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Sleep duration and mortality: a systematic review and meta-analysis

LISA GALLICCHIO and BINDU KALESAN
The Prevention and Research Center, The Weinberg Center for Women's Health & Medicine, Mercy Medical Center, Baltimore, MD, USA

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SUMMARY Epidemiologic studies have shown that sleep duration is associated with overall mortality. We conducted a systematic review of the associations between sleep duration and all-cause and cause-specific mortality. PubMed was systematically searched up to January, 2008 to identify studies examining the association between sleep duration and mortality (both all-cause and cause-specific) among adults. Data were abstracted serially in a standardized manner by two reviewers and analyzed using random-effects meta-analysis. Twenty-three studies assessing the associations between sleep duration and mortality were identified. All examined sleep duration measured using participant self-report. Among the 16 studies which had similar reference categories and reported sufficient data on short sleep and mortality for meta-analyses, the pooled relative risk (RR) for all-cause mortality for short sleep duration was 1.10 [95% confidence interval (CI): 1.06, 1.15]. For cardiovascular-related and cancer-related mortality, the RRs associated with short sleep were 1.06 (95% CI: 0.94, 1.18) and 0.99 (95% CI: 0.88, 1.13), respectively. Similarly, among the 17 studies reporting data on long sleep duration and mortality, the pooled RRs comparing the long sleepers with medium sleepers were 1.23 (95% CI: 1.17, 1.30) for all-cause mortality, 1.38 (95% CI: 1.13, 1.69) for cardiovascular-related mortality, and 1.21 (95% CI: 1.11, 1.32) for cancer-related mortality. Our findings indicate that both short sleepers and long sleepers are at increased risk of all-cause mortality. Further research using objective measures of sleep duration is needed to fully characterize these associations.

KEYWORDS cancer, cardiovascular, meta-analysis, mortality, sleep duration, systematic review

INTRODUCTION

In some but not all industrialized societies, there is a trend towards fewer hours of sleep each night due, to the most part, to longer work schedules and a greater allotment of time to leisure time activities (Akerstedt and Nilsson, 2003; Ferrie *et al*., 2007). This decrease in the amount of sleep time is troublesome as accumulating evidence suggests that sleep is an important determinant of health. Specifically, studies have shown that 'short sleepers', generally defined as individuals who report sleeping less than 7 h on average per night are at higher risk for a number of adverse health conditions, including coronary heart disease and diabetes, compared with individuals reporting 7 or 8 h of sleep per night (Ayas *et al*., 2003a,b; Van Cauter *et al*., 2007). Further, large prospective cohort studies have shown that 'short sleep' is associated with a higher risk of mortality (Ferrie *et al*., 2007; Hublin *et al*., 2007; Lan *et al*., 2007).

Conversely, the epidemiologic evidence also indicates that 'long sleepers', generally defined as individuals who report sleeping more than 9 h on a typical night are also at increased risk of disease and death compared with 'average sleepers' (Lan *et al*., 2007; Patel *et al*., 2004; Tamakoshi and Ohno, 2004). Less attention has been directed at the health consequences of long sleep although the body of research suggests that long sleep is more strongly associated with mortality than short sleep. Possible explanations for the associations between

Correspondence: Lisa Gallicchio, PhD, Epidemiologist, The Prevention and Research Center, The Weinberg Center for Women's Health and Medicine, Mercy Medical Center, 227 St. Paul Place, 6th Floor, Baltimore, MD 21202, USA. Tel.: 410-951-7956; fax: 410-951-7989; e-mail: Lgallic@mdmercy.com

long sleep and morbidity and mortality have been proposed but there is a general lack of knowledge as to the underlying mechanisms behind these associations (Grandner and Drummond, 2007).

Although several reviews have been published examining the literature pertaining to sleep duration and mortality (Grandner and Drummond, 2007; Institute of Medicine, 2006; Youngstedt and Kripke, 2004), to our knowledge there has been no published systematic review of the literature that has characterized the magnitude of these associations. Therefore the purpose of this report was to systematically review the epidemiologic evidence on the association between sleep duration and the risk of mortality, both qualitatively and quantitatively. For this review, we focused on both the 'short sleepers' and the 'long sleepers' in comparison with those individuals reporting a 'medium' amount of sleep each night.

METHODS

Study search

We searched PubMed for articles on the associations between sleep duration and mortality (all-cause or cause-specific) that were reported in cohort studies. The search strategy was as follows: (('sleep'[MeSH Terms] OR Sleep[Text Word])) OR (('sleep initiation and maintenance disorders'[TIAB] NOT Medline[SB]) OR 'sleep initiation and maintenance disorders'[MeSH Terms] OR Insomnia[Text Word])) AND (('mortality'[Subheading] OR 'mortality'[MeSH Terms] OR Mortality[Text Word]) OR ('death'[MeSH Terms] OR death[Text Word]) OR fatal[All Fields])) NOT (('sudden infant death'[TIAB] NOT Medline[SB]) OR 'sudden infant death'[MeSH Terms] OR sudden infant death syndrome[Text Word]) AND ('humans'[MeSH Terms] AND English[lang] AND 'adult'[MeSH Terms])). The search included all studies published in PubMed up to October 31, 2007 and was limited to humans, adults, and articles written in English. In addition, the study team hand-searched the references in the articles chosen for data abstraction and in the relevant review articles identified in the PubMed search. After the original search, we updated the PubMed search through January 2008.

Study selection and data abstraction

The following exclusion criteria were applied to the abstracts identified in the literature search: (i) no original data (reviews, editorials); (ii) studies not addressing the association between sleep duration and mortality; and (iii) studies not in human adults. The full-text articles of all references selected after applying these criteria were reviewed using the same criteria. If separate references examining the same association in the same study were identified, the report with the most updated data was selected for inclusion, or in the case of duplicate publication, only one publication was included. The eligibility of each abstract or full-text article was assessed independently in a standardized manner by two reviewers.

Data abstraction for selected articles was performed serially by two reviewers using an electronic abstraction database created in Microsoft Excel (Microsoft Corporation, Seattle, WA). Information abstracted included year of publication, country of data collection, study design, and sample characteristics. Disagreements between reviewers were resolved by consensus.

Statistical analysis

Relative risks (RR) and 95% confidence intervals (CI) for all-cause, cardiovascular-related, and cancer-related mortality outcomes were abstracted from each included study. Data on other mortality outcomes such as external causes were also abstracted but were not considered for meta-analyses because either there were too few studies reporting the outcome or because the outcome, in general, was non-specific. When several RR estimates for an outcome were reported in a study, we selected the RR that was adjusted for the most covariates and that was derived using data from the most subjects in the study. Pooled RR estimates were obtained using inverse-variance weights in random-effects models.

Relative risks for the mortality outcomes and short sleep and long sleep time were pooled for studies with similar reference categories. When multiple categories of short sleep and long sleep time were reported for an individual study (e.g., <3, 3 to 5.9, and 6 to 6.9 h, etc.), these categories were pooled for that individual study to comprise a single short sleep group (<7 h for the majority of studies), or similarly, a single long sleep group (≥ 9 h for the majority of studies).

Meta-analyses were conducted for all studies reporting RRs and estimates of variance using a similar reference category among all participants and for males and females separately. As one study, Kripke *et al.* (2002), comprised greater than 20% of the pooled estimate weight in each of the conducted meta-analyses and was limited by being drawn from a 'convenience population' (Allen, 2002), secondary analyses were conducted excluding this study. Further, because other medical conditions are considered to be strong confounders of the association between sleep duration and mortality, meta-analyses were also conducted for only those studies that adjusted for other medical conditions.

Heterogeneity was assessed using the DerSimonian and Laird's Q statistic and the I^2 statistic. Publication bias was examined using funnel plots. In the case where statistical heterogeneity was statistically significant in unstratified analyses, meta-regression was conducted to explore the sources of statistical heterogeneity. Variables included in the analysis were country of study (United States/other), number of deaths ($<1000/\geq 1000$), years of study follow-up (<10 years/≥ 10 years), age of study participants (only 60 years or older included/other), and reference category used (7 to 7.9 h/other). All analyses were conducted using STATA version 9.2 (StataCorp, College Station, TX, USA).

RESULTS

Search results

The PubMed search yielded 1370 references, of which 1345 were excluded after abstract and full-text review (Fig. 1). Among the remaining 25 articles, 5 were excluded because more updated results were presented in a separate publication (Ayas *et al*., 2003b; Belloc, 1973; Breslow and Enstrom, 1980; Wingard and Berkman, 1983; Wingard *et al*., 1982). Two additional articles were identified based on hand-searching of existing reviews on sleep and mortality (Hammond, 1964; Heslop *et al*., 2002), of which one was determined to be a duplicate of a study identified using the PubMed search (Hammond, 1964). In the updated search, two articles published after the original search date were found and included in the review (Ferrie *et al*., 2007; Hublin *et al*., 2007). Therefore, in all 23 articles, detailing results from 23 unique studies were included in this systematic review.

Study characteristics

All of the 23 studies selected for inclusion into the systematic review were prospective studies (Table 1). Eight of the studies were conducted in the United States, five in Japan, five in Great Britain, and one each in Taiwan, Israel, Spain, Finland, and Sweden. All but one of the studies included both men and women; the remaining study enroled only women (Nurses' Health Study) (Patel *et al*., 2004). The cohorts varied in size from 184 (Dew *et al*., 2003) to 1116936 (Kripke *et al*., 2002), and the number of deaths ranged from 66 (Dew *et al*., 2003) to 77640 (Kripke *et al*., 2002). All cohorts primarily included members of the general population; seven of the cohorts enroled only individuals 60 years of age or older (Branch and Jette, 1984; Gale and Martyn, 1998; Goto *et al*., 2003; Lan *et al*., 2007; Pollak *et al*., 1990; Ruigomez *et al*., 1995; Rumble and Morgan, 1992).

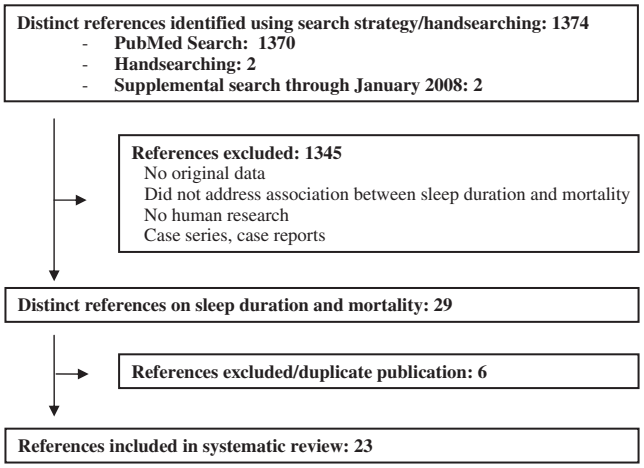

Figure 1. Study selection process.

Sleep duration was assessed by self-report using a single survey item in all of the 23 identified studies. The outcomes studied were all-cause mortality in 23 studies, cardiovascular or coronary heart disease mortality in nine studies (Amagai *et al*., 2004; Burazeri *et al*., 2003; Ferrie *et al*., 2007; Heslop *et al*., 2002; Kripke, 1979; Kripke *et al*., 2002; Lan *et al*., 2007; Mallon *et al*., 2002; Patel *et al*., 2004), and cancer mortality in six studies (Amagai *et al*., 2004; Kripke, 1979; Kripke *et al*., 2002; Lan *et al*., 2007; Mallon *et al*., 2002; Patel *et al*., 2004). Other outcomes included deaths from respiratory diseases (Lan *et al*., 2007), from external causes (including homicide or suicide) (Amagai *et al*., 2004; Kripke *et al*., 2002), from non-cardiovascular disease (Burazeri *et al*., 2003; Ferrie *et al*., 2007), from stroke (Amagai *et al*., 2004; Kripke, 1979), and from 'other' causes (Amagai *et al*., 2004; Lan *et al*., 2007; Mallon *et al*., 2002; Patel *et al*., 2004).

The reference category for analyses was 7 to 7.9 h of sleep for 7 studies (Amagai *et al*., 2004; Ferrie *et al*., 2007; Kripke, 1979; Kripke *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004; Tamakoshi and Ohno, 2004), 7 to 8.9 h for 2 studies (Branch and Jette, 1984; Heslop *et al*., 2002; Hublin *et al*., 2007; Kaplan *et al*., 1987; Kojima *et al*., 2000; Tsubono *et al*., 1993), 7 to 8 h for 4 studies (Branch and Jette, 1984; Heslop *et al*., 2002; Hublin *et al*., 2007; Kaplan *et al*., 1987; Kojima *et al*., 2000; Tsubono *et al*., 1993), 6 to 7.9 h for 2 studies (Goto *et al*., 2003; Mallon *et al*., 2002), 6 to 8.9 h for 2 studies (Huppert and Whittington, 1995; Qureshi *et al*., 1997), 7 to 9 h for 1 study (Ruigomez *et al*., 1995), 6 to 8 h for 1 study (Burazeri *et al*., 2003), 9 to 9.9 h for 1 study (Gale and Martyn, 1998), 4 to 9.9 h for 1 study (Rumble and Morgan, 1992), and ≥6 h for 1 study (Dew *et al*., 2003). Pollak *et al*. (1990) analyzed sleep duration as a continuous variable. Sixteen of the 23 studies adjusted for or stratified on comorbid conditions in the analyses (Amagai *et al*., 2004; Burazeri *et al*., 2003; Dew *et al*., 2003; Ferrie *et al*., 2007; Gale and Martyn, 1998; Goto *et al*., 2003; Heslop *et al*., 2002; Huppert and Whittington, 1995; Kojima *et al*., 2000; Kripke *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004; Pollak *et al*., 1990; Qureshi *et al*., 1997; Rumble and Morgan, 1992; Tamakoshi and Ohno, 2004), all adjusted for participant age.

Quantitative analysis

Short sleep

Nineteen studies reported RR and 95% CI for the association between short sleep and all-cause mortality, 16 of which had similar reference categories and reported data sufficient for meta-analyses (Fig. 2). Thirteen of the RRs were in the direction of increased risk, 4 of the RRs were statistically significant. The pooled all-cause mortality RR comparing the category for short sleep to the reference category in each study was 1.10 (95% CI: 1.06, 1.15), with little evidence of statistical heterogeneity [$Q(15) = 18.47$, $P = 0.24$] (Table 2). The pooled all-cause mortality RR remained elevated and statistically significant after excluding Kripke *et al*. (2002) (RR:

Table 1 Description of prospective cohort studies examining the association between sleep duration and mortality

Author, year	*Study*	*Country*	*Population description*	*% Male*	*Mean age (range) in years*	*Cohort size*	*Years of follow up*	*Number of deaths*	*Comorbidities considered*[a]	*Types of mortality examined*
Ferrie *et al.*, 2007	Whitehall II study	Great Britain	London-based office staff	67.7	35–55	9781	17	566	BP, cholesterol, diabetes, respiratory illness, GHQ, CHD	All-cause, CVD, non-CVD
Hublin *et al.*, 2007	Finnish Twin Cohort	Finland	Adult twins born before 1958 with both co-twins alive in 1975	47.7	40.7 (24–101)	21368	22	3700	[b]	All-cause
Lan *et al.*, 2007	Survey of Health and Living Status of the Elderly	Taiwan	General population	56.8	71.3 (64+)	3079	10	1338	CHD, stroke, cancer, depression	All-cause, cancer, CVD, respiratory, other
Amagai *et al.*, 2004	Jichi Medical School Cohort Study	Japan	General population; no history of CVD or cancer at baseline	39.0	55.1 (19–93)	11325	Mean = 8.2	495	BP, cholesterol, CVD, cancer	All-cause, CVD, stroke, cancer, external causes, other
Patel *et al.*, 2004	Nurses' Health Study	United States	Female, registered nurses	0	53 (40–65)	82969	14	5409	Cancer, CVD, BP, diabetes, depression	All-cause, CVD, cancer, other
Tamakoshi and Ohno, 2004	Japan Collaborative Cohort Study	Japan	General population	42.2	56.6 (40–79)	104010	Mean = 9.9	11071	Depressive symptoms, stroke, MI, cancer	All-cause
Goto *et al.*, 2003		Japan	General population	65.3	73 (65 to 97)	724	12	305	CHD	All-cause
Burazeri *et al.*, 2003	Kiryat Yovel Community Health Study	Israel	General population	45.7	63 (50+)	1842	10	403	CHD, BP, diabetes, CHF	All-cause, CVD, non-CVD
Dew *et al.*, 2003		United States	Healthy older adults	46.2	74.5 (58–91)	184	Mean = 12.8	66	Cumulative Illness Rating Scale (Miller *et al.*, 1992)	All-cause
Heslop *et al.*, 2002		Scotland	Population-based sample of workers	85.6	Women: <60; men: <65	6797	25	2565	BP, cholesterol	All-cause, CVD
Mallon *et al.*, 2002		Sweden	General population	48.4	56 (45–65)	1870	12	266	None	All-cause, CAD, cancer, other
Kripke *et al.*, 2002	Cancer Prevention Study II	United States	Primarily friends and relatives of American Cancer Society volunteers	43.1	57 (30–102)	1116936	6	77640	'Sick now', leg pain, CHD, BP, cancer, stroke, diabetes, bronchitis, emphysema, kidney disease	All-cause, accidents, cancer, heart disease, suicide, homicide
Kojima *et al.*, 2000		Japan	General population	45.8	47.3 (20–67)	5322	Mean = 11.9	258	BP, cerebrovascular, CHD, renal disease, diabetes	All-cause
Gale and Martyn, 1998		Great Britain	General population	NR	75.0 (65+)	1229	23	1158	Cognitive function, BP	All-cause
Qureshi *et al.*, 1997	National Health and Nutrition Examination Survey	United States	General population without history of stroke or CHD	36.3	(32+)	7844	10	NR	BP, cholesterol, diabetes	All-cause
Huppert and Whittington, 1995	Health and Lifestyle Survey	Great Britain	General population	44.3	(18+)	6096	7	474	'Limiting disease'	All-cause

Table 1 (Continued)

Author, year	*Study*	*Country*	*Population description*	*% Male*	*Mean age (range) in years*	*Cohort size*	*Years of follow up*	*Number of deaths*	*Comorbidities considered*[a]	*Types of mortality examined*
Ruigomez *et al.*, 1995	Health Interview Survey of Barcelona	Spain	General population	39.0	(65–97)	1219	Mean = 4.6	224	None	All-cause
Tsubono *et al.*, 1993	National Collaborative Cohort Study: Wakuya Town site	Japan	General population	39.8	(40+)	4318	4	207	None	All-cause
Rumble and Morgan, 1992	Nottingham Longitudinal Study of Activity and Ageing	England	General population	NR	(65+)	1042	5	352	Stroke, CHD, BP, diabetes	All-cause
Pollak *et al.*, 1990		United States	Elderly residents of an urban community	[c]	75.4 (65–98)	1855	3.5	338	Hypnotic use, cognitive impairment, depression	All-cause
Kaplan *et al.*, 1987	Alameda County Study	United States, California	General population	NR	(38+)	4174	17	1219	None	All-cause
Branch and Jette, 1984	Massachusetts Health Care Panel Study	United States	General population	38	(66+)	1235	5	275	None	All-cause
Kripke, 1979	Cancer Prevention Study I	United States	Primarily friends and relatives of American Cancer Society volunteers	44.5	(30+)	823065	6	14866	None	All-cause, CHD, stroke, cancer, suicide

NR, not reported; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; GHQ, General Health Questionnaire; MI, myocardial infarction.

[a]Adjusted for in the model or excluded in analysis/design.

[b]No adjustments or exclusions based on comorbid conditions; however, study sample included those in a 1975 cohort that were alive (and completed a study questionnaire) in 1981.

[c]Numbers included by gender do not equal stated cohort size of 1855; study enroled both males and females.

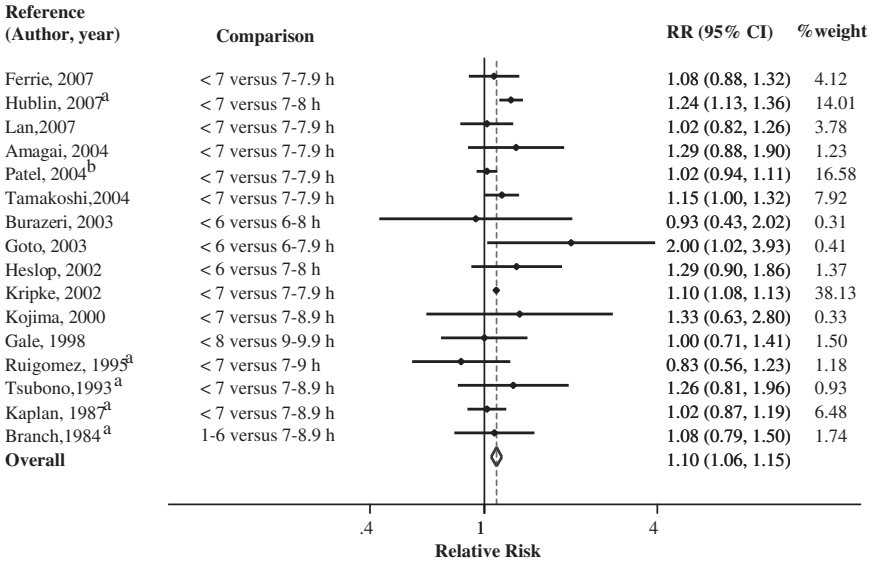

Figure 2. Forest plot of relative risks (RR) and 95% confidence intervals (CI) for short sleep duration versus reference category among prospective studies. [a]No adjustment for or exclusions based on comorbid conditions; [b]study enroled women only.

Table 2 Random effect estimates for short sleep and mortality among studies with similar comparison categories

	No. of studies	*References*	*RR (95% CI)*	I^2 *statistic*	*Q test, P*-value
All-cause mortality					
All studies	16	Amagai *et al*., 2004; Branch and Jette, 1984; Burazeri *et al*., 2003; Ferrie *et al*., 2007; Gale and Martyn, 1998; Goto *et al*., 2003; Heslop *et al*., 2002; Hublin *et al*., 2007; Kaplan *et al*., 1987; Kojima *et al*., 2000; Kripke *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004; Ruigomez *et al*., 1995; Tamakoshi and Ohno, 2004; Tsubono *et al*., 1993	1.10 (1.06, 1.15)	18.8	0.24
Males only	11	Amagai *et al*., 2004; Branch and Jette, 1984; Burazeri *et al*., 2003; Goto *et al*., 2003; Heslop *et al*., 2002; Hublin *et al*., 2007; Kojima *et al*., 2000; Kripke *et al*., 2002; Lan *et al*., 2007; Ruigomez *et al*., 1995; Tamakoshi and Ohno, 2004	1.13 (1.07, 1.19)	11.3	0.34
Females only	12	Amagai *et al*., 2004; Branch and Jette, 1984; Burazeri *et al*., 2003; Goto *et al*., 2003; Heslop *et al*., 2002; Hublin *et al*., 2007; Kojima *et al*., 2000; Kripke *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004; Ruigomez *et al*., 1995; Tamakoshi and Ohno, 2004	1.10 (1.00, 1.21)	57.9	0.01
Cardiovascular-related mortality					
All studies	5	Burazeri *et al*., 2003; Ferrie *et al*., 2007; Heslop *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004	1.06 (0.94, 1.18)	0.0	0.86
Males only	4	Amagai *et al*., 2004; Burazeri *et al*., 2003; Heslop *et al*., 2002; Lan *et al*., 2007	1.29 (0.83, 1.98)	46.5	0.13
Females only	4	Burazeri *et al*., 2003; Heslop *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004	1.04 (0.72, 1.50)	49.9	0.12
Cancer-related mortality					
All studies	3	Amagai *et al*., 2004; Lan *et al*., 2007; Patel *et al*., 2004	0.99 (0.88, 1.13)	0.0	0.39
Males only	2	Amagai *et al*., 2004; Lan *et al*., 2007	1.13 (0.72, 1.78)	0.0	0.79
Females only	3	Amagai *et al*., 2004; Lan *et al*., 2007; Patel *et al*., 2004	0.98 (0.86, 1.12)	0.0	0.47

RR = relative risk; CI, confidence interval.

1.10; 95% CI: 1.04, 1.18), the study with the largest influence, and when limiting the analysis to only those studies that adjusted for or excluded based on comorbid conditions (RR: 1.10; 95% CI: 1.07, 1.12). Pooled all-cause mortality RRs associated with short sleep were similar for males (RR: 1.13; 95% CI: 1.07, 1.19) and females (RR: 1.10; 95% CI: 1.00,

1.21). The all-cause mortality analyses funnel plots for all studies as well as for males and females only showed no evidence of publication bias.

The pooled RRs for cardiovascular-related and cancer-related mortality were 1.06 (95% CI: 0.94, 1.18) and 0.99 (95% CI: 0.88, 1.13), respectively (Table 2). None of the gender-specific pooled RRs for cardiovascular-related and cancer-related mortality were statistically significant, although the RRs were elevated among men for cardiovascular-related mortality (RR: 1.29; 95% CI: 0.83, 1.98) and cancer-related mortality (RR: 1.13; 95% CI: 0.72, 1.78).

Long sleep

Nineteen studies reported RR and 95% CI for the association between long sleep and all-cause mortality, 17 of which had similar reference categories and reported data sufficient for meta-analyses (Fig. 3). Sixteen of the adjusted RRs were in the direction of increased risk, 8 of the RRs were statistically significant. The pooled all-cause mortality RR comparing long sleep duration with the reference category was 1.23 (95% CI: 1.17, 1.30), with little evidence of statistical heterogeneity [$Q(16) = 20.01$, $P = 0.22$] (Table 3). The pooled all-cause mortality RR remained elevated and statistically significant after excluding Kripke *et al.* (2002) (RR: 1.24; 95% CI: 1.16, 1.32) the study with the largest influence, and when limiting the analysis to only those studies that adjusted for or excluded based on comorbid conditions (RR: 1.25; 95% CI: 1.19, 1.32). Pooled all-cause mortality RRs associated with long sleep were similar for males (RR: 1.23; 95% CI: 1.14, 1.32) and females (RR: 1.27; 95% CI: 1.14, 1.43) (Table 3). The all-cause mortality analyses funnel plots for all studies as well as for results pertaining to males and females only showed no evidence of publication bias.

The pooled RRs for cardiovascular-related and cancer-related mortality were 1.38 (95% CI: 1.13, 1.69) and 1.21 (95% CI: 1.11, 1.32), respectively. For both males and females, the pooled RRs for cardiovascular-related mortality were elevated, although not significantly (males: RR, 1.34; 95% CI: 0.79, 2.28; females: RR, 1.45; 95% CI: 0.93, 2.28). For cancer-related mortality, the pooled RR for females but not males was statistically significant (males: RR, 1.20; 95% CI: 0.96, 1.49; females: RR, 1.21; 95% CI: 1.10, 1.34).

DISCUSSION

Summary of findings

In this systematic review, we identified 23 prospective cohort studies that examined the associations between sleep duration and all-cause and/or cause-specific mortality. Findings from the quantitative analyses indicate that among both males and females, short sleepers and long sleepers are at increased risk for all-cause mortality compared to individuals who report, on average, a 'medium' amount of sleep per night (generally defined as 7 to 7.9 h). Less evidence exists to draw conclusions regarding the associations between duration of sleep and specific types of mortality, although the pooled risk estimates for short sleep among men were in the direction of increased risk compared with average sleepers for cardiovascular-related mortality, and the pooled risk estimates for long sleep among men and women were in the direction of increased risk compared with average sleepers for both cardiovascular-related and cancer-related mortality.

Sleep and all-cause mortality

The accumulated evidence suggests that sleep duration is significantly associated with all-cause mortality, with the relationship between sleep duration and mortality being U-shaped. Despite the consistency of this evidence, there has been some debate in the literature as to whether these increases in mortality risk among the short sleepers and long sleepers compared to individuals reporting a 'medium' amount of sleep

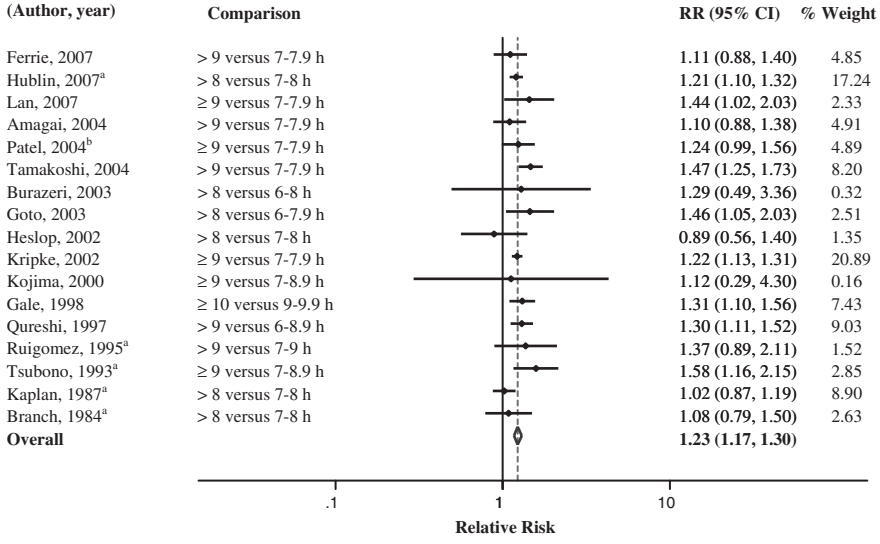

Figure 3. Forest plot of relative risks (RR) and 95% confidence intervals (CI) for long sleep duration versus reference category among prospective studies. [a]No adjustment for or exclusions based on comorbid conditions; [b]study enroled women only.

Table 3 Random effect estimates for long sleep and mortality among studies with similar comparison categories

	No. of studies	*References*	*RR (95% CI)*	I^2 *statistic*	*Q test P*-value
All-cause mortality					
All studies	17	Amagai *et al*., 2004; Branch and Jette, 1984; Burazeri *et al*., 2003; Ferrie *et al*., 2007; Gale and Martyn, 1998; Goto *et al*., 2003; Heslop *et al*., 2002; Hublin *et al*., 2007; Kaplan *et al*., 1987; Kojima *et al*., 2000; Kripke *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004; Qureshi *et al*., 1997; Ruigomez *et al*., 1995; Tamakoshi and Ohno, 2004; Tsubono *et al*., 1993	1.23 (1.17, 1.30)	20.0	0.22
Males only	11	Amagai *et al*., 2004; Branch and Jette, 1984; Burazeri *et al*., 2003; Goto *et al*., 2003; Heslop *et al*., 2002; Hublin *et al*., 2007; Kojima *et al*., 2000; Kripke *et al*., 2002; Lan *et al*., 2007; Ruigomez *et al*., 1995; Tamakoshi and Ohno, 2004	1.23 (1.14, 1.32)	12.8	0.32
Females only	12	Amagai *et al*., 2004; Branch and Jette, 1984; Burazeri *et al*., 2003; Goto *et al*., 2003; Heslop *et al*., 2002; Hublin *et al*., 2007; Kojima *et al*., 2000; Kripke *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004; Ruigomez *et al*., 1995; Tamakoshi and Ohno, 2004	1.27 (1.14, 1.43)	43.5	0.05
Cardiovascular-related mortality					
All studies	5	Burazeri *et al*., 2003; Ferrie *et al*., 2007; Heslop *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004	1.38 (1.13, 1.69)	23.8	0.26
Males only	4	Amagai *et al*., 2004; Burazeri *et al*., 2003; Heslop *et al*., 2002; Lan *et al*., 2007	1.34 (0.79, 2.28)	56.2	0.08
Females only	5	Amagai *et al*., 2004; Burazeri *et al*., 2003; Heslop *et al*., 2002; Lan *et al*., 2007; Patel *et al*., 2004	1.45 (0.93, 2.28)	62.6	0.03
Cancer-related mortality					
All studies	2	Amagai *et al*., 2004; Lan *et al*., 2007; Patel *et al*., 2004	1.21 (1.11, 1.32)	0.0	0.93
Males only	2	Amagai *et al*., 2004; Lan *et al*., 2007	1.20 (0.96, 1.49)	0.0	0.48
Females only	3	Amagai *et al*., 2004; Lan *et al*., 2007; Patel *et al*., 2004	1.21 (1.10, 1.34)	0.0	0.91

RR, relative risk; CI, 95% confidence interval.

per night are real. Much of the data indicates that some but not all of the excess mortality among the long and short sleepers is due to differences in the characteristics of the individuals who comprise these groups; for example, individuals who report shorter and longer sleep times are more likely to be in poorer overall health and to have been diagnosed with medical conditions, including depression, than individuals who report average sleep times (Ayas *et al*., 2003a; Ferrie *et al*., 2007; Kohatsu *et al*., 2006; Patel *et al*., 2006). Further, lower income has been shown to be associated with both shorter and longer sleep (Ferrie *et al*., 2007; Patel *et al*., 2006); therefore, it has been hypothesized that the association between short sleep and mortality may be due to socio-economic status. However, recent studies have taken into account comorbid conditions, socio-economic status or factors, and lifestyle factors in the analyses and have shown that these factors do not explain all of the association between sleep duration and mortality (Ferrie *et al*., 2007; Hublin *et al*., 2007). While this does not rule out the potential influence of unmeasured factors due to residual confounding or the existence of undetected disease affecting sleep (Hublin *et al*., 2007), the results from these recent studies as well as the consistency of the evidence overall suggest a real increase in the risk of mortality among short and long sleepers compared with the average sleepers.

Biological plausibility of the association

The specific mechanisms underlying the association between sleep duration and mortality are unclear. A number of experimental studies have shown that short sleep causes potentially adverse endocrinologic, immunologic, and metabolic effects (Akerstedt and Nilsson, 2003; Knutson *et al*., 2007; Spiegel *et al*., 2005). For example, Spiegel *et al*. (2005) showed in a laboratory-based study that restricted sleep among 11 healthy men was associated with impaired glucose tolerance, higher evening cortisol levels, alterations in sympathetic nervous system activity, and a reduction in leptin secretion. It has also been suggested that the mechanism behind the association between sleep duration and mortality could be chronic inflammation as clinical studies have reported elevated inflammatory markers, including high-sensitivity C-reactive protein and interleukin-6, during sleep deprivation conditions (Meier-Ewert *et al*., 2004; Shearer *et al*., 2001). It should be noted that in experimental studies, 'short sleep' has,

in general, been defined as short-term forced sleep deprivation, and the biological effects of this type of short sleep may differ from those associated with chronic sleep deprivation. However, all of the above proposed mechanisms are consistent with evidence linking chronic short sleep to the development of adverse health conditions, such as diabetes, high blood pressure, and obesity (Ayas *et al*., 2003a,b; Van Cauter *et al*., 2007), all of which are associated with subsequent mortality.

Less research has focused on potential mechanisms behind the association between long sleep and mortality even though the body of evidence suggests that long sleep may be more detrimental in terms of mortality than short sleep. Unlike short sleep, long sleep has not consistently been shown to be associated with certain adverse medical conditions such as diabetes and hypertension, although studies have reported that long sleep is associated with obesity and stroke (Chen *et al*., 2008; Marshall *et al*., 2008). Further, adjustment for health conditions in studies examining the association between long sleep and mortality has not resulted in an attenuation of the association. Hence, the mechanism underlying the association may be different than that which underlies the association between short sleep and mortality. A number of mechanisms for the association between long sleep and mortality were hypothesized in a recent review by Grandner and Drummond (2007) entitled 'Who are the long sleepers? Towards and understanding of the mortality relationship'. These include: (i) an increased amount of sleep fragmentation which has been shown to be associated with a number of negative health outcomes; (ii) changes in cytokine levels that influence mortality risk; and (iii) lack of physiological challenge such that long sleepers are not exposed to potentially beneficial mild stressors. Further, Grandner and Drummond (2007) also speculated that individuals with self-reported long sleep duration experience a shorter photoperiod (ratio of daylight to darkness) than individuals with an average sleep time; a shorter photoperiod among other species (chickens) has been shown to increase the risk of death. All of these hypothesized mechanisms are in line with the theory that longer sleep duration may be the result of a physiological deviation from normal aging, thus placing long sleepers at risk for premature death (Lan *et al*., 2007).

Limitations

Despite the increasing evidence of a U-shaped association between sleep duration and mortality, it is difficult to accurately characterize the number of hours of sleep associated with increased mortality risk due to the limitations of the epidemiologic literature. First, all of the studies included in this review measured sleep duration using a single self-reported survey item which may not capture the actual amount (or quality) of sleep per night. For example, Lauderdale *et al*. (2006) found that actigraph-measured sleep duration was shorter than self-reported sleep duration (6.06 h versus 6.65 h on a weekday). Similar findings were reported by investigators of the Sleep Heart Health Study which compared self-reported sleep duration to sleep duration measured using polysomnography in healthy adults (Walsleben *et al*., 2004). There are also data suggesting that prospective assessment of sleep using sleep diaries may also provide more accurate information regarding sleep duration habits than the single self-reported survey item which calls for a retrospective recall (Morin *et al*., 2003). Sleep diaries have become a standard assessment measure in insomnia outcome research (Morin *et al*., 2003) and could be considered, if practical, in the context of a large prospective cohort study, to collect better data pertaining to sleep duration.

Second, the studies included both in the overall systematic review and the meta-analyses varied in their initial exclusion criteria and their inclusion of adjustment factors in the analyses. For example, Lan *et al*. (2007) adjusted for cardiovascular disease, stroke, cancer, and depression while Pollak *et al*. (1990) adjusted for hypnotic use, cognitive impairment and depression; 7 studies did not adjust for or exclude participants based on any comorbid conditions. Because comorbid conditions may be important confounders of the association between sleep duration and mortality, we conducted meta-analyses including all studies and also limited to only those studies that considered comorbid conditions; however, we found no difference in the results. It remains a possibility that residual confounding across the studies caused overestimation of the associations, therefore leading to overall statistically significant findings in the meta-analyses. Finally, in general, the studies included in this review used different category cut-points in their analyses, hence precluding our ability to examine the associations between sleep duration and mortality at individual hour or smaller sleep duration categories. As suggested by the results of individual studies, a stronger association between sleep duration and mortality may exist with shorter (e.g., less than 5 h per night) and longer (e.g., greater than 10 h per night) sleep times. Based on the categories reported in the studies in this review, we attempted to combine categories into 'overall' short and long sleep categories – these would not be sufficient to provide sleep duration recommendations to be put into public health practice.

CONCLUSIONS

Sleep is a common under-recognized public health issue in industrialized countries across the globe. Our findings indicate that both short sleepers and long sleepers are at increased risk of all-cause mortality; this is consistent with results from studies examining sleep duration and the development of health conditions as well as the limited evidence pertaining to the physiological effects of sleep at various durations. However, our results must be considered in the context of the inherent limitations of the research pertaining to sleep duration, including the use of a single survey item to assess sleep duration and the lack of consistency in controlling for comorbid conditions. In terms of strength of association, the calculated

estimate for short sleep showed a relatively small increase in all-cause mortality (RR: 1.10) compared with estimates reported for the known mortality risk factors such as obesity [RR: 1.27; (McGee, 2005)], cigarette smoking [RR: 1.78; (Khaw *et al*., 2008)], and physical inactivity [RR: 1.49; (Nocon *et al*., 2008)]. The long sleep association was stronger than that reported for short sleep but this association is more likely to be confounded by unmeasured health problems or habits.

However, in terms of public health implications, the prevalence of sleep duration disorders is increasing and therefore increases in mortality attributable to short or long sleep will also likely occur. Hence, the management and treatment of sleep duration disorders should be addressed by physicians (Institute of Medicine, 2006) in addition to the management and treatment of factors such as obesity that are known to increase the risk of mortality. As stated in a recent United States Institute of Medicine report on sleep and health, increasing the awareness and improving the diagnosis and treatment of sleep disorders is needed, especially in terms of public education, training for health professionals, and surveillance and monitoring (Institute of Medicine, 2006). This should include more research on the associations between sleep duration and mortality, both all-cause and cause-specific, using measures that more accurately measure sleep duration such as polysomnography. Additional research into the mechanisms underlying the associations should also be conducted.

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