Stroke

CLINICAL AND POPULATION SCIENCES

Sleep Duration and Stroke

Prospective Cohort Study and Mendelian Randomization Analysis

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BACKGROUND AND PURPOSE: Studies of sleep duration in relation to specific types of stroke are scarce. Moreover, the results are inconclusive and causality remains unclear. Our objective was to investigate whether sleep duration is associated with risk of stroke and its types using observational and Mendelian randomization designs.

METHODS: The prospective study included 79 881 women and men (45–79 years of age) who were followed up for incident stroke or death over a mean follow-up of 14.6 years (1 164 646 person-years) through linkage to Swedish Registers. For the Mendelian randomization study, single-nucleotide polymorphisms associated with sleep duration were identified from a genome-wide association study. Summarized data for genetic associations with stroke were obtained from publicly available data of the MEGASTROKE and the International Stroke Genetics Consortia.

RESULTS: Compared with normal sleep duration, long sleep (≥9 hours per day) was associated with increased risk of total and ischemic stroke (hazard ratios [95% CI], 1.12 [1.03–1.22] and 1.14 [1.03–1.24], respectively), whereas short sleep (<7 h/d) was linked to higher risk of intracerebral hemorrhage (hazard ratio [95% CI], 1.21 [1.03–1.41]). The 2-sample Mendelian randomization analysis supported no causal association of short or long sleep duration with ischemic stroke as a whole.

CONCLUSIONS: In a prospective study, long sleep duration was associated with increased risk of total and ischemic stroke, whereas short sleep was linked to increased risk of intracerebral hemorrhage. However, the Mendelian randomization analysis did not show a significant detrimental effect of short or long sleep duration on the risk of total stroke or stroke types.

Key Words: Mendelian randomization analysis ■ polymorphisms, single-nucleotide ■ risk ■ sleep ■ Sweden

Stroke is one of the leading causes of death and disability worldwide and primary prevention is essential. A growing evidence suggests a multifactorial origin but traditional risk factors, such as diabetes mellitus, unhealthy dietary choices, smoking, and a sedentary lifestyle do not explain the entire stroke risk.[1] Observational studies indicate that sleep outside the recommended sleep duration hours is associated with the most common clinical risk factors for cardiovascular pathologies, such as hypertension, obesity, diabetes mellitus, and dyslipidemia,[2] and thus may be implicated in the development of stroke. Some prospective studies have investigated the link between sleep duration and risk of stroke.[3] However, the results remain inconsistent indicating either a curvilinear relationship with higher risk of stroke among short and long sleepers,[4] higher incidence of stroke only among those who reported short sleep[5] or long sleep duration,[6,7] or a null association.[8,9] A recent dose-response meta-analysis of 16 prospective studies, demonstrated a significantly higher risk of stroke among long sleepers compared with those sleeping 7 hours.[3]

Studies on the effect of sleep duration on specific types of stroke and ischemic stroke subtypes are scarce,[3] and only few studies, mainly in Asian populations, have investigated the link between sleep duration and hemorrhagic stroke. For example, a Japanese

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Nonstandard Abbreviations and Acronyms

ICH	intracerebral hemorrhage
LAS	large-artery atherosclerotic stroke
MR	Mendelian randomization
SNP	single nucleotide polymorphism

prospective study of 27 896 adults showed that long sleep duration (defined as ≥9 hours) compared with 7 hours of sleep was associated with 51% higher risk of total stroke mortality and 65% higher risk of ischemic stroke mortality, respectively.[10] The same study found a reduced risk of hemorrhagic stroke mortality in those who reported short sleep duration (≤6 hours) compared with 7 hours of sleep with a more pronounced association in men (hazard ratio, 0.31 [95% CI, 0.16–0.64]).[10] The inconsistency in the results from observational studies could be explained by low number of incident cases of stroke types in some studies, differences in the definition of short and long sleep duration, or reporting bias. Moreover, it remains unclear whether the association between sleep duration and risk of stroke is causal as observational studies are susceptible to confounding and reverse causality.

Mendelian randomization (MR) is an epidemiological study design in which genetic variants associated with the modifiable risk factor (eg, sleep traits) are used as proxy indicators to establish causal effect on outcomes.[11] The MR design reduces confounding by environmental factors because alleles are randomly allocated at conception, and it avoids reverse causation bias because disease cannot affect genotype.[11,12] None of the previous studies on sleep duration and stroke used the MR design.

In the present study, we aimed to investigate the association between sleep duration and risk of different stroke types in a prospective cohort study of 79 881 Swedish men and women. In addition, we performed a 2-sample MR study to explore whether sleep duration is causally associated with overall stroke or any stroke subtype.

METHODS

Data Availability

The data that support findings of the prospective cohort study are available upon application to the Swedish Infrastructure for Medical Population-Based Life-Course Environmental Research (https://www.simpler4health.se). Data used for the MR analyses are publicly available from the MEGASTROKE consortium (https://www.megastroke.org/)[13] and the International Stroke Genetics Consortium (https://strokegenetics.org/).[14]

Study Population

In the primary analysis, we used data from the Swedish Infrastructure for Medical Population-Based Life-course Environmental Research, which consists of data from 2 prospective cohorts, including the Swedish Mammography Cohort (N=39 227 women aged 49–83 years in 1997) and the Cohort of Swedish Men (N=48 850 men aged 45–79 in 1997). In 1997, participants completed a questionnaire about possible risk factors for aging-associated diseases. In the present analysis, we excluded individuals with an erroneous or a missing personal identity number (as they could not be followed up through population-based registers); those who died or had a previous diagnosis of stroke or cancer before 1 January 1998; and those who had missing information on sleep duration (Figure I in the Data Supplement). Data from 79 881 participants (35 696 women and 44 185 men) with a mean baseline age of 61 (45–83) years were available for the analysis. The study was approved by the Swedish Ethical Review Authority.

Ascertainment of Stroke Cases and Follow-Up

Information on incident stroke cases was obtained by record linkage with the Swedish National Patient Register, which covers in-patient care in Sweden since 1987 and outpatient visits from private and public caregivers since 2001. Information on deaths within the cohort was obtained from the Swedish Cause of Death Register. Stroke types were classified according to the *International Classification of Diseases*, *Tenth Revision*: ischemic stroke (code I63), intracerebral hemorrhage (ICH; I61), subarachnoid hemorrhage (I60), and unspecified stroke (I64). Participants were followed up from January 1, 1998 to the date of diagnosis of stroke, death from any cause, or December 31, 2014, whichever occurred first.

Assessment of Sleep Duration and Potential Confounders

Information on sleep duration and potential confounders, including education, weight, height, physical activity, smoking status and history, alcohol consumption, and history of hypertension, high cholesterol levels, and diabetes mellitus was obtained from the questionnaire completed by the participants in the autumn of 1997. Participants were asked to indicate how many hours per day they usually sleep. In the main analyses, sleep duration was divided into 3 categories: short sleep, <7 hours per day; normal sleep, 7 to <9 hours of sleep; and long sleep, ≥9 hours of sleep. Pack-years of smoking were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years of smoking. For descriptive statistics, alcohol consumption in current drinkers was calculated by multiplying the frequency of consumption of beer, wine, and liquor by the amount consumed at each occasion.

Two-Sample MR Analysis

We used publicly available summarized data for genetic associations with stroke from the MEGASTROKE consortium[13] and the International Stroke Genetics consortium.[14] Studies included in the consortia were approved by local research ethics committees and institutional review boards and all participants provided written informed consent.[13] The MEGASTROKE

consortium included 446 696 individuals of European ancestry (406 111 noncases and 40 585 cases of any stroke); the number of cases of ischemic stroke were 34 217 overall, 4373 for large-artery atherosclerotic stroke (LAS), 5386 for small vessel stroke, and 7193 for cardioembolic stroke. The Trial of ORG 10172 in Acute Stroke Treatment criteria was used to subtype ischemic stroke. Summary statistics data for ICH were available from a genome-wide association meta-analysis of 3026 European-descent individuals (1545 cases and 1481 noncases).[14] The present MR analysis was approved by the Swedish Ethical Review Authority.

Instrumental Variable Selection

We selected single-nucleotide polymorphisms (SNPs) previously shown to be associated with the sleep traits at the level of genome-wide significance ($P<5\times10^{-8}$) among 446 118 UK Biobank participants of European ancestry.[15] The number of identified SNPs were 27 for short sleep duration (n=106 192 cases with <7 hours of sleep relative to 305 742 controls with 7–8 hours of sleep) and 8 for long sleep (n=34 184 cases with ≥9 hours of sleep).[15] One to 2 SNPs were unavailable in the MEGASTROKE consortium data sets. Thus, estimates for 26 SNPs were included in the analysis of short sleep duration and all stroke, all ischemic stroke, cardioembolic stroke, and small vessel stroke; 27 SNPs in the analysis of short sleep and LAS; and 6 SNPs in the analysis of long sleep and all stroke outcomes. In relation to ICH, 4 to 12 SNPs were unavailable in the data set obtained from the International Stroke Genetics Consortium. Details of the SNPs used as instrumental variables are available in Table I in the Data Supplement.

Statistical Analysis

In our analysis based on observational data, Cox proportional hazards regression models were used to obtain hazard ratios with 95% CI with age as the time variable and adjusted for sex (as a stratification variable) in the basic model. In a multivariable model, we further adjusted for education (less than high school, high school, or university), smoking status and pack-years of smoking (never, former <20 pack-years, former ≥20 pack-years, current <20 pack-years, or current ≥20 pack-years), alcohol intake (never drinkers, past drinkers, <1 drink/wk, 1–6 drinks/wk, 7–14 drinks/wk, 15–21 drinks/wk or >21 drinks/wk), walking/bicycling (hardly ever, <20 min/d, 20–40 min/d, >40 min/d), exercise (<1 h/wk, 1 h/wk, 2–3 h/wk, ≥4 h/wk), body mass index (weight divided by the square of height; <22.5, 22.5–24.9, 25.0–29.9, or ≥30 kg/m^2), and history of hypertension (yes/no), hypercholesterolemia (yes/no), and diabetes mellitus (yes/no) at baseline. Potential confounders were selected using directed acyclic graphs[16] based on our a priori knowledge of the relationships among potential confounders, intermediates, exposure, and outcome variables, as well as on existing information regarding factors associated with stroke and sleep duration.[1,2] There was no evidence of significant violation of the proportional hazards assumption, as determined by a test based on Schoenfeld residuals. In a sensitivity analysis, we divided sleep duration into 5 categories: very short sleep, <6 hours; short sleep, 6 to <7 hours; normal sleep, 7 to <9 hours; long sleep, 9 to <10 hours; and very long sleep, ≥10 hours of sleep per day. *P* values below 0.05 were considered statistically significant. The analyses were conducted using SAS (SAS Institute, Inc, Cary, NC).

The random-effects inverse-variance weighted method was used in the main MR analyses and the weighted median method as complementary analyses. The MR Pleiotropy Residual Sum and Outlier method[17] was used to evaluate potential outlier SNPs. Additionally, we used the MR-Egger method to assess directional pleiotropy.[18] Reported odds ratios with their 95% CI are per genetically predicted one unit increase in log odds of short and long sleep duration. All statistical tests are 2-tailed. The MR analysis was performed using the mrrobust package in Stata (StataCorp LP, College Station, TX)[19] and MR package for R (R Foundation for Statistical Computing, Vienna, Austria).[20]

RESULTS

Prospective Cohort Study

Baseline characteristics of the study participants by category of sleep duration are presented in Table 1. Compared with those who reported 7 to <9 hours of sleep per day, individuals with reports of short or long sleep duration were on average older, had lower educational attainment, were more likely to be current smokers, had higher body mass index, and were more likely to have history of hypertension, high cholesterol levels, and diabetes mellitus. Long sleepers had higher alcohol consumption and were less physically active than those who habitually slept between 7 to <9 hours per day (Table 1). The mean follow-up was 14.6 years (1 164 646 person-years). During this period, 8091 participants were diagnosed with stroke. Among them 6041 had ischemic stroke; 1062 had hemorrhagic stroke (826 ICH; 236 subarachnoid hemorrhage); and 988 had undefined type of stroke. The mean age at diagnosis of any stroke was 75.9 (SD, 9.0) years.

Table 1. Baseline Characteristics According to Sleep Duration in 79 881 Swedish Adults

	Habitual Sleep Duration, h/d		
Characteristics*	<7	7–<9	≥9
No. of participants	18 679	56 361	4841
Age, y	61.4±9.9	60.3±9.2	64.1±9.3
Alcohol intake in current drinkers, g/d	6.6±11.5	6.6±9.2	8.1±23.2
Postsecondary education, %	16.3	18.1	15.7
Current smokers, %	25.2	23.7	26.5
Walk/bicycle ≥40 min/d, %	41.7	40.4	39.7
Exercise ≥2 h/wk, %	66.0	67.6	65.0
Body mass index ≥30 kg/m^2, %	12.2	9.3	14.7
Hypertension, %	24.4	22.0	26.1
Hypercholesterolemia, %	13.3	12.5	14.4
Diabetes mellitus, %	6.5	5.6	8.5

*Values are means±SD or percentages.

In the basic model adjusted for age and sex, both short and long sleep duration was associated with a modest increased risk of total stroke compared with normal sleep duration. Further adjustment for potential confounders attenuated the associations and only the association with long sleep duration persisted (Table 2). A 21% higher risk of ischemic stroke was observed in those who reported habitual long sleep duration compared with those who slept 7 to <9 hours per day. This association was attenuated but remained statistically significant in the multivariable model. In contrast, short sleep duration was associated with an increased risk of ICH compared with normal sleep duration in both models. No association between sleep duration and total hemorrhagic stroke or subarachnoid hemorrhage was observed.

In a sensitivity analysis, the results of multivariable analyses were similar after dividing sleep duration into 5 groups, although the associations of sleep duration and total and ischemic stroke were not statistically significant in the small group of participants (1.7%) who reported ≥10 hours of sleep (Table II in the Data Supplement).

Two-Sample MR Analysis

There was no association of genetic liability to short or long sleep duration with overall stroke (Figures 1 and 2). However, there was suggestive evidence for an association of short sleep duration with higher odds of LAS (odds ratio, 1.41 [95% CI, 1.02–1.95]; *P*=0.04; Figure 1). This association was similar in the sensitivity analysis utilizing the weighted median method, though the estimate was less precise (odds ratio, 1.44 [95% CI, 0.91–2.27]; *P*=0.117; Figure 1). No associations of sleep duration with other stroke subtypes were observed (Figures 1 and 2). There was no evidence of directional pleiotropy (Table III in the Data Supplement). The link between genetically predicted sleep traits and ICH is presented in Table III in the Data Supplement due to low precision.

DISCUSSION

Principal Findings

The present study utilized a prospective cohort study design as well as MR technique to evaluate the link

Table 2. HR (95% CI) of Stroke According Sleep Duration in 79 881 Swedish Adults, 1998–2014

	Habitual Sleep Duration, h/d		
Outcome and model	<7	7 to <9	≥9
Total stroke*			
Total no. of cases	2031	5417	643
Total person-years of follow-up	267 881	832 675	64 090
Age and sex-adjusted model	1.07 (1.02–1.13)†	1.00 (reference)	1.19 (1.10–1.29)†
Multivariable model‡	1.04 (0.99–1.09)	1.00 (reference)	1.12 (1.03–1.22)†
Total ischemic stroke			
Total no. of cases	1501	4051	489
Age and sex-adjusted model	1.06 (1.00–1.13)	1.00 (reference)	1.21 (1.10–1.33)†
Multivariable model‡	1.03 (0.96–1.32)	1.00 (reference)	1.14 (1.03–1.24)†
Total hemorrhagic stroke			
Total no. of cases	275	712	75
Age and sex-adjusted model	1.15 (1.00–1.32)	1.00 (reference)	1.14 (0.90–1.43)
Multivariable model‡	1.13 (0.98–1.30)	1.00 (reference)	1.09 (0.86–1.39)
ICH			
Total no. of cases	225	540	61
Age and sex-adjusted model	1.22 (1.05–1.43)†	1.00 (reference)	1.17 (0.90–1.53)
Multivariable model‡	1.21 (1.03–1.41)†	1.00 (reference)	1.12 (0.86–1.46)
SAH			
Total no. of cases	50	172	14
Age and sex-adjusted model	0.89 (0.65–1.23)	1.00 (reference)	1.01 (0.59–1.74)
Multivariable model‡	0.88 (0.64–1.21)	1.00 (reference)	1.00 (0.58–1.73)

HR indicates hazard ratio; ICH, intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.

*Includes ischemic stroke, ICH, SAH, and undefined type of stroke.

†*P* values <0.05.

‡The Cox proportional hazards regression model was adjusted for age (underlying time scale), sex (as a stratification variable), education, smoking status and pack-years of smoking, alcohol intake, walking/bicycling, exercise, body mass index, and history of hypertension, hypercholesterolemia, and diabetes mellitus.

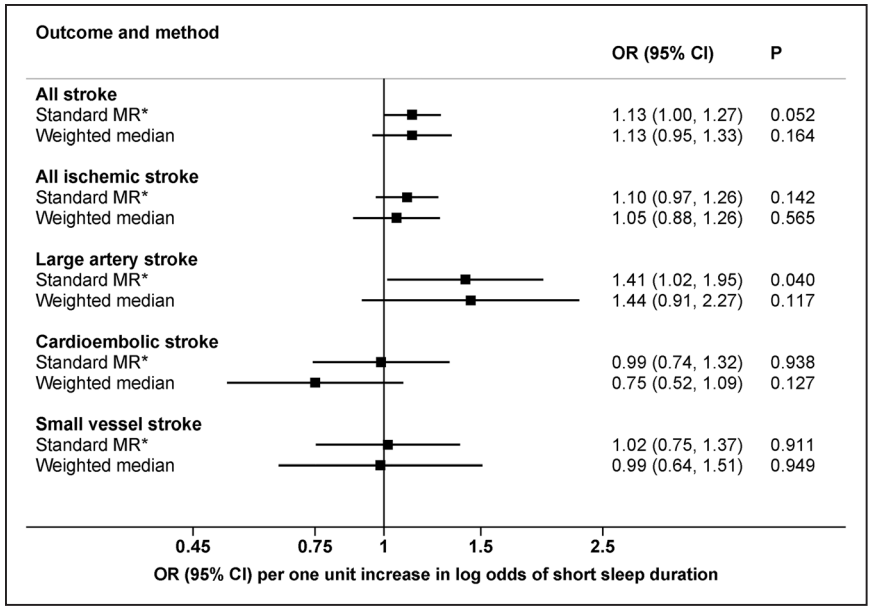

Figure 1. Associations of genetic liability to short sleep duration with overall stroke, ischemic stroke, and its subtypes.
Odds ratios (OR) are per one unit increase in log odds of short sleep duration. MR indicates Mendelian randomization. *Random-effects inverse-variance weighted method.

between sleep duration and risk of total stroke and specific stroke types and subtypes. In the cohort study, long sleep duration was associated with an increased risk of total stroke and ischemic stroke, whereas short sleep duration was associated with an increased risk of ICH. The MR analyses did not confirm these observational findings but suggested an association between short sleep duration and increased risk of LAS.

Comparisons With Other Studies

Findings of our cohort study are consistent with other observational studies[4,6,7,21] and demonstrate an increased risk of total stroke and ischemic stroke associated with long sleep, though the association was rather weak. However, our MR analyses did not confirm the observational findings which may indicate that residual confounding (eg, from chronic health conditions, such as obesity or obstructive sleep apnea) may have biased the results of observational studies. Long sleep may be an early sign of health deterioration, which increases risk of stroke. In the MR analysis, we observed a suggestive association between genetic liability to short sleep duration and higher odds of LAS, suggesting biological heterogeneity of the effect of sleep on different ischemic stroke subtypes. The mechanism underlying the associations between short sleep and stroke is likely multifactorial, especially considering that sleep deprivation is associated with common risk factors of cardiovascular events such as impaired glucose and insulin metabolism,[22] increase caloric intake and unhealthy food choices,[23,24] and hypertension.[25] A study in mice showed that sleep deprivation resulted in increased blood pressure, endothelial dysfunction, and markers of oxidative stress and

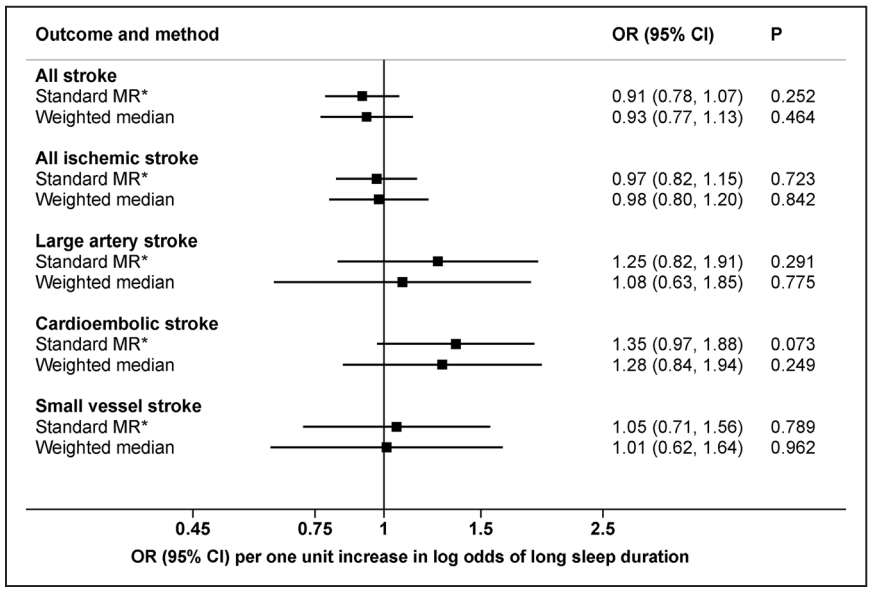

Figure 2. Associations of genetic liability to long sleep duration with overall stroke, ischemic stroke, and its subtypes.
Odds ratios (OR) are per one unit increase in log odds of long sleep duration. MR indicates Mendelian randomization. *Random-effects inverse-variance weighted method.

inflammation.[26] Due to variations in stroke cause, there might be differences in the contribution of risk factors to the pathophysiology of ischemic stroke subtypes.[1] For example, a recent MR study provided evidence for a robust association between genetic liability to insomnia and increased odds of LAS but not small vessel stroke or cardioembolic stroke.[12]

Only one prospective study, to date, has investigated the link between sleep duration and subtypes of hemorrhagic stroke.[21] In our study, a 21% increased risk of ICH was observed in participants who reported short sleep duration (defined as <7 hours), compared with normal sleep, after adjustment for potential confounders. In contrast, a previous study of 3135 Chinese adults found an increased risk of total hemorrhagic stroke in women who reported long sleep duration (>8 hours per night) compared with those who indicated 6 to 8 hours of sleep (hazard ratio, 3.58 [95% CI, 1.28–10.06]) but showed no association with short sleep.[27] A Japanese prospective study of 27 896 adults demonstrated a reduced risk of hemorrhagic stroke mortality among individuals who reported short sleep duration (≤6 hours) compared with 7 hours of sleep.[10] A recent study of 31 750 participants found no evidence of the association between sleep duration and risk of total hemorrhagic stroke or ICH and subarachnoid hemorrhage.[21] The discrepancy in results of observational studies in relation to hemorrhagic stroke could be due to differences in the definition of short and long sleep duration; ethnical and cultural diversity and number of incident cases of specific stroke subtypes. Our secondary MR analyses of sleep duration and ICH showed no significant association between short sleep duration and ICH, but the direction of the association in the inverse-variance weighted and weighted median analyses was consistent with a detrimental effect. However, these findings should be interpreted with caution due to the small sample size and low precision.

Strengths and Limitations

Important strengths of our prospective cohort study are large sample size and large number of incident stroke cases objectively assessed through linkage to linkage to nationwide population-based registers. In addition, we investigated the association of sleep duration with several stroke subtypes. Several limitations, however, apply to our observational study. Similar to other prospective studies, sleep duration was based on self-reports. It has been previously shown that self-reported sleep duration has a tendency to overestimation compared with objectively measured sleep (eg, with actigraphy).[28] However, dividing sleep duration into more extreme categories revealed similar results of a null association between very short sleep duration (<6 hours) and the risk of stroke compared with a reference group of 7 to <9 hours. Another limitation is that no particular time frame was specified in the question about sleep duration. Observational and interventional studies on the association between objectively measured sleep duration and risk of stroke are needed to confirm our findings. In addition, sleep duration might change during the follow-up period. However, a meta-analysis of 65 studies that measured sleep characteristics by polysomnography or actigraphy in 3577 participants aged 5 to 102 years, demonstrated that after 60 years of age total sleep time remained unchanged.[29] Other potential confounders, such as occupational status, could not be controlled for in the present analysis. Moreover, the incidence of subarachnoid hemorrhage in the present study was low which could increase the risk of type 2 error. Due to observational nature of this study, we cannot rule out residual and unmeasured confounding.

The main strength of our MR study includes the large number of overall stroke and total ischemic stroke cases and data on etiologic subtypes of ischemic stroke. In addition, our MR analysis was restricted to European-descent individuals which reduced potential bias due to population stratification. Finally, we have used methods to correct for possible pleiotropy and identify potential outliers SNPs (MR-Egger and MR Pleiotropy Residual Sum and Outlier). However, our MR study has several limitations. One of the limitations is that the analyses of the associations between genetically predicted sleep traits and ICH were based on a small sample, and we cannot exclude that weak associations might be overlooked. Further large MR studies in other populations are warranted. Another limitation is the relatively small number of SNPs in particular for long sleep duration. This reduced the precision in our MR analyses and we can therefore not exclude that we may have missed weak associations. In addition, suggestive evidence of the association of genetically predicted short sleep duration with increased risk of LAS should be investigated further.

In conclusion, our prospective cohort study indicated that long sleep duration is associated with increased risk of total and ischemic stroke. In addition, short sleep was linked to increased risk of ICH. However, 2-sample MR analysis did not support these findings but provided suggestive evidence that genetically predicted short sleep duration is associated with an increased risk of LAS. Given the variations in stroke cause, analyses of the effect of modifiable risk factors on stroke subtypes might be beneficial for better understanding therapeutic and preventive strategies.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Figure I
Tables I–III

REFERENCES

1. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. *Circ Res*. 2017;120:472–495. doi: 10.1161/CIRCRESAHA.116.308398
2. Phua CS, Jayaram L, Wijeratne T. Relationship between sleep duration and risk factors for stroke. *Front Neurol*. 2017;8:392. doi: 10.3389/fneur.2017.00392
3. He Q, Sun H, Wu X, Zhang P, Dai H, Ai C, Shi J. Sleep duration and risk of stroke: a dose-response meta-analysis of prospective cohort studies. *Sleep Med*. 2017;32:66–74. doi: 10.1016/j.sleep.2016.12.012
4. Fang J, Wheaton AG, Ayala C. Sleep duration and history of stroke among adults from the USA. *J Sleep Res*. 2014;23:531–537. doi: 10.1111/jsr.12160
5. von Ruesten A, Weikert C, Fietze I, Boeing H. Association of sleep duration with chronic diseases in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. *PLoS One*. 2012;7:e30972. doi: 10.1371/journal.pone.0030972
6. Kakizaki M, Kuriyama S, Nakaya N, Sone T, Nagai M, Sugawara Y, Hozawa A, Fukudo S, Tsuji I. Long sleep duration and cause-specific mortality according to physical function and self-rated health: the Ohsaki Cohort Study. *J Sleep Res*. 2013;22:209–216. doi: 10.1111/j.1365-2869.2012.01053.x
7. Leng Y, Cappuccio FP, Wainwright NW, Surtees PG, Luben R, Brayne C, Khaw KT. Sleep duration and risk of fatal and nonfatal stroke: a prospective study and meta-analysis. *Neurology*. 2015;84:1072–1079. doi: 10.1212/WNL.0000000000001371
8. Helbig AK, Stöckl D, Heier M, Ladwig KH, Meisinger C. Symptoms of insomnia and sleep duration and their association with incident strokes: findings from the population-based MONICA/KORA Augsburg Cohort Study. *PLoS One*. 2015;10:e0134480. doi: 10.1371/journal.pone.0134480
9. Westerlund A, Bellocco R, Sundström J, Adami HO, Åkerstedt T, Trolle Lagerros Y. Sleep characteristics and cardiovascular events in a large Swedish cohort. *Eur J Epidemiol*. 2013;28:463–473. doi: 10.1007/s10654-013-9802-2
10. Kawachi T, Wada K, Nakamura K, Tsuji M, Tamura T, Konishi K, Nagata C. Sleep duration and the risk of mortality from stroke in Japan: the Takayama Cohort Study. *J Epidemiol*. 2016;26:123–130. doi: 10.2188/jea.JE20140272
11. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32:1–22. doi: 10.1093/ije/dyg070
12. Larsson SC, Markus HS. Genetic liability to insomnia and cardiovascular disease risk. *Circulation*. 2019;140:796–798. doi: 10.1161/CIRCULATIONAHA.119.041830
13. Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese AK, van der Laan SW, Gretarsdottir S, et al; AFGen Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; INVENT Consortium; STARNET; BioBank Japan Cooperative Hospital Group; COMPASS Consortium; EPIC-CVD Consortium; EPIC-InterAct Consortium; International Stroke Genetics Consortium (ISGC); METASTROKE Consortium; Neurology Working Group of the CHARGE Consortium; NINDS Stroke Genetics Network (SiGN); UK Young Lacunar DNA Study; MEGASTROKE Consortium. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet*. 2018;50:524–537. doi: 10.1038/s41588-018-0058-3
14. Woo D, Falcone GJ, Devan WJ, Brown WM, Biffi A, Howard TD, Anderson CD, Brouwers HB, Valant V, Battey TW, et al; International Stroke Genetics Consortium. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J Hum Genet*. 2014;94:511–521. doi: 10.1016/j.ajhg.2014.02.012
15. Dashti HS, Jones SE, Wood AR, Lane JM, van Hees VT, Wang H, Rhodes JA, Song Y, Patel K, Anderson SG, et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat Commun*. 2019;10:1100. doi: 10.1038/s41467-019-08917-4
16. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology*. 2011;22:745. doi: 10.1097/EDE.0b013e318225c2be
17. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50:693–698. doi: 10.1038/s41588-018-0099-7
18. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44:512–525. doi: 10.1093/ije/dyv080
19. Spiller W, Davies NM, Palmer TM. Software application profile: Mrrobust - a tool for performing two-sample summary mendelian randomization analyses. *Int J Epidemiol*. 2019;48:684–690.
20. Yavorska OO, Burgess S. MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. *Int J Epidemiol*. 2017;46:1734–1739. doi: 10.1093/ije/dyx034
21. Zhou L, Yu K, Yang L, Wang H, Xiao Y, Qiu G, Liu X, Yuan Y, Bai Y, Li X, et al. Sleep duration, midday napping, and sleep quality and incident stroke: the Dongfeng-Tongji cohort. *Neurology*. 2020;94:e345–e356.
22. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. 1999;354:1435–1439. doi: 10.1016/S0140-6736(99)01376-8
23. Brondel L, Romer MA, Nougues PM, Touyarou P, Davenne D. Acute partial sleep deprivation increases food intake in healthy men. *Am J Clin Nutr*. 2010;91:1550–1559. doi: 10.3945/ajcn.2009.28523
24. Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. *Nat Commun*. 2013;4:2259. doi: 10.1038/ncomms3259
25. Palagini L, Bruno RM, Gemignani A, Baglioni C, Ghiadoni L, Riemann D. Sleep loss and hypertension: a systematic review. *Curr Pharm Des*. 2013;19:2409–2419. doi: 10.2174/1381612811319130009
26. Kröller-Schön S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S, Heimann A, Schmidt FP, Pinto A, Kvandova M, et al. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. *Eur Heart J*. 2018;39:3528–3539. doi: 10.1093/eurheartj/ehy333
27. Song Q, Liu X, Zhou W, Wang L, Zheng X, Wang X, Wu S. Long sleep duration and risk of ischemic stroke and hemorrhagic stroke: the Kailuan Prospective Study. *Sci Rep*. 2016;6:33664. doi: 10.1038/srep33664
28. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? *Epidemiology*. 2008;19:838–845. doi: 10.1097/EDE.0b013e318187a7b0
29. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*. 2004;27:1255–1273. doi: 10.1093/sleep/27.7.1255