Nature and Science of Sleep

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Healthy Sleep Pattern, Metabolic Diseases, and Risk of Stroke: The Kailuan Cohort Study

Lili Huang[1,*], Yesong Liu[2,*], Tingting Geng[1,*], Nannan Zhang[2], Liang Sun[1], Shouling Wu[3], Xiang Gao[1]

[1]Department of Nutrition and Food Hygiene, School of Public Health, Institute of Nutrition, Fudan University, Shanghai, People's Republic of China; [2]Department of Neurology, Kailuan General Hospital, Tangshan, People's Republic of China; [3]Department of Cardiology, Kailuan General Hospital, Tangshan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiang Gao, Department of Nutrition and Food Hygiene, School of Public Health, Institute of Nutrition, Fudan University, 130 Dongan Road, Shanghai, 200032, People's Republic of China, Email xiang_gao@fudan.edu.cn; Shouling Wu, Department of Cardiology, Kailuan General Hospital, 57 Xinhua East Road, Tangshan, 063000, People's Republic of China, Tel +86 315 3025655, Fax +86 315 3725312, Email drwusl@163.com

Background: Sleep complaints were reported to be associated with stroke, however, the evidence on the association between healthy sleep pattern and stroke risk in Chinese is limited.

Objective: The aim of this study was to investigate the association between healthy sleep pattern and stroke in Chinese, and the influence of metabolic diseases on the association.

Methods: A total of 11,851 participants from the Kailuan study in China without stroke at baseline were included. We calculated a healthy sleep score according to four sleep factors, and defined the low-risk groups as follows: no insomnia, no excessive daytime sleepiness, no frequent snoring, and sleep 7–8h/d. Each low-risk sleep factor was assigned a score of 1. Cox proportional hazard models were used to assess the association between healthy sleep score and stroke. Mediation analysis was used to estimate the role of metabolic diseases (obesity, diabetes, and hypertension) in the healthy sleep score-stroke association.

Results: During a mean follow-up period of 7.7 years, 504 cases of stroke were identified. A higher healthy sleep score was associated with a lower risk of stroke in a dose-response manner (*P*-trend=0.03). The adjusted hazard ratio (HR) for participants with a healthy sleep score of 4 versus ≤2 was 0.75 (95% confidence interval [CI]: 0.56, 0.96). In addition, obesity, diabetes, and hypertension collectively explained 21.9% (95% CI: 17.2, 26.5) of the association between healthy sleep score and stroke.

Conclusion: Adherence to healthy sleep pattern was associated with a lower risk of stroke, and the favorable association was partially mediated by metabolic diseases.

Keywords: healthy sleep pattern, metabolic disease, stroke, mediation

Introduction

Evidence has demonstrated that sleep complaints, including short or long sleep duration, insomnia, frequent snoring, and excessive daytime sleepiness, have an impact on the risk of stroke.[1,2] This could be due to their effects on sympathetic nervous system activity,[3] glucose homeostasis,[4,5] and vascular structure and function.[6] These sleep behaviors do not occur in isolation, and modifications in one sleep behavior usually lead to compensatory changes in other sleep behaviors.[7] Therefore, combining various sleep behaviors into sleep patterns could reflect real-world sleep conditions. However, data on relationship between sleep pattern and risk of stroke are limited and mainly conducted in Western populations.[8–10] Moreover, the association between sleep complaints and stroke subtypes has not been well-studied,[11,12] and few studies were conducted in Asian populations.

In addition, the associations between individual sleep complaints and metabolic diseases, including obesity, diabetes, and hypertension, have been well-established.[13,14] Furthermore, these metabolic diseases are also risk factors for

Received: 12 March 2024
Accepted: 16 July 2024
Published: 5 August 2024

stroke[15–17] and thus may be involved in the association between sleep and stroke risk. To date, no data have explored to which extent the association between sleep pattern and stroke risk could be interpreted by these metabolic abnormalities.

To address these research gaps, we used data from the Kailuan study, a large community-based cohort in China, to examine the association of a healthy sleep score (combination of major sleep behaviors) with the risk of total stroke and subtypes of stroke. We also examined the role of metabolic diseases in the relationship between sleep pattern and risk of stroke.

Methods

Participants

In this analysis, participants were derived from the Kailuan study, an ongoing cohort from 2006–2007 with 101,510 Chinese adults aged 18–98 years recruited. The study design has been described in detail in previous studies.[18–20] Participants were recruited from Kailuan general hospital and 10 hospitals responsible for the healthcare of the community. All participants completed questionnaire assessments (ie socioeconomic status, lifestyles, and history of diseases), clinical, and laboratory examinations. The same assessments were conducted every two years afterwards. In 2012, information on sleep complaints was collected among 12,990 participants;[21,22] thus, the survey in 2012 was regarded as the baseline survey in this study.

We excluded those with cancer and cardiovascular disease (n=504) at baseline, without completed sleep data (n=265) or covariates (n=370), resulting in 11,851 participants for the present analysis. The study was approved by the Ethics Committee of the Kailuan General Hospital (approval number: 2006-05), and all participants provided written informed consent.

Assessment of Sleep Complaints

Sleep complaints, including insomnia, daytime sleepiness, sleep duration, and snoring, were collected via questionnaires. The detailed information has been described in previous studies.[23,24] Insomnia was assessed using the Chinese version of the Athens Insomnia Scale (AIS), comprising eight items evaluating insomnia symptoms over the past three months. Each item was scored from 0 to 3 (0=no event, 1= mild, 2= moderate, and 3= severe), with a total AIS score of ≥6 indicating insomnia. Daytime sleepiness was assessed via the Chinese version of the Epworth Sleepiness Scale (ESS) with eight items. Each item scored 0–3, representing the probability of falling asleep while engaged in specific daily life situations, with a total ESS score ≥10 indicating excessive daytime sleepiness. Sleep duration was collected via the question "usual total hours of actual sleep during the night over the past one month". Snoring was collected by self-reported snoring frequency as never/rare, occasional, or frequent during the last month.

Definition of Healthy Sleep Score

We then constructed a healthy sleep score using the above four sleep behaviors. According to the previous studies[8] and the recommendation of the American Academy of Sleep Medicine and Sleep Research Society,[25] we defined low-risk sleep factors as follows: no excessive daytime sleepiness, no insomnia, sleep 7–8 h per day, and no frequent snoring. Each low-risk sleep factor was assigned a score of 1 and 0 otherwise. Then, all component scores were summed to obtain a healthy sleep score ranging from 0 to 4, with higher scores indicating a healthier sleep pattern. The healthy sleep score was categorized into three groups according to the data distribution: healthy sleep score≤2, healthy sleep score of 3, and healthy sleep score of 4.

Assessment of Outcome-Incident Stroke Cases

The outcome was the first occurrence of stroke, including ischemic stroke and hemorrhagic stroke, according to the World Health Organization criteria.[26] The detailed adjudication of incident stroke in the Kailuan study was described previously.[22,27] In brief, participants were followed up by face-to-face interviews at biennial routine medical examinations until 31 December, 2020. The outcome was further confirmed by checking discharge summaries from the 11 hospitals and medical records from medical insurance. Outcome information was obtained directly by checking death

certificates from provincial vital statistics offices, discharge summaries, and medical records for the participants without face-to-face follow-ups.

Assessment of Metabolic Conditions and Other Related Factors

The weight and height of each participant were measured by trained study staff. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI≥28kg/m^2, aligning with the Chinese criteria.[28] The blood pressure (BP) was taken using a calibrated mercury sphygmomanometer, with at least two readings after 5 minutes of rest; the average value was used for hypertension diagnosis. Following the Seventh Report of the Joint National Committee recommendation,[29] hypertension was defined as BP measurement ≥140/90 mmHg or the self-reported use of antihypertensive medication. Fasting (8–12h) blood samples were collected in the morning and then stored at −80°C at the central laboratory of Kailuan general hospital. An auto-analyzer (Hitachi 747; Hitachi, Tokyo) was used to measure fasting blood glucose (FBG) with the hexokinase/glucose-6-phosphate dehydrogenase method. The coefficient of variation using blind quality control specimens was <2.0%.[30] Diabetes was defined as an FBG value ≥7.0 mmol/L, use of hypoglycemic drugs, or self-reported physician-diagnosed diabetes.[30] We also combined obesity, diabetes, and hypertension, and defined a composite index with values ranging from 0 to 3, representing the range from no disease to the presence of the three metabolic diseases.

Information on age, sex, education, average income per month, occupation, alcohol consumption, smoking, and physical activity were also obtained via a questionnaire by well-trained health workers.[23] Serum creatinine was measured using the sarcosine oxidase assay method (creatinine kit; BioSino Bio-technology and Science Inc., Beijing, China), with ≤6% intra- and inter-assay variable coefficients. The estimated glomerular filtration rate (eGFR) was computed according to the chronic kidney disease (CKD) Epidemiology Collaboration equation.[23] Proteinuria was assessed using the dry-chemistry method (H12-MA test strips; Changchun Dirui Medical Technology Co., Ltd., Changchun, China). In this study, participants with eGFR <60mL/min per 1.73 m^2 or proteinuria ≥2+ (>300mg/dl) were considered to have CKD.[23]

Statistical Analysis

Baseline characteristics were described across healthy sleep score, and differences among groups were tested by one-way ANOVA, Kruskal–Wallis test, or chi-square tests where appropriate. Person years were calculated from baseline until the date of stroke diagnosis, death, or 31 December 2020, whichever occurred first. Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of total stroke and stroke subtypes (ischemic and hemorrhagic stroke). The linear trend in risk across healthy sleep pattern groups was tested by using the median value for each group and treating them as continuous variables.

Based on existing literature, we adjusted for age and sex in Model 1; occupation (coal miners, other blue miners, white miners), education (illiterate and primary, middle school, high school and above), average income per month (≤1000, 1000–3000, >3000RMB), alcohol consumption (never and past, current and light drink, current and moderate and above), smoking (never, past, current), physical activity (no, occasional, frequent), use of sleep medication (no, yes) and CKD (no, yes) were further adjusted in Model 2. Obesity (no, yes), hypertension (no, yes), and diabetes (no, yes) were further adjusted in Model 3 to examine the influence of these metabolic diseases on the association between healthy sleep score and stroke. We also analyzed the association of individual low-risk sleep factors with total stroke and its subtypes.

To investigate the consistency of our findings across different demographics, subgroup analyses were performed based on age (<60 and ≥60 years), sex (men and women), education (illiterate and primary, middle school, high school and above), average income per month (≤1000, 1000–3000, >3000RMB), physical activity (no, occasional, frequent), alcohol consumption (never and past, current and light drink, current and moderate and above), smoking status (never, past, current), and CKD (no, yes). An interaction analysis between healthy sleep score and metabolic diseases was conducted using likelihood ratio tests.

Mediation effects of metabolic diseases on the association between healthy sleep score and stroke risk were evaluated using mediation package in R. Indirect, direct, and total effects for each mediator were computed via combining the mediator and outcome models with the adjustment of all the covariates in Model 2. The joint associations were also

assessed. The participants were classified into nine groups according to number of healthy sleep factors (≤2, 3, 4) and the number of metabolic diseases (0, 1, and ≥2), with number of healthy sleep factors≤2 and metabolic diseases≥2 as the reference group.

We performed several sensitivity analyses to test the robustness of our findings. First, we excluded incident cases during the first two years of follow-up, considering the possibility of reverse causality. Second, we excluded participants with CKD. Third, we excluded coal miners (41.3%), considering the generalization of results.

All analyses were conducted by R (version 4.2.0), and a two-sided *P* value<0.05 was considered significant.

Results

Characteristics of the Study Population

Among the 11,851 participants (mean age: 53.8±10.4 years; 82.4% of men), 1468 (12.4%) participants had ≤2 healthy sleep factors, 6349 (53.6%) had 4 healthy sleep factors (Table 1). Participants with higher healthy sleep score were younger, more likely to be women, White-collar workers, and less likely to consume alcohol or smoke, and had a lower proportion of obesity, hypertension, and diabetes compared to those with lower healthy sleep score (Table 1).

Table 1 Baseline Characteristics Across Healthy Sleep Score

	All	Healthy Sleep Score			
		≤2	3	4	*P*
N	11851	1468	4034	6349	
Age, year	53.8±10.4	54.5±10.10	53.7±10.9	53.6±11.4	0.02
Men, %	9764 (82.4)	1262 (86.0)	3398 (84.2)	5104 (80.4)	<0.001
Education level, %					
Illiterate and primary	748 (6.3)	99 (6.7)	260 (6.4)	389 (6.1)	<0.001
Middle school	10036 (84.7)	1279 (87.1)	3425 (84.9)	5332 (84.0)	
High school and above	1067 (9.0)	90 (6.1)	349 (8.7)	628 (9.9)	
Occupation, %					
Coalminers	4890 (41.3)	716 (48.8)	1830 (45.4)	2344 (36.9)	<0.001
Other blue collars	6106 (51.5)	687 (46.8)	11,986 (49.2)	3433 (54.1)	
White collars	855 (7.2)	65 (4.4)	218 (5.4)	572 (9.0)	
Average income per month, RMB, %					
≤1000	3473 (29.3)	346 (23.6)	1081 (26.8)	2046 (32.2)	<0.001
1001–3000	7612 (64.2)	1060 (72.2)	2705 (67.1)	3847 (60.6)	
>3000	766 (6.5)	62 (4.2)	248 (6.1)	456 (7.2)	
Alcohol consumption, %					
Never	7046 (59.5)	661 (45.0)	2140 (53.0)	4245 (66.9)	<0.001
Current, light	3475 (29.3)	539 (36.7)	1290 (32.0)	1646 (25.9)	
Current, moderate	1033 (8.7)	205 (14.0)	456 (11.3)	372 (5.9)	
Current, heavy	179 (1.5)	36 (2.5)	92 (2.3)	51 (0.8)	
Current, unknown	50 (0.4)	8 (0.5)	24 (0.6)	18 (0.3)	
Past	66 (0.6)	19 (1.3)	32 (0.8)	15 (0.1)	
Smoke, %					
Never	6661 (56.2)	612 (41.7)	1962 (48.6)	4087 (64.4)	<0.001
Past	664 (5.6)	128 (8.7)	249 (6.2)	287 (4.5)	
Current	4526 (38.2)	728 (49.6)	1823 (45.2)	1975 (31.1)	
Physical activity, %					
No	5622 (47.4)	720 (49.0)	1921 (47.6)	2981 (47.0)	<0.001
Occasional	4467 (37.7)	433 (29.5)	1356 (33.6)	2678 (42.2)	
Frequent	1762 (14.9)	315 (21.5)	757 (18.8)	690 (10.9)	

(*Continued*)

Table 1 (Continued).

	All	Healthy Sleep Score			
		≤2	3	4	*P*
Use of sleep medication	1260 (10.6)	167 (11.4)	315 (7.8)	778 (12.3)	<0.001
BMI, kg/m^2	25.0±3.38	25.6±3.56	25.1±3.34	24.8±3.22	<0.001
CKD, %	451 (3.8)	57 (3.9)	149 (3.7)	245 (3.9)	0.89
Obesity, %	1891 (15.9)	327 (22.3)	681 (16.9)	883 (13.9)	<0.001
Hypertension, %	4905 (41.4)	681 (46.4)	1683 (41.7)	2541 (40.0)	<0.001
Diabetes, %	1332 (11.2)	211 (14.4)	458 (11.4)	663 (10.4)	<0.001

Notes: Continuous variables were expressed as: mean ±SD, Categorical variables were expressed as: n (%).
Abbreviations: BMI, body mass index; CKD:, chronic kidney disease.

Association Between Healthy Sleep Pattern and Stroke Risk

During a mean follow-up period of 7.7±1.0 years, 504 incident cases of stroke were identified. We observed a higher healthy sleep score was associated with a lower risk of stroke in a dose-response manner. The adjusted HR of stroke was 0.86 (95% CI: 0.70, 0.94) for each healthy sleep score increment based on Model 2 (Table 2). Compared to healthy sleep score≤2, the adjusted HR of stroke was 0.71 (95% CI: 0.55, 0.91) for healthy sleep score of 4. The association (HR: 0.75, 95% CI: 0.56, 0.96) was slightly attenuated when further adjusting for obesity, diabetes, and hypertension. The associations were also observed in stroke subtype, with the estimated effect on hemorrhagic stroke (each healthy sleep score increment, HR: 0.62, 95% CI: 0.46, 0.83) were more pronounced than ischemic stroke (each healthy sleep score increment, HR: 0.88, 95% CI: 0.78, 0.99; Table 2).

Association Between Low-Risk Sleep Factors and Stroke Risk

The analyses of individual low-risk sleep factors showed that no excessive daytime sleepiness (HR: 0.60, 95% CI: 0.37, 0.97) and no frequent snoring (HR: 0.69, 95% CI: 0.56, 0.86) were associated with lower risk of total stroke (Table 3). The two sleep factors were also associated with stroke subtypes, with the estimated effect on hemorrhagic stroke (no excessive daytime sleepiness, HR: 0.28, 95% CI: 0.10, 0.79; no frequent snoring, HR: 0.46, 95% CI: 0.25, 0.83) were more pronounced compared to ischemic stroke (no excessive daytime sleepiness, HR: 0.64, 95% CI: 0.38, 1.05; no frequent snoring, HR: 0.73, 95% CI: 0.58, 0.92).

Table 2 The Association Between Healthy Sleep Score and Risk of Stroke

	Healthy Sleep Score, HR (95% CI)				
	≤2	3	4	Each Score Increase	*P* for Trend
Total stroke					
Case/person-year	84/11,368	177/31,278	243/48,720		
Model 1	1.00 (reference)	0.78 (0.60, 1.01)	0.68 (0.53, 0.88)	0.84 (0.76, 0.94)	0.002
Model 2	1.00 (reference)	0.78 (0.60, 1.01)	0.71 (0.55, 0.91)	0.86 (0.70, 0.94)	0.007
Model 3	1.00 (reference)	0.81 (0.63, 1.05)	0.75 (0.56, 0.96)	0.88 (079, 0.98)	0.03
Ischemic stroke					
Case/person-year	72/11,418	166/31,322	225/48,806		
Model 3	1.00 (reference)	0.86 (0.65, 1.13)	0.76 (0.58, 0.99)	0.88 (0.78, 0.99)	0.04
Hemorrhagic stroke					
Case/person-year	15/11,617	20/31,879	23/49,566		
Model 3	1.00 (reference)	0.49 (0.25, 0.95)	0.35 (0.18, 0.68)	0.62 (0.46, 0.83)	0.001

Notes: Model 1: adjusted for age, sex (men or women); Model 2: model 1 additionally adjusted for education (illiterate and primary, middle school, high school and above), average income per month (≤1000, 1000–3000, >3000RMB), occupation (coalminers, other blue collars, white collars), physical activity (no, occasion, frequent), alcohol drinking (never and past, light drinking, moderate-heavy drinking), smoking (never, past, current), use of sleep medication (no or yes), and CKD (no, yes). Model 3: model 2 additionally adjusted for obesity (no, yes), hypertension (no, yes) and diabetes (no, yes).

Table 3 The Association Between Low-Risk Sleep Factors and Risk of Stroke

Low-Risk Sleep Factors	HR (95% CI)		
	Total Stroke	Ischemic Stroke	Hemorrhagic Stroke
No excessive daytime sleepiness	0.60 (0.37, 0.97)	0.64 (0.38, 1.05)	0.28 (0.10, 0.79)
No insomnia	0.85 (0.65, 1.10)	0.87 (0.66, 1.15)	0.72 (0.34, 1.52)
Sleep 7–8h/day	0.97 (0.80, 1.18)	1.00 (0.82, 1.22)	0.62 (0.36, 1.06)
No frequent snoring	0.69 (0.56, 0.86)	0.73 (0.58, 0.92)	0.46 (0.25, 0.83)

Notes: Model was adjusted for age, sex (men or women), education (illiterate and primary, middle school, or high school and above), average income per month (≤1000, 1000–3000, >3000RMB), occupation (coalminers, other blue collars, white collars), physical activity (no, occasion, frequent), alcohol drinking (never and past, light drinking, moderate-heavy drinking), smoking (never, past, current), use of sleep medication (no or yes) and CKD (no, yes).

Subgroup Analysis

The association between healthy sleep score and stroke risk remained consistent in participants aged ≥60, men, those with low income, no physical activity, no alcohol drinking and smoking, and without CKD, but the interaction test did not reach statistical significance (P for interaction>0.05 for all; Figure S1).

Mediation Analysis and Joint Analysis

In the mediation analysis, the association between healthy sleep score and stroke risk was mediated by obesity, diabetes, and hypertension with the proportion of mediation effect ranging from 4.4% to16.1%. Collectively, the three mediators explained 21.9% (95% CI: 17.2, 26.5) of the association between healthy sleep score and stroke risk (Table 4). The joint analysis showed that compared with participants with number of healthy sleep factors≤2 and metabolic diseases≥2, participants with 4 healthy sleep factors and no metabolic diseases had a substantially lower risk of stroke (HR: 0.27, 95% CI: 0.16, 0.44; Figure 1).

In the sensitivity analyses, the results were generally robust when excluding incident cases occurring during the first two years of follow-up, coal miners, patients with CKD (Table S1).

Discussion

In this large-scale community-based study conducted in China, we found that higher healthy sleep score (combination of no insomnia, no excessive daytime sleepiness, sleep 7–8h/d, and no frequent snoring), was associated with lower total stroke and its subtypes risk. For each number increment in low-risk sleep factor, there was an 14% lower risk of total stroke. In addition, the metabolic disease, including obesity, diabetes, and hypertension, collectively explained 21.9% of the association between healthy sleep score and stroke. In addition, individuals with 4 healthy sleep factors and no metabolic diseases had approximately 70% lower risk of stroke than those with number of healthy sleep factors≤2 and metabolic diseases≥2.

Table 4 Association of Healthy Sleep Score with Total Stroke Mediated by Metabolic Diseases

	Total Effect	Natural Direct Effect	Natural Indirect Effect	Proportion Eliminated
	HR (95% CI)	HR (95% CI)	HR (95% CI)	% (95% CI)
Obesity	0.855 (0.781, 0.930)	0.879 (0.797, 0.960)	0.973 (0.968, 0.979)	16.1 (12.7, 24.5)
Diabetes	0.863 (0.783, 0.943)	0.872 (0.793, 0.951)	0.990 (0.988, 0.992)	6.2 (3.0, 9.4)
Hypertension	0.856 (0.728, 0.984)	0.862 (0.740, 0.984)	0.992 (0.984, 0.998)	4.4 (3.1, 5.7)
Total mediation	–	–	–	21.9 (17.2, 26.5)

Notes: Model was adjusted for age, sex (men or women), education (illiterate and primary, middle school, or high school and above), average income per month (≤1000, 1000–3000, >3000RMB), occupation (coalminers, other blue collars, white collars), physical activity (no, occasion, frequent), alcohol drinking (never and past, light drinking, moderate-heavy drinking), smoking (never, past, current), use of sleep medication (no or yes) and CKD (no, yes).

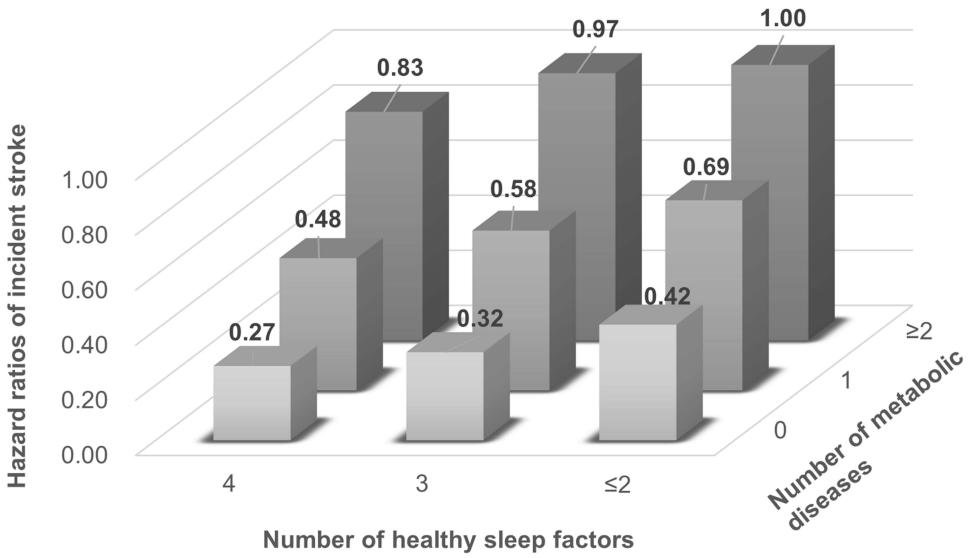

Figure 1 The joint association of healthy sleep score and metabolic diseases with stroke. Model was adjusted for age, sex (men or women), education (illiterate and primary, middle school, high school or college and above), average income per month (≤1000, 1000–3000, >3000RMB), occupation (coalminers, other blue collars, white collars), physical activity (no, occasion, frequent), alcohol drinking (never and past, light drinking, moderate-heavy drinking), smoking (never, past, current), use of sleep medication (no or yes), and CKD (no, yes).

Our study contributes to the literature regarding the influence of sleep patterns on stroke risk, which were mainly conducted in Western populations. A study using data from the UK Biobank creating a healthy sleep score using chronotype, duration, insomnia, snoring, and excessive daytime sleepiness, also found that participants with higher sleep pattern scores (healthy sleep pattern) had a 34% (95% CI: 25%, 42%) lower risk of stroke.[8] A recent retrospective case-control study also found a graded association between the accumulation of sleep disturbance symptoms (included extreme sleep duration, sleep onset latency, waking more than once, napping for >1h, unplanned napping and presence or uncertainty surrounding snorting, snorting or gasping and breathing cessation or choking) and stroke risk.[10] Compared with participants with 0–1 sleep disturbance symptoms, participants with an increased number of sleep disturbance symptoms had a graded increase in stroke risk (2–3: OR: 1.63, 95% CI: 1.36–1.96; 4–5: OR: 3.08, 95% CI: 2.49–3.80; >5: OR: 5.38, 95% CI: 4.03–7.18).[10] Our findings, together with these studies, suggest that the comprehensive index constructed using multi-dimensional sleep parameters could be useful to identify high-risk populations for stroke event.

The association between individual sleep complaints and stroke has been widely discussed. However, the conclusions were still controversial. Our study found that participants without excessive daytime sleepiness or frequent snoring were associated with a lower risk of stroke, while we did not observe significant associations of insomnia or sleep duration with risk of stroke, which were found in other studies.[31,32] Nevertheless, this also provides evidence to support the notion that using a sleep pattern may help us find a stable estimate of the sleep-stroke relationship.

Few studies have specifically explored the relationship between sleep and stroke subtypes. The Dongfeng-Tongji cohort, using a single question to assess sleep quality over the past six months, found a significant association between poor sleep quality and increased risk of ischemic and hemorrhagic strokes.[11] Similarly, a large retrospective case-control study found a dose-response association of sleep disturbance symptoms with ischemic and hemorrhagic stroke.[10] Consistent with these studies, our study also found an association of healthy sleep score with ischemic and hemorrhagic stroke. Notably, our study, together with the above-mentioned studies, observed the effect of sleep on hemorrhagic stroke was more pronounced than ischemic stroke. The pathogenesis of stroke may provide some insight. The increased risk of hemorrhagic stroke induced by sleep disturbances may be largely attributed to its direct impact on blood pressure, as hypertension is a major risk factor for cerebral hemorrhage.[33] However, due to the small sample size of incident hemorrhagic stroke cases, we cannot exclude the possibility of chance findings, and the results should be interpreted with caution.

Our mediation analyses contribute to better understanding the lower risk of stroke associated with healthy sleep pattern. Our data showed that the association between healthy sleep pattern and stroke may be explained by metabolic disease, including obesity, hypertension, and diabetes. These metabolic conditions are well-established risk factors of stroke.[17,34,35] Sleep complaints were also reported to be associated with these chronic conditions.[13,36] Experimental studies demonstrated that poor sleep quality might induce leptin production, insulin resistance, and increased sympathetic nervous system activity, which could result in the aforementioned metabolic abnormalities.[3–5,37–39] However, the moderate mediation proportion (21.9%) in this study indicated other crucial factors need to be identified. Nevertheless, in joint associations, we found that the individuals with 4 healthy sleep factors and no metabolic diseases had approximately 70% lower risk of stroke. Our findings support the importance of maintaining healthy sleep pattern and metabolic health simultaneously in stroke prevention.

Several limitations in this study should be noted. Firstly, the incident case number of hemorrhagic stroke were small, and future studies with a larger sample size are required to replicate our findings. Secondly, information on chronic conditions was collected at baseline, which may affect the inference of causal association. Thirdly, we evaluated the association between baseline sleep patterns and future stroke risk without accounting for changes in sleep habits, potentially leading to non-differential misclassification.[40] Additionally, sleep complaints were self-reported via questionnaire, introducing the possibility of measurement errors. Fourthly, because most of the participants from the Kailuan study were men (82.4%), they cannot be viewed as a representative sample of the general Chinese population. However, studying such a population could reduce residual confounding due to diverse socioeconomic factors and lifestyle patterns. Finally, residual confounding cannot be completely ruled out because of the limitation of observational study design, despite comprehensive adjustment for the potential confounders.

Conclusion

In this large cohort study in China, our findings suggested that adherence to a healthy sleep pattern, including no insomnia, no excessive daytime sleepiness, sleep 7–8h/d, and no frequent snoring, was associated with a lower risk of stroke. In addition, our data showed significant mediation effect of metabolic diseases on the association between healthy sleep pattern and stroke risk. Our findings highlight the importance of maintaining both healthy sleep pattern and normal metabolism to reduce the risk of stroke.

Data Sharing Statement

The data are available from the corresponding authors upon reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of the Kailuan General Hospital (approval number: 2006-05) and conformed to the tenets of the Declaration of Helsinki. All data from this study were published with the consent of the participants.

Acknowledgments

We thank all study participants, their relatives, the members of the survey teams at the 11 regional hospitals of the Kailuan Medical Group, and the project development and management teams at the Beijing Tiantan Hospital and the Kailuan Group.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Startup grant at Fudan University JIF201036Y.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ke J, Liu X, Ruan X, et al. Short sleep duration associated with the incidence of cardio-cerebral vascular disease: a prospective cohort study in Shanghai, China. *BMC Cardiovasc Disord*. 2023;23(1):177. doi:10.1186/s12872-023-03205-y
2. Zhou B, Jiang C, Zhang W, et al. Association of sleep duration and napping with stroke mortality in older Chinese: a 14-year prospective cohort study of the Guangzhou Biobank Cohort study. *Sleep Med*. 2023;101:384–391. doi:10.1016/j.sleep.2022.11.026
3. Coy TV, Dimsdale JE, Ancoli-Israel S, Clausen J. Sleep apnoea and sympathetic nervous system activity: a review. *J Sleep Res*. 1996;5(1):42–50. doi:10.1046/j.1365-2869.1996.00006.x
4. Schmid SM, Hallschmid M, Jauch-Chara K, et al. Disturbed glucoregulatory response to food intake after moderate sleep restriction. *Sleep*. 2011;34(3):371–377. doi:10.1093/sleep/34.3.371
5. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes*. 2010;59(9):2126–2133. doi:10.2337/db09-0699
6. Calvin AD, Covassin N, Kremers WK, et al. Experimental sleep restriction causes endothelial dysfunction in healthy humans. *J Am Heart Assoc*. 2014;3(6):e001143. doi:10.1161/jaha.114.001143
7. Wallace ML, Stone K, Smagula SF, et al. Which sleep health characteristics predict all-cause mortality in older men? An application of flexible multivariable approaches. *Sleep*. 2018;41(1). doi:10.1093/sleep/zsx189
8. Fan M, Sun D, Zhou T, et al. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK biobank participants. *Eur Heart J*. 2020;41(11):1182–1189. doi:10.1093/eurheartj/ehz849
9. Li J, Yin J, Luo Y, et al. Association of healthy sleep pattern with the risk of cardiovascular disease and all-cause mortality among people with diabetes: a prospective cohort study. *Diabet Res Clin Pract*. 2022;186:109822. doi:10.1016/j.diabres.2022.109822
10. Mc Carthy CE, Yusuf S, Judge C, et al. Sleep patterns and the risk of acute stroke: results from the INTERSTROKE International Case-Control Study. *Neurology*. 2023;100(21). doi:10.1212/wnl.0000000000207249
11. Zhou L, Yu K, Yang L, et al. Sleep duration, midday napping, and sleep quality and incident stroke: the Dongfeng-Tongji cohort. *Neurology*. 2020;94(4):e345–e356. doi:10.1212/wnl.0000000000008739
12. Chen JC, Brunner RL, Ren H, et al. Sleep duration and risk of ischemic stroke in postmenopausal women. *Stroke*. 2008;39(12):3185–3192. doi:10.1161/strokeaha.108.521773
13. Reutrakul S, Van Cauter E. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metabolism*. 2018;84:56–66. doi:10.1016/j.metabol.2018.02.010
14. Rahim A, McIsaac MA, Aronson KJ, Smith PM, Tranmer JE. The associations of shift work, sleep quality, and incidence of hypertension in Ontario adults: a population-based study. *Can J Cardiol*. 2021;37(3):513–518. doi:10.1016/j.cjca.2020.09.003
15. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. *Lancet*. 2014;383(9921):970–983. doi:10.1016/s0140-6736(13)61836-x
16. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet*. 2014;383(9933):1973–1980. doi:10.1016/s0140-6736(14)60040-4
17. Turin TC, Okamura T, Afzal AR, et al. Hypertension and lifetime risk of stroke. *J Hypertens*. 2016;34(1):116–122. doi:10.1097/hjh.0000000000000753
18. Zhang Q, Zhou Y, Gao X, et al. Ideal cardiovascular health metrics and the risks of ischemic and intracerebral hemorrhagic stroke. *Stroke*. 2013;44(9):2451–2456. doi:10.1161/STROKEAHA.113.678839
19. Wu Z, Huang Z, Lichtenstein AH, et al. The risk of ischemic stroke and hemorrhagic stroke in Chinese adults with low-density lipoprotein cholesterol concentrations < 70 mg/dL. *BMC Med*. 2021;19(1):142. doi:10.1186/s12916-021-02014-4
20. Wang L, Lee Y, Wu Y, et al. A prospective study of waist circumference trajectories and incident cardiovascular disease in China: the Kailuan Cohort Study. *Am J Clin Nutr*. 2021;113(2):338–347. doi:10.1093/ajcn/nqaa331
21. Wong JC, Li J, Pavlova M, et al. Risk factors for probable REM sleep behavior disorder: a community-based study. *Neurology*. 2016;86(14):1306–1312. doi:10.1212/wnl.0000000000002414
22. Ma C, Pavlova M, Liu Y, et al. Probable REM sleep behavior disorder and risk of stroke: a prospective study. *Neurology*. 2017;88(19):1849–1855. doi:10.1212/wnl.0000000000003902
23. Li J, Huang Z, Hou J, et al. Sleep and CKD in Chinese adults: a cross-sectional study. *Clin J Am Soc Nephrol*. 2017;12(6):885–892. doi:10.2215/cjn.09270816
24. Gao Y, Li J, Cheng FW, et al. Poor sleep quality is associated with altered taste perception in Chinese adults. *J Acad Nutr Diet*. 2021;121(3):435–445. doi:10.1016/j.jand.2020.06.019
25. Watson NF, Badr MS, Belenky G, et al. Joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. *Sleep*. 2015;38(8):1161–1183. doi:10.5665/sleep.4886
26. WHO Task Force. Stroke–1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke*. 1989;20(10):1407–1431. doi:10.1161/01.str.20.10.1407
27. Li Y, Huang Z, Jin C, et al. Longitudinal change of perceived salt intake and stroke risk in a Chinese population. *Stroke*. 2018;49(6):1332–1339. doi:10.1161/strokeaha.117.020277

28. Mu L, Liu J, Zhou G, et al. Obesity prevalence and risks among Chinese adults: findings from the China PEACE Million Persons Project, 2014–2018. *Circ Cardiovasc Qual Outcomes*. 2021;14(6):e007292. doi:10.1161/circoutcomes.120.007292
29. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560–2572. doi:10.1001/jama.289.19.2560
30. Jin C, Li G, Rexrode KM, et al. Prospective study of fasting blood glucose and intracerebral hemorrhagic risk. *Stroke*. 2018;49(1):27–33. doi:10.1161/strokeaha.117.019189
31. Wu MP, Lin HJ, Weng SF, Ho CH, Wang JJ, Hsu YW. Insomnia subtypes and the subsequent risks of stroke: report from a nationally representative cohort. *Stroke*. 2014;45(5):1349–1354. doi:10.1161/strokeaha.113.003675
32. Titova OE, Michaëlsson K, Larsson SC. Sleep duration and stroke: prospective cohort study and Mendelian randomization analysis. *Stroke*. 2020;51(11):3279–3285. doi:10.1161/strokeaha.120.029902
33. Magid-Bernstein J, Girard R, Polster S, et al. Cerebral hemorrhage: pathophysiology, treatment, and future directions. *Circ Res*. 2022;130(8):1204–1229. doi:10.1161/circresaha.121.319949
34. Curioni C, André C, Veras R. Weight reduction for primary prevention of stroke in adults with overweight or obesity. *Cochrane Database Syst Rev*. 2006;2006(4):Cd006062. doi:10.1002/14651858.CD006062.pub2
35. Bradley SA, Spring KJ, Beran RG, Chatzis D, Killingsworth MC, Bhaskar SMM. Role of diabetes in stroke: recent advances in pathophysiology and clinical management. *Diabetes Metab Res Rev*. 2022;38(2):e3495. doi:10.1002/dmrr.3495
36. Mansukhani MP, Covassin N, Somers VK. Apneic sleep, insufficient sleep, and hypertension. *Hypertension*. 2019;73(4):744–756. doi:10.1161/hypertensionaha.118.11780
37. Broussard JL, Kilkus JM, Delebecque F, et al. Elevated ghrelin predicts food intake during experimental sleep restriction. *Obesity*. 2016;24(1):132–138. doi:10.1002/oby.21321
38. Stern JH, Grant AS, Thomson CA, et al. Short sleep duration is associated with decreased serum leptin, increased energy intake and decreased diet quality in postmenopausal women. *Obesity*. 2014;22(5):E55–E61. doi:10.1002/oby.20683
39. Cui H, López M, Rahmouni K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. *Nat Rev Endocrinol*. 2017;13(6):338–351. doi:10.1038/nrendo.2016.222
40. Leng Y, Cappuccio FP, Wainwright NW, et al. Sleep duration and risk of fatal and nonfatal stroke: a prospective study and meta-analysis. *Neurology*. 2015;84(11):1072–1079. doi:10.1212/wnl.0000000000001371