CLINICAL AND POPULATION SCIENCES

Sleep Duration and Stroke
Prospective Cohort Study and Mendelian Randomization Analysis

Olga E. Titova, PhD; Karl Michaëlsson, PhD, MD; Susanna C. Larsson, PhD

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 (1164,646 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. 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, and thus may be implicated in the development of stroke. Some prospective studies have investigated the link between sleep duration and risk of stroke. However, the results remain inconsistent indicating either a curvilinear relationship with higher risk of stroke among short and long sleepers, higher incidence of stroke only among those who reported short sleep or long sleep duration, or a null association. 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. Studies on the effect of sleep duration on specific types of stroke and ischemic stroke subtypes are scarce, 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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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. 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]). 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 (e.g., sleep traits) are used as proxy indicators to establish causal effect on outcomes. 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. 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/) and the International Stroke Genetics Consortium (https://strokegenetics.org/).

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 and the International Stroke Genetics consortium. Studies included in the consortia were approved by local research ethics committees and institutional review boards and all participants provided written informed consent. The MEGASTROKE
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 was used to evaluate potential outlier SNPs. Additionally, we used the MR-Egger method to test for directional pleiotropy. Reported odds ratios with their 95% CI were 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) and MR package for R (R Foundation for Statistical Computing, Vienna, Austria).

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 |
|-------------------------------------------------|------|------|------|
| 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/m², %                   | 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 between sleep duration and stroke risk. The results indicated that both short and long sleep durations were associated with an increased risk of total stroke, with a more pronounced effect for long sleep duration. In contrast, short sleep duration was associated with an increased risk of ICH, while there were no significant associations with total hemorrhagic stroke or subarachnoid hemorrhage.

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

| Outcome and model | Habital Sleep Duration, h/d | <7 | 7 to <9 | ≥9 |
|-------------------|-----------------------------|--|--|---|
| Total stroke*     |                             | 2031 | 5417 | 643 |
| Total no. of cases|                             | 287 881 | 832 675 | 64 090 |
| Total person-years of follow-up |             | 37 881 | 103 675 | 12 090 |
| 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 |                           | 1501 | 4051 | 489 |
| Total no. of cases |                             | 275 | 712 | 75 |
| 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 |                           | 275 | 712 | 75 |
| 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) |
| ICH |                             | 50 | 172 | 14 |
| Total no. of cases |                             | 225 | 540 | 61 |
| Age and sex-adjusted model |                | 0.89 (0.85–1.23) | 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.
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 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, increase caloric intake and unhealthy food choices, and hypertension. A study in mice showed that sleep deprivation resulted in increased blood pressure, endothelial dysfunction, and markers of oxidative stress and

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**Table 1.** Associations of genetic liability to short sleep duration with overall stroke, ischemic stroke, and its subtypes.

| Outcome and method          | OR (95% CI) | P   |
|-----------------------------|-------------|-----|
| All stroke                  |             |     |
| Standard MR                 | 0.91 (0.78, 1.07) | 0.252 |
| Weighted median             | 0.93 (0.77, 1.13)  | 0.464 |
| All ischemic stroke         |             |     |
| Standard MR                 | 0.97 (0.82, 1.15)  | 0.723 |
| Weighted median             | 0.98 (0.80, 1.20)  | 0.842 |
| Large artery stroke         |             |     |
| Standard MR                 | 1.25 (0.82, 1.91)  | 0.291 |
| Weighted median             | 1.08 (0.83, 1.38)  | 0.775 |
| Cardioembolic stroke        |             |     |
| Standard MR                 | 1.35 (0.97, 1.88)  | 0.073 |
| Weighted median             | 1.28 (0.84, 1.94)  | 0.249 |
| Small vessel stroke         |             |     |
| Standard MR                 | 1.05 (0.71, 1.56)  | 0.789 |
| Weighted median             | 1.01 (0.62, 1.64)  | 0.962 |

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**Table 2.** Associations of genetic liability to long sleep duration with overall stroke, ischemic stroke, and its subtypes.

| Outcome and method          | OR (95% CI) | P   |
|-----------------------------|-------------|-----|
| All stroke                  |             |     |
| Standard MR                 | 1.13 (1.00, 1.27) | 0.052 |
| Weighted median             | 1.13 (0.95, 1.33)  | 0.164 |
| All ischemic stroke         |             |     |
| Standard MR                 | 1.10 (0.97, 1.26)  | 0.142 |
| Weighted median             | 1.05 (0.88, 1.26)  | 0.565 |
| Large artery stroke         |             |     |
| Standard MR                 | 1.41 (1.02, 1.95)  | 0.040 |
| Weighted median             | 1.44 (0.91, 2.27)  | 0.117 |
| Cardioembolic stroke        |             |     |
| Standard MR                 | 0.99 (0.74, 1.32)  | 0.938 |
| Weighted median             | 0.75 (0.52, 1.09)  | 0.127 |
| Small vessel stroke         |             |     |
| Standard MR                 | 1.02 (0.75, 1.37)  | 0.911 |
| Weighted median             | 0.99 (0.64, 1.51)  | 0.949 |

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**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.

**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. Due to variations in stroke cause, there might be differences in the contribution of risk factors to the pathophysiology of ischemic stroke subtypes. 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.

Only one prospective study, to date, has investigated the link between sleep duration and subtypes of hemorrhagic stroke. 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. A Japanese prospective study of 27896 adults demonstrated a reduced risk of hemorrhagic stroke mortality among individuals who reported short sleep duration (≤6 hours) compared with 7 hours of sleep. A recent study of 31750 participants found no evidence of the association between sleep duration and risk of total hemorrhagic stroke or ICH and subarachnoid hemorrhage. 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; ethnic 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). 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. 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

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