Sleep Duration and Risk of Stroke Mortality Among Chinese Adults
Singapore Chinese Health Study

An Pan, PhD; Deidre Anne De Silva, MBBS, FRCP; Jian-Min Yuan, MD, PhD;
Woon-Puay Koh, MBBS, PhD

Background and Purpose—Prospective relation between sleep duration and stroke risk is less studied, particularly in Asians. We examined the association between sleep duration and stroke mortality among Chinese adults.

Methods—The Singapore Chinese Health Study is a population-based cohort of 63,257 Chinese adults aged 45 to 74 years enrolled during 1993 through 1998. Sleep duration at baseline was assessed via in-person interview, and death information during follow-up was ascertained via record linkage with the death registry up to December 31, 2011. Cox proportional hazard models were used to calculate hazard ratios with adjustment for other comorbidities and lifestyle risk factors of stroke mortality.

Results—During 926,752 person-years of follow-up, we documented 1381 stroke deaths (322 from hemorrhagic and 1059 from ischemic or unspecified strokes). Compared with individuals with 7 hours per day of sleep, the multivariate-adjusted hazard ratio (95% confidence interval) of total stroke mortality was 1.25 (1.05–1.50) for ≤5 hours per day (short duration), 1.01 (0.87–1.18) for 6 hours per day, 1.09 (0.95–1.26) for 8 hours per day, and 1.54 (1.28–1.85) for ≥9 hours per day (long duration). The increased risk of stroke death with short (1.54; 1.16–2.03) and long durations of sleep (1.95; 1.48–2.57) was seen among subjects with a history of hypertension, but not in those without hypertension. These findings were limited to risk of death from ischemic or unspecified stroke, but not observed for hemorrhagic stroke.

Conclusions—Both short and long sleep durations are associated with increased risk of stroke mortality in a Chinese population, particularly among those with a history of hypertension. (Stroke. 2014;45:1620-1625.)

Key Words: Asian continental ancestry group ■ cohort studies ■ hypertension ■ sleep ■ stroke

Short and long sleep durations are associated with adverse health outcomes, including diabetes mellitus,1 coronary heart disease (CHD),2 and total mortality.3 However, the prospective relation between sleep duration and stroke is less studied. A meta-analysis4 of 4 prospective cohorts among US4,5 and Japanese adults6,7 reported that both short and long sleep durations were associated with a 15% and 65% increase in the risk of developing or dying of stroke, respectively. Two recent publications also reported similar relations in European8 and multiethnic American populations.9 In all studies, long sleep duration has been associated with an increased risk; however, the results for short sleep duration were inconsistent.4,9

Few studies have investigated ischemic and hemorrhagic strokes separately and tested the potential risk modification by comorbid conditions, given the concern that longer sleep duration may reflect the presence of comorbidity or unhealthy status. Most previous studies were limited in the sample size of stroke outcomes for the short sleep duration category.4,6–8 No study has been done in the Chinese population, where disease burden from stroke is increasing rapidly in the past several decades.9 We have previously shown that both short (≤5 hours per day) and long (≥9 hours per day) sleep durations were related to an increased risk of CHD mortality among Singaporean Chinese.11 Thus, using data from the same cohort with longer duration of follow-up, we aimed to examine the prospective association between sleep duration and stroke mortality in the first such study among a Chinese population.
Materials and Methods

Study Population

The Singapore Chinese Health Study was established between 1993 and 1998 with 63,257 Chinese (27,954 men and 35,303 women) in Singapore, aged 45 to 74 years. The study subjects were recruited from 2 major dialect groups in Singapore, Hokkiens and Cantonese, who originated from Fujian and Guangdong provinces in Southern China, respectively. During the enrollment period, all study participants were residents of government housing estates, where 86% of the Singapore population resided at the time of recruitment. The Institutional Review Board of the National University of Singapore approved this study, and all enrolled subjects gave informed consent.

Ascertainment of Sleep Duration and Covariates

At recruitment, trained interviewers conducted face-to-face interviews using a structured questionnaire and obtained information on height, weight, cigarette smoking, habitual physical activity, alcohol drinking, and habitual dietary intake (by a validated 165-item food frequency questionnaire). Body mass index (in kg/m²) was calculated by body weight in kilograms divided by square of height in meters. Participants were asked about their history of medical conditions diagnosed by physicians, including diabetes mellitus, hypertension, CHD, and stroke, and unknown status of these conditions was coded as not on the questionnaires. History of cancer was ascertained by self-reports and record linkage with the Singapore Cancer Registry. Sleep duration was assessed by the following question: “On the average, during the last year, how many hours in a day did you sleep?” with the following responses: ≤5 hours, 6 hours, 7 hours, 8 hours, 9 hours, ≥10 hours.

Ascertainment of Stroke Mortality

Deaths were identified through record linkage with the Singapore Registry of Births and Deaths up to December 31, 2011. Underlying death causes were coded according to the International Classification of Diseases, Ninth Revision (ICD-9): codes 430 to 438 for all stroke deaths, 430 to 432 for hemorrhagic stroke, and 433 to 438 for ischemic or otherwise unspecified stroke. We have tried to verify unspecified stroke cases through sources of medical records in a previous pilot study: among 308 cases with available medical records, 86% were ischemic strokes and 14% were hemorrhagic strokes. This suggested that a majority of strokes classified as unspecified were actually ischemic strokes (unpublished data). As of December 31, 2011, only 47 subjects from this cohort were known to be lost to follow-up because of migration out of Singapore or for other reasons. Therefore, emigration among participants seems to be negligible in this cohort, and vital statistics during follow-up was virtually complete.

Statistical Analysis

We chose a reference category of 7 hours per day because most subjects were in this category, as well as to be consistent with previous studies. Person-years for each participant were calculated from the date of recruitment until date of death, lost to follow-up, or December 31, 2011, whichever occurred first. Cox proportional hazard regressions were used to calculate hazard ratio (HR) and 95% confidence interval (CI) for stroke mortality associated with different categories of sleep duration (≤5, 6, 8, 9, ≥10 hours relative to ≥7 hours per day). We adjusted for age, year of recruitment, sex, dialect group, level of education, body mass index, alcohol drinking, smoking intensity (number of cigarettes per day) and duration (number of years of smoking), level of moderate physical activity, and daily intakes of total calorie, vegetables, fruits, dietary fiber, and polyunsaturated fatty acids. In a separate model, we further adjusted for history of hypertension, diabetes mellitus, CHD, stroke, and cancer, because these comorbidities could be potential mediators in the pathway between sleep duration and stroke death. Additionally, we tested the interactions between sleep duration (5 categories) and these comorbidities or overweight/obesity status on the risk of stroke mortality and performed stratified analysis by these variables. We also tested the curvilinear relation by including linear and quadratic terms of sleep duration in the regression model. Statistical computing was conducted using SAS version 9.1 (SAS Institute Inc, Cary, NC), and 2-sided P values <0.05 were considered statistically significant.

Results

Among the 63,257 participants, 32.6% slept 7 hours per day, followed by 8 hours per day (27.4%) and 6 hours per day (23.3%). There was only 9.7% with ≤5 hours per day and 7.8% with ≥9 hours per day of sleep. Compared with people with 7 hours per day of sleep, individuals with short (≤5 hours per day) or long (≥9 hours per day) durations were older and more likely to have a history of hypertension, CHD, stroke, and cancer (Table I). Participants with short sleep duration were less educated, and those with long sleep duration were more likely to be ever-smokers. There were no statistically significant differences in body mass index, physical activity, and dietary habits among the different categories of sleep duration.

During a mean follow-up duration of 14.7 years, 1381 stroke deaths (322 hemorrhagic and 1059 ischemic or unspecified strokes) occurred among cohort participants. Compared with sleeping for 7 hours per day, both short and long durations were associated with increased risk of stroke mortality (Table 2), and the relations were slightly attenuated after adjustment for comorbidities. Compared with the reference group, the multivariate-adjusted HR (95% CI) of total stroke mortality was 1.25 (1.05–1.50) for ≤5 hours per day, 1.01 (0.87–1.18) for 6 hours per day, 1.09 (0.95–1.26) for 8 hours per day, and 1.54 (1.28–1.85) for ≥9 hours per day (P for quadratic effect <0.001). These associations were mainly limited to ischemic or unspecified stroke mortality, but not hemorrhagic stroke mortality (Table 2). The results were similar in men and women (Table I in the online-only Data Supplement).

We also performed stratified analysis by baseline comorbidities (Table 3). No significant interaction was found for any of the comorbidities, and the results were similar when stratified by baseline overweight/obesity status or history of diabetes mellitus. However, when stratified by baseline history of cardiovascular disease, the association between long sleep duration and stroke mortality was marginally stronger in those with baseline cardiovascular disease (HR, 2.35; 95% CI, 1.54–3.60) than those without (1.43; 1.16–1.76; P for difference=0.07). When stratified by baseline hypertension status, the U-shaped association with stroke mortality was found for short (HR, 1.54; 95% CI, 1.16–2.03) and long (1.95; 1.48–2.57) sleep durations among participants with a history of hypertension (P for quadratic effect <0.001), but not among those who did not report a history of hypertension (P for difference=0.087 and 0.042 for short and long sleep durations, respectively). Compared with those without hypertension and having 6 to 8 hours of sleep per day, HR (95% CI) was 2.13 (1.68–2.70) for individuals with hypertension and having ≤5 hours of sleep per day, and 2.69 (2.12–3.42) for individuals with hypertension and having ≥9 hours of sleep per day (Table II in the online-only Data Supplement).

Discussion

In this large cohort of Chinese adults, we found that both short and long sleep durations were significantly associated with an increased risk of stroke mortality. The associations were...
observed in mortality from ischemic or unspecified stroke, but not in mortality from hemorrhagic stroke. The significant associations with short and long sleep durations were only observed among hypertensive subjects, but not among those without hypertension.

The relation between sleep duration and stroke has been investigated in several cohort studies, and ours is the first in a Chinese population. The finding of increased stroke risk with long sleep duration is largely consistent with previous investigations in US populations, Japanese, and German adults, where <6 hours per day of sleep was related to 2-fold increased stroke risk. Earlier studies have shown a nonsignificant increased risk (HR, 1.14; 95% CI, 0.97–1.33) among postmenopausal women in the United States and a nonsignificant increased risk among men (2.00; 0.93–4.31), but not women (0.97; 0.39–2.41), in Japan. However, several other studies failed to observe significant relations between short sleep duration and stroke risk. Nevertheless, these previous studies may be limited by small sample size in the short sleep category: <60 cases in several studies and 99 cases in the Women’s Health Initiative (WHI) study. Short sleep duration could lead to increased risk of stroke through several biological and behavioral pathways by increasing 24-hour blood pressure and heart rate, elevating sympathetic nervous system activity, dysregulating hormonal control of appetite (reduced leptin and elevated ghrelin), increasing body weight, activating proinflammatory pathways, and affecting the activity of major neuroendocrine stress systems. Individuals with insufficient sleep may also be more likely to have sleep disorders or mental distress, which may mediate the association with stroke risk or mortality. Previous studies have demonstrated that obstructive sleep apnoea syndrome is independently associated with an increased risk of stroke and all-cause mortality. However, in studies that had information on depression as a comorbidity, the association was not materially changed after adjustment for depression. The magnitude of the association between short sleep duration and stroke mortality was weak (HR, 1.25) in our study, and the results should be interpreted cautiously, and unmeasured confounders (eg, sleep quality, sleep disorders, mental status, and depression) may mediate the association with stroke risk or mortality.

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occupational characteristics) may contribute to the observed relation. Additional studies need to clarify whether short sleep duration is an independent risk factor for stroke mortality.

Although most studies did not distinguish between ischemic and hemorrhagic strokes, the Japan Collaborative Cohort Study (JACC) study examined deaths from ischemic and hemorrhagic strokes, and the WHI study specifically evaluated the relation with ischemic stroke. In the JACC study, long sleep duration (≥10 hours per day) was associated with ischemic and hemorrhagic strokes separately, and the WHI study, although the association between short sleep duration and risk of ischemic stroke in the latter did not reach statistical significance. We acknowledge that with 322 hemorrhagic stroke deaths, our null results could be because of low statistical power from small sample size. Future studies investigating whether the relation could be modified or mediated by these factors may contribute to the observed relation. Additional studies need to clarify whether short sleep duration is an independent risk factor for stroke mortality.

A novel finding in this study is that the increased risk with short or long duration was more prominent among participants with hypertension, and individuals with both hypertension and short or long sleep duration had substantially higher risk of stroke mortality. This finding suggests that optimal sleep duration is particularly important for patients with hypertension. Hypertension is the single most important risk factor for stroke, and the mechanism linking sleep duration to stroke risk could be through the effects of blood pressure.

Recent studies suggest that short or long sleep duration may be related to arterial stiffness and subclinical atherosclerosis manifested by increased carotid intima media thickness, both of which are known to be induced by high blood pressure as well. Meanwhile, arterial stiffness and increased carotid intima media thickness have been shown to be potential mechanisms for stroke development. Thus, hypertension and sleep duration may have a synergistic effect on stroke risk through the common pathways of inducing arterial stiffening and atherosclerosis, both of which are more closely linked with ischemic rather than hemorrhagic stroke.

The strengths of this study are its large sample size, long follow-up, and inclusion of many known vascular risk factors as possible covariates. There are several limitations of our study. First, as the outcome was stroke mortality, we are uncertain whether the results are applicable to nonfatal stroke. There was a large proportion of unspecified strokes in our study, although our previous pilot study suggested that a majority of them were ischemic strokes. This is consistent with data from the national registry that 80% of all strokes in Singapore are ischemic strokes. Moreover, the lack of comprehensive information on sleep disorders and sleep quality limits us to further investigate whether the relation could be modified or mediated by these factors. We did not collect information on working status and job characteristics (eg, shift work) in the study, which may confound the results because they are related to both sleep duration and stroke risk. Furthermore, because we measured sleep duration by self-report and only at a single time point, any subsequent change in sleep duration after recruitment could lead to nondifferential misclassification and potentially underestimate the sleep–stroke association. Finally, because this is an
Conclusions

Both short and long sleep durations are associated with an increased risk of stroke mortality in the Chinese population. This relationship was more prominent among participants with baseline hypertension compared with their normotensive counterparts. Our findings of significant association between sleep duration and ischemic stroke mortality, but not for hemorrhagic stroke mortality, also need to be confirmed in future studies.

Acknowledgments

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Disclosures
None.

References
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http://stroke.ahajournals.org/content/suppl/2014/04/17/STROKEAHA.114.005181.DC1

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### Supplemental Table I. Hazard ratio (95% confidence intervals) of stroke mortality according to sleep duration: stratified by gender.

**Daily sleep duration**

<table>
<thead>
<tr>
<th></th>
<th>≤5 hours</th>
<th>6 hours</th>
<th>7 hours</th>
<th>8 hours</th>
<th>≥9 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/person-years</td>
<td>75/31179</td>
<td>143/91355</td>
<td>202/131562</td>
<td>183/114192</td>
<td>90/25362</td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.13 (0.86-1.47)</td>
<td>0.93 (0.75-1.16)</td>
<td>1.00</td>
<td>0.98 (0.80-1.20)</td>
<td>1.49 (1.16-1.92)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/person-years</td>
<td>104/54584</td>
<td>148/124618</td>
<td>178/177415</td>
<td>183/141504</td>
<td>75/34990</td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.37 (1.08-1.75)</td>
<td>1.10 (0.88-1.37)</td>
<td>1.00</td>
<td>1.23 (1.00-1.51)</td>
<td>1.62 (1.24-2.13)</td>
</tr>
<tr>
<td><strong>Ischemic or unspecified stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/person-years</td>
<td>61/31179</td>
<td>101/91355</td>
<td>148/131562</td>
<td>141/114192</td>
<td>75/25362</td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.25 (0.92-1.69)</td>
<td>0.90 (0.69-1.15)</td>
<td>1.00</td>
<td>1.03 (0.82-1.30)</td>
<td>1.64 (1.23-2.17)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/person-years</td>
<td>84/54584</td>
<td>120/124618</td>
<td>130/177415</td>
<td>139/141504</td>
<td>60/34990</td>
</tr>
</tbody>
</table>
**SUPPLEMENTAL MATERIAL**

<table>
<thead>
<tr>
<th>Hemorrhagic stroke</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/person-years</td>
<td>14/31179</td>
<td>42/91355</td>
<td>54/131562</td>
<td>42/114192</td>
<td>15/25362</td>
</tr>
<tr>
<td>Multivariate model</td>
<td>0.80 (0.44-1.44)</td>
<td>1.04 (0.69-1.55)</td>
<td>1.00</td>
<td>0.85 (0.57-1.27)</td>
<td>1.04 (1.58-1.86)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/person-years</td>
<td>20/54584</td>
<td>28/124618</td>
<td>20/177415</td>
<td>44/141504</td>
<td>15/34990</td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.07 (0.63-1.81)</td>
<td>0.78 (0.49-1.24)</td>
<td>1.00</td>
<td>1.13 (0.75-1.70)</td>
<td>1.30 (0.72-2.33)</td>
</tr>
</tbody>
</table>

*No significant interaction was found for total stroke mortality (*P*-interaction=0.53), deaths from ischemic or unspecified stroke (*P*-interaction=0.45), and deaths from hemorrhagic stroke (*P*-interaction=0.43). The multivariate model adjusted for age at recruitment, year of recruitment (1993-1995, 1996-1998), dialect (Hokkien, Cantonese), education (no formal education, primary school, secondary school or higher), body mass index (<20.0, 20.0-23.9, 24.0-27.9, and ≥28.0 kg/m²), alcohol drinking (none, monthly, weekly, daily), years of smoking (never, <20, 20-39, and ≥40 years), dose of smoking (never, ≤12, 13-22, 23-32, ≥33 cigarettes/day), moderate activity (<0.5, 0.5-3.9, and ≥4.0 hours/week), energy intake (kcal/day), dietary intakes of vegetables, fruits, fiber, polyunsaturated fatty acids (g/day, quartiles), self-reported history of physician-diagnosed hypertension, diabetes, stroke and coronary heart disease, and history of cancer reported by the nationwide cancer registry.*
Supplemental Table II. Hazard ratio (95% confidence intervals) of stroke mortality according to joint association between sleep duration and baseline hypertension status.*

<table>
<thead>
<tr>
<th>Daily sleep duration</th>
<th>Without previous hypertension</th>
<th>With previous hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/person-years</td>
<td>Multivariate model</td>
</tr>
<tr>
<td><strong>Total stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 hours</td>
<td>97/62600</td>
<td>1.16 (0.94-1.44)</td>
</tr>
<tr>
<td>6-8 hours</td>
<td>627/610999</td>
<td>1.00</td>
</tr>
<tr>
<td>≥9 hours</td>
<td>82/44695</td>
<td>1.38 (1.09-1.74)</td>
</tr>
<tr>
<td><strong>Ischemic or unspecified stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 hours</td>
<td>78/62600</td>
<td>1.23 (0.97-1.57)</td>
</tr>
<tr>
<td>6-8 hours</td>
<td>469/610999</td>
<td>1.00</td>
</tr>
<tr>
<td>≥9 hours</td>
<td>64/44695</td>
<td>1.42 (1.09-1.85)</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 hours</td>
<td>19/62600</td>
<td>0.95 (0.59-1.52)</td>
</tr>
<tr>
<td>6-8 hours</td>
<td>158/610999</td>
<td>1.00</td>
</tr>
<tr>
<td>≥9 hours</td>
<td>18/44695</td>
<td>1.26 (0.77-2.06)</td>
</tr>
</tbody>
</table>
The multivariate model adjusted for age at recruitment, year of recruitment (1993-1995, 1996-1998), dialect (Hokkien, Cantonese), education (no formal education, primary school, secondary school or higher), body mass index (<20.0, 20.0-23.9, 24.0-27.9, and ≥28.0 kg/m²), alcohol drinking (none, monthly, weekly, daily), years of smoking (never, <20, 20-39, and ≥40 years), dose of smoking (never, ≤12, 13-22, 23-32, ≥33 cigarettes/day), moderate activity (<0.5, 0.5-3.9, and ≥4.0 hours/week), energy intake (kcal/day), dietary intakes of vegetables, fruits, fiber, polyunsaturated fatty acids (g/day, quartiles), self-reported history of physician-diagnosed diabetes, stroke and coronary heart disease, and history of cancer reported by the nationwide cancer registry.