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CLINICAL PAPER

Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies

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Aims To assess the relationship between duration of sleep and morbidity and mortality from coronary heart disease (CHD), stroke, and total cardiovascular disease (CVD).

Methods and results We performed a systematic search of publications using MEDLINE (1966–2009), EMBASE (from 1980), the Cochrane Library, and manual searches without language restrictions. Studies were included if they were prospective, follow-up >3 years, had duration of sleep at baseline, and incident cases of CHD, stroke, or CVD. Relative risks (RR) and 95% confidence interval (CI) were pooled using a random-effect model. Overall, 15 studies (24 cohort samples) included 474 684 male and female participants (follow-up 6.9–25 years), and 16 067 events (4169 for CHD, 3478 for stroke, and 8420 for total CVD). Sleep duration was assessed by questionnaire and incident cases through certification and event registers. Short duration of sleep was associated with a greater risk of developing or dying of CHD (RR 1.48, 95% CI 1.22–1.80, $P < 0.0001$), stroke (1.15, 1.00–1.31, $P = 0.047$), but not total CVD (1.03, 0.93–1.15, $P = 0.52$) with no evidence of publication bias ($P = 0.95$, $P = 0.30$, and $P = 0.46$, respectively). Long duration of sleep was also associated with a greater risk of CHD (1.38, 1.15–1.66, $P = 0.0005$), stroke (1.65, 1.45–1.87, $P < 0.0001$), and total CVD (1.41, 1.19–1.68, $P < 0.0001$) with no evidence of publication bias ($P = 0.92$, $P = 0.96$, and $P = 0.79$, respectively).

Conclusion Both short and long duration of sleep are predictors, or markers, of cardiovascular outcomes.

Keywords Sleep duration • Cardiovascular disease • Meta-analysis

Introduction

Quantity and quality of sleep show secular trends alongside changes in modern society requiring longer hours of work, more shift-work, and 24-7 availability of commodities, reducing the average duration of sleep across westernized populations with increased reporting of fatigue, tiredness, and excessive daytime sleepiness.[1] Lack of sleep exerts deleterious effects on a variety of systems with detectable changes in metabolic, endocrine[2] and immune pathways.[3] Too little or too much sleep are associated with adverse health outcomes, including total mortality,[4] type 2 diabetes,[5] hypertension[6,7] and respiratory disorders,[8] obesity in both children and adults,[9] and poor self-rated health.[10] The relationship between duration of sleep and vascular events is U-shaped, suggesting that different mechanisms may operate at either end of the distribution of sleep duration.[11]

The aims of this study were to systematically review prospective population-based studies, to carry out a meta-analysis to assess the evidence in support of the presence of a relationship between either short or long duration of sleep and incidence of CHD, stroke, and total cardiovascular disease (CVD) and to obtain a quantitative estimate of the risk.

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Methods

A systematic review and meta-analysis was carried out with methods described in detail elsewhere.[4] In brief, we searched longitudinal population studies (published up to June 2009) reporting the association between duration of sleep and fatal and non-fatal coronary heart disease (CHD), stroke, and total CVD events (Supplementary material online, Appendix S1). Studies met the following criteria: original article, prospective cohort design, assessment of duration of sleep as baseline exposure, cause-specific death or non-fatal incident case of CHD, stroke or CVD recorded prospectively as outcome, follow-up of at least 3 years, adult population, and indication of the number of subjects exposed and of the rate or number of events in different sleep duration categories. Studies were excluded if a case–control design was used. If multiple published reports from the same study were available, we included only the one with the most detailed information for both exposure and outcome. Data were extracted independently by two investigators (F.P.C. and D.C.) and differences were resolved by discussion with a third investigator (M.A.M.). In each study, we identified the reference category, being 7–8 h per night in the majority of studies (*Table 1* and *Figures 1–3*). In most studies, 'short' sleep was defined as ≤5–6 h per night and 'long' sleep as >8–9 h per night.

Statistical analysis

Full methods are reported elsewhere.[4] The quality of the studies was evaluated by the Downs and Black Quality Index score system.[12] Relative risks (RR) or hazard ratios were extracted as a measure of the relationship between sleep duration and incidence of disease. Pooled RR [and 95% confidence interval (CI)] was estimated using a weighted random-effect model. By comparison with the reference category of sleep duration, we estimated the pooled RR (and 95% CI) of disease for the 'short' and the 'long' sleep category, separately. We tested for heterogeneity among studies,[13] publication bias by funnel plot asymmetry and Egger's test.[14] We carried out sensitivity and subgroup analyses.[4] All statistical analyses were performed using MIX software version 1.7.[15] The study adheres to the PRISMA Statement guidelines (Supplementary material online, Appendix S2).

Results

Characteristics of the study cohorts

Fifteen studies were included (Supplementary material online, Appendices S3 and S4). Where results were reported for men and women separately, they were entered into the analyses as separate cohorts. Eleven studies recruited both men and women, whereas four studies only women (*Table 1*). Nine reported outcomes separately for men and women (18 cohorts). Thus, 24 cohorts were included in the meta-analysis. They included 474 684 participants from eight different countries (five from USA, three from Japan, two from UK, and one from Sweden, Germany, Singapore, Israel, and Taiwan). Follow-up ranged from 6.9 to 25 years. All studies assessed death through death certificates (*Table 1*). Non-fatal incident cases of vascular events were recorded through disease registers. Sleep duration was assessed by questionnaire in all studies. The total number of events reported was 16 067 (4169 CHD, 3478 stroke, and 8420 total CVD).

Sleep duration and coronary heart disease

In the pooled analysis, short duration of sleep was associated with a greater risk of developing or dying of CHD (RR 1.48, 95% CI 1.22–1.80, $P < 0.0001$) with no evidence of publication bias ($P = 0.95$) and some heterogeneity between studies ($I^2 = 44\%$, $Q = 17.7$, $P = 0.059$) (*Figure 1A*). Long duration of sleep was associated with a greater risk of developing or dying of CHD (1.38, 1.15–1.66, $P = 0.0005$) with no evidence of publication bias ($P = 0.92$) and some heterogeneity between studies ($I^2 = 49\%$, $Q = 21.6$, $P = 0.028$) (*Figure 1B*).

Sleep duration and stroke

In the pooled analysis, short duration of sleep was associated with a greater risk of developing or dying of stroke (RR 1.15, 1.00–1.31, $P = 0.047$) with no evidence of publication bias ($P = 0.30$) and no heterogeneity between studies ($I^2 = 0\%$, $Q = 4.34$, $P = 0.50$) (*Figure 2A*). Long duration of sleep was associated with a greater risk of developing or dying of stroke (1.65, 1.45–1.87, $P < 0.0001$) with no evidence of publication bias ($P = 0.96$) and no heterogeneity between studies ($I^2 = 0\%$, $Q = 1.44$, $P = 0.92$) (*Figure 2B*).

Sleep duration and total cardiovascular disease

In the pooled analysis, short duration of sleep was weakly and not significantly associated with a greater risk of developing or dying of total CVD (RR 1.03, 0.93–1.15, $P = 0.52$) with no evidence of publication bias ($P = 0.46$) and no heterogeneity between studies ($I^2 = 0\%$, $Q = 3.42$, $P = 0.97$) (*Figure 3A*). Long duration of sleep was associated with a greater risk of developing or dying of total CVD (1.41, 1.19–1.68, $P < 0.0001$) with no evidence of publication bias ($P = 0.79$) and heterogeneity between studies ($I^2 = 61\%$, $Q = 30.7$, $P = 0.002$) (*Figure 3B*).

Sources of heterogeneity

For both short and long sleep and in relation to all outcomes considered, the heterogeneity of effect was not due to differences in gender, duration of follow-up, or geographical location (*Table 2*).

Discussion

This study shows an increased risk of developing or dying of CHD and stroke on either end of the distribution of sleep duration. Pooled analyses indicate that short sleepers have a greater risk of CHD and stroke than those sleeping 7–8 h per night. Furthermore, long sleepers also show an increased risk for these events, confirming the presence of a U-shape association, with some heterogeneity among studies for CHD and CVD outcomes, no presence of publication bias, high statistical power, no difference between men and women, or by the duration of follow-up. Results for total cardiovascular events were less consistent with no detectable effect in short sleepers and a statistically significant increased risk in long sleepers.

The associations are consistent in different populations, as suggested by the sensitivity analysis and the absence of publication

Table 1 Description of the studies included in the meta-analysis

Author	Year, publication	Country	Cohort	Year, baseline	Sleep category	Total events CHD/ stroke/ CVD	Age (years)	Quality Score[12]	Exposure assessment	Outcome assessment	Adjusted variables
Qureshi	1997	USA	NHANES I (NHEFS)	1982	<6 h >8 h	413/285/—	31+[a]	17	Questionnaire	Hospitalizations and death certificates	Age, sex, race, BMI, education, smoking, SBP, cholesterol, diabetes
Heslop	2002	Scotland	Scottish workplaces	1970–74	<7 h >8 h	—/—/1182 —/—/117	<66	16	Questionnaire	Death certificate	Age, marital status, social class, risk factors, self-perceived stress
Mallon	2002	Sweden	County of Dalarna	1983	<6 h >8 h	71/—/— 20/—/—	45–65	18	Questionnaire	Death certificate	Age
Ayas	2003	USA	Nurses' Health Study	1986	≤5 h >9 h	934/—/—	40–65[b]	18	Questionnaire	National Death Index plus Medical Records	Age, shift work, high cholesterol, BMI, diabetes, hypertension, smoking, snoring, exercise, alcohol consumption, depression, aspirin use, HRT, FH of MI
Burazeri	2003	Israel	Kiryat Yovel Community Health Study	1985–88	— >8 h	—/—/77 —/—/93	50+	17	Questionnaire	Death certificate	Age, sex, social class, country origin, smoking, alcohol use, physical activity, self appraised health status, diabetes, CHD, stroke, congestive heart failure, blood pressure, BMI, serum glucose, creatinine, albumin, total and HDL cholesterol. thiocyanate, plasma homocysteine
Amagai	2004	Japan	Jichi medical school cohort study	1992–95	<6 h ≥9 h	26/34/— 28/29/—	40–69	15	Questionnaire	Death certificate	Age, SBP, total cholesterol, BMI, smoking, alcohol consumption, education, marital status
Patel	2004	USA	Nurses' Health Study	1986	≤5 h ≥9 h	—/—/1084	30–55[b]	17	Questionnaire	National Death Index	Age, smoking, alcohol consumption, physical activity, depression, snoring, BMI, Hx cancer, CVD, hypertension, diabetes, shift work
Ferrie	2007	England	Whitehall II Study	1985–88	≤5 h ≥9 h	—/—/168	35–55[a]	18	Questionnaire	Death certificate	Age, sex, marital status, employment grade, smoking, physical activity, alcohol consumption, self-rated health, BMI, SBP, total cholesterol, physical illness, GHQ, prevalent CHD
Lan	2007	Taiwan	Survey of Health and Living Status of the Elderly	1993–94	<7 h ≥10 h	—/—/209 —/—/170	64+	17	Questionnaire	Death certificate	Age, marital status, income, smoking, alcohol, BMI, exercise, depression

Continued

Table 1 *Continued*

Author	Year, publication	Country	Cohort	Year, baseline	Sleep category	Total events CHD/ stroke/ CVD	Age (years)	Quality Score[12]	Exposure assessment	Outcome assessment	Adjusted variables
Meisinger	2007	Germany	MONICA/ KORA Augsburg study	1984–95	≤5 h ≥9 h	295/—/— 85/—/—	45–74	17	Questionnaire	Death certificate and coronary event registry	Age, survey, BMI, education, dyslipidaemia, alcohol intake, FH of MI, physical activity, smoking, hypertension, diabetes, (menopause in women)
Chen	2008	USA	Women's Health Initiative	1994–98	≤5 h ≥10 h	—/1166/—	50–79[b]	17	Questionnaire	Death certificate or self-reporting	Age, race, socio-economic status, depression, smoking, exercise, hormone replacement, previous CVD, diabetes, hypertension, BMI, high cholesterol
Shankar	2008	Singapore	Singapore Chinese Health Study	1993–99	≤5 h ≥9 h	846/—/— 570/—/—	45–74	17	Questionnaire	Death certificate	Age, dialect, year of recruitment, BMI, smoking, alcohol intake, physical activity, dietary calories, fruits, vegetables, fibre, fat & cholesterol, vitamin suppl.
Ikehara	2009	Japan	JACC study	1988–91	≤4 h >10 h	508/1038/ 2297 373/926/ 1990	40–79	18	Questionnaire	Death certificate	Age, BMI, PH of hypertension, diabetes, alcohol, smoking, education, exercise, employment, mental stress, depression, fresh fish intake
Stone	2009	USA	SOF study	1993–94	<6 h >8 h	—/—/723	69+[b]	18	Questionnaire	Death certificate	Age, BMI, PH diabetes, Parkinson's, dementia, COPD, non-skin cancer, osteoarthritis, CVD, hypertension, walks, alcohol use, smoking, depression, cognitive status, oestrogen and hypnotic use
Suzuki	2009	Japan	Shizuoka study	1999	≤5 h ≥10 h	—/—/184 —/—/126	65–85	18	Questionnaire	National Vital Statistics Database	Age, sex, smoking, alcohol consumption, BMI, physical activity, SES, mental status, hypertension, diabetes

[a]Men and women combined.
[b]Women only.

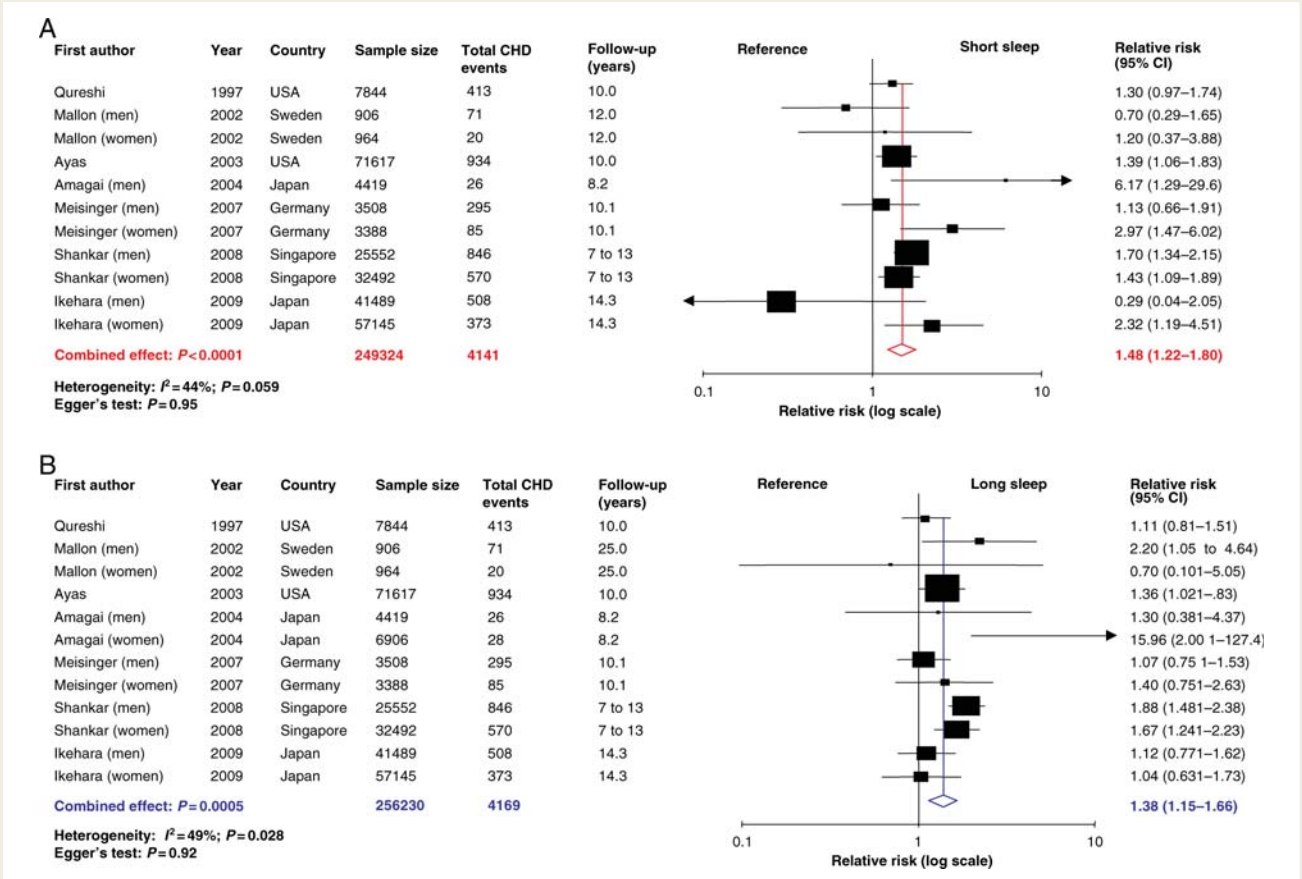

Figure 1 Forest plots of the risk of developing or dying of coronary heart disease associated with (*A*) short duration of sleep compared with the reference group and (*B*) long duration of sleep compared with the reference group. Results are expressed as relative risk and 95% confidence intervals.

bias, particularly for the effects in short sleepers across all endpoints and for stroke among long sleepers; moreover, the consistency of the method of assessments of the duration of sleep by questionnaire and outcomes across studies limits the variability due to differences in methods.

The study has limitations: we included adjusted estimates from multivariate models from each contributing study. However, residual confounding and bias remain a possibility. Moreover, the results can only be representative of the studies that have been included and are unable to provide a representative inference of all studies published, but not included. Although there was no statistical evidence of publication bias, some studies could have been missed out from the analysis. Given the conservative random-effects model adopted and in view of the results of numerous subgroup and sensitivity analyses, it is unlikely that any addition to the reviewed studies would have generated summary estimates outside the reported 95% CIs. The studies did not exclude subjects with obstructive sleep apnoea–hypopnoea syndrome (OSAS). These would represent ~4% of middle-aged men and 2% of middle-aged women.[16,17] Obstructive sleep apnoea–hypopnoea syndrome is associated with obesity, disrupted and short sleep, excessive daytime sleepiness, and high rates of morbidity and mortality, predominantly due to CVD.[18]

Self-reported sleep duration was assessed by questionnaire. This method often did not allow (unless explicitly built as additional questions) to differentiate time asleep from time in bed or to estimate the number and duration of naps. It is not usually feasible to obtain more detailed and objective measures of sleep in large prospective population studies. Sleep diaries, actigraphy, and polysomnography from some large population and small-scale investigations have shown high correlations between subjective estimates of sleep duration and the more direct assessments.[19,20] Furthermore, assessments of sleep durations in the primary healthcare setting rely on self-reported data from patients.

It is possible that a single measure of exposure may not fully capture the sustained effects of sleep duration over time when relating them to long-term disease incidence. Changes in sleep duration over time may represent a better measure of exposure in this context. Two studies have addressed this issue by measuring changes in sleep duration over time as a proxy for prolonged exposure to short or long sleep duration in relation to vital outcomes.[21,22]

Our results are, in part, consistent with other evidence of increased risk of cardiovascular risk factors like coronary artery calcifications,[23] hypertension,[6,7,24] obesity,[9] type 2 diabetes[5] or impaired glucose control,[25] and atherogenic lipid profile[26] with

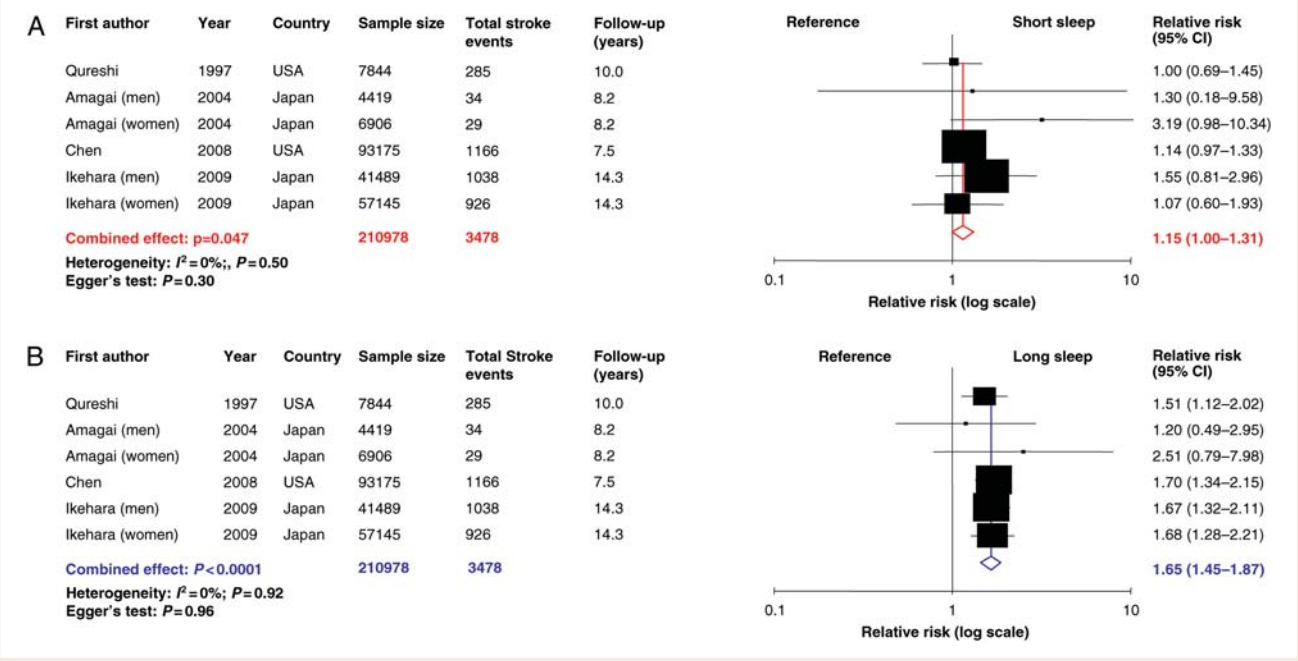

Figure 2 Forest plots of the risk of developing or dying of stroke associated with (*A*) short duration of sleep compared with the reference group and (*B*) long duration of sleep compared with the reference group. Results are expressed as relative risk and 95% confidence intervals.

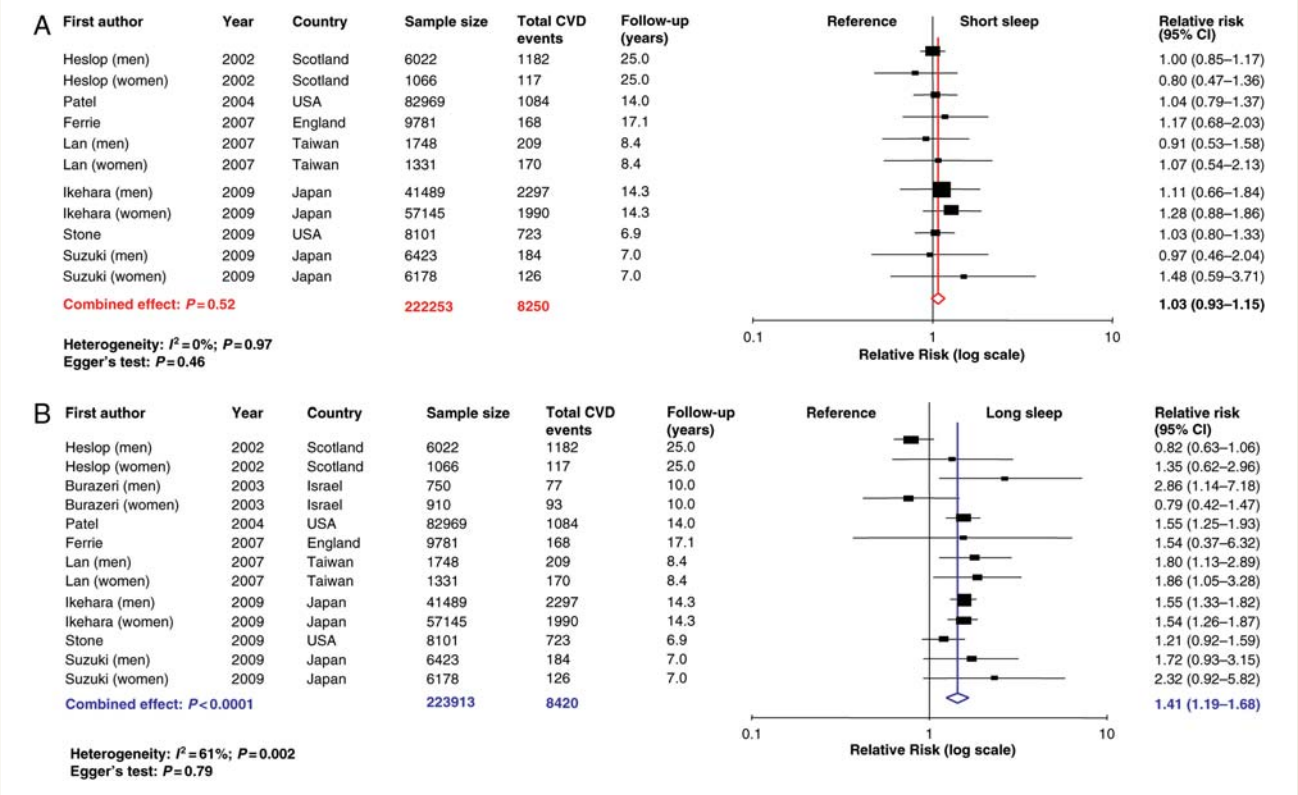

Figure 3 Forest plots of the risk of developing or dying of total cardiovascular disease associated with (*A*) short duration of sleep compared with the reference group and (*B*) long duration of sleep compared with the reference group. Results are expressed as relative risk and 95% confidence intervals.

Table 2 Subgroup analyses to explore source of heterogeneity

Subgroups	CHD		Stroke		CVD	
	Cohorts	RR (95% CI), *P* for heterogeneity	Cohorts	RR (95% CI), *P* for heterogeneity	Cohorts	RR (95% CI), *P* for heterogeneity
Short sleep						
Gender						
Men	5	1.28 (0.74–2.22)	2	1.53 (0.82–2.82)	4	1.00 (0.87–1.15)
Women	5	1.60 (1.24–2.06)	3	1.21 (0.86–1.70)	6	1.06 (0.91–1.24)
		$P = 0.48$		$P = 0.51$		$P = 0.57$
Duration of follow-up						
≤10 years	5	1.49 (1.26–1.75)	4	1.14 (0.93–1.39)	5	1.03 (0.84–1.26)
>10 years	6	1.36 (0.80–2.32)	2	1.27 (0.82–1.96)	6	1.03 (0.92–1.16)
		$P = 0.75$		$P = 0.65$		$P = 1.00$
Location						
Europe	4	1.33 (0.72–2.46)	—	—	3	0.99 (0.86–1.15)
USA	2	1.35 (1.10–1.65)	2	1.17 (0.97–1.29)	2	1.03 (0.86–1.25)
East Asia	5	1.68 (1.22–2.31)	4	1.41 (0.95–2.11)	6	1.13 (0.90–1.42)
		$P = 0.49$		$P = 0.40$		$P = 0.64$
Long sleep						
Gender						
Men	5	1.43 (1.03–2.00)	2	1.63 (1.30–2.05)	5	1.48 (1.00–2.19)
Women	6	1.43 (1.09–1.89)	3	1.71 (1.43–2.04)	7	1.44 (1.23–1.68)
		$P = 1.00$		$P = 0.74$		$P = 0.89$
Duration of follow-up						
≤10 years	6	1.53 (1.18–1.99)	4	1.62 (1.35–1.93)	7	1.53 (1.16–2.02)
>10 years	6	1.17 (0.95–1.44)	2	1.67 (1.40–2.00)	6	1.34 (1.06–1.70)
		$P = 0.11$		$P = 0.81$		$P = 0.45$
Location						
Europe	4	1.28 (0.92–1.77)	—	—	5	1.12 (0.72–1.73)
USA	2	1.24 (1.00–1.53)	2	1.62 (1.35–1.95)	2	1.39 (1.09–1.77)
East Asia	6	1.50 (1.11–2.03)	4	1.67 (1.40–1.98)	6	1.59 (1.42–1.78)
		$P = 0.58$		$P = 0.81$		$P = 0.22$

shorter duration of sleep. However, in our analysis, while the pooled estimates for CHD and stroke were statistically significant, that for total CVD was not. Residual confounding and lack of specificity of the outcome measures may explain the findings. Short duration of sleep has been recently associated with vascular damage. In the Chicago cohort of the CARDIA study, short duration of sleep measured by actigraphy was associated with a greater 5-year incidence of coronary artery calcifications measured by computed tomography.[23] In a population study in Germany, both short and long duration of sleep were associated with an increased risk of atherosclerosis, as measured by the intima–media thickness of the common carotid arteries.[27] Finally, recent data from the Whitehall II study suggest that the effect of short sleep on CHD risk may be mediated by poor sleep quality.[28]

The risk associated with changes in sleep duration varies by gender.[7,29–32] In our analyses, no gender differences were detected in association with either short or long duration of sleep and cardiovascular outcomes. Ideally, long follow-up durations would be appropriate to assess the influence of sleep duration on health over the life course.[33] We excluded a priori short follow-up studies (<3 years) to avoid that disease status might have affected sleep patterns. Furthermore, a stratified analysis by the duration of follow-up was carried out, which did not suggest any trend. We were unable to stratify studies by age bands due to the inconsistent reporting of age in the published reports.

The mechanisms that underlie these associations are not fully understood. Causative mechanisms relating short duration of sleep to adverse health outcomes include reciprocal changes in circulating levels of leptin and ghrelin,[34,35] which in turn would increase appetite, caloric intake, reduce energy expenditure,[2] and facilitate the development of obesity[35] and impaired glycaemic control[36] with increased cardiovascular risk. Increased cortisol secretion and altered growth hormone metabolism have also been implicated.[37] Low-grade inflammation is also activated during short sleep, with possible implications not only for CVD but also for other chronic conditions including cancer.[3]

Conversely, no studies published to date have demonstrated a possible mechanism mediating the effect of long duration of sleep as a cause of CVD. The association between long duration

of sleep and cardiovascular morbidity and mortality may be explained by residual confounding and co-morbidities[38–40] In particular, depressive symptoms, low socio-economic status, unemployment, low level of physical activity, and undiagnosed health conditions have all been shown to be associated with long duration of sleep and to confound the association with morbidity and mortality.[38,40] It is conceivable that the associations between long duration of sleep and the different cardiovascular outcomes may reflect the role of long sleep as a marker, rather than as a cause, of these chronic conditions.[11] A recent intervention study of weight reduction, healthy diet, and increased physical activity showed, compared with a control group, a significant reduction in the 7-year incidence of type-2 diabetes among long sleepers,[41] supporting the view that long sleep may be an indicator of risk, reversible upon changes in the risk factors.

Conclusions

Currently, there is no evidence that sleeping habitually between 6 and 8 h per day in an adult is associated with harm and long-term health consequences. However, sleeping 9 h or more per night may represent a useful diagnostic tool for detecting subclinical or undiagnosed co-morbidity. People reporting consistently sleeping 5 h or less per night should be regarded as a higher risk group for cardiovascular morbidity and mortality.

Authors' contribution

F.P.C. and M.A.M. conceived the study aims and design, contributed to the systematic review and data extraction, performed the analysis and interpreted the results. F.P.C. drafted the manuscript. D.C., L.D., and P.S. contributed to the data extraction, interpretation of results, and to the revision of the manuscript.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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