Self-Reported Sleep Duration and Quality and Cardiovascular Disease and Mortality: A Dose-Response Meta-Analysis

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Background—There is growing evidence that sleep duration and quality may be associated with cardiovascular harm and mortality.

Methods and Results—We conducted a systematic review, meta-analysis, and spline analysis of prospective cohort studies that evaluate the association between sleep duration and quality and cardiovascular outcomes. We searched MEDLINE and EMBASE for these studies and extracted data from identified studies. We utilized linear and nonlinear dose-response meta-analysis models and used DerSimonian–Laird random-effects meta-analysis models of risk ratios, with inverse variance weighting, and the I^2 statistic to quantify heterogeneity. Seventy-four studies including 3 340 684 participants with 242 240 deaths among 2 564 029 participants who reported death events were reviewed. Findings were broadly similar across both linear and nonlinear dose-response models in 30 studies with >1 000 000 participants, and we report results from the linear model. Self-reported duration of sleep >8 hours was associated with a moderate increased risk of all-cause mortality, with risk ratio, 1.14 (1.05–1.25) for 9 hours, risk ratio, 1.30 (1.19–1.42) for 10 hours, and risk ratio, 1.47 (1.33–1.64) for 11 hours. No significant difference was identified for periods of self-reported sleep <7 hours, whereas similar patterns were observed for stroke and cardiovascular disease mortality. Subjective poor sleep quality was associated with coronary heart disease (risk ratio, 1.44; 95% confidence interval, 1.09–1.90), but no difference in mortality and other outcomes.

Conclusions—Divergence from the recommended 7 to 8 hours of sleep is associated with a higher risk of mortality and cardiovascular events. Longer duration of sleep may be more associated with adverse outcomes compared with shorter sleep durations. (*J Am Heart Assoc*. 2018;7:e008552. DOI: 10.1161/JAHA.118.008552.)

Key Words: cardiac risk factors • coronary artery disease • meta-analysis • prevention

Cardiovascular disease (CVD) causes over 787 000 deaths in the United States.[1] Whereas sleep duration is generally not considered a traditional risk factor for cardiovascular disease (CVD), growing evidence supports its association with cardiovascular risk (CVR) factors[2–7] and disease,[8–11] and quality of sleep appears to contribute to CVR.[10,12] Yet, current guidelines for the risk reduction of CVD make limited recommendations about quality or duration of sleep.[13,14]

The National Sleep Foundation recommends 7 to 9 hours of sleep for people aged 26 to 64 years and 7 to 8 hours of sleep for people aged ≥65 years,[14] and the Centers for Disease Control and Prevention has similar recommendations for adults.[15] Whether adults sleep the recommended hours is influenced by cultural, social, psychological, behavioral, pathophysiological, and environmental influences.[16,17] Sleep duration may be reduced

Clinical Perspective

What Is New?

- In this meta-analysis of 74 studies representing over 3 million participants, we found a J-shaped relationship between sleep duration and mortality and incident cardiovascular disease.
- Duration of sleep >8 hours of sleep was associated with increased risk of mortality.
- No significant effect was identified for periods of sleep <7 hours. Similar patterns were observed for stroke and cardiovascular disease mortality.
- Subjective poor sleep quality was associated with a significant increase in coronary heart disease, but not other outcomes.

What Are the Clinical Implications?

- Our study suggests that abnormal sleep is a marker of elevated cardiovascular risk.
- Future work should evaluate whether attention to optimizing the duration and quality of sleep may help reduce the burden of cardiovascular disease.

because of irregular working and shift-work patterns and round-the-clock availability of commodities of modern society.[18] However, guidelines make no specific reference with regard to sleeping beyond the recommended limit. Long sleep duration may be associated with obstructive sleep apnea, heart disease, and failing health[19] or may represent a symptom of early "latent" disease preceding a formal diagnosis.[20]

Although previous reviews have evaluated sleep duration and mortality and cardiovascular outcomes,[10,16] these reviews have not quantified the CVR associated with each hour deviation below or above the recommended sleep duration. In addition, none of the previous reviews assessed the influence of sleep quality.[10,16] Thus, we conducted a systematic review and meta-analysis of the impact of sleep duration and quality on CVD and mortality.

Methods

Data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

The full methods, including detailed eligibility criteria, search strategy, data selection, extraction, and analysis, are reported in Data S1. The article was prepared according the guidance of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement (Data S2).

Eligibility Criteria

We selected prospective cohort studies that reported on participants who quantified their duration of sleep or quality of sleep, and their association with subsequent CVD and mortality. The primary outcome was all-cause mortality, and secondary outcomes were CVD and mortality.

Search Strategy

We searched Medline and Embase using Ovid SP (from inception to the end of October 2015) using the search terms in Data S3.

Study Selection and Data Extraction

Two reviewers (C.S.K. and A.M.) checked all titles and abstracts for studies that could potentially meet the inclusion criteria. Data extraction and risk of bias assessment were performed independently by at least 2 reviewers (C.S.K., G.K., or M.G.). Publication bias was assessed using funnel plots.

Statistical Analysis

We used Stata software (version 14; StataCorpLP, College Station, TX) to perform regression analysis with random-effects dose-response meta-analysis models to estimate the association between hours of sleep and adverse outcomes, using 7 hours of sleep as the reference category. The linear model represents the primary analysis, and the cubic model was included as a supplemental analysis.

Conventional random-effects meta-analysis was performed as a secondary analysis using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). We decided to use random-effects models because they are more conservative compared with fixed-effect models, in the presence of any heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic. The details of the main and sensitivity analyses are described in Data S1. We also performed analysis of sleep quality (Data S4) in relation to mortality and cardiovascular outcomes.

Results

Description of Included Studies

A total of 74 studies met the inclusion criteria; the process of study selection is shown in Figure 1.[8,9,11,12,21–90] Study design and participant characteristics are shown in Table 1. The included studies were dated 1970–2017, which represented 3 340 684 participants. Among studies that reported crude events, there were 242 240 all-cause deaths in 2 564 029 participants from 44 studies (9.4%), 5435 coronary heart disease (CHD) deaths in 741 695 participants from
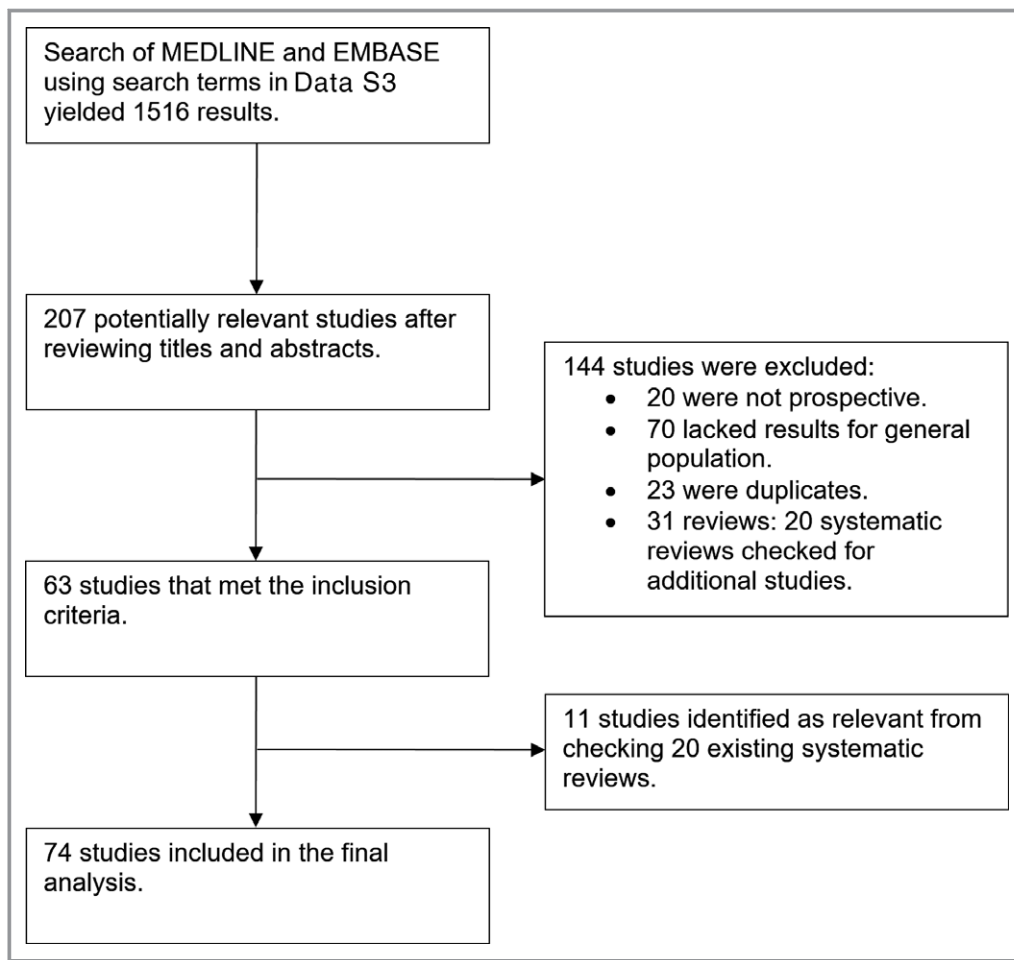
Figure 1. Flow diagram of study inclusion.

7 studies (0.7%), 6380 stroke deaths in 374 728 participants from 5 studies (1.7%), 32 988 cardiovascular deaths in 759 939 participants from 14 studies (4.3%), 32 084 CHD events in 540 538 participants from 14 studies (5.9%), 14 946 stroke events in 525 620 participants from 11 studies (2.8%), and 4160 CVD events in 97 832 participants from 6 studies (4.3%). Data S5 shows the prevalence of CVD and CVR factor profiles for each cohort.

Quality Assessment of Included Studies

The quality assessment is shown in Data S6. Studies used questionnaires or direct questioning to ascertain information about sleep quality or sleep duration. Methods used to estimate outcomes included population registries, death certification, questionnaires, and review of medical records or patient through interview or telephone call. Most studies adjusted for potential confounders, but the factors adjusted for varied across studies. Loss to follow-up was unclear in 30 studies, and 12 studies had 10% or more loss to follow-up or missing data. The study reference group and studies included for each analysis are shown in Data S7.

Sleep Duration and All-Cause Mortality

Numeric results of analyses are shown in Tables 2 and 3. For the spline analysis, a total of 30 studies* reported data that could be used for the all-cause mortality analysis. When spline analysis was applied using a linear model, incremental deviation <7 hours of self-reported sleep was not associated with increased risk of all-cause mortality, but sleep durations >8 hours were associated with increased risk of all-cause mortality (Figure 2). The cubic spline analysis model is shown in Data S8.

Pooled risk of all-cause mortality for the entire cohort (Figure 2, Data S9) and the subgroup of men and women only are shown in Data S10. There were a total of 39 studies included in the analysis.** The funnel plot for sleep duration and mortality did not suggest that there was publication bias. Deviation from self-reported sleep duration of 7 or 8 hours appeared to be associated with all-cause mortality, where

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*References 11, 21, 23, 25, 26, 29, 32, 33, 36, 41, 44, 47–49, 52, 55–57, 60, 64, 66, 68, 70, 71, 79, 80, 84, 86–88.
**References 11, 21, 23, 25–27, 29, 32–34, 36, 39–41, 44, 46–49, 51–54, 56, 57, 61, 64, 66, 68, 70–72, 77, 79, 80, 84, 86–88.

Table 1. Study Design and Demographics Table

Study ID	Design; Country; Year	No. of Participants	Mean Age, y	% Male	Participant Inclusion Criteria
Akersted, 2017[21]	Prospective cohort study; Sweden; 1997–2010	43 868	51	36	Participants were aged >18 y in the Swedish National March study.
Amagai, 2010[22]	Prospective cohort study; Japan; April 1992 to July 1995	11 367	55	39	Participants were adults of varying ages in 12 rural areas of Japan from the Jichi Medical School Cohort Study.
Aurora, 2016[23]	Prospective cohort study; USA; 1995–2011	5784	64	46	Participants were aged 40 y and not treated for sleep-disordered breathing in the Sleep Heart Health Study.
Ayas, 2003[24]	Prospective cohort study; USA; 1986–1996	71 617	Unclear	0	Participants were US female health professionals aged 45 to 65 y who were enrolled in the Nurses' Health Study.
Bellavia, 2014[25]	Prospective cohort study; Sweden; 1998–2012	70 973	Unclear	53	Participants were Swedish males and aged 45 to 79 y and females aged 39 to 76 y from the population-based Cohort of Swedish Men and the Swedish Mammography Cohort.
Burazeri, 2003[26]	Prospective cohort study; Israel; 1985 with up to 11 years' follow-up	1842	Unclear	46	Participants were aged >50 y in West Jerusalem in the Kiryat Yovel Community Health Study.
Cai, 2015[27]	Prospective cohort study; China; 1996–2010	113 138	54	41	Participants were Chinese men and women in Shanghai, China in the Shanghai Women's Health Study and the Shanghai Men's Health Study.
Canivet, 2014[28]	Prospective cohort study; Sweden; 1991–2005	13 617	Unclear	43	Participants were all people between the ages of 45 and 65 residing in Malmo, Sweden from the Malmo Diet and Cancer Study 1991.
Castro-Costa, 2011[29]	Prospective cohort study; Brazil; 1997–2005	1512	Median 69	38	Participants were all residents of Bambui city, Brazil aged ≥60 years on January 1, 1997 and part of the Bambui Cohort Study.
Chandola, 2010[30]	Prospective cohort study; England; 1985–1988	10 308	Unclear	67	Participants were adults aged 35 to 55 y from 20 London-based civil service departments in the Whitehall II Cohort.
Chen, 2008[31]	Prospective cohort study; USA; 1994–1998	93 175	Unclear	0	Participants were postmenopausal women aged 50 to 79 y from all over the United States in the Women's Health Initiative Observational study cohort.
Chen, 2013[32]	Prospective cohort study; Taiwan; 1999–2002	4064	73.8	56	Participants were residents of the Shih-Pai area of Taipei, Taiwan who were aged >65 y and part of the Shih-Pai Sleep Study.
Chien, 2010[33]	Prospective cohort study; Taiwan; 1990–1991	3430	54.8	50	Participants were adults aged >35 years in the Chin-Shan Community Cardiovascular Cohort study and of Chinese ethnicity living in Chin-Shan township, Taiwan.
Cohen-Mansfeld, 2012[34]	Prospective cohort study; Israel; 1989–1992	1166	83	55	Participants were older Jewish adults aged >75 y in the Cross-Sectional and Longitudinal Aging Study.
Ensrud, 2012[35]	Prospective cohort study; USA; 2003–2005	2505	76	100	Participants were nonfrail males aged ≥65 y, recruited by the prospective Osteoporotic Fractures in Men study.
Gangwisch, 2008[36]	Prospective cohort study; USA; 1982–1992	9789	Unclear	37	Participants were men and women aged 25 to 74 y in the NHANES I epidemiological follow-up study.

Table 1. Continued

Study ID	Design; Country; Year	No. of Participants	Mean Age, y	% Male	Participant Inclusion Criteria
Garde, 2013[37]	Prospective cohort study; Denmark; 1970–2001	5249	49	100	Participants were in the Copenhagen Male Study who were all men aged 40 to 59 y at 14 companies were invited.
Gianfagna, 2016[38]	Prospective cohort study; Italy; 1986–2008	2277	51	100	Participants were men aged 35 to 74 y and CVD free in the MONICA-Brianza and PAMELA population based cohorts.
Goto, 2013[39]	Prospective cohort study; Japan; 1987–1999	724	Unclear	65	Participants were aged ≥65 y in Okinawa Japan.
Hale, 2013[40]	Prospective cohort study; USA; 1993–2009	3942	62	0	Participants were in the Women's Health Initiative clinical trial and observational study who were postmenopausal women aged 50 to 79 y and did not have history of CHD.
Hall, 2015[41]	Prospective cohort study: USA; 1997 start follow-up of 9 years	3013	73.6	48.6	Participants were adults in the Health, Aging and Body Composition Study.
Hamazaki, 2011[42]	Prospective cohort study; Japan; 1994–2008	2282	44	100	Participants were men aged 35 to 54 y at a light metal factory (Japan) who did not have previous cardiovascular events or missing information at baseline survey.
Helbig, 2015[43]	Prospective cohort study; Germany; 1984–2001	17 604	48	50	Participants were age 25 to 74 y in the Monitoring Trends and Determinants in Cardiovascular Disease/Cooperative Health Research in the Region of Augsburg study.
Heslop, 2002[44]	Prospective cohort study; Scotland; 1970–1995	3030	Unclear	85	Participants were working Scottish men and women recruited between 1970 and 1973.
Hoevenaar-Blom, 2011[12]	Prospective cohort study; Netherlands; 1993–2012	20 432	42	45	Participants were aged 20 to 65 y in the MORGEN study.
Huang, 2013[45]	Prospective cohort study; Taiwan; 1999–2010	1901	Unclear	51	Participants were aged ≥65 y in the Elderly Nutrition and Health Survey in Taiwan.
Hublin, 2007[46]	Prospective cohort study; Finland; 1975–2003	21 268	41	48	Participants were in Finnish Twin Cohort who were all Finnish twin pairs of the same sex born before 1958 with both co-twins alive in 1975.
Ikehara, 2009[47]	Prospective cohort study; Japan; 1988–2003	98 634	Unclear	42	Participants were in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk where were aged 40 to 79 y and living in Japan.
Jung, 2013[48]	Prospective cohort study; USA; 1984–2001	2001	74	44	Participants were in the community-dwelling adults aged 60 to 96 y in The Rancho Bernardo Study.
Kakizaki, 2013[49]	Prospective cohort study; Japan; 1994–2008	49 256	60	48	Participants were aged 40 to 79 y in the Ohsaki Cohort Study.
Kawachi, 2016[50]	Prospective cohort study; Japan; 1992–2008	27 896	54	54	Participants were men and women aged ≥35 y in the Takayama Cohort Study.
Kim, 2013[51]	Prospective cohort study; USA; 1993–2007	135 685	Unclear	46	Participants were aged 45 to 75 y in the Multiethnic Cohort Study from Hawaii and Los Angeles.
Kojima, 2000[52]	Prospective cohort study; Japan; 1982–1996	5322	47	46	Participants were aged 20 to 76 y from Shirakawa town, Japan.
Kripke, 2002[53]	Prospective cohort study; USA; 1982–1988	1 116 936	57	43	Participants were aged 30 to 102 y in the Cancer Prevention Study II mainly friends/relatives of American Cancer Society volunteers.
Lan, 2007[54]		3079	71	55	

Table 1. Continued

Study ID	Design; Country; Year	No. of Participants	Mean Age, y	% Male	Participant Inclusion Criteria
	Prospective cohort study; Taiwan; 1993–2003				Participants were ≥64 y in the Survey of Health and Living Status of the Elderly in Taiwan.
Lee, 2014[55]	Prospective cohort study; Hong Kong; 2001–2010	3427	74	51	Participants were men and women in Hong Kong aged ≥65 y.
Lee, 2017[56]	Prospective cohort study; Taiwan; 2006–2010	937	65	55	Participants were Taiwanese aged ≥53 y in the Social Environment and Biomarkers of Aging Study.
Leng, 2015[9]	Prospective cohort study; United Kingdom; 1998–2009	9692	62	46	Participants were adults aged 42 to 81 y in the European Prospective Investigation into Cancer-Norfolk cohort.
Li, 2013[57]	Prospective cohort study; Japan; 1983–1990	12 489	Unclear	38	Participants were residents aged 20 to 79 y in the Minami Saku area of Japan who were a part of the SAKUCESS project.
Liu, 2014[58]	Prospective cohort study; USA; 1971–2007	3381	45	48	Participants were aged >30 y and were free from CHD in the Framingham Offspring Study.
Magee, 2011[59]	Prospective cohort study; Australia; 2006–2009	218 155	63	47	Participants were Australian adults aged ≥45 y, residing in the state of New South Wales and part of the 45 and Up study.
Magee, 2013[60]	Prospective cohort study; Australia; 2006–2009	227 815	Unclear	46.3	Participants were Australian adults aged ≥45 y, residing in the state of New South Wales and part of the 45 and Up study.
Mallon, 2002[61]	Prospective cohort study; Sweden; 1983–1995	1870	56	48	Participants were a random adults aged 45 to 65 y in the population register of the County of Dalarna in Sweden.
Martin, 2011[62]	Prospective cohort study; USA; Unclear	245	81	62	Participants were adults aged ≥65 y admitted to postacute rehabilitation sites in the Los Angeles area in the USA.
Meisinger, 2007[63]	Prospective cohort study; Germany; 1984–1995	6896	58	50.9	Participants were German adults aged 45 to 74 y who were part of the MONICA Augsburg project.
Mesas, 2010[64]	Prospective cohort study; Spain; 2001–2008	3820	71.8	44	Participants were noninstitutionalized adults aged ≥60 y living in Spain.
Pan, 2014[65]	Prospective cohort study; Singapore; 1993–1998	63 257	57	44	Participants were Chinese adults in Singapore aged 45 to 74, recruited from Hokkiens and Cantonese dialect groups residing in government housing estates.
Patel, 2004[66]	Prospective cohort study; USA; 1986–2000	82 969	53	0	Participants were women aged 30 to 55 y and residing in 11 US states that were part of the Nurses' Health Study.
Pollak, 1990[67]	Prospective cohort study; USA; 1984–1985	1855	75	Unclear	Participants were elderly residents of an urban community aged 65 to 98 y.
Qiu, 2011[68]	Prospective cohort study; China; 2005–2008	12 671	86	57	Participants were elderly Chinese adults from 22 provinces in China in the Chinese Longitudinal Healthy Longevity Survey.
Qureshi, 1997[69]	Prospective cohort study; USA; 1982–1992	7844	Unclear	36	Participants were US civilian noninstitutionalized adults aged >31 y and in the NHANES I Epidemiologic Follow-up Study (NHEFS).
Rhee, 2012[70]	Prospective cohort study; Korea; 1992–2008	14 533	51	100	Participants were male subjects aged 40 to 59 y in the Seoul Male Cohort Study.

Table 1. Continued

Study ID	Design; Country; Year	No. of Participants	Mean Age, y	% Male	Participant Inclusion Criteria
Rod, 2014[71]	Prospective cohort study; UK; 1985–2010	9098	45	67	Participants were in the Whitehall II Cohort Study who were London-based office staff aged 35 to 55 y working in 20 civil service departments in 1985.
Ruigomez, 1995[72]	Prospective cohort study; Spain; 1986–1991	1219	Unclear	39	Participants were an elderly population in the 1986 Health Interview Survey of Barcelona.
Ruiter Petrov, 2014[73]	Prospective cohort study; USA; 2003–2010	5666	61	44	Participants were aged ≥45 y in the Reasons for Geographic And Racial Differences in Stroke study.
Sands-Lincoln, 2013[74]	Prospective cohort study; USA; 1993–2009	86 329	63	0	Participants were in the Women's Health Initiative clinical trial and observational study who were postmenopausal women aged 50 to 79 y and did not have a history of CHD.
Shankar, 2008[75]	Prospective cohort study; Singapore; 1993–2006.	58 044	56	44	Participants were Chinese adults aged 45 to 75 y in the Singapore Chinese Health Study.
Song, 2016[76]	Prospective cohort study; China; 2006–2010	95 203	51	79	Participants were aged 18 to 98 y in the Kailuan study.
Stone, 2009[77]	Prospective cohort study; USA; Unclear	6107	80	50	Participants were community-dwelling older adults participating in the Study of Osteoporotic Fractures and the Outcomes of Sleep Disorders in Older Men Study.
Strand, 2016[78]	Prospective cohort study; Taiwan; 1998–2011	392 164	40	49	Participants were Taiwanese adults aged 20 y who were participants in a health check-up program run by MJ Health Management Institution.
Suzuki, 2009[11]	Prospective cohort study; Japan; 1999–2006	12 601	74	51	Participants were elderly residents aged 65 to 85 y in the Shizuoka Study.
Tamakoshi, 2004[79]	Prospective cohort study; Japan; 1988–1999	104 010	58	42	Participants were aged 40 to 79 y in the Japan Collaborative Cohort Study on Evaluation of Cancer Risk study.
Tsubono, 1993[80]	Prospective cohort study; Japan; 1988–1992	4318	Unclear	40	Participants were aged ≥40 y in Japan who participated in the annual health examination program implemented by the Town Council.
Tu, 2012[81]	Prospective cohort study; China; 1997–2006	68 832	60	0	Participants were women aged 40 to 70 y in the Shanghai Women's Health Study.
Twig, 2016[82]	Prospective cohort study; Israel; unclear	23 690	30	100	Participants were men aged >25 y in the Israeli Defense Forces who were in the MELANY cohort study.
Von Ruesten, 2012[83]	Prospective cohort study; Germany; 1994–2007	23 620	49	39	Participants were in the European Prospective Investigation into Cancer and Nutrition (EPIC) study in Potsdam.
Wang, 2016[84]	Prospective cohort study; China; 2006–2010	95 903	51	80	Participants were aged 18 to 98 y in the Kailuan study.
Werle, 2011[85]	Prospective cohort study; Brazil; 1994–2009	187	84	36	Participants were aged >80 y in the city of Veranopolis, Brazil.
Westerlund, 2013[8]	Prospective cohort study; Sweden; 1997–2010	41 192	Unclear	35	Participants were aged ≥18 y in the Swedish National March Cohort Study.
Wingard, 1983[86]	Prospective cohort study; USA; 1965–1974	6928	Unclear	47	Participants were aged 30 to 69 y of age in 1965 in California.
Xiao, 2014[87]	Prospective cohort study; USA; 1995–2011	239 896	63	56	Participants were aged 51 to 72 y in the NIH AARP Diet and Health Study.

Continued

Table 1. Continued

Study ID	Design; Country; Year	No. of Participants	Mean Age, y	% Male	Participant Inclusion Criteria
Yeo, 2013[88]	Prospective cohort study; Korea; 1993–2010	13 164	55	41	Participants were aged ≥20 y in the Korean Multi-center Cancer Cohort study.
Zawisza, 2015[89]	Prospective cohort study; Poland; 1986–2008	2449	72	35	Participants were aged ≥65 y from Krakow city centre in Poland.
Zuubier, 2015[90]	Prospective cohort study; Netherlands; 2004–2013	1734	62	47	Participants were aged ≥45 y in the Rotterdam Study.

CHD indicates coronary heart disease; CVD, cardiovascular disease; MELANY, Metabolic Lifestyle and Nutrition Assessment in Young Adults; MONICA-Brianza, Monitoring of Cardiovascular Disease-Brianza; MORGEN, Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands; NHANES, National Health and Nutrition Examination Survey; PAMELA, Pressioni Arteriose Monitorate E Loro Associazioni; SAKUCESS, Saku Cancer Etiology Surveillance Study.

longer sleep durations are associated with greater mortality compared with small increases for shorter durations. The similar J-shaped relationship was observed for the subgroup of men and women.

Sleep Duration and CHD Mortality and CHD

A total of 5[37,47,49,75,78] and 12[***] studies were included in spline analysis for CHD mortality and CHD, respectively. Linear spline analysis failed to demonstrate any significant difference for both outcomes for self-reported shorter and longer sleep durations (Figure 3, cubic model in Data S8).

For the meta-analysis, there were 7 studies[37,47,49,51,61,75,78] (Data S11) and 15 studies[****] (Data S12) for CHD mortality and CHD, respectively. Although there were fewer studies, a similar J-shaped pattern was observed where there was greater risk of CHD mortality and events with incremental deviation from the reference 7 to 8 hours of self-reported sleep (a modest increase for 6 hours and greater increase for ≤5 hours; Data S10). The funnel plot for self-reported sleep duration and CHD mortality suggested a possible publication bias whereas for CHD the plot did not suggest that there was a publication bias.

Sleep Duration and Stroke Mortality and Stroke

Linear spline analysis for stroke mortality and stroke included 3[47,49,65] and 9[8,22,31,42,43,50,69,76,83] studies, respectively. There was no difference in stroke events associated with self-reported sleep duration shorter or longer than 7 hours, but a moderate increase in stroke mortality if sleep duration was >7 hours (Figure 3, Data S8).

Meta-analysis of 5 studies[27,47,49,51,65] were included in the analysis of stroke mortality (Data S10). For stroke events, there were 13 studies.[†] The funnel plot for sleep duration and stroke mortality did not suggest a publication bias. For stroke

mortality, there appeared to be no difference in events with self-reported sleep duration <7 hours, but significant and moderate increase in events with longer sleep duration >8 hours (Data S13). However, for stroke events, the increase in event rates are preserved for both sleep duration <7 hours (modest for 6 hours and a greater increase for ≤5 hours) and a moderate increase for >8 hours (Data S14). The funnel plot for sleep duration and stroke did not suggest a publication bias.

Sleep Duration and Cardiovascular Mortality and CVD

Spline analysis using linear models did not shown any difference in events with shorter duration than 7 hours for both cardiovascular mortality (8 studies)[11,25,44,47,49,71,87,88] and CVD (7 studies).[8,12,22,33,38,42,74] However, longer self-reported sleep duration >7 hours appeared to be associated with a moderate increase in greater stroke mortality (cubic model shown in Data S8).

There were 16 studies[‡] (Data S15) that evaluated CVD mortality and 8 studies[8,12,22,28,33,38,42,74] (Data S16) that evaluated CVD events. The J-shaped pattern was observed for self-reported sleep duration and CVD mortality, but this was not the case for CVD events, but there were fewer studies in the event analysis. The funnel plot for sleep duration and CVD mortality and CVD did not suggest a publication bias. Incremental decrease in hours of sleep was associated with significant increase in mortality (Data S10).

Sleep Quality and Mortality and Adverse Cardiovascular Outcomes

A total of 17 studies[§] were included in the analysis of subjective sleep quality and adverse outcomes (Data S10 and Data S17). For all-cause mortality, there were 12 652 deaths

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[***]References 8, 12, 22, 24, 38, 42, 58, 63, 69, 74, 83, 84.
[****]References 8, 12, 22, 24, 38, 40, 42, 58, 59, 63, 69, 74, 81, 83, 84.
[†]References 8, 9, 22, 31, 42, 43, 59, 69, 73, 76, 81, 83.

[‡]References 8, 11, 25–27, 32, 44, 47, 49, 51, 54, 57, 66, 71, 87, 88.
[§]References 8, 11, 12, 30, 32, 35, 38, 43, 45, 46, 52, 61–63, 68, 71, 78, 82.

Table 2. Study Cohort, Follow-up and Results for Studies With Authors Akersted to Akersted

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
Akersted, 2017[21]	13 y	All-cause mortality: 3548/39 191	Sleep duration and mortality: ≤5 h: aHR 1.12 (0.99–1.27), 6 h: aHR 0.98 (0.88–1.09), 7 h: aHR 1.00, ≥8 h: aHR 1.10 (1.00–1.20).
Amagai, 2010[22]	10.7 y	CVD events: 481/11 367. MI: 80/11 367. Stroke: 411/11 367	Sleep duration and CVD in males: <5.9 h: aHR 2.14 (1.11–4.13), 6.0 to 6.9 h: aHR 1.04 (0.61–1.76), 7.0 to 7.9 h: aHR 1.00, 8.0 to 8.9 h: aHR 0.98 (0.69–1.40), ≥9.0 h: aHR 1.33 (0.93–1.92). Sleep duration and CVD in females: <5.9 h: aHR 1.46 (0.70–3.04), 6.0 to 6.9 h: aHR 0.64 (0.38–1.10), 7.0 to 7.9 h: aHR 1.00, 8.0 to 8.9 h: aHR 0.85 (0.60–1.20), ≥9.0 h: aHR 1.28 (0.88–1.87). Sleep duration and MI in men: <5.9 h: aHR 1.78 (0.50–6.28), 6.0 to 6.9 h: aHR 0.77 (0.25–2.33), 7.0 to 7.9 h: aHR 1.00, 8.0 to 8.9 h: aHR 0.69 (0.34–1.41), ≥9.0 h: aHR 0.99 (0.47–2.06). Sleep duration and MI in women: <5.9 h: aHR 4.93 (1.31–18.61), 6.0 to 6.9 h: aHR 0.59 (0.13–2.73), 7.0 to 7.9 h: aHR 1.00, 8.0 to 8.9 h: aHR 0.59 (0.21–1.66), ≥9.0 h: aHR 0.84 (0.27–2.62). Sleep duration and stroke in men: <5.9 h: aHR 2.00 (0.93–4.31), 6.0 to 6.9 h: aHR 1.13 (0.63–2.03), 7.0 to 7.9 h: aHR 1.00, 8.0 to 8.9 h: aHR 1.03 (0.69–1.53), ≥9.0 h: aHR 1.39 (0.92–2.10). Sleep duration and stroke in women: <5.9 h: aHR 0.97 (0.39–2.41), 6.0 to 6.9 h: aHR 0.68 (0.39–1.18), 7.0 to 7.9 h: aHR 1.00, 8.0 to 8.9 h: aHR 0.86 (0.60–1.23), ≥9.0 h: aHR 1.29 (0.86–1.91).
Aurora, 2016[23]	10.8 y	All-cause mortality: 1509/5784	Sleep duration and mortality: <7 h: aHR 0.98 (0.87–1.10), 7 to 8 h: aHR 1.00, ≥9 h: aHR 1.25 (1.05–1.47).
Ayas, 2003[24]	10 y	CHD: 934/71 617	Sleep duration and CHD: ≤5 h: aOR 1.39 (1.05–1.84), 6 h: aOR 1.18 (0.98–1.43), 7 h: aOR 1.10 (0.92–1.31), 8 h: aOR 1.00, >9 h: aOR 1.37 (1.02–1.85).
Bellavia, 2014[25]	15 y	All-cause mortality 13 450/70 973. CVD mortality: 3981/70 973	Sleep duration and all-cause mortality: <6 h: aHR 1.25 (1.13–1.37), 6 to 6.5 h: aHR 1.10 (1.04–1.17), 6.6 to 7.4 h: aHR 1.00 (reference), 7.5 to 8 h: aHR 1.03 (0.98–1.08), >8 h: aHR 1.14 (1.05–1.24). Sleep duration and CVD mortality: <6 h: aHR 1.44 (1.20 to 1.73), 6 to 6.5 h: aHR 1.23 (1.09–1.38), 6.6 to 7.4 h: aHR 1.00, 7.5 to 8 h: aHR 1.02 (0.92–1.12), >8 h: aHR 1.11 (0.95–1.31).
Burazeri, 2003[26]	10 y	All-cause mortality: 403/1842	Total sleep duration and all-cause mortality in men: <6 h: aHR 1.00, 6 to 8 h: aHR 1.41 (0.83–2.39), >8 h: aHR 2.13 (1.23–3.71). Total sleep duration and all-cause mortality in women: <6 h: aHR 1.00, 6 to 8 h: aHR 0.63 (0.42–0.97), >8 h: aHR 0.80 (0.51–1.24). Total sleep duration and CVD mortality in men: <6 h: aHR 1.00, 6 to 8 h: aHR 1.54 (0.75–3.15), >8 h: aHR 2.02 (1.01–4.03). Total sleep duration and CVD mortality in women: <6 h: aHR 1.00, 6 to 8 h: aHR 0.69 (0.37–1.29), >8 h: aHR 0.79 (0.42–1.48).
Cai, 2015[27]	Median 6 to 7 y	All-cause mortality: 4277/113 138	Sleep duration and all-cause mortality: 4 to 5 h: aHR 1.11 (1.00–1.23), 6 h: aHR 1.06 (0.97–1.16), 7 h: aHR 1.00, 8 h: aHR 1.15 (1.05–1.26), 9 h: aHR 1.34 (1.17–1.54), ≥10 h: 1.81 (1.59–2.06). Sleep duration and all-cause mortality in men: 4 to 5 h: aHR 1.06 (0.90–1.25), 6 h: aHR 1.07 (0.94–1.23), 7 h: aHR

Table 2. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
			1.00, 8 h: aHR 1.13 (1.00–1.28), 9 h: aHR 1.34 (1.10–1.62), ≥10 h: aHR 1.55 (1.29–1.86). Sleep duration and all-cause mortality in women: 4 to 5 h: aHR 1.15 (1.01–1.32), 6 h: aHR 1.06 (0.94–1.20), 7 h: aHR 1.00, 8 h: aHR 1.17 (1.04–1.32), 9 h: aHR 1.36 (1.13–1.64), ≥10 h: aHR 2.11 (1.77–2.52). Sleep duration and cardiovascular mortality: 4 to 5 h: aHR 1.05 (0.87–1.26), 6 h: aHR 1.10 (0.94–1.29), 7 h: aHR 1.00, 8 h: aHR 1.22 (1.05–1.43), 9 h: aHR 1.47 (1.17–1.85), ≥10 h: aHR 2.04 (1.65–2.53). Sleep duration and cardiovascular mortality in men: 4 to 5 h: aHR 1.09 (0.82–1.46), 6 h: aHR 1.06 (0.83–1.34), 7 h: aHR 1.00, 8 h: aHR 1.25 (1.00–1.56), 9 h: aHR 1.68 (1.23–2.30), ≥10 h: aHR 1.58 (1.14–2.18). Sleep duration and cardiovascular mortality in women: 4 to 5 h: aHR 1.02 (0.80–1.30), 6 h: aHR 1.12 (0.91–1.39), 7 h: aHR 1.00, 8 h: aHR 1.20 (0.96–1.50), 9 h: aHR 1.28 (0.91–1.82), ≥10 h: aHR 2.64 (1.99–3.52). Sleep duration and stroke mortality: 4 to 5 h: aHR 0.91 (0.70–1.18), 6 h: aHR 0.99 (0.79–1.23), 7 h: aHR 1.00, 8 h: aHR 1.28 (1.04–1.58), 9 h: aHR 1.31 (0.94–1.82), ≥10 h: aHR 2.35 (1.78–3.09). Sleep duration and stroke mortality in men: 4 to 5 h: aHR 0.93 (0.62–1.40), 6 h: aHR 0.78 (0.55–1.10), 7 h: aHR 1.00, 8 h: 1.20 (0.89–1.62), 9 h: aHR 1.62 (1.06–2.48), ≥10 h: aHR 1.73 (1.14–2.64). Sleep duration and stroke mortality in women: 4 to 5 h: aHR 0.92 (0.65–1.29), 6 h: aHR 1.14 (0.85–1.52), 7 h: aHR 1.00, 8 h: aHR 1.36 (1.01–1.82), 9 h: aHR 0.98 (0.58–1.66), ≥10 h: aHR 3.09 (2.14–4.47).
Canivet, 2014[28]	14 y	Unclear	Sleep duration and cardiovascular events in men: ≤6 h: aHR 1.1 (0.96–1.3), 7 to 8 h: aHR 1.0, ≥9 h:aHR 1.3 (1.01–1.7). Sleep duration and cardiovascular events in women: ≤6 h: aHR 1.3 (1.1–1.5), 7 to 8 h: aHR 1.0, ≥9 h: aHR 1.5 (1.1–2.1).
Castro-Costa, 2011[29]	Unclear	All-cause mortality: 440/ 1512	Night-time sleep duration and all-cause mortality: <6 h: aHR 1.09 (0.78–1.53), 6 to 7 h: aHR 0.84 (0.60–1.17), 7 to 8 h: aHR 1.00 (reference), 8 to 9 h: aHR 1.31 (0.97–1.78), ≥9 h: aHR 1.53 (1.12–2.09).
Chandola, 2010[30]	15 y	CHD mortality, MI, angina: 1205/8998	Sleep duration and CHD mortality, MI and angina: <5 h: aRR 1.05 (0.92–1.20), 6 h: aRR 0.98 (0.83–1.16), 7 h: aRR 1.00, >8: aRR 0.99 (0.77–1.27). Poor sleep quality (more than usual restless, disturbed nights) and CHD mortality, MI, and angina: aRR 1.36 (1.10–1.68).
Chen, 2008[31]	7.5 y	Ischaemic stroke: 1166/ 93 175	Sleep duration and ischemic stroke: <6 h: aHR 1.14 (0.97–1.33), 7 h: aHR 1.00, 8 h: aHR 1.24 (1.04–1.47), >9 h: aHR 1.70 (1.32–2.21).
Chen, 2013[32]	9 y	All-cause mortality: 1004/4064. CVD mortality: 259/4064	Sleep duration and all-cause mortality: <4 h: aHR 1.00 (0.75–1.33), 5 h: aHR 0.92 (0.74–1.15), 6 h: aHR 0.88 (0.73–1.06), 7 h: aHR 1.00, 8 h: aHR 1.26 (1.04–1.53), >9 h: aHR 1.66 (1.28–2.17). Sleep duration and CVD mortality: <4 h: aHR 1.05 (0.61–1.79), 5 h: aHR 0.95 (0.62–1.48), 6 h:aHR 0.79 (0.54–1.16), 7 h: aHR 1.00, 8 h: aHR 1.36 (0.92–2.01), >9 h: aHR 2.36 (1.46–3.80). Poor sleep quality (subjective) and all-cause mortality: aHR 0.81 (0.47–1.38). Poor sleep quality (subjective) and CVD mortality: aHR 0.60 (0.19–1.93).

Continued

Table 2. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
Chien, 2010[33]	Median 15.9 y	All-cause mortality: 901/3430. CVD events: 420/3430	Sleep duration and all-cause mortality: <5 h: aRR 1.15 (0.9–1.46), 6 h: aRR 0.97 (0.79–1.21), 7 h: aRR 1, 8 h: aRR 1.04 (0.86–1.27), ≥9 h: aRR 1.34 (1.08–1.67). Sleep duration and CVD event: <5 h: aRR 0.94 (0.65–1.35), 6 h: aRR 0.91 (0.67–1.24), 7 h: aRR 1, 8 h: aRR 1.05 (0.80–1.39), >9 h: aRR 1.12 (0.81–1.55).
Cohen-Mansfeld, 2012[34]	20 y	All-cause mortality: 1108/1166	Sleep duration and mortality: <7 h: aHR 0.98 (0.84–1.13), 7 to 9 h: 1.00, >9 h: aHR 1.32 (1.09–1.58).
Ensrud, 2012[35]	3.4 y	All-cause mortality: 180/2505	Poor sleep quality (PSQI score >5) and all-cause mortality: >5 81/1018 vs ≤5 99/1487, aOR 1.02 (0.73–1.42). Sleep duration and all-cause mortality: ≤5 h: 21/269 vs 159/2236, aOR 1.08 (0.65–1.80).
Gangwisch, 2008[36]	Up to 10 y	All-cause mortality: 1877/9789	Sleep duration and all-cause mortality: ≤5 h: aHR 1.17 (0.99–1.39), 6 h: aHR 0.95 (0.81–1.11), 7 h: aHR 1.00, 8 h: aHR 1.23 (1.08–1.39), ≥9 h: aHR 1.34 (1.15–1.56).
Garde, 2013[37]	30 y	All-cause mortality: 2643/5249. Ischaemic heart disease mortality: 587/5249	Sleep duration on all-cause mortality in men: <6 h: aHR 1.06 (0.90–1.25). 6 to 7 h: aHR 1.00. ≥8 h: aHR 0.99 (0.84 to 1.09). Sleep duration and ischemic heart disease mortality in men: <6 h: aHR 1.46 (1.07–2.00). 6 to 7 h: aHR 1.00. ≥8 h: aHR 1.20 (0.97–1.49).
Gianfagna, 2016[38]	Median 17 y	CVD event: 293/2277. CHD event: 214/2277	Sleep duration and CVD event: ≤6 h: aHR 1.14 (0.84–1.53), 7 to 8 h: aHR 1.00, ≥9 h: aHR 1.55 (1.08–2.21). Sleep duration and CHD event: ≤6 h: aHR 1.14 (0.80–1.61), 7 to 8 h: aHR 1.00, ≥9 h: aHR 1.32 (0.85–2.07). Sleep disturbance on CVD event vs none/some: moderate aHR 1.14 (0.74–1.77), severe aHR 1.80 (1.07–3.03). Sleep disturbance on CHD event vs none/some: moderate aHR 1.35 (0.83–2.21), severe aHR 1.83 (0.98–3.41).
Goto, 2013[39]	12 y	All-cause mortality: 305/724	Sleep duration and all-cause mortality in men: aHR <6 h: aHR 1.29 (0.50–3.34), 6 to 7 h: aHR 1.00, >7 h: aHR 1.54 (092–2.58). Sleep duration and all-cause mortality in women: aHR <6 h: aHR 2.62 (1.36–5.07), 6 to 7 h: aHR 1.00, >7 h: aHR 1.40 (0.91–2.15).
Hale, 2013[40]	Up to 16 y	All-cause mortality: 335/3942. CHD: 132/3942	Sleep duration and all-cause mortality: ≤5 h: aOR 1.01 (0.68–1.51), 6 h: aOR 0.94 (0.71–1.24), 7 to 8 h: aOR 1.00, ≥9 h: aOR 1.55 (0.92–2.60). Sleep duration and CHD: ≤5 h: aOR 1.09 (0.63–1.89), 6 h: aOR 0.66 (0.42–1.04), 7 to 8 h: aOR 1.00, ≥9 h: aOR 1.88 (0.92–3.83).
Hall, 2015[41]	9 y	All-cause mortality: 953/3075	Sleep duration and all-cause mortality: <6 h: aHR 1.06 (0.83–1.34), 6 h: aHR 1.00 (0.82–1.22), 7 h: aHR 1.00, 8 h: aHR 1.10 (0.91–1.33), >8 h: aHR 1.23 (0.93–1.63).
Hamazaki, 2011[42]	14 y	CVD events: 64/2282. Stroke: 30/2282. Coronary events: 27/2282	Sleep duration and CVD events: <6 h: aHR 3.49 (1.30–9.40), 6 to 6.9 h: aHR 1.11 (0.55–2.25), 7 to 7.9 h: aHR 1.00, ≥8 h: aHR 1.71 (0.90–3.24). Sleep duration and stroke: <6 h: aHR 1.84 (0.23–14.90), 6 to 6.9 h: aHR 0.96 (0.30–3.10), 7 to 7.9 h: aHR 1.00, ≥8 h: aHR 2.25 (0.91–5.57). Sleep duration and coronary events: <6 h: aHR 4.95 (1.31–18.73), 6 to 6.9 h: aHR 1.12 (0.40–3.13), 7 to 7.9 h: aHR 1.00 (reference), ≥8 h: aHR 1.78 (0.67–4.76).

Table 2. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
Helbig, 2015[43]	14 y	Stroke: 917/17 604	Sleep duration and strokes in men: ≤5 h: aHR 1.36 (0.95–1.94), 6 h: aHR 0.92 (0.70–1.22), 7 to 8 h: aHR 1.00, 9 h: aHR 1.05 (0.78–1.43), ≥10 h: aHR 1.38 (0.98–1.94). Sleep duration and strokes in women: ≤5 h: aHR 0.68 (0.40–1.18), 6 h: aHR 1.25 (0.91–1.70), 7 to 8 h: aHR 1.00, 9 h: aHR 1.09 (0.76–1.57), ≥10 h: aHR 0.91 (0.55–1.51). Poor sleep quality (difficulty staying asleep) and stroke in men: aHR 1.06 (0.87–1.30). Poor sleep quality (difficulty staying asleep) and stroke in women: aHR 0.87 (0.68–1.10).
Heslop, 2002[44]	25 y	All-cause mortality: 1062/7028. CVD mortality: 557/7028	Sleep duration and all-cause mortality in men: <7 h: aHR 1.15 (0.93–1.42), 7 to 8 h: aHR 1.00, >8 h: aHR 0.91 (0.57–1.46). Sleep duration and all-cause mortality in women: <7 h: aHR 1.73 (0.99–3.03), 7 to 8 h: 1.00, >8 h: aHR 0.58 (0.08–4.22). Sleep duration and CVD mortality in men: <7 h: aHR 1.19 (0.90–1.58), 7 to 8 h: aHR 1, >8 h: aHR 0.63 (0.30–1.34). Sleep duration and CVD mortality in women: <7 h: aHR 2.30 (0.94–5.60), 7 to 8 h: aHR 1, >8 h: aHR 1.53 (0.20–11.8).
Hoevenaar-Blom, 2011[12]	11.9 y	CVD events: 1486/ 20 432. CHD: 1148/ 20 432	Sleep duration on incident CVD: ≤6 h: aHR 1.11 (0.97–1.27), 7 h: aHR 1.00, 8 h: aHR 0.95 (0.84–1.08), ≥9 h: aHR 0.96 (0.77–1.18). Sleep duration and incident CHD: ≤6 h: aHR 1.19 (1.00–1.40), 7 h: aHR 1.00, 8 h: aHR 0.85 (0.73–1.00), ≥9 h: aHR 0.78 (0.58–1.04). Poor sleep quality and incident CVD: aHR 1.04 (0.87–1.26). Poor sleep quality and incident CHD: aHR 1.19 (0.96–1.50).
Huang, 2013[45]	10 y	All-cause mortality: 182/ 1865	Poor sleep quality (good vs poor) and all-cause mortality in men: aHR 0.60 (0.42–0.87). Poor sleep quality (good vs poor) and all-cause mortality in women: aHR 0.99 (0.68–1.45).
Hublin, 2007[46]	22 y	All-cause mortality: 3700/21 268	Sleep duration and all-cause mortality in men: <7 h: aHR 1.26 (1.11–1.43), 7 to 8 h: aHR 1.00, >8 h: aHR 1.24 (1.09–1.41). Sleep duration and all-cause mortality in women: <7 h: aHR 1.21 (1.05–1.40), 7 to 8 h: aHR 1.00, >8 h: aHR 1.17 (1.03–1.34). Poor sleep quality and all-cause mortality in men: aHR 1.10 (0.87–1.39). Poor sleep quality and all-cause mortality in women: aHR 0.99 (0.77–1.27).
Ikehara, 2009[47]	Median 14.3 y	All-cause mortality 14 540/98 634. CVD mortality 4287/ 98 634. Stroke mortality: 1964/ 98 634. CHD mortality 881/98 634	Sleep duration and all-cause mortality in men: ≤4 h: aHR 1.29 (1.02–1.64), 5 h: aHR 1.02 (0.90–1.16), 6 h: aHR 1.08 (1.00–1.16), 7 h: aHR 1.00, 8 h: aHR 1.06 (1.00–1.12), 9 h: aHR 1.13 (1.05–1.22), ≥10 h: aHR 1.41 (1.29–1.54). Sleep duration and all-cause mortality in women: ≤4 h: aHR 1.28 (1.03–1.60), 5 h: aHR 1.11 (0.98–1.25), 6 h: aHR 1.05 (0.97–1.14), 7 h: aHR 1.00, 8 h: aHR 1.16 (1.08–1.24), 9 h: aHR 1.32 (1.20–1.45), ≥10 h: aHR 1.56 (1.40–1.75). Sleep duration and CVD mortality in men: ≤4 h: aHR 1.11 (0.67–1.83), 5 h: aHR 0.99 (0.77–1.27), 6 h: aHR 1.01 (0.87–1.18), 7 h: aHR 1.00, 8 h: aHR 1.11 (1.00–1.24), 9 h: aHR 1.14 (0.99–1.32), ≥10 h: aHR 1.56 (1.33–1.83).

Continued

Table 2. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
			Sleep duration and CVD mortality in women: ≤4 h: aHR 1.28 (0.88–1.86), 5 h: aHR 1.22 (1.00–1.50), 6 h: aHR 1.00 (0.86–1.16), 7 h: aHR 1.00, 8 h: aHR 1.28 (1.14–1.44), 9 h: aHR 1.37 (1.17–1.62), ≥10 h: aHR 1.54 (1.28–1.86). Sleep duration and stroke mortality in men: ≤4 h: aHR 1.56 (0.82–2.94), 5 h: aHR 0.85 (0.58–1.26), 6 h: aHR 0.95 (0.76–1.20), 7 h: aHR 1.00, 8 h: aHR 1.11 (0.95–1.30), 9 h: aHR 1.14 (0.92–1.42), ≥10 h: aHR 1.66 (1.31–2.08). Sleep duration and stroke mortality in women: ≤4 h: aHR 1.07 (0.59–1.91), 5 h: aHR 0.99 (0.72–1.37), 6 h: aHR 0.93 (0.75–1.16), 7 h: aHR 1.00, 8 h: aHR 1.24 (1.05–1.47), 9 h: aHR 1.29 (1.01–1.64), ≥10 h: aHR 1.69 (1.29–2.20). Sleep duration and CHD mortality in men: ≤4 h: aHR 0.29 (0.04–2.05), 5 h: aHR 1.02 (0.62–1.70), 6 h: aHR 0.86 (0.63–1.19), 7 h: aHR 1.00, 8 h: aHR 1.02 (0.82–1.27), 9 h: aHR 0.96 (0.70–1.31), ≥10 h: aHR 1.12 (0.77–1.63). Sleep duration and CHD mortality in women: ≤4 h: aHR 2.32 (1.19–4.50), 5 h: aHR 1.64 (1.07–2.53), 6 h: aHR 1.23 (0.88–1.72), 7 h: aHR 1.00, 8 h: aHR 1.24 (0.94–1.64), 9 h: aHR 1.52 (1.05–2.19), ≥10 h: aHR 1.04 (0.63–1.72).
Jung, 2013[48]	Up to 19 y	All-cause mortality: 1224/2001	Night-time sleep duration and all-cause mortality in men: <6 h: aHR 0.98 (0.673–1.43), 6.0 to 6.9 h: aHR 1.12 (0.85–1.48) 7.0–7.9 h: aHR 1.0, 8.0–8.9 h: aHR 0.98 (0.79–1.22), ≥9 h: aHR 1.09 (0.82–1.45). Night-time sleep duration and all-cause mortality in women: <6 h: aHR 1.11 (0.77–1.60), 6.0–6.9 h: aHR 1.17 (0.85–1.61) 7.0–7.9 h: aHR 1.0, 8.0–8.9 h: aHR 1.19 (0.90–1.57), ≥9 h: aHR 1.51 (1.05–2.18).
Kakizaki, 2013[49]	13 y	All-cause mortality 8447/49 256. CVD mortality 2549/49 256. Stroke mortality 1165/49 256. IHD mortality 561/49 256	Sleep duration and all-cause mortality: ≤6 h: aHR 1.01 (0.93–1.09), 7 h: aHR 1.00, 8 h: aHR 1.07 (1.01–1.14), 9 h: aHR 1.14 (1.06–1.24), ≥10 h: aHR 1.37 (1.27–1.47). Sleep duration on CVD mortality: ≤6 h: aHR 1.10 (0.96–1.28), 7 h: aHR 1.00, 8 h: aHR 1.21 (1.08–1.36), 9 h: aHR 1.32 (1.15–1.52), ≥10 h: aHR 1.49 (1.30–1.71). Sleep duration and stroke mortality: ≤6 h: aHR 1.05 (0.84–1.30), 7 h: aHR 1.00, 8 h: aHR 1.17 (0.99–1.39), 9 h: aHR 1.30 (1.06–1.60), ≥10 h: aHR 1.51 (1.24–1.85). Sleep duration and IHD mortality: ≤6 h: aHR 1.38 (1.02–1.86), 7 h: aHR 1.00, 8 h: aHR 1.36 (1.06–1.73), 9 h: aHR 1.49 (1.10–2.02), ≥10 h: aHR 1.41 (1.04–1.92).
Kawachi 2016[50]	Up to 16 y	Stroke mortality: 611/27 896	Sleep duration and stroke mortality: ≤6 h: aHR 0.77 (0.59–1.01), 7 h: aHR 1.00, 8 h: aHR 1.13 (0.91–1.40), ≥9 h: aHR 1.51 (1.16–1.97). Sleep duration and stroke mortality in men: ≤6 h: aHR 0.51 (0.34–0.77), 7 h: aHR 1.00, 8 h: aHR 0.88 (0.66–1.17), ≥9 h: aHR 1.23 (0.90–1.69). Sleep duration and stroke mortality in women: ≤6 h: aHR 1.06 (0.75–1.50), 7 h: aHR 1.00, 8 h: aHR 1.50 (1.10–2.04), ≥9 h: aHR 1.93 (1.38–2.70).
Kim, 2013[51]	13 y	All-cause mortality: 19 335/135 685. CVD mortality 6610/135 685. Stroke mortality: 1259/135 685. MI mortality: 1188/135 685	Sleep duration and all-cause mortality in men: aHR ≤5 h: 1.15 (1.06–1.23), 6 h: aHR 1.04 (0.99–1.10), 7 h: aHR 1.00, 8 h: 1.07 (1.01–1.12), ≥9 h: 1.19 (1.12–1.27). Sleep duration and all-cause mortality in women: aHR ≤5 h: 1.14 (1.06–1.23), 6 h: aHR 1.05 (0.99–1.12), 7 h: aHR 1.00, 8 h: 1.02 (0.96–1.08), ≥9 h: 1.22 (1.13–1.31). Sleep duration and CVD mortality in men: aHR ≤5 h: 1.13 (1.00–1.28), 6 h: aHR 1.01 (0.92–1.11), 7 h: aHR 1.00, 8 h: 1.05 (0.96–1.14), ≥9 h: 1.22 (1.09–1.35).

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Table 2. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
			Sleep duration and CVD mortality in women: aHR ≤5 h: 1.20 (1.05–1.36), 6 h: aHR 1.06 (0.96–1.18), 7 h: aHR 1.00, 8 h: 1.08 (0.98–1.20), ≥9 h: 1.29 (1.13–1.47). Sleep duration and stroke mortality in men: aHR ≤5 h: 1.02 (0.74–1.40), 6 h: aHR 1.10 (0.88–1.37), 7 h: aHR 1.00, 8 h: 1.13 (0.91–1.39), ≥9 h: 1.35 (1.03–1.75). Sleep duration and stroke mortality in women: aHR ≤5 h: 1.16 (0.88–1.52), 6 h: aHR 0.99 (0.79–1.23), 7 h: aHR 1.00, 8 h: 1.07 (0.87–1.33), ≥9 h: 1.39 (1.06–1.83). Sleep duration and MI mortality in men: aHR ≤5 h: 1.24 (0.94–1.64), 6 h: aHR 0.92 (0.74–1.15), 7 h: aHR 1.00, 8 h: 0.98 (0.80–1.20), ≥9 h: 1.16 (0.89–1.50). Sleep duration and MI mortality in women: aHR ≤5 h: 1.18 (0.87–1.59), 6 h: aHR 1.23 (0.96–1.56), 7 h: aHR 1.00, 8 h: 1.10 (0.86–1.40), ≥9 h: 1.29 (0.95–1.75).
Kojima, 2000[52]	12 y	All-cause mortality: 256/5322	Sleep duration and all-cause mortality in men: <7 h: aRR 1.93 (1.12–3.35), 7.0 to 8.9 h: aRR 1.00, 9.0 to 9.9 h: aRR 1.15 (0.74–1.77), ≥10.0 h: aRR 1.77 (0.88–3.54). Sleep duration and all-cause mortality in women: <7 h: aRR 0.90 (0.50–1.61), 7.0 to 8.9 h: aRR 1.00, 9.0 to 9.9 h: aRR 1.07 (0.58–1.95), ≥10.0 h: aRR 0.40 (0.06–2.92). Poor sleep quality (waking up feeling bad) on all-cause mortality (Male): aRR 1.13 (0.60–2.12). Poor sleep quality (waking up feeling bad) on all-cause mortality (Female): aRR 2.03 (1.10–3.74).
Kripke, 2002[53]	Up for 6 y	All-cause mortality: 77 640/1 116 936	Sleep duration and all-cause mortality in men: 3 h: aHR 1.19 (0.96–1.47), 4 h: aHR 1.17 (1.06–1.28), 5 h: aHR 1.11 (1.05–1.18), 6 h: aHR 1.08 (1.04–1.11), 7 h: aHR 1.00 (ref), 8 h: aHR 1.12 (1.09–1.15), 9 h: aHR 1.34 (1.28–1.40), ≥10 h: 1.08 (1.01–1.16). Sleep duration and all-cause mortality in women: 3 h: aHR 1.33 (1.08–1.64), 4 h: aHR 1.11 (1.01–1.22), 5 h: aHR 1.07 (1.01–1.13), 6 h: 1.07 (1.03–1.11), 7 h: aHR 1.00 (ref), 8 h: aHR 1.13 (1.09–1.16), 9 h: 1.23 (1.17–1.28), ≥10 aHR 1.41 (1.34–1.50).
Lan, 2007[54]	8 y	All-cause mortality: 1338/3079. CVD mortality: 379/3079	Sleep duration and all-cause mortality in men: <7 h: aHR 0.98 (0.76–1.25), 7 h: aHR 1.00, 8 h: aHR 1.09 (0.89–1.33), 9 h: aHR 1.14 (0.91–1.42), ≥10 h: aHR 1.51 (1.19–1.92). Sleep duration and all-cause mortality in women: <7 h: aHR 1.14 (0.77–1.67), 7 h: aHR 1.00, 8 h: aHR 1.36 (1.01–1.84), 9 h: aHR 1.86 (1.36–2.53), ≥10 h: aHR 2.06 (1.50–2.83). Sleep duration and CVD mortality in men: <7 h: aHR 0.91 (0.53–1.57), 7 h: aHR 1.00, 8 h: aHR 1.40 (0.93–2.10) 9 h: aHR 1.26 (0.80–1.98), ≥10 h: aHR 1.81 (1.13–2.89). Sleep duration and CVD mortality in women: <7 h: aHR 1.07 (0.54–2.15), 7 h: aHR 1.00, 8 h: aHR 1.77 (1.05–2.98), 9 h: aHR 1.75 (1.00–3.07), ≥10 h: aHR 1.85 (1.04–3.27).
Lee, 2014[55]	61.7 months	All-cause mortality: 297/3427	Night time sleep duration ≥10 h and mortality in men: aHR 1.75 (1.09–2.81). Night time sleep duration ≥10 h and mortality in women: aHR 2.88 (1.01–8.18).
Lee, 2017[56]	4.7 y.	All-cause mortality: 72/937.	Sleep duration and all-cause mortality: <6 h: aHR 1.21 (0.67–2.17), 6 to 7 h: aHR 1.00, ≥8 h: aHR 2.11 (1.19–3.76).

Table 2. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
Leng, 2015[9]	9.5 y	Stroke 346/9692	Sleep duration and stroke: <6 h: aHR 1.18 (0.91–1.53), 6 to 8 h: aHR 1.00, >8 h: aHR 1.46 (1.08–1.98). Sleep duration and stroke in men: <6 h: aHR 1.08 (0.75–1.57), 6 to 8 h: aHR 1.00, >8 h: aHR: 1.21 (0.80–1.82). Sleep duration and stroke in women: <6 h: aHR 1.25 (10.86–1.83), 6 to 8 h: aHR 1.00, >8 h: aHR: 1.80 (1.13–2.85).
Li, 2013[57]	7 y	All-cause mortality: 312/ 12 489	Sleep duration and all-cause mortality in men: <5 h: aHR 1.44 (0.65–3.19), 6 h: aHR 0.86 (0.50–1.48), 7 h: aHR1.00, 8 h: aHR 1.05 (0.72–1.53), >9 h: aHR 1.70 (1.07–2.70). Sleep duration and all-cause mortality in women: <5 h: aHR 1.01 (0.42–2.39), 6 h: aHR 1.31 (0.78–2.21), 7 h: aHR 1.00, 8 h: aHR 1.01 (0.63–1.60), >9 h: aHR 1.85 (1.09–3.13). Sleep duration and CVD mortality in men: <5 h: aHR 1.57 (0.35–7.15), 6 h: aHR 0.60 (0.17–2.15), 7 h: aHR 1.00, 8 h: aHR 1.04 (0.49–2.21), >9 h: aHR 2.73 (1.22–6.11). Sleep duration and CVD mortality in women: <5 h: aHR 0.80 (0.18–3.47), 6 h: aHR 0.91 (0.38–2.23), 7 h: aHR 1.00, 8 h: aHR 1.13 (0.57–2.23), >9 h: aHR 1.72 (0.76–3.89).
Liu, 2014[58]	Over 20 y	CHD: 491/3381	Sleep duration and CHD: ≤6 h: aHR 1.29 (1.03–1.61), 7 to 8 h: aHR 1.00, ≥9 h: aHR 1.13 (0.81–1.58).

aHR indicates adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; CHD, coronary heart disease; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; PSQI, Pittsburgh Sleep Quality Index.

among 73 702 participants from 10 studies, and the pooled results suggest that poor subjective quality of sleep was not associated with significant increase in mortality (risk ratio, 1.03; 95% confidence interval, 0.93–1.14). Poor sleep quality was associated with a significant and moderate increase in coronary heart disease (risk ratio, 1.44 95% confidence interval, 1.09–1.90) but not for any other outcomes. The funnel plot for sleep quality did not suggest publication bias.

Sensitivity Analysis Excluding Studies That Did Not Exclude Baseline CVD, Adjust for Cardiac Risk Factors, and Adjusted for Snoring or Obstructive Sleep Apnea

Sensitivity analysis was performed on the meta-analysis data (Data S18). After exclusion of studies that included participants with baseline CVD, there was a significant increase in all-cause mortality with longer and shorter self-reported hours of sleep (small for 6 hours, modest for 5 and 9 hours, and moderate for 4 and 10 hours) and moderate increase in CVD mortality and stroke mortality with longer hours of sleep. Similar observations were found for studies that adjusted for CVR factors. For the analysis of CHD and stroke, there were significant and moderate increases in events when baseline CVD was excluded with 5-hour duration of sleep. For the adjustments for obstructive sleep apnea analysis, some of the

results were no longer statistically significant because there were fewer studies.

Discussion

In this meta-analysis of 60 studies representing over 3 million participants, we observed that divergence from the recommended 7 to 8 hours of sleep was significantly associated with a moderate increase in mortality and incident CVD. We observed a J-shaped relationship between sleep duration and mortality, and incident adverse cardiovascular events were observed. When spline analysis was applied to evaluate the incremental association of sleep duration and adverse events, our results suggest that longer than the recommended duration of 7 to 8 hours of sleep may be associated with a moderate degree of harm, compared with those who slept for durations shorter than that recommended.

Our study provides evidence that may contribute to important clinical and public health messages. First, we observed through spline analysis a more-precise estimation of the risk gradient of CVD and mortality on the greater side of the recommended 7 to 8 hours of sleep compared to existing studies. Second, deviations in sleep duration and quality may be a nonspecific marker for increased CVR that might warrant determination of CVR. In particular, clinicians may need to be aware that the risk gradient appears to be

Table 3. Study Cohort, Follow-up and Results for Studies With Authors Magee to Zuubier

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
Magee, 2011[59]	Unclear	Stroke 6541/218 155. Heart disease 25 669/218 155	Sleep duration and stroke: <6 h: aOR 1.54 (1.36–1.75), 6 h: aOR 1.25 (1.14–1.38), 7 h: aOR 1.00, 8 h: aOR 1.08 (1.01–1.17), ≥9 h: 1.50 (1.38–1.62). Sleep duration and heart disease: <6 h: aOR 1.23 (1.15–1.33), 6 h: aOR 1.11 (1.06–1.17), 7 h: aOR 1.00, 8 h: aOR 1.01 (0.97–1.05), ≥9 h: aOR 1.14 (1.09–1.19).
Magee, 2013[60]	2.8 y	All-cause mortality 8782/227 815	Sleep duration and all-cause mortality: <6 h: aHR 1.13 (1.01–1.25), 6 h: aHR 0.99 (0.91–1.06), 7 h: aHR 1.00, 8 h: aHR 1.02 (0.96–1.08), 9 h: aHR 1.04 (0.96–1.12), >10 h: aHR 1.26 (1.16–1.36).
Mallon, 2002[61]	12 y	All-cause mortality 266/2663. Coronary artery disease mortality: 91/2663.	Sleep duration and all-cause mortality in men: <6 h: aRR 1.1 (0.6–7.0), 7 to 8 h: aRR 1.00, >8 h: aRR 2.0 (1.2–3.2). Sleep duration and all-cause mortality in women: <6 h: aRR 1.0 (0.6–1.8), 7 to 8 h: aRR 1.00, >8 h: aRR 1.3 (0.6–2.6). Sleep duration and coronary artery disease mortality in men: <6 h: aRR 0.7 (0.3–1.7), 7 to 8 h: aRR 1.00, >8 h: aRR 2.2 (1.0–4.4). Sleep duration and coronary artery disease mortality in women: <6 h: aRR 1.2 (0.4–4.2), 7 to 8 h: aRR 1.00, >8 h: aRR 0.7 (0.1–5.2). Poor sleep quality (difficulty maintaining sleep) and all-cause mortality in men: aRR 1.4 (1.1–1.9). Poor sleep quality (difficulty maintaining sleep) and coronary artery disease mortality in men: aRR 1.2 (0.7–1.9). Poor sleep quality (difficulty maintaining sleep) and all-cause mortality in women: aRR 1.1 (0.7–1.7). Poor sleep quality (difficulty maintaining sleep) and coronary artery disease mortality in women: aRR 1.1 (0.5–2.9).
Martin, 2011[62]	1 y	All-cause mortality: 57/245	Sleep quality (high PQSI 7-day score) and all-cause mortality: aHR 1.12 (1.04–1.21).
Meisinger, 2007[63]	Unclear	Acute coronary event: 295/6896	Sleep duration and acute coronary event in men: ≤5 h: aHR 1.13 (0.66–1.92), 6 h: aHR 1.05 (0.71–1.55), 7 h: aHR 1.22 (0.92–1.61), 8 h: aHR 1.00 (reference), ≥9 h: aHR 1.07 (0.75–1.53). Sleep duration and acute coronary event in women: ≤5 h: aHR 2.98 (1.48–6.03), 6 h: aHR 1.05 (0.49–2.27), 7 h: aHR 1.34 (0.75–2.40), 8 h: aHR 1.00 (reference), ≥9 h: aHR 1.40 (0.74–2.64). Poor sleep quality (difficulty maintaining sleep) and acute coronary events in men: aHR 1.12 (0.84–1.48). Poor sleep qualtiy (difficulty maintaining sleep) and acute coronary events in women: aHR 1.53 (0.99–2.37).
Mesas, 2010[64]	6.8 y	All-cause mortality: 897/3820	Sleep duration and all-cause mortality: <5 h: aOR 1.42 (1.04–1.96), 6 h: aOR 1.23 (0.90–1.69), 7 h: aOR 1.00, 8 h: aOR 1.34 (1.02–1.76), 9 h: aOR 1.48 (1.12–1.96), 10 h: aOR 1.73 (1.30–2.29), >11 h: aOR 1.66 (1.23–2.24).
Pan, 2014[65]	Up to 8 y	Stroke mortality: 1381/63 257	Sleep duration and stroke deaths: <5 h: aHR 1.25 (1.05–1.50), 6 h: aHR 1.01 (0.87–1.18), 7 h: aHR 1.00, 8 h: aHR 1.09 (0.95–1.26), >9 h: aHR 1.54 (1.28–1.85). Sleep duration and ischaemic or unspecified stroke deaths: <5 h: aHR 1.37 (1.12–1.68), 6 h: aHR 1.04 (0.87–1.24), 7 h: aHR 1.00, 8 h: aHR 1.14 (0.96–1.34), >9 h: aHR 1.68 (1.36–2.06). Sleep duration and hemorrhagic stroke death: <5 h: aHR 0.92 (0.62–1.36), 6 h: aHR 0.91 (0.67–1.24), 7 h: aHR 1.00, 8 h: aHR 0.97 (0.73–1.29), >9 h: aHR 1.14 (0.76–1.72).
Patel 2004[66]	14 y	All-cause mortality: 5409/82 969. CVD mortality: 1084/82 969	Sleep duration and all-cause mortality: <5 h: aRR 1.08 (0.96–1.22), 6 h: aRR 0.99 (0.92–1.06), 7 h: aRR 1.00, 8 h: aRR 1.11 (1.03–1.19), >9 h: aRR 1.40 (1.25–1.55). Sleep duration and cardiovascular mortality: <5 h: aRR 1.04 (0.79–1.35), 6 h: aRR

Table 3. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
			1.06 (0.91–1.25), 7 h: aRR 1.00, 8 h: aRR 1.12 (0.95–1.31), >9 h: aRR 1.56 (1.25–1.96).
Pollak, 1990[67]	3.5 y	All-cause mortality: 309/1855	Incremental increase in h of sleep and all-cause mortality in men: HR 0.96 (0.66–1.39). Incremental increase in h of sleep and all-cause mortality in women: HR 1.11 (0.80–1.54).
Qiu, 2011[68]	3 y	All-cause mortality: 5199/12 671	Sleep duration and all-cause mortality: <5 h: aHR 0.97 (0.88–1.08), 6 h: aHR 1.05 (0.95–1.16), 7 h: aHR 1.00 (0.90–1.11), 9 h: aHR 0.95 (0.83–1.07), >10 h: aHR 1.09 (1.00–1.18). Sleep duration and all-cause mortality and men: <5 h: aHR 1.17 (1.01–1.38), 6 h: aHR 1.06 (0.91–1.25), 7 h: aHR 1.17 (0.99–1.37), 9 h: aHR 1.08 (0.89–1.31), >10 h: aHR 1.22 (1.08–1.38). Sleep duration and all-cause mortality and women: <5 h: aHR 0.85 (0.75–0.98), 6 h: aHR 1.02 (0.90–1.15), 7 h: aHR 0.88 (0.76–1.01), 9 h: aHR 0.86 (0.72–1.02), >10 h: aHR 1.00 (0.90–1.11). Sleep quality (poor vs good) and all-cause mortality: aHR 0.91 (0.83–1.00). Sleep quality (poor vs good) and all-cause mortality in men: aHR 1.11 (0.95–1.30). Sleep quality (poor vs good) and all-cause mortality in women: aHR 0.81 (0.71–0.91).
Qureshi, 1997[69]	10 y	Stroke 322/7844. CHD: 474/7844	Sleep duration and risk for stroke: <6 h: aOR 1.0 (0.7–1.5), 6 to 8 h: aOR 1.0, >8 h: aOR 1.5 (1.1–2.0). Sleep duration and CHD: <6 h: aOR 1.3 (1.0–1.8), 6 to 8 h: aOR 1.0, >8 h: aOR 1.1 (0.8–1.5).
Rhee, 2012[70]	Up to 15 y	All-cause mortality: 990/14 533	Sleep duration and all-cause mortality: ≤5 h: aHR 1.53 (1.11–2.12), 6 to 7 h: aHR 1.04 (0.88–1.22), ≥8 h: aHR 1.00.
Rod, 2014[71]	22 y.	All-cause mortality: 804/9098. CVD mortality: 221/9098	Sleep duration and all-cause mortality in men: ≤5 h: aHR 1.11 (0.73–1.68), 6 h: aHR 1.23 (1.01–1.50), 7 h: aHR 1.00, 8 h: aHR 1.18 (0.92–1.50), >9 h: aHR 1.44 (0.59–3.50). Sleep duration and all-cause mortality in women: ≤5 h: aHR 1.21 (0.76–1.91), 6 h: aHR 1.14 (0.86–1.52), 7 h: aHR 1.00, 8 h: aHR 0.91 (0.63–1.30), >9 h: aHR 1.48 (0.60–3.65). Sleep duration and CVD mortality: ≤6 h: aHR 1.18 (0.87–1.63), 7 to 8 h: aHR 1.00, >9 h: aHR 1.61 (0.40–6.59). Poor sleep quality (disturbed sleep) and all-cause mortality in men: aHR 0.85 (0.62–1.16). Poor sleep quality (disturbed sleep) and all-cause mortality in women: aHR 1.03 (0.70–1.52). Poor sleep quality (disturbed sleep) and CVD mortality: aHR 1.04 (0.72–1.49).
Ruigomez, 1995[72]	55.7 months	All-cause mortality 224/1219	Sleep duration and all-cause mortality: <7 h: aRR 0.83 (0.56–1.23), 7 to 9 h: aRR 1.00, >9 h: aRR 1.37 (0.89–2.11). Sleep duration and all-cause mortality in men: <7 h: aRR 1.06 (0.61–1.83), 7 to 9 h: aRR 1.00, >9 h: 1.30 (0.71–2.38). Sleep duration and all-cause mortality in women: <7 h: aRR 0.66 (0.37–1.16), 7 to 9 h: aRR 1.00, >9 h: 1.46 (0.79–2.70).
Ruiter Petrov, 2014[73]	2 y	Stroke (at least 1 symptom): 224/5666	Sleep duration on stroke symptoms: <6 h: aHR 1.47 (0.89–2.45), 6 h: aHR 1.22 (0.82–1.81), 7 h: aHR 1.00, 8 h: aHR 1.30 (0.92–1.83), ≥9 h: aHR 1.42 (0.82–2.45).
Sands-Lincoln, 2013[74]	10.3 y	CVD events: 7257/86 329	Sleep duration and CVD: ≤5 h: aHR 1.06 (0.96–1.16), 6 h: aHR 1.00 (0.95–1.06), 7 to 8 h: aHR 1.00, 9 h: aHR 0.95 (0.83–1.08), ≥10 h: aHR 1.23 (0.89–1.70).

Continued

SYSTEMATIC REVIEW AND META-ANALYSIS

Table 3. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
			Sleep duration and CHD: ≤5 h: aHR 1.08 (0.96–1.20), 6 h: aHR 1.00 (0.94–1.07), 7 to 8 h: aHR 1.00, 9 h: aHR 0.93 (0.80–1.08), ≥10 h: aHR 1.33 (0.94–1.88).
Shankar, 2008[75]	13 y	CHD mortality: 1416/58 044	Sleep duration and CHD mortality: ≤5 h: aRR 1.57 (1.32–1.88), 6 h: aRR 1.13 (0.98–1.31), 7 h: aRR 1.00, 8 h: aRR 1.12 (0.97–1.29), ≥9 h: aRR 1.79 (1.48–2.17).
Song, 2016[76]	7.9 y	Stroke: 3135/95 023	Sleep duration and stroke: <6 h: aHR 0.92 (0.81–1.05), 6 to 8 h: aHR 1.00, >8 h: aHR 1.29 (1.01–1.64). Sleep duration and stroke in men: <6 h: aHR 0.90 (0.78–1.03), 6 to 8 h: aHR 1.00, >8 h: aHR 1.24 (0.96–1.60). Sleep duration and stroke in women: <6 h: aHR 1.09 (0.75–1.60), 6 to 8 h: aHR 1.00, >8 h: aHR 1.91 (0.98–3.74).
Stone, 2009[77]	Up to 4.1 y	All-cause mortality: 793/6107	Sleep duration and all-cause mortality in men: <5 h: RH 1.2 (0.8–1.8), 7 to 8 h: RH 1.00. Sleep duration and all-cause mortality in women: <5 h: RH 1.8 (1.3–2.5), 7 to 8 h: RH 1.00.
Strand, 2016[78]	9.7 y	CHD mortality: 711/392 164	Sleep duration and CHD mortality: <4 h: aHR 1.36 (0.88–2.10), 4 to 6 h: aHR 1.03 (0.85–1.24), 6 to 8 h: aHR 1.00, <8 h: aHR 1.28 (1.05–1.56). Sleep duration and CHD mortality in men: <4 h: aHR 1.03 (0.53–2.00), 4 to 6 h: aHR 1.06 (0.85–1.32), 6 to 8 h: aHR 1.00, <8 h: aHR 1.11 (0.88–1.41). Sleep duration and CHD mortality in women: <4 h: aHR 1.84 (1.03–3.29), 4 to 6 h: aHR 0.99 (0.72–1.37), 6 to 8 h: aHR 1.00, <8 h: aHR 1.81 (1.28–2.56). Difficulty getting to sleep and CHD mortality: aHR 1.01 (0.80–1.26).
Suzuki, 2009[11]	6 y	All-cause mortality: 1004/14 001. CVD mortality: 310/14 001	Sleep duration and all-cause mortality: ≤5 h: aHR 0.92 (0.66–1.28), 6 h: aHR 1.06 (0.80–1.39), 7 h: aHR 1.00, 8 h: aHR1.36 (1.09–1.70), 9 h: aHR 1.41 (1.05–1.90), ≥10 h: aHR 1.96 (1.49–2.57). Sleep duration and all-cause mortality in men: ≤5 h: aHR 1.08 (0.72–1.61), 6 h: aHR 1.05 (0.75–1.47), 7 h: aHR 1.00, 8 h: aHR 1.36 (1.04–1.78), 9 h: aHR 1.52 (1.08–2.15), ≥10 h: aHR 1.86 (1.34–2.56). Sleep duration and all-cause mortality in women: ≤5 h: aHR 0.71 (0.39–1.29), 6 h: aHR 1.08 (0.67–1.74), 7 h: aHR 1.00, 8 h: aHR 1.39 (0.92–2.09), 9 h: aHR 1.15 (0.64–2.09), ≥10 h: aHR 2.27 (1.37–3.76). Sleep duration and CVD mortality: ≤5 h: aHR 1.10 (0.62–1.93), 6 h: aHR 0.85 (0.50–1.45), 7 h: aHR 1.00, 8 h: aHR 1.52 (1.01–2.29). 9 h: aHR 1.55 (0.91–2.63), ≥10 h: aHR 1.95 (1.18–3.21). Sleep duration and CVD mortality in men: ≤5 h: aHR 0.97 (0.46–2.05), 6 h: aHR 0.75 (0.38–1.48), 7 h: aHR 1.00, 8 h: aHR 1.05 (0.63–1.75). 9 h: aHR 1.26 (0.65–2.45), ≥10 h: aHR 1.71 (0.94–3.11). Sleep duration and CVD mortality in women: ≤5 h: aHR 1.48 (0.59–3.67), 6 h: aHR 1.08 (0.44–2.66), 7 h: aHR 1.00, 8 h: aHR 2.83 (1.39–5.76). 9 h: aHR 2.32 (0.93–5.77), ≥10 h: aHR 2.31 (0.91–5.82). Poor sleep quality (frequent awakening) and all-cause mortality: aHR 0.99 (0.83–1.18). Poor sleep quality (frequent awakening) and all-cause mortality in men: aHR 1.00 (0.81–1.24). Poor sleep quality (frequent awakening) and all-cause mortality in women: aHR 0.96 (0.69–1.31). Poor sleep quality (frequent awakening) and CVD mortality: aHR 0.91 (0.66–1.26).

Continued

Table 3. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
			Poor sleep quality (frequent awakening) and CVD mortality in men: aHR 0.97 (0.64–1.48). Poor sleep quality (frequent awakening) and CVD mortality in women: aHR 0.81 (0.49–1.35).
Tamakoshi, 2004[79]	9.9 y	All-cause mortality: 11 071/ 104 010	Sleep duration and all-cause mortality in men: ≤4 h: aRR 0.88 (0.44–1.78), 5 h: aRR 1.07 (0.83–1.38), 6 h: aRR 1.11 (0.95–1.28), 7 h: aRR 1.00, 8 h: aRR 1.19 (1.07–1.32), 9 h: aRR 1.27 (1.08–1.48), ≥10 h: aRR 1.75 (1.46–2.09). Sleep duration and all-cause mortality in women: ≤4 h: aRR 1.83 (1.20–2.81), 5 h: aRR 1.18 (0.90–1.53), 6 h: aRR 1.17 (0.99–1.39), 7 h: aRR 1.00, 8 h: aRR 1.35 (1.17–1.56), 9 h: aRR 1.57 (1.26–1.96), ≥10 h: aRR 2.12 (1.67–2.68).
Tsubono 1993[80]	4 y	All-cause mortality: 207/4318	Sleep duration and all-cause mortality: ≤6 h: aRR 1.26 (0.81–1.97), 7 to 8 h: aRR 1.00, ≥9 h: aRR 1.58 (1.16–2.15).
Tu, 2012[81]	4 y	Unclear	Sleep duration and CHD in women: ≤4 h: aOR 1.46 (1.26–1.70), 5 h: aOR 1.28 (1.15–1.43), 6 h: aOR 1.11 (1.02–1.21), 7 h: aOR 1.00, 8 h: aOR 0.95 (0.86–1.03), 9 h: aOR 1.07 (0.92–1.25), ≥10 h: aOR 1.41 (1.19–1.67). Sleep duration and stroke in women: ≤4 h: aOR 1.75 (1.49–2.07), 5 h: aOR 1.37 (1.21–1.55), 6 h: aOR 1.16 (1.05–1.29), 7 h: aOR 1.00, 8 h: aOR 1.05 (0.94–1.17), 9 h: aOR 1.07 (0.89–1.29), ≥10 h: aOR 1.88 (1.56–2.27).
Twig, 2016[82]	6.4 y	Coronary artery disease 92/26 023	Poor sleep quality (highest vs lowest quartile) and coronary artery disease: aHR 2.38 (1.37–4.11).
Von Ruesten, 2012[83]	8 y	Stroke 169/23 620. MI 197/23 620	Sleep duration and MI: <6 h: aHR 1.44 (0.85–2.43) 6 h: aHR 0.80 (0.53–1.20), 7 h: aHR 1.00, 8 h: aHR 0.82 (0.56–1.19), ≥9 h: aHR 0.89 (0.54–1.49). Sleep duration and strokes: <6 h: aHR 2.06 (1.18–3.59), 6 h: aHR 1.13 (0.72–1.77), 7 h: aHR 1.00, 8 h: aHR 1.16 (0.77–1.73), ≥9 h: aHR 1.65 (1.00–2.73).
Wang, 2016[84]	3.98 y	MI: 423/101 510. All-cause mortality: 1793/101 510	Sleep duration and MI: ≤5 h: aHR 0.89 (0.60–1.30), 6 h: aHR 0.84 (0.61–1.16), 7 h: aHR 1.00, 8 h: aHR 0.86 (0.66–1.13), ≥9 h: aHR 1.12 (0.58–2.16). Sleep duration and all-cause mortality: ≤5 h: aHR 1.23 (1.03–1.80), 6 h: aHR 1.95 (0.81–1.12), 7 h: aHR 1.00, 8 h: aHR 1.06 (0.92–1.20), ≥9 h: aHR 1.65 (1.22–2.22).
Werle, 2011[85]	9 y	All-cause mortality: 141/187. CV mortality: 56/187	Incremental increase in h of sleep and all-cause mortality: aHR 0.95 (0.89–1.02). Incremental increase in h of sleep and cardiovascular mortality: aHR 0.83 (0.73–0.95).
Westerlund 2013[8]	13 y	CVD mortality: 857/41 192. Stroke: 1685/41 192. MI: 1908/41 192	Sleep duration and CVD mortality: ≤5 h: aHR 1.11 (0.76–1.64), 6 h: aHR 1.17 (0.88–1.55), 7 h: aHR 1.00, ≥8 h: aHR 1.12 (0.85–1.47). Sleep duration and CVD: ≤5 h: aHR 1.05 (0.88–1.26), 6 h: aHR 0.97 (0.86–1.09), 7 h: aHR 1.00, ≥8 h: aHR 1.00 (0.89–1.13). Sleep duration and stroke: ≤5 h: aHR 1.05 (0.80–1.37), 6 h: aHR 0.95 (0.79–1.14), 7 h: aHR 1.00, ≥8 h: aHR 0.87 (0.72–1.04). Sleep duration and MI: ≤5 h: aHR 1.19 (0.92–1.55), 6 h: aHR 1.05 (0.88–1.25), 7 h: aHR 1.00, ≥8 h: aHR 1.19 (1.00–1.41). Poor sleep quality (difficulty maintaining sleep) and CVD mortality: mostly/always aHR 0.97 (0.77–1.20).
Wingard, 1983[86]	9 y	All-cause mortality: 369/6928	Sleep duration and all-cause mortality in men: ≤6 h: 52/352, 7 to 8 h: 142/1735, ≥9 h: 15/132. Sleep duration and all-cause mortality in women: ≤6 h: 35/386, 7 to 8 h: 107/1902, ≥9 h: 17/200.

Continued

Table 3. Continued

Study ID	Follow-up Duration	Outcomes and Crude Rate of Outcomes	Results
Xiao, 2014[87]	14 y	All-cause mortality: 44 100/ 239 896. CVD mortality: 11 635/ 239 896	Sleep duration and all-cause mortality: <5 h: aRR 1.16 (1.11–1.26), 5 to 6 h: aRR 1.04 (1.02–1.06), 7 to 8 h: aRR 1.00, ≥9 h: aRR 1.11 (1.06–1.19). Sleep duration and CVD mortality: <5 h: aRR 1.25 (1.13–1.38), 5 to 6 h: aRR 1.06 (1.02–1.10), 7 to 8 h: aRR 1.00, ≥9 h: aRR 1.07 (0.97–1.17).
Yeo, 2013[88]	9 y	All-cause mortality: 1580/13 164. CVD mortality: 363/13 164	Sleep duration and all-cause mortality: ≤5 h: aHR 1.21 (1.03–1.41), 6 h: aHR 1.10 (0.95–1.27), 7 h: aHR 1.00, 8 h: aHR 1.03 (0.89–1.19), 9 h: aHR 1.36 (1.11–1.67), ≥10 h: aHR 1.36 (1.07–1.72). Sleep duration on CVD mortality: ≤5 h: aHR 1.40 (1.02–1.93), 6 h: aHR 1.25 (0.92–1.69), 7 h: aHR 1.00, 8 h: aHR 1.04 (0.76–1.42), 9 h: aHR 1.26 (0.81–1.96), ≥10 h: aHR 1.37 (0.82–2.29).
Zawisza, 2015[89]	10.8 y	All-cause mortality 2093/2449.	Incremental increase in h of sleep and all-cause mortality: aHR 1.04 (1.003–1.075).
Zuubier, 2015[90]	7.3 y	All-cause mortality: 154/1734.	Sleep duration and all-cause mortality: <6 h: aHR 1.12 (0.77–1.65), 6 to 7.5 h: aHR 1.00, ≥7.5 h: 1.18 (0.70–1.98).

aHR indicates adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PSQI, Pittsburgh Sleep Quality Index; RH, relative hazard.

steeper for long sleep duration compared with short duration, so individuals with excessive sleeping patterns may warrant further clinical assessment. Third, we provide updated evidence that supports the J-shaped relationship where longer sleep is associated with significantly higher mortality and CVD and further the knowledge by highlighting that excess sleep is possibly associated with a greater likelihood of harm than less sleep with spline analysis. In addition, we found that sleep *quality* emerged as an important risk factor for CHD, so clinicians should consider nonrestorative sleep (or "waking up unrefreshed") during patient assessment. Finally, our study highlights current evidence that sleep may be an important factor for individuals who wish to adopt a healthier lifestyle—our findings support public health campaigns promoting good sleep practices and behaviors and the importance of the clinician discussing sleep in primary care consultations.

St-Onge et al recently published a scientific statement on behalf of the American Heart Association.[91] Their review surveyed the literature and found that sleep duration, mostly short sleep, and sleep disorders are related to adverse cardiometabolic risk, such as obesity, hypertension, type 2 diabetes mellitus, and CVD. Unlike their review, we focused on mortality and CVD and quantitatively pooled the impact of individual hours of sleep duration and these events. We were able to show, with metaregression, that the association of short sleep duration and adverse events was lost, but the association of long sleep duration and adverse events still persists. It is possible that the adverse outcomes associated with short sleep duration may be manifested through the risk factors described by St-Onge's review. Our findings support

the clinical recommendations of the American Heart Association, in which sleep behaviors should be addressed to promote cardiac health, and public health campaigns addressing sleep behavior should include explicit guidelines for adequate sleep.

Our meta-analysis results show a possible increase in mortality with both long and short duration of sleep relative to 7 or 8 hours, but after spline analysis, there is no difference in mortality for patients with shorter sleep duration. The spline regression is the gold standard for metaregression for nonlinear relationships to model exposures and outcomes. We further used this method to perform analysis on the subgroups studies that had more-complete reporting that include crude event rates.

The exact mechanisms that underlie the association between sleep and CVD and mortality are not fully understood. Short sleep duration has been shown to increase levels of leptin and ghrelin,[92,93] which leads to increased appetite, caloric intake, reduce energy expenditure, and facilitates the development of obesity[80] and impaired glycemic control.[94] Cortisol also increases with reduced sleep, and altered growth hormone metabolism may increase CVR.[95] Low-grade inflammation occurs with reduced sleep, which may be associated with CVD and cancer. Long sleep duration may be associated with an increased risk of CVD because of an adverse CVR factor profile or prevalent comorbidities that lead to fatigue, such as chronic inflammatory disorders and anemia. Depressive symptoms, low socioeconomic status, unemployment, and low physical activity are also associated with long sleep duration, which may confound the association of long sleep with morbidity and mortality.[20]
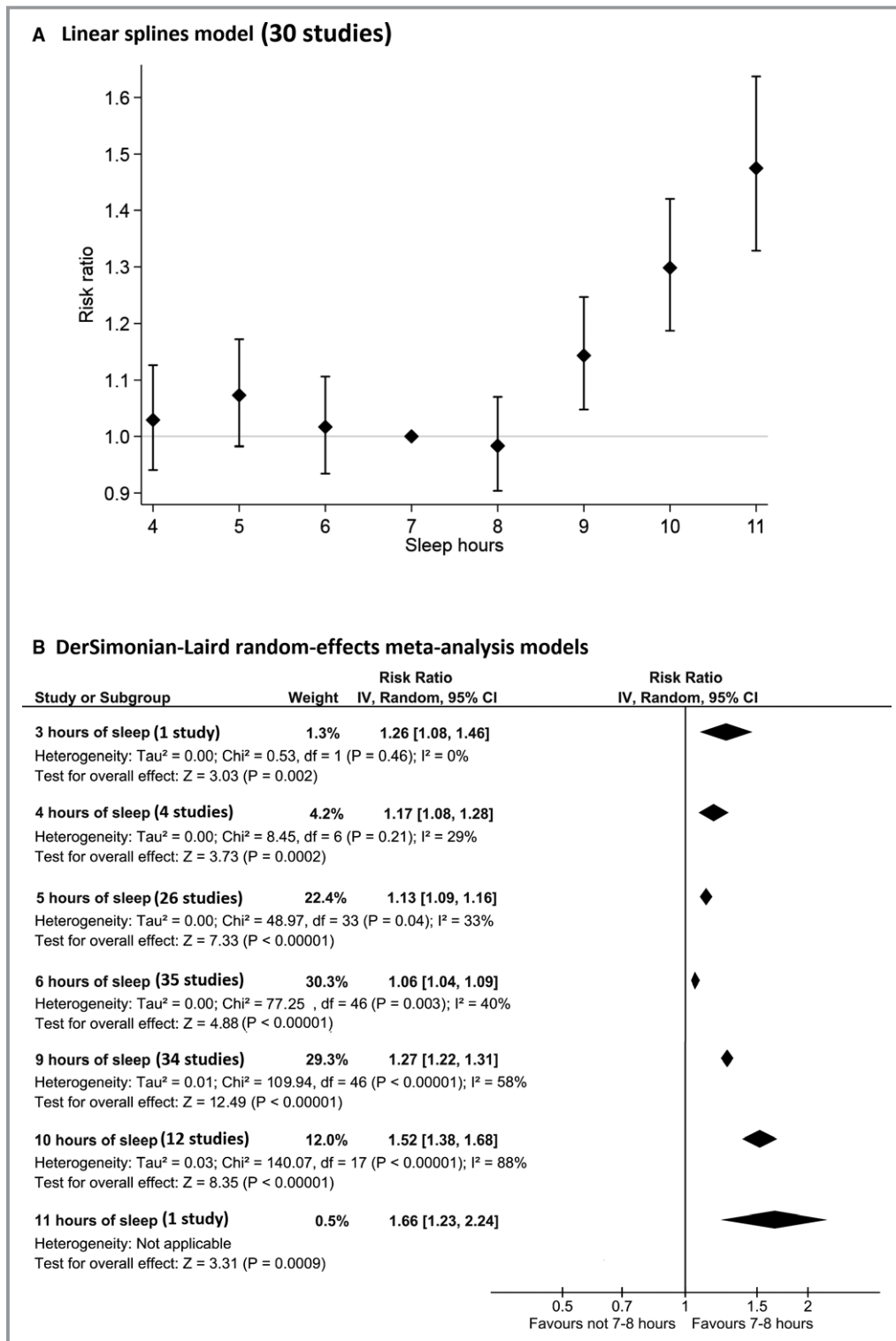
Figure 2. Sleep duration and risk of all-cause mortality with linear and cubic splines. A, Linear splines model (30 studies). B, DerSimonian–Laird random-effects meta-analysis models. CI indicates confidence interval.

An important consideration in the temporal relationship between sleep and adverse outcomes is the potential influence of CVR factors. For example, a Japanese study observed that sleep disturbances were associated with a higher risk of later-onset of type 2 diabetes mellitus.[96] In addition, it is unclear whether abnormal sleep is a marker of
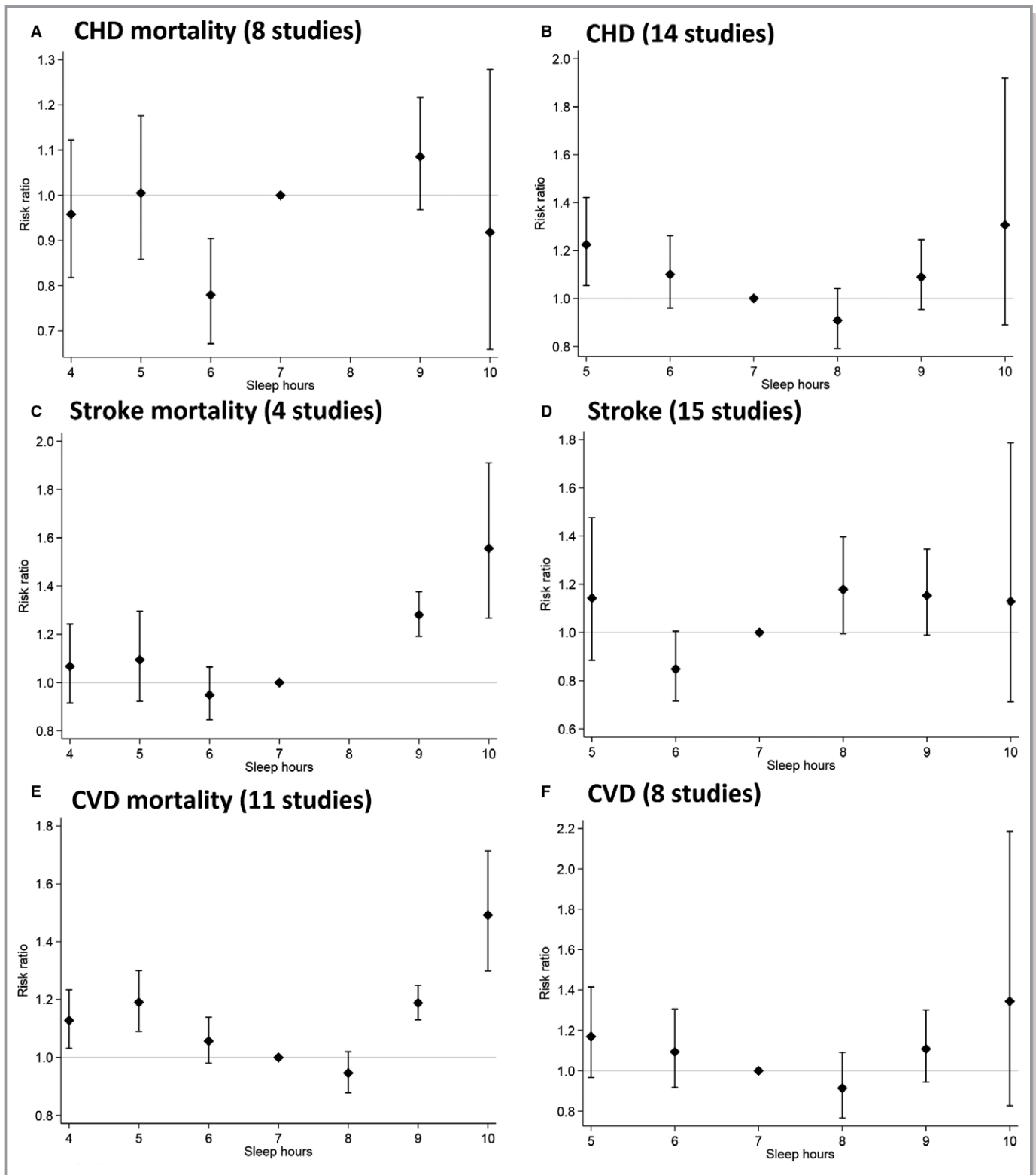
Figure 3. Linear models for adverse cardiovascular events. A, CHD mortality (8 studies). B, CHD (14 studies). C, Stroke mortality (4 studies). D, Stroke (15 studies). E, CVD mortality (11 studies). F, CVD (8 studies). CHD indicates coronary heart disease; CVD, cardiovascular disease.

undiagnosed prevalent CVDs or of early/latent disease that subsequently manifests in adverse cardiovascular outcomes and death. Some studies have attempted to reduce the effect of baseline prevalent CVD by excluding patients with these conditions whereas other studies adjusted for these factors. Despite our sensitivity analysis considering exclusion

and adjustments, there may still be residual confounding given that there may be undiagnosed or latent disease or risk factors because some of these population-based studies do investigate patients at baseline for these variables and rely on self-reporting. The other important consideration is whether the increased incident CVR is causally related to sleep directly or whether abnormal sleep patterns may contribute to adverse health behaviors that increase CVR thereby contributing to the increase in cardiovascular events.

Several studies have evaluated the mismatch between self-reported sleep and more-objective measures. An analysis of 669 participants in the CARDIA (Coronary Artery Risk Development in Young Adults) Sleep Study suggests a moderate correlation between self-reported and objectively measured sleep duration with evidence of systematic errors in the mean and calibration.[97] Another study of 2086 Hispanic Americans suggests a moderate correlation between self-reported sleep and actigraphy results.[98] A smaller study that compared self-reported sleep and actigraphy in 56 participants reported a poor agreement between sleep duration and quality, as assessed by a questionnaire and objectively measured sleep.[99] In addition, a different analysis of 63 patients who were overweight and obese individuals and who underwent actigraphy also reported a weak correlation between usual sleep time and actigraph estimates.[100] With respect to CVR, studies suggest that self-reported sleep duration is different from objectively assess sleep duration.[101,102] Although the exact reasons for discrepancies between subjective and objective measures are not clear, it appears that self-reported sleep is only, at best, moderately correlated with objective measures of sleep and perhaps multiple measures of sleep duration should be recommended for future studies.

In the current analysis, the study by Kripke et al[53] represented more than one third of the entire cohort, and this large study has implications to the interpretation of the results. This cohort was a diverse group of adults who were friends or relatives of American of Cancer Society volunteers who were aged between 30 and 102 years. The mean age in this study was 57 years and 43% of participants were female, which were both slightly lower than the average of 60 years of age and 52% female in all the included studies. In addition, the study took place in the 1980s, which may affect the applicability of its findings to the current population. Collectively, these findings may limit the generalizability of the current study.

Our study has a number of limitations. Although we used adjusted estimates where available, there are likely to be residual or unmeasured confounding and bias. For example, an underlying physical or mental health condition may be the driver behind extreme sleep patterns. A key limitation was that sleep duration was assessed by self-reported questionnaires. It is unclear whether this is truly reflective of actual sleep patterns given that there are studies that clearly show that with respect to CVR, self-reported sleep duration and objectively assessed sleep duration are significantly different.[101,102] Another limitation was the absence of individual patient-level data, so we could not make assumptions about the CVR factor profiles of patients based on their sleep duration or quality. Some studies did report baseline risk factors for patients, but every study reported different risk factors, and the combinations of the risk-factor profiles reported were too heterogeneous to make general assumptions. Although we demonstrated an association between sleep quality, duration, and outcomes, these relationships cannot infer causality and it is unclear whether sleep duration or quality is a marker of prevalent CVR, an adverse CVR factor profile, or adverse health behaviors that contribute to the adverse outcomes reported.

Conclusion

In conclusion, we found a significant association between deviations in sleep duration and both mortality and adverse cardiovascular outcomes. National guidelines should consider advocating this as the recommended sleep duration. We also found evidence that sleep duration above the recommended level of 7 to 8 hours was associated with a moderate degree of harm compared with sleeping less than the suggested duration. Furthermore, the greater the divergence from the recommended durations of sleep, the greater the association for cardiovascular harm and mortality. Our study suggests that abnormal sleep is a marker of elevated CVR—and greater consideration should be given in exploring during patient consultations in both the duration and quality of sleep.

Acknowledgments

Disclosures

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