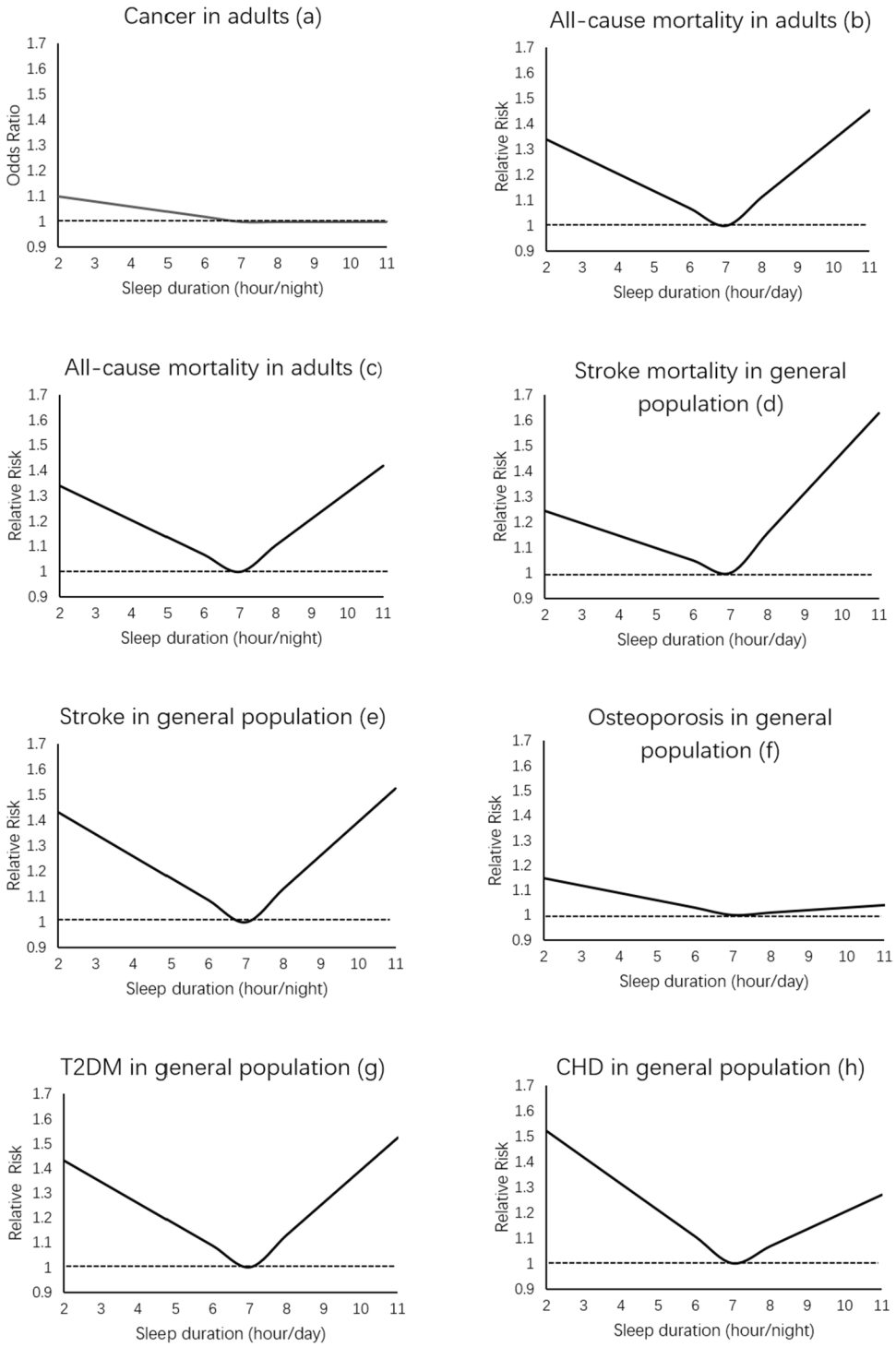

Fig. 3 Nonlinear dose–response analyses of sleep duration and risk of cancer in adults (**a**), all-cause mortality in adults (**b**, **c**), stroke mortality in general population (**d**), stroke in general population (**e**), osteoporosis in general population (**f**), T2DM in general population (**g**), CHD in general population (**h**). CHD, coronary heart disease; T2DM, type 2 diabetes mellitus

Publication bias

Of all meta-analyses, 5 reported significant publication bias by Egger's test including all-cause mortality, ADHD, GDM in adults, and obesity/overweight in children. Of the included articles, 62% were not linked to a significant publication bias and 30% did not report the publication bias.

AMSTAR2 scores and GRADE classification

The results of AMSTAR 2 of the included meta-analyses are shown in Tables 6 and 7. Among the studies focusing on cancers and mortality, about 10% of the studies were classified by GRADE into "moderate," 17% were classified into "low," and 73% were "critically low." In studies related to non-cancer field, about 1%, 21%, and 78% studies were rated as "moderate," "low," and "critically low." Most studies did not meet the requirements that studies need for comprehensive reporting of the prior design, excluded assays, and funding information in detail as well as accounting for bias in individual studies. The detailed results of each item of AMSTAR 2 for the included meta-analyses are available in Table S6 and S7, Supplementary data.

As for the quality of outcomes concerning cancers and mortality, about 67% were graded as "very low," 30% graded as "low," and 3% graded as "moderate." With respect to non-cancer outcomes, 79%, 16%, and 5% were rated as "very low," "low," and "moderate" regarding quality of evidence, respectively. None were stratified as "high" because most of the meta-analyses contained studies bearing serious risk of bias and imprecision while lacking plausible confounding analysis, magnitude, and dose–response ingredients. The detailed information about GRADE is shown in Table S8 and S9, Supplementary data.

Discussion

This umbrella review is the first systematic review of meta-analyses of associations between duration of sleep and health consequences in population-based studies. According to the recommendations from the expert panel of the NSF [1, 2], the reference sleep duration for infants is between 12 and 15 h, pre-school children between 10 and 13 h, and school-aged children between 9 and 11 h. For adults, a sleep duration of 7 to 9 h and for older adults 7 to 8 h are considered appropriate. At present, maintaining an appropriate sleep duration has become a critical public health issue and mastering the effect of inappropriate sleep durations on health outcomes constitutes a key success factor for promoting general health.

From this umbrella review, we observed a strong nonlinear U-shaped or V-shaped association for the relationship between sleep duration and CVD, cognitive decline, CHD, depression, falls, frailty, lung cancer, MS, and stroke among adults. Yet, no associations were found between sleep durations and the risk of cancers (except lung cancer), cancer-specific mortality, CHD mortality, dyslipidemia (including high LDL cholesterol, fatty liver disease, high total cholesterol, high triglycerides, and low HDL cholesterol). Short sleep duration was linked with 19–47% higher risk of ADHD, NFLD, proteinuria, and T2DM in general population, 16% higher risk of hypertension in adults, and 55–58% higher risk of mood deficits and obesity. Furthermore, the most recent studies found that long sleep duration was associated with an increased risk by 63–77% of all-cause dementia and AD in general population as well as 5–37% all-cause mortality, cancer-related mortality, GDM, and osteoporosis in adults. Extreme sleep durations (including shortest and longest sleep duration) were more likely to be associated with an elevated risk of all-cause mortality, AD, cognitive decline, cognitive disorders, CHD and T2DM in general population, and CVD in adults. We observed a J-shaped dose–response relationship revealing that 1-h reduction per day or night was associated with 3–11% higher risk of all-cause mortality, CHD, osteoporosis, stroke, and T2DM among short sleepers. Apart from that, a 1 h increment per day or night also linearly increased the risk of stroke mortality, CHD, stroke, and T2DM by 7–17%.

To a large extent, neurologic outcomes were significantly influenced by sleep durations, though a fair number of the studies had moderate heterogeneity that may not be balanced by the population, region, sex, or other determinants. Reference sleep duration (7 h/night or 7–8 h/night) in adults is associated with decreased dementia, cognitive decline, and cognitive disorders [37, 54], but the effects of inappropriate sleep durations are controversial. Some studies alleged that only long [55] or short [56] sleep time was linked to cognitive diseases. Two large studies from China in 2011 and from the USA in 2016 respectively demonstrated a significant U-shaped and V-shaped association between sleep duration and cognitive function [57, 58]. From this umbrella review, cognitive decline was affected by both long and short sleep durations. In 2019, a meta-analysis containing 7 studies for dementia and 6 for AD suggested that longer sleep time was associated with a higher risk of dementia and AD by 77% and 63%, respectively. However, shorter sleep duration was insignificantly associated with a 20% (1.20, 0.91–1,59) increased risk of dementia and 18% (1.18, 0.91–1.54) increased risk of AD [36]. Furthermore, short sleep time represented a hazard of ADHD for children under 18 years old.

There are several plausible mechanisms for the effect of sleep duration. First, short sleep time was associated with cerebral white matter atrophy or lesions [59, 60], a direct cause for the cognitive disorders. Secondly, deprived and prolonged sleep contributed to neuroinflammation of the cerebral structure [36]. An elevated tumor necrosis factor alpha (TNF-α) level caused by insufficient sleeping is associated with longer reaction times, memory problems, and damaged attention [61]. Furthermore, both short and long sleepers were found to be associated with an elevated level of pro-inflammatory cytokines, including interleukin (IL)-6 and high-sensitivity C-reactive protein (hsCRP) [62, 63].

IL-6 and hsCRP can negatively influence synaptic plasticity and neurogenesis and are predictors for AD and vascular dementia as well as ADHD in children [64, 65]. Third, inappropriate sleep durations may involve the process of amyloid clearance [57]. Appropriate clearance of amyloid is the premise of normal function of the brain. It is widely acknowledged that excessive β-amyloid peptide (Aβ) triggers amyloid cascade theory and consequently results in AD. The accumulation of Aβ, stimulated by sleep deprivation may in turn reciprocally aggravate sleep disruption, commencing a vicious cycle of cognition disorders [66]. Consistent stimulation of inflammation factors and the recruitment of immune cells activated by long hours of sleep may to some extent give rise to cognition impairment and AD [67, 68].

In terms of cardiovascular disorders, sleep durations were tightly linked to a wide range of diseases including CVD, CHD, and hypertension. Inadequate sleep may boost the activity of the sympathetic nervous system, and therefore stimulate the renin–angiotensin–aldosterone system to increase catecholamines [69, 70]. Accumulating catecholamines may contribute to the constriction of blood vessels and onset of hypertension. Thus, a vicious circle may be formed as a stimulated sympathetic nervous system in turn shortens sleep time. On the other hand, magnesium is thought be a trace element essential for human as well as a physiologic calcium antagonist to decrease vascular tension. Intracellular magnesium may decrease with severe sleep deprivation [71]. Thus, inadequate sleep with low levels of intracellular magnesium may act as a potential indicator for hypertension. Although from this umbrella review, longer sleep time was not significantly linked with the risk of hypertension in adults, other studies have demonstrated that long sleep duration was a risk factor for the onset of hypertension [72, 73]. Mechanisms are not yet fully understood, though there are many hypotheses that long sleepers include subjects with obstructive sleep apnea, fatigue, depression [74], and low socioeconomic and employment status [75]. As such, longer sleep duration may not necessarily signal better sleep quality. Interestingly, one study reported that patients with chronic heart failure did not have better sleep efficiency as the self-reported sleep time increased [76]. Conversely, when using objective measurement like polysomnography, only objective short sleep duration or poor sleep quality were associated with higher risk of cardiovascular outcomes [76]. Higher risk of CHD and CVD may result from short or long sleep duration, increases or decreases in sleep time, and extreme sleep durations. The development of cardiovascular disorders may not only include the direct effect of sleep duration change but also include altered insulin sensitivity [77], glucose intolerance [78], impaired glycemic control [9, 79], growth hormone metabolic activities [7, 9], and fluctuation of leptin, ghrelin, and cortisol secretion [75, 80]. Further exploration into the relationship between long sleep duration and cardiovascular outcomes should focus on (a) the accompanying symptoms with long sleep rather than durations alone and (b) the difference between subjective and objective sleep durations.

Meaningful associations between sleep duration and cancer-related outcomes were relatively few. Most meta-analyses did not demonstrate a significant association between inappropriate sleep durations and the oncogenesis and progression of the carcinoma [19, 29–31]. However, this umbrella review did demonstrate a slightly positive association that long sleep duration was a risk factor for lung cancer. In a synthetic analysis curtailing 1,500,000 study individuals from 13 countries [81], the RRs of colorectal and lung cancer were 1.08 (95% CI: 1.03–1.13) and 1.11 (95% CI: 1.00–1.22) in long sleepers, which was consistent with our conclusions.

Mechanisms underlying these associations are underexplored, yet the melatonin hypothesis may play a part in oncogenesis of the cancers. Melatonin has a pivotal role in the circadian cycle, and the level is proportional to the length of sleep [19, 82]. Shorter sleep means a greater possibility of nighttime activities and a greater chance of exposure to light at night, subsequently resulting in decreased melatonin levels [83]. Melatonin plays an anti-cancer role experimentally by suppressing the initial phase of cell proliferation and stimulating differentiation and apoptosis, whereas decreased or insufficient melatonin may promote tumor growth [83, 84]. Furthermore, melatonin is intricately linked with sex hormone levels [31]. For example, inappropriate melatonin secretion may induce estrogen levels to increase, which has been reported to be a contributing factor to the aggressiveness of breast cancer [85]. The combined mechanisms mentioned above may disproportionately trigger the tumorigenesis of gastrointestinal [86], colorectal cancers [87], and the progression of hormone-related cancers including breast [88], prostate [19], and ovarian cancers [89]. Additionally, short sleep duration together with long sleep duration is potentially associated with circadian rhythm, mood changes, activities alteration, and occupational demands, which also take part in the oncogenesis and progression of cancers. Short sleep time considerably contributes to excessive caloric intake [90], having an indirect effect on human insulin metabolism. Impaired glucose metabolism may elevate levels of insulin-like growth factor-1, a modifier for the increased risk of colorectal cancer [91, 92]. Inappropriate sleep durations may stimulate ulcers and gastrointestinal dysfunctions and subsequently predispose individual to a higher risk of gastrointestinal cancer [90]. Of note, people may be inclined to switch their sleep patterns including the length of sleep. Fluctuations and alterations may therefor confound the exact relationship between sleep durations and the risk of cancers.

Due to the fact that sleep disorders and circadian rhythm may not be easily and comprehensively quantified by hour or degree, we did not include them in the umbrella review. Alternatively, we reported sleep duration both as a night metric and day metric for dose-analysis calculation. Normal sleep–wake rhythms and healthy sleep behaviors play a pivotal role in maintaining and boosting functioning [93]. The effect of sleep disorders and circadian rhythm may exert their influence through impaired immunity [94], increased inflammation and oxidative stress [95], dysfunctional catabolic process, and hormone release [96, 97]. In a study in which some workers were assigned to work on a night shift work, their waketime blood pressure and average systolic and diastolic blood pressure was higher than the control group [98]. The disruption of circadian rhythm may also attenuate the cardioprotective vagal modulation [99]. Furthermore, the misalignment of circadian rhythm may accompany the loss of PER2 and the increase of β-catenin protein in breast cancer and intestinal cancer [100]. In 2015, a study reported that individuals suffering from insomnia, parasomnia, or obstructive sleep apnea were at higher risk of developing nasal cancer, oral cancer, breast cancer, and prostate cancer than patients without sleep disturbances [26].

Strengths and limitations

An umbrella review is thought to represent one of the highest levels of synthesis of comprehensive evidence [24]. There has been no previous attempt to conduct an overview assessing whether or not sleep duration has an effect on health and well-being. This newly developed approach helps to assess any harm that may be related to inappropriate sleep duration and provides future direction in sleep investigation. We utilized the up-to-date AMSTAR2 appraisal tool and GRADE classifications to assess the quality and validity of the included studies.

However, possible limitations should be acknowledged in the interpretation of this umbrella review. First, based on the definition of sleep duration, there may be variations of objective and subjective sleep durations. Night shifts and sleep disorders as mentioned were confounding factors potentially contributing to bias. Secondly, we did not include sleep quality in our umbrella review. Sleep quality was assessed by questionnaires of various types and could not be separated from sleep duration. Lack of dose–response analysis on quality of sleep is another consideration. Third, AMSTAR and GRADE classifications of the mentioned studies were relatively low. Low AMSTAR grades were explained by the fact that many included meta-analyses did not satisfy the principal criteria in terms of their description of excluded studies and funding sources. On the other hand, more than half of the studies included in this umbrella review were meta-analyses of observational studies which contributed to low GRADE classifications due to their low-quality evidence. Fourth, the number of cases in each subgroup was often ambiguous. This was caused by the phenomenon that source papers usually reported the total numbers of patients rather than the exact numbers in subgroups. Also, studies on cancer-related outcomes were not able to develop a consensus despite the fact that potential mechanisms are being discovered gradually. These findings suggest that more research is needed to address the the association between sleep duration and lung cancer mortality.

Conclusion

Inappropriate sleep durations exhibit considerable associations with outcomes of non-cancer conditions. Long and short sleep duration increased the risk for cognitive diseases and other chronic diseases. Increased sleep hours in long sleepers and decreased hours in short sleepers did more harm to patients than good . Future large and robustly designed studies may continue to clarify the effect of sleep duration on different aspects of human health.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11325-021-02458-1.

Author contribution JL and DHC searched, collected, analyzed the data, and wrote the manuscript. LRL and QW designed the study, supervised the project, and revised the manuscript. BC and YH assisted with detailed statistical analysis. ZYC, RYW, and QD helped with data extraction. All authors read and approved the final draft.

Funding This study was funded by the National Natural Science Foundation of China (Grant Numbers 81974098, 81770756) and Program from Department of Science and Technology of Sichuan Province (Grant Number 2020YJ0054), Post-Doctor Research Project, West China Hospital, Sichuan University (Grant Number 2019HXBH089), and Health Commission of Sichuan province (20PJ036).

Data availability The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability.
Not applicable.
Ethics approval and consent to participate.
Not applicable.
Consent for publication.
Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

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