Sleep duration and risk of fatal and nonfatal stroke

A prospective study and meta-analysis

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ABSTRACT

Objective: To study the association between sleep duration and stroke incidence in a British population and to synthesize our findings with published results through a meta-analysis.

Methods: The prospective study included 9,692 stroke-free participants aged 42–81 years from the European Prospective Investigation into Cancer–Norfolk cohort. Participants reported sleep duration in 1998–2000 and 2002–2004, and all stroke cases were recorded until March 31, 2009. For the meta-analysis, we searched Ovid Medline, EMBASE, and the Cochrane Library for prospective studies published until May 2014, and pooled effect estimates using a weighted random-effect model.

Results: After 9.5 years of follow-up, 346 cases of stroke occurred. Long sleep was significantly associated with an increased risk of stroke (hazard ratio [HR] = 1.46 [95% confidence interval (CI) 1.08, 1.98]) after adjustment for all covariates. The association remained robust among those without preexisting diseases and those who reported sleeping well. The association for short sleep was smaller (and not statistically significant) (HR = 1.18 [95% CI 0.91, 1.53]). There was a higher stroke risk among those who reported persistently long sleep or a substantial increase in sleep duration over time, compared to those reporting persistently average sleep. These were compatible with the pooled HRs from an updated meta-analysis, which were 1.15 (1.07, 1.24) and 1.45 (1.30, 1.62) for short and long sleep duration, respectively.

Conclusions: This prospective study and meta-analysis identified prolonged sleep as a potentially useful marker of increased future stroke risk in an apparently healthy aging population. ***Neurology*®** **2015;84:1072–1079**

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **CVD** = cardiovascular disease; **DBP** = diastolic blood pressure; **HR** = hazard ratio; ***ICD-9*** = *International Classification of Diseases–9*; ***ICD-10*** = *International Classification of Diseases–10*; **MDD** = major depressive disorder; **MI** = myocardial infarction; **SBP** = systolic blood pressure.

Sleep is increasingly suggested as a predictor of cardiovascular events,[1,2] and stroke is an outcome of particular interest. One meta-analysis in 2009[2] included 4 studies on sleep and stroke[3–6] and concluded a U-shaped relationship, with both short and long sleep being associated with an increased stroke risk.

Increasing numbers of prospective studies have examined this association in the past 5 years.[7–10] These studies have examined various types of populations with different follow-up durations, with inconsistent results. While several earlier studies observed strong effects for long sleep and suggested a J-shaped relationship,[3,4,11] the most recent study found a U-shaped association between sleep duration and risk of stroke mortality in a large sample of Chinese adults.[8] It is unclear whether this association is applicable to nonfatal stroke, and if this could be modified by sleep quality. Meanwhile, evidence is lacking from the British population, and no study has examined change in sleep duration over time and subsequent stroke risk. Understanding this relationship is potentially important for the early detection of stroke, especially in older populations. Therefore, we aimed to update the meta-analysis, and to study the effects of

Editorial, page 1066

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sleep duration and change in sleep duration on stroke incidence in a middle- to older-aged British population. We evaluated both fatal and nonfatal stroke and explored whether the associations varied by follow-up length, stroke subtypes, and sleep quality.

METHODS

Study population. The study population was drawn from the European Prospective Investigation of Cancer–Norfolk cohort study. Details about study design have been described previously.[12] Briefly, we recruited 25,639 men and women aged 40–79 years using general practice age–sex registers from Norfolk, UK, during 1993–1997, and followed them up for health outcomes. As part of the follow-up, participants were sent questionnaires for completion.

Standard protocol approvals, registrations, and patient consents. The Norwich District Ethics Committee approved the study and all participants gave signed informed consent.

Measures of sleep. During 1998–2000, 16,643 people answered the following question: "On average, how many hours do you sleep in a 24-hour period?" with 6 response options: <4, 4–6, 6–8, 8–10, 10–12, and >12. This question was repeated during 2002–2004.

In addition, participants were asked "Do you generally sleep well?" with response alternatives "yes" and "no."

Ascertainment of stroke cases. At baseline, we excluded participants with self-reported history of doctor-diagnosed stroke or those whose date of stroke onset was before the date of sleep report. All stroke cases to March 31, 2009, were taken as the first occurrence of either hospital admission or death due to stroke. We defined nonfatal stroke as hospital admission due to stroke that did not lead to death (in the same month), and recorded information through linkage with the National Health Services district database. We obtained information on fatal stroke through linkage with the UK Office of National Statistics. Stroke cases were classified according to *ICD-9* as codes 430-438 (hemorrhagic stroke 430-432; cerebral infarction 433-435; stroke unspecified or other 436-438) or according to *ICD-10* as codes I60-I69 (hemorrhagic stroke I60-I62; ischemic stroke I63, I65, and I66; stroke unspecified or other I64 and I67-I69).

Covariates. We chose all covariates a priori based on literature and relevance to sleep and stroke. Those reported from questionnaires included age, sex, social class (professionals, managerial, and technical occupations, skilled workers subdivided into nonmanual and manual, partly skilled workers, and unskilled manual workers), education (no qualifications, educated to age 16, educated to age 18, and educated to degree level), marital status (single, married, widowed, separated, and divorced), smoking (current, former, and nonsmokers), alcohol intake (units of alcohol per week), family history of stroke, hypnotic drug use, physical activity (inactive, moderately inactive, moderately active, active), major depressive disorder (MDD) in the previous year, preexisting myocardial infarction (MI) and diabetes, and use of antihypertension drugs.

Other objectively measured confounders included body mass index (BMI; weight in kilograms divided by height in meters squared); systolic blood pressure (SBP) and diastolic blood pressure (DBP), both in mm Hg, based on the mean of 2 readings taken by trained nurses; and serum cholesterol level estimated from nonfasting blood samples taken by venepuncture, using colorimetry (RA 1000, Bayer Diagnostics, Basingstoke, UK).

Statistical analysis. We defined the response categories for sleep duration as short (<6 hours), average (6–8 hours), and long (>8 hours) due to the low frequency of extreme sleep durations. First, we compared baseline characteristics of the participants by sleep duration using χ^2 test. Cox proportional hazard models were fitted to obtain hazard ratios (HR), with average sleep being the reference group. We constructed models with progressive adjustment of the covariates to show the associations explained by the covariates and performed the analysis in those with complete data on all covariates (A) adjusted for age and sex; (B) further adjusted for social class, education, marital status, smoking, alcohol intake, hypnotic drug use, and family history of stroke; and (C) further adjusted for BMI, physical activity, MDD, SBP, DBP, preexisting MI and diabetes, serum cholesterol level, and hypertension drug use. We repeated these analyses for fatal and nonfatal stroke, and presented the results by sex.

Change in sleep duration from 1998–2000 to 2002–2004 was modeled through combinations of the 3 duration categories during each time period, giving 9 subcategories. The association between change in sleep duration and overall incidence risk of stroke was examined using model C, with "constantly average" being the reference group, and was conducted in the whole sample to retain power. Finally, we performed subgroup analysis according to follow-up length, sleep quality, preexisting diseases, stroke subtypes, and other potential effect modifiers using model B. Analyses were implemented in STATA, version 12.0 (StataCorp LP, College Station, TX).

Meta-analysis of prospective studies on the association between sleep duration and stroke incidence. We conducted an updated systematic review and meta-analysis using methods described in detail elsewhere.[2] We searched longitudinal population studies (published up to May 2014) reporting the association between sleep duration and fatal and nonfatal stroke (appendix e-1 on the *Neurology*® Web site at Neurology.org), with the following restrictions: original article, prospective cohort design, and adult population. Studies with no complete information presented for stroke events were contacted, and were excluded if no additional estimates could be obtained. Data were extracted independently by 2 investigators (Y.L. and F.P.C.). Short sleep was defined as ≤5–6 hours and long sleep as ≥8–9 hours. When multiple multivariate models were fitted, we extracted the estimates that were least likely to have been confounded (models with most covariates). Effect estimates were pooled using a weighted random-effect model. We tested for heterogeneity among studies,[13] publication bias by funnel plot asymmetry and Egger test,[14] and carried out sensitivity analyses.[2] All analyses were performed using Review Manager software (v5) (Copenhagen, 2011). We evaluated the quality of studies,[15] and the study adheres to the PRISMA Statement guidelines for nonrandomized studies.[16]

RESULTS

After excluding participants with self-reported preexisting stroke (n = 438) and those whose date of stroke onset was before the date of sleep report (n = 623), the final study sample included 9,692 participants who had complete data on all covariates.

At baseline, the participants were aged from 42 to 81 years (mean 61.6). A total of 6,684 (69%) of the participants reported sleeping for 6–8 hours per day, while 10% reported sleeping for >8 hours. Table 1 shows baseline characteristics by sleep duration.

Table 1 Baseline characteristics by sleep duration in the European Prospective Investigation of Cancer–Norfolk study, 1998–2000

	Total, n (%)	<6 h (n = 2,022), n (%)	6–8 h (n = 6,684), n (%)	>8 h (n = 986), n (%)
Age, y				
42–52	1,819	333 (16.5)[a]	1,324 (19.8)	162 (16.4)
52–62	3,384	702 (34.7)	2,374 (35.5)	308 (31.2)
62–72	3,140	634 (31.4)	2,158 (32.3)	348 (35.3)
72–82	1,349	353 (17.5)	828 (12.4)	168 (17.0)
Male sex	4,444	807 (39.9)[a]	3,204 (47.9)	433 (43.9)
Nonmanual social class	6,359	1,267 (62.7)[b]	4,448 (66.5)	644 (65.3)
A-level and higher education	5,733	1,086 (53.7)[a]	4,060 (60.7)	587 (59.5)
Married	8,012	1,559 (77.1)[a]	5,617 (84.0)	836 (84.8)
Current or former smoker	4,983	1,047 (51.8)	3,423 (51.2)	513 (52.0)
Alcohol intake ≥8 units/wk[c]	4,655	924 (45.7)	3,248 (48.6)	483 (49.0)
Hypnotics use	145	80 (4.0)[a]	59 (0.9)	6 (0.6)
Family history of stroke	7,291	501 (24.8)	1,655 (24.8)	245 (24.8)
BMI >26.5[c]	4,757	1,028 (50.8)	3,228 (48.3)	501 (50.8)
Physical activity				
Inactive	2,383	570 (28.2)[a]	1,548 (23.2)	265 (26.9)
Moderately inactive	2,912	578 (28.6)	2,048 (30.6)	286 (29.0)
Moderately active	2,429	484 (23.9)	1,715 (25.7)	230 (23.3)
Active	1,968	390 (19.3)	1,373 (20.5)	205 (20.8)
Major depressive disorder	441	138 (6.8)[a]	248 (3.7)	55 (5.6)
Hypertension drug use	2,039	493 (24.4)[a]	1,323 (19.8)	223 (22.6)
Systolic blood pressure ≥137 mm Hg[c]	4,842	1,019 (50.4)	3,301 (49.4)	522 (52.9)
Cholesterol level ≥5.9 mmol/L[c]	4,650	974 (48.2)	3,192 (47.8)	484 (49.1)
Self-reported diabetes	254	49 (2.4)	177 (2.6)	28 (2.8)
Self-reported heart attack	293	70 (3.5)	185 (2.8)	38 (3.9)

Abbreviation: BMI = body mass index.
[a] $p < 0.005$.
[b] $p < 0.01$.
[c] Cutoff by median.

Participants with <6 hours or >8 hours of sleep were older, more likely to be women, less active, to have MDD, and to be taking antihypertensive drugs. No significant association was found between sleep duration and BMI, SBP, or preexisting diabetes or MI.

A total of 346 participants had at least one incident fatal or nonfatal stroke during a mean of 9.5 years of follow-up. There were 67 fatal stroke and 300 hospital admissions, with 21 participants being admitted to hospital before subsequent death. Univariate analysis suggested that those who reported <6 hours and >8 hours of sleep had 32% and 71% increased risk of having a stroke incident, respectively. Table 2 summarizes the adjusted HRs associated with short and long sleep. After adjustment for age and sex, short and long sleep were associated with 19% and 45% increase in the risk of stroke, respectively. These estimates were hardly changed after further adjustment for potential confounders. The association was stronger for women, although a formal test for sex difference was not statistically significant ($p = 0.24$). When we examined stroke outcomes separately, the association was more pronounced for fatal stroke (table e-1).

Table 3 shows the association between change in sleep duration and stroke risk. The risk doubled for those reporting persistently long sleep, compared to those with persistently average sleep duration. This risk was even greater for those whose reported sleep increased from short to long over the 4 years (HR = 3.75 [95% confidence interval (CI), 1.17, 12.05]). Finally, subgroup analysis (table e-2) suggested that the association remained among those without preexisting diseases, did not attenuate by increasing

Table 2 Hazard ratios (95% confidence intervals) of sleep duration for stroke incidence, 1998–2009

		<6 h			>8 h		
	No. of patients	HR	95% CI	6–8 h, referent	HR	95% CI	Overall p[a]
All (n = 9,692)	346						
Model 1[b]		1.19	(0.92, 1.53)	1.00	1.45	(1.07, 1.97)	0.05
Model 2[c]		1.16	(0.90, 1.51)	1.00	1.45	(1.07, 1.97)	0.05
Model 3[d]		1.18	(0.91, 1.53)	1.00	1.46	(1.08, 1.98)	0.05
Men (n = 4,444)	198						
Model 1[b]		1.14	(0.80, 1.63)	1.00	1.24	(0.82, 1.87)	0.52
Model 2[c]		1.07	(0.74, 1.54)	1.00	1.24	(0.82, 1.87)	0.59
Model 3[d]		1.08	(0.75, 1.57)	1.00	1.21	(0.80, 1.82)	0.67
Women (n = 5,248)	148						
Model 1[b]		1.24	(0.86, 1.79)	1.00	1.83	(1.16, 2.89)	0.04
Model 2[c]		1.26	(0.86, 1.84)	1.00	1.78	(1.12, 2.82)	0.05
Model 3[d]		1.25	(0.86, 1.83)	1.00	1.80	(1.13, 2.85)	0.05

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Tested by likelihood ratio test.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, social class, education, marital status, smoking, alcohol intake, hypnotic drug use, and family history of stroke.
[d] Adjusted for age, sex, social class, education, marital status, smoking, alcohol intake, hypnotic drug use, family history of stroke, body mass index, physical activity, depression, hypnotic drug use, systolic blood pressure, diastolic blood pressure, preexisting diabetes and myocardial infarction, cholesterol level, and hypertension drug use.

length of follow-up, and was more pronounced for those who reported sleeping well (p for interaction = 0.01). The association for short sleep was strong among younger people (HR = 1.87 [0.97, 3.60]) and the association for long sleep was only significant among those aged 63 years and older (HR = 1.50 [1.09, 2.05]) (p for interaction = 0.98). The association was stronger between short sleep and ischemic stroke and between long sleep and hemorrhagic stroke.

Systematic review and meta-analysis. Eleven studies[3–8,10,11,17–19] identified from the search along with the current study were included (table e-3) in the meta-analysis. Six studies reported outcomes separately for men and women, and were entered as separate

Table 3 Change in sleep duration over 2 measurements and stroke incidence, 1998–2009

Sleep duration[a]			Stroke incidence risk	
1998–2000	2002–2004	No. of patients	HR	95% CI
Average	Average	6,646	1.00	Referent
Short	Average	905	1.30	(0.74, 2.18)
Long	Average	608	1.33	(0.74, 2.38)
Short	Short	1,759	1.11	(0.71, 1.73)
Average	Short	1,161	1.12	(0.66, 1.88)
Long	Short	45	1.36	(0.18, 9.91)
Average	Long	825	1.53	(0.96, 2.44)
Long	Long	648	2.01[b]	(1.26, 3.23)
Short	Long	52	3.75[c]	(1.17, 12.05)

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Short: <6 hours; average: 6–8 hours; long: >8 hours.
[b] $p < 0.01$.
[c] $p < 0.05$ adjusted for age, sex, social class, education, marital status, smoking, alcohol intake, hypnotic drug use, family history of stroke, body mass index, physical activity, depression, hypnotic drug use, systolic blood pressure, diastolic blood pressure, preexisting diabetes and myocardial infarction, cholesterol level, and hypertension drug use.

cohorts. The final analysis included 559,252 participants from 7 countries. All studies measured sleep duration by questionnaire, and 6 only reported fatal stroke events. Over a follow-up of 7.5–35 years, a total of 11,695 stroke events were reported. The figure shows the pooled effects for short (A) and long (B) sleep, respectively. The addition of the current study did not alter the overall estimates of effect for both short and long sleep. For short sleep, the pooled relative risk (RR) was 1.15 (95% CI, 1.07, 1.24; $p = 0.0002$), with no evidence of heterogeneity. For long sleep, the pooled RR was 1.45 (1.30, 1.62), with significant between-study heterogeneity ($I^2 = 54\%$; $p = 0.003$). After repeating the meta-analysis excluding the study by Westerlund et al.,[7] the heterogeneity disappeared (RR, 1.53; 95% CI, 1.42, 1.65; $p < 0.00001$; $I^2 = 0\%$).

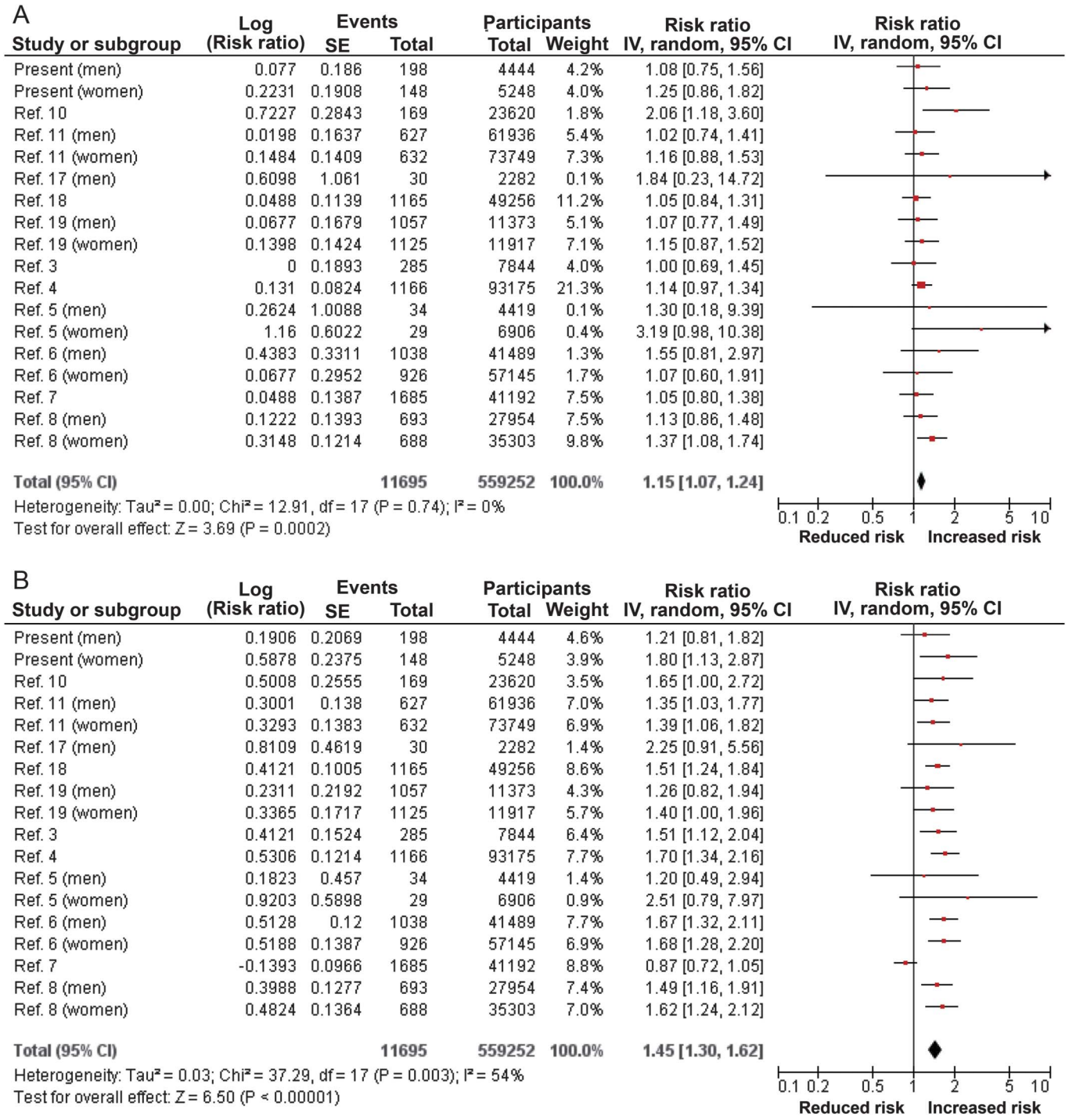
DISCUSSION In this middle-to older-aged British population, we observed a J-shaped relationship between daily sleep duration and 9.5-year stroke risk. Those with short sleep had an 18% increased stroke risk (not statistically significant), while long sleep was associated with a 46% increase in stroke risk after adjustment for conventional cardiovascular disease (CVD) risk factors and comorbidities. Those who reported persistently long sleep and those who reported substantially increased sleep had at least double the stroke risk compared to those with persistently average sleep duration. Our findings are compatible with an updated meta-analysis, which suggested a pooled RR of 1.15 (1.07, 1.24) and 1.45 (1.30, 1.62) for short and long sleep, respectively.

This study benefits from the prospective design, particularly the ability to examine the longitudinal change in sleep duration. Both fatal and nonfatal stroke events were examined, and sex-specific estimates were provided. The study also explored whether the association differed by comorbidities, general sleep quality, and stroke subtypes, which helps to provide more insights into potential mechanisms. The meta-analysis including over 8,000 stroke cases, substantially greater than that included in previous work,[2] provides external validity to our findings. There are several limitations. First, this study included 9,692 stroke-free participants who were younger and had higher social class and educational level compared to the baseline population, but the external validity is supported by the agreement with the meta-analysis. As with previous studies, sleep duration was reported via a single question, which might reflect perception of sleep rather than biological sleep. It should be noted that one's perception of sleep could be influenced by poor cognitive function or physical health.[20,21] This is potentially problematic for older adults and for those with preclinical minor stroke, whose perception of sleep might be impaired due to cognitive factors. However, examination of change in sleep duration was in line with results on a single measure of sleep at baseline. From a practical standpoint, evaluation of sleep durations using self-reported data are more feasible in primary care settings. Although a range of potential confounders were included in the analysis, we could not rule out the possibility of residual confounding. For example, the effects of unmeasured health or sleep problems (e.g., obstructive sleep apnea or snoring) cannot be overlooked, particularly on the association for long sleep. We evaluated general sleep quality by asking if one generally sleeps well. This is a relatively crude measure, and we were unable to differentiate between short sleep due to poor sleep quality or time constraints and natural short sleepers. However, our observation on the interaction between perception of sleep duration and general sleep quality provides interesting insights to the problem and stresses the need for further studies. Finally, failure to reach statistical significance in the short sleep group may reflect low statistical power due to the small number of events. In order to retain power, we have defined short sleepers as those who reported sleeping less than 6 hours, and might have failed to detect the association for extremely short sleepers as reported by previous studies.[22,23] While the association for short sleep could have been underestimated, the point estimate was compatible with that of the meta-analysis.

In accordance with previous studies,[3,4,6,8,11] we found a robust association between long sleep and increased stroke risk. The Women's Health Initiative study has shown similar results on the risk of ischemic stroke among postmenopausal women.[4] We extended the analysis to all stroke events in both sexes, and suggested a stronger association among women. The Singapore Chinese Health Study[8] found both short and long sleep to be associated with mortality from ischemic or unspecified stroke, while our study suggested an association between short sleep and risk of ischemic stroke, and between long sleep and hemorrhagic stroke. It is unclear why different sleep lengths might be associated with different stroke subtypes. Notably, the numbers in each subtypes of stroke were relatively small, and larger studies are required to replicate our findings and help to inform mechanisms.

A few studies on middle-aged participants have reported either no association between sleep duration and stroke risk[7,17] or association only for short sleep.[10] A recent study suggested an increased risk of stroke associated with insomnia, particularly in young adults.[9] Consistent with these studies, we found the association for short sleep stronger among younger participants, but for long sleep more pronounced among the older ones, although test for interaction

Figure Forest plot of the risk of stroke associated with sleep duration



Association between short (A) and long (B) sleep duration and risk of stroke. Results are presented as pooled relative risk and 95% confidence interval (CI).

was not statistically significant. Short and long sleep might have different implications in different age groups, and the interaction by age needs to be tested by larger studies in the future. Although it is possible for older people to sleep more due to less work and social demands, we have previously suggested decreased self-reported sleep duration for older participants despite long time spent in bed in this cohort.[24] Therefore, it is worth noting excessive sleep as an early sign of increased stroke risk, particularly among older people. This study suggests that those who reported persistently long sleep or substantially increased sleep had a much higher stroke risk. This again points to the importance of detecting prolonged sleep among the aging population. While there are no other studies with which to directly compare our

findings, stability of sleep as a trait is important[25] and future studies are needed to explore this matter.

The underlying mechanisms are not fully understood. Sleep deprivation has been linked to disrupted metabolism and increased cortisol secretion, sympathetic nervous activity, and low-grade inflammation, which might lead to elevated blood pressure, interrupted blood flow, and increased stroke risk.[26–28] The present prospective study and the updated meta-analysis, however, have both suggested a stronger association for long sleep duration, independent of conventional CVD risk factors. This raises the question of whether long sleep could be a cause, consequence, or early marker of ill health.[29] One important biological pathway is through inflammation, as long sleep has been associated with an increased level of inflammatory biomarkers.[30,31] Interestingly, a number of studies have associated long sleep with cardiovascular conditions including carotid artery atherosclerosis, atrial fibrillation, white matter hyperintensity volume, and left ventricular mass, which might have predisposed one to the risk of stroke.[32–37] These further supported the assumption of long sleep being a risk factor for stroke. Meanwhile, some studies suggested an association for long sleep and stroke only among those with limited physical function[18] or with a history of hypertension.[8] The First National Health and Nutrition Examination Survey (NHANES I) concluded that long sleep might represent underlying sleep-specific disease.[3] Notably, our study remained robust among those without comorbidities or who reported sleeping well, and did not attenuate with increasing length of follow-up, which makes reverse causality an unlikely explanation. Long sleep might be an early sign of system dysregulation and future stroke risk in an apparently healthy, aging population. Further targeted research is needed to examine the additional contribution of habitual sleep duration to existing risk prediction models of stroke. The mechanisms for the health risk associated with long sleep duration should be investigated using experimental designs.[38]

This prospective study and meta-analysis suggested a significant increase in stroke risk among long sleepers and a modest increase among short sleepers. Persistently long sleep or marked increase in sleep duration were associated with subsequent risk of stroke. The underlying mechanism needs further investigation. Prolonged sleep might be a useful marker of increased stroke risk in older people, and should be tested further for its utility in clinical practice.

AUTHOR CONTRIBUTIONS

The work presented here was carried out in collaboration among all authors. Drafting/revising the manuscript for content, including medical writing for content: Y.L., F.P.C., N.W.J.W., P.G.S., R.L., C.B., K.-T.K. Study concept or design: Y.L., F.P.C., N.W.J.W., P.G.S., C.B., K.-T.K. Analysis or interpretation of data: Y.L., F.P.C., N.W.J.W., P.G.S., C.B., K.-T.K. Acquisition of data: R.L. Statistical analysis: Y.L., F.P.C. Study supervision or coordination: K.-T.K. Obtaining funding: K.-T.K.

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