Sleep Duration and Risk of Ischemic Stroke in Postmenopausal Women

Jiu-Chiuan Chen, MD, MPH, ScD; Robert L. Brunner, PhD; Hong Ren, MS; Sylvia Wassertheil-Smoller, PhD; Joseph C. Larson, MS; Douglas W. Levine, PhD; Matthew Allison, MD, MPH; Michelle J. Naughton, PhD; Marcia L. Stefanick, PhD

Background and Purpose—Many studies have shown a U-shape association between sleep duration and mortality, but epidemiological evidence linking cardiovascular diseases with habitual sleep patterns is limited and mixed.

Methods—We conducted a prospective study on 93 175 older women (aged 50 to 79 years) in the Women’s Health Initiative Observational study cohort to examine the risk of ischemic stroke in relation to self-reported sleep duration. Cox models were used to investigate the putative associations, adjusting for multiple sociodemographic and lifestyle factors, depression, snoring, sleepiness symptoms, and other cardiovascular disease-related clinical characteristics.

Results—At baseline, 8.3% of subjects had reported their sleep duration as ≤5 hours per night and 4.6% reported long duration of sleep (≥9 hours/night). After an average of 7.5 years of follow-up, 1166 cases of ischemic stroke had occurred. Multivariable-adjusted relative risk (RR) and 95% CI for ischemic stroke (using a sleep time of 7 hours/night as the reference) were 1.14 (0.97, 1.33), 1.24 (1.04, 1.47), and 1.70 (1.32, 2.21) for women reporting ≤6, 8, and ≥9 hours of sleep. A modestly stronger association with sleep duration ≤6 hours per night (RR, 1.22; 1.03, 1.44) was noted among women without prevalent cardiovascular disease at baseline. Our analyses also reveal that the adverse effect of long sleep is likely independent of the increased risk for ischemic stroke associated with frequent snoring and sleepiness (RR, 1.31; 1.00, 1.72).

Conclusions—Habitual sleep patterns are important neurobehavioral determinants of risk for ischemic stroke in postmenopausal women. The underlying neurobiology and mechanistic mediators for the putative adverse effect of long sleep (≥9 hours/night) need further elucidation. (Stroke. 2008;39:3185-3192.)

Key Words: cerebral infarction ■ cohort studies ■ risk factors ■ sleep disorders

Increases in mortality associated with either shortened sleep (sleep duration ≤6 hours/night) or long sleep duration (sleep duration ≥9 hours/night) have consistently been found in many population-based studies.1–3 What accounts for this association is not fully understood. Three previous studies, the follow-up of First National Health and Nutrition Examination Survey (NHANES-I) participants, the Nurses’ Health study, and the Monitoring Trends and Determinants on Cardiovascular Diseases Augsburg cohort study, have investigated the putative effect of habitual sleep duration on the risk of coronary heart disease (CHD), with mixed results.4–6 Both the Nurses’ Health study and NHANES-I follow-up study reported an increased CHD risk associated with habitual sleep duration <6 hours, which also increased the MI risk among middle-aged women in the Monitoring Trends and Determinants on Cardiovascular Diseases Augsburg cohort.

Long sleep duration (≥9 hours/night) was associated with increased CHD risk in the Nurses’ Health study, but it was associated with statistically nonsignificant increase in MI risk among women in the recent Monitoring Trends and Determinants on Cardiovascular Diseases Augsburg cohort analysis, with no association found in NHANES-I follow-up study. Epidemiological data relating habitual sleep duration to the risk of stroke are very sparse, and only the NHANES-I follow-up study reported an increased risk of stroke in long-duration sleepers (>8 hours), but not in short-duration sleepers (<6 hours).4 Causal inference cannot be drawn from these studies, and the reported analyses did not fully account for potential confounding by individual attributes that are common determinants of both sleep duration and risk of cardiovascular diseases (CVD), such as race/ethnicity, socioeconomic position, lifestyle factors, and depressive symp-
toms. Although some studies on mortality have reported a larger effect size for long sleep than for short sleep, it has been argued that the observed detrimental health effects of long sleep are likely confounded by depression or socioeconomic status (eg, unemployment status). In addition, previous studies did not distinguish ischemic stroke from hemorrhagic events, even though there is little neurobiological rationale to suggest that hemorrhagic stroke would be associated with either short or long sleep duration.

To address the aforementioned uncertainty in relating sleep duration to increased risk of stroke, we conducted a longitudinal analysis focusing primarily on ischemic stroke, using the comprehensive data from the Women’s Health Initiative Observational Study (WHI-OS), a long-term (1994 to 2005) prospective cohort study designed to identify and assess the relationships of biological, lifestyle, biochemical, and genetic factors to the risks of heart disease, cancer, fracture, and other major health problems of older women.

Subjects and Methods

Study Population

Detailed information about the study population, recruitment methods, and measurement protocols of the WHI-OS has been published previously. Briefly, the WHI-OS population is a multiethnic cohort (0.5% American Indian or Alaskan Native, 8.2% African American, 2.9% Asian-Pacific Islander, 3.9% Hispanic, 83.3% white, and 1.4% unknown) of 93,676 women who were aged 50 to 79 at study inception and recruited from the areas surrounding 40 clinical centers in 24 states and District Columbia, between September 1, 1994 and December 31, 1998. The recruitment areas covered a variety of communities including urban, suburban, and rural populations. Women were eligible to participate in WHI-OS if they were postmenopausal; unlikely to change residence or die within 3 years of enrollment; did not have complicated conditions such as alcoholism, drug dependence, or dementia; and were not enrolled in the WHI or any other clinical trials. Participants entered the WHI-OS by expressing initial interest in either the diet modification or hormone therapy arms of the WHI Clinical Trials but proved ineligible or unwilling to participate or responded to a direct invitation to be screened for the WHI-OS. All participants provided written informed consent, approved by the Institutional Review Board at each participating center.

Study Variable

The measures of sleep disturbance in WHI cohort were developed by sleep researcher consultants to the WHI Behavioral Advisory Committee. As part of the baseline examination, each WHI participant was asked to report “hours of sleep on a typical night during the past 4 weeks” (5, 6, 7, 8, 9, ≥10). Levine et al have assessed the psychometric properties of these sleep measures and noted that sleep duration did not strongly correlate with other construct of sleep disturbance, such as insomnia. Analyses of their data also indicated very good test–retest reliability for both self-reported sleep duration (Spearman R = 0.97 for same-day administration and 0.89 for 8 to 14 days).

Ascertainment of Health Outcome

The diagnosis of ischemic stroke followed the established protocols that have been published elsewhere. In brief, potential stroke outcomes in WHI-OS, including fatal and nonfatal events, were queried initially through self-reports at annual contacts. When a potential outcome was identified, medical records and death certificates were requested and assembled. The diagnosis of stroke was based on rapid onset of a persistent neurological deficit attributed to the brain arterial system lasting >24 hours (unless death supervenes) without evidence for other cause, such as brain trauma, tumor, or infection. Stroke outcomes were classified as ischemic stroke if the clinical diagnosis revealed the occlusion of cerebral or precerebral arteries with infarction (cerebral thrombosis, cerebral embolism, lacunar infarction). Cases with hemorrhagic stroke or other acute but ill-defined cerebrovascular diseases and those resulting from iatrogenic complications were considered as nonischemic stroke in the present study. At each clinical center, the local physician adjudicator reviewed the medical records and, using these standardized criteria, determined the diagnosis of ischemic stroke. The estimated proportion of WHI stroke case classification based on CT or MRI findings was high (>95%), and there were only few cases that were classified according to the specific clinical information (eg, surgical evidence) or did not have neuroimaging studies available (eg, fatal strokes). In a subset of locally adjudicated ischemic stroke cases (n = 926) called for central review, 91% agreed with central adjudication.

Measurement of Pertinent Covariates

At the baseline visit, participants completed structured questionnaires to solicit information on demographic features, socioeconomic status, lifestyle factors (eg, smoking, physical activity), and relevant clinical characteristics, including use of menopausal hormone therapy, histories of CHD/CVD, and related clinical risk factors. Physical measures of weight, height, and blood pressure were taken at baseline. Individuals were classified into the following BMI (in kg/m²) categories: underweight (<18.5), normal (18.5 to 24.9), overweight (25.0 to 29.9), obesity I (30.0 to 34.9), obesity II (35.0 to 39.9), and obesity III (≥40). Hypertension was defined as having a physician diagnosis plus receiving medications, or having elevated blood pressure (systolic ≥140, diastolic ≥90 mm Hg, or both). Women were classified as having treated diabetes mellitus (DM) if they had a physician diagnosis plus receiving oral medications or insulin. CHD was defined as having previous MI, coronary angioplasty, or coronary artery bypass graft. Histories of CVD include having previous CHD, stroke, or TIA. Good reliability and validity of these self-reported clinical characteristics and physical measures have been documented. Depressive symptoms were assessed with a scale that used 6 items from the 20-item Center for Epidemiological Studies Depression Scale (CES-D). To avoid collinearity between measures of sleep measures and depressive symptoms, we excluded 1 item about poor sleep (“your sleep was restless”) and used the 5-item CES-D score to adjust for the effect of depressive symptoms in our main analyses. Two items from the Diagnostic Interview Schedule were used to assess feelings of sadness or depression for ≥2 weeks in the past year and feelings of sadness on most days for ≥2 weeks. Subjects responding “yes” to both items were classified as having “history of depression.” The participants also rated the frequency of snoring (“did you snore”) and sleeplessness (“falling asleep during quiet activities like reading, watching TV, or riding in a car”), based on a 5-point scale (0, <1, 1 to 2, 3 to 4, ≥5 times/week) over the past 4 weeks, with an additional choice of “don’t know” for self-reported snoring. We classified participants as having frequent snoring or sleepiness if they reported more than once per week of indicated sleep disturbance. There was also good test–retest reliability for the frequency of snoring (Spearman R = 0.98 for same-day administration and 0.81 for 8 to 14 days).

Statistical Analyses

We compared the distributions of sleep duration across different population characteristics using χ² tests. Follow-up time for each woman was accrued from enrollment to the event date with ischemic stroke loss to follow-up, or the end of current study on September 12, 2005, whichever came first. According to the WHI protocol, women who had nonischemic stroke during the follow-up would not enter adjudication again. Although nonischemic stroke is not the outcome of interest in the present analyses, these women were also censored at the time of nonischemic stroke. Based on the time-to-event analyses, crude event rates were then calculated and compared across subgroups with different sleep duration. Cox proportional hazard models were used to estimate hazard ratios for having ischemic stroke associated with habitual sleep duration, adjusting for potential confounders. A full set of participants characteristics were
included in the multivariable analyses regardless of their respective associations with ischemic stroke in our study population, including age, race–ethnicity, socioeconomic status (education, family income, employment), lifestyle factors (smoking, physical activity), depressive symptoms, hormone therapy usage, and other clinical characteristics (previous CVD, hypertension, DM, high cholesterol level requiring medication, and obesity). We also stratified the effect estimates by clinical characteristics to assess whether the putative effects persist in those without previous comorbid conditions (CVD/CHD, DM, hypertension) predisposing to sleep disturbance and the study end point.

Several sensitivity analyses were performed to evaluate whether the observed associations were sensitive to excluding ischemic stroke events that occurred during the early course (within the first 6 months) of follow-up, including 6-item CES-D score, or further accounting for history of depression in the multivariable-adjusted models. Additional analyses jointly modeling the effect of habitual sleep duration and “frequent snoring and sleepiness” were also conducted to explore the independent effects of different subconstructs of sleep disturbance. All these statistical analyses were performed using the SAS System for Windows, version 9 (SAS Institute).

Results

Table 1 presents the population distribution of sleep duration in relation to selected baseline (1994 to 1998) sociodemographics and lifestyle factors. Approximately 8.3% reported short sleep duration ≤5 hours per night, whereas 4.6% were long-duration sleepers (≥9 hours/night). A higher proportion of non-white women had short sleep, compared to 6.7% of white, as follows: black (19.0%), Hispanic (13.8%), American Indian (14.8%), and Asian/Pacific Islander (14.9%). Low socioeconomic status (educational attainment, family income) was associated with high prevalence of short sleep duration ≤5 hours per night. Prevalence of short sleep duration ≤5 hours per night was much higher in women who were physically inactive, when compared to their counterparts. The prevalence of being long sleepers (≥9 hours/night) also differed by individual socioeconomic status. There was also a graded increase in the prevalence of being long-duration sleepers as the family income decreased. Women who retired or were not currently working were more likely than employed women to have long sleep duration. Being a current smoker or less physically active was associated with a slightly higher prevalence of being long-duration sleepers.

As shown in Table 2, clinical characteristics were important determinants of sleep duration. Increasing BMI, above the normal category (18.5 to 24.9 kg/m²), was associated with increased prevalence of short sleep duration ≤5 hours per night. Current hormone therapy users were less likely to have short sleep duration than noncurrent users. Participants with existing CHD/CVD, treated DM, hypertension, hypercholesterolemia, or depression were more likely to report short sleep duration ≤5 hours per night than those without these comorbid conditions. Women with existing CHD/CVD, treated DM, hypertension, hypercholesterolemia, or depressive symptoms were more likely to have long sleep duration than those without these comorbid conditions, although such differences were not as prominent as those with short sleep duration ≤5 hours per night.

We noted that self-reported sleep duration had a nonlinear relation with the frequency of snoring as well as with the frequency of sleepiness. Compared to women in the other categories of sleep duration, women with 8 to 9 hours of sleep were the least likely to have frequent sleepiness (42% to 44% vs 48% to 61%) and women with 7 hours of sleep were the least likely to report frequent snoring (20% vs 21% to 30%). Higher prevalence of having both “frequent snoring and sleepiness” was found in participants with ≤5 hours of sleep (15%) or ≥10 hours of sleep (17%), compared to the others (11% to 14%).

A total of 1166 cases of ischemic stroke occurred during an average of 7.5 years of follow-up. There was a suggested U-shape relation between sleep duration and risk of ischemic stroke (Table 3). Women with sleep duration of 7 hours per night had the lowest risk for ischemic stroke; the risk was higher in women with sleep ≥6 hours per night, and a graded increase in risk was noted for women with increasing sleep duration beyond 7 hours per night. Given the relatively small number of cases among those with longest (n=16 with sleep ≥10 hours/night) or shortest sleep (n=99 with sleep ≤5 hours/night), we combined these 2 distributional extremes with their adjacent categories in the further adjusted analyses. Results of the multi-variable adjusted Cox models were also presented in Table 3. Using women with sleep duration of 7 hours per night as the referent, we found a 19% (95% CI, 3% to 37%) increase in relative risk (RR) in women with sleep ≥6 hours per night, after adjustment for age and race. However, the increased RR associated with sleep duration ≤6 hours per night was slightly diminished and became statistically nonsignificant (Model-IV: RR, 1.14; 95% CI, 0.97, 1.33) after additionally accounting for socioeconomic status, depressive symptoms, hormone therapy use, and conventional CVD risk factors. In contrast, there was a consistent and graded increase in RR observed for women with sleep of 8 hours per night and for those with sleep ≥9 hours per night. These elevated RRs among women with sleep duration >7 hours per night remained fairly stable in all the adjusted models, with the RR increased by ≈25% among women with sleep duration of 8 hours per night and by 70% in those with sleep ≥9 hours per night. We also noted the increase in ischemic stroke risk among women with frequent snoring and sleepiness. Compared to those reporting no or <1 occurrence per week in both snoring and sleepiness, women with both “frequent snoring and sleepiness” had an elevated but statistically nonsignificant risk for ischemic stroke (RR, 1.28; 95% CI, 0.98 to 1.68), adjusting for the same set of confounders in Model-IV, with a stronger association (RR, 1.51; 95% CI, 1.11, 2.06) noted in women without prevalent CVD.

We found only very little changes to the effect estimates (comparing either short- or long-duration sleepers to those with sleep of 7 hours/night), and the U-shape relationship between habitual sleep patterns and ischemic stroke remained in the sensitivity analyses. After we excluded the events that occurred within the first 6 months of follow-up, an increased risk for ischemic stroke was observed among participants reporting ≤6 hours (RR, 1.15; 95% CI, 0.98 to 1.35), 8 hours (RR, 1.22; 95% CI, 1.03 to 1.45), and ≥9 hours (RR, 1.71; 95% CI, 1.32 to 2.23), adjusting for the same set of confounders in Model-IV. In the multivariable-adjusted model including 6-item CES-D, we still observed an increased risk for ischemic stroke in short-duration sleepers (RR, 1.15; 95% CI,
0.98 to 1.36) and in those with sleep duration of 8 hours (RR, 1.21; 95% CI, 1.02 to 1.44) or ≥9 hours (RR, 1.71, 95% CI, 1.32 to 2.19).

Similarly, after we substituted the “depressive symptoms” with “history of depression” in the multivariable-adjusted analyses, an increased risk for ischemic stroke remained for women reporting 6 hours (RR, 1.11; 95% CI, 0.95 to 1.30), 8 hours (RR, 1.22; 95% CI, 1.03 to 1.45), and ≥9 hours (RR, 1.60; 95% CI, 1.23 to 2.08). In our exploratory analysis that jointly modeled the presumed independent effects of “frequent snoring/sleepiness” and habitual sleep duration, the modest increase in risk was still noted in short-duration sleepers (RR, 1.14; 95% CI, 0.97 to 1.35), and there were statistically significant associations both with long sleep (RR, 1.66; 95% CI, 1.27, 2.16) and with “frequent snoring and sleepiness” (RR, 1.31; 95% CI, 1.00, 1.72).

### Table 1. Population Distribution* of Sleep Duration in Relation to Sociodemographics and Lifestyle Factors in the Women’s Health Initiative Observational Study Cohort, 1994–2005

<table>
<thead>
<tr>
<th>Hours of Sleep/Night</th>
<th>N†</th>
<th>≤5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>93 175</td>
<td>7738 (8.3%)</td>
<td>25 077 (26.9%)</td>
<td>34 902 (37.5%)</td>
<td>21 158 (22.7%)</td>
<td>3758 (4.0%)</td>
<td>542 (0.6%)</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>29 559</td>
<td>2503 (8.5%)</td>
<td>8268 (27.6%)</td>
<td>11 506 (38.9%)</td>
<td>6128 (20.9%)</td>
<td>1029 (3.5%)</td>
<td>171 (0.6%)</td>
</tr>
<tr>
<td>60–69</td>
<td>40 984</td>
<td>3177 (7.8%)</td>
<td>10 660 (26.0%)</td>
<td>15 298 (37.3%)</td>
<td>9907 (24.2%)</td>
<td>1704 (4.2%)</td>
<td>238 (0.6%)</td>
</tr>
<tr>
<td>70–79</td>
<td>22 632</td>
<td>2058 (9.1%)</td>
<td>6249 (27.6%)</td>
<td>8089 (35.8%)</td>
<td>5069 (22.4%)</td>
<td>1025 (4.5%)</td>
<td>133 (0.6%)</td>
</tr>
</tbody>
</table>

*The data represented the number of subjects (%) belonging to each level of sleep duration, given for each subcategory of individual characteristics (all P<0.001).
†The total number of subjects summed up across each subcategory varies slightly because of missing values.
In Table 4, the estimated associations with habitual sleep patterns were further stratified by the presence of previous CVD/CHD, DM, or hypertension. The increased RR for ischemic stroke in women with sleep ≥9 hours per night were very consistent and did not depend on these clinical comorbidities. The positive association with sleep ≤6 hours per night remained among those without the indicated comorbidities predictive of sleep deprivation, and the modest increase in RR of ischemic stroke became statistically significant among women without existing CVD (RR, 1.26; 95% CI, 1.06, 1.50) or DM (RR, 1.22; 95% CI, 1.03, 1.44) at baseline.

Discussion

Our study results corroborate and extend the previous observation of Qureshi et al in the NHANES-I follow-up study. In their 10-year longitudinal analyses of the national cohort of 7844 adults (aged 25 to 74 at baseline), long-duration sleepers (>8 hours/night) had increased stroke risk (RR, 1.5; 95% CI, 1.1 to 2.0) compared to those with sleep of 6 to 8 hours per night. However, the ascertained outcome in the NHANES-I did not differentiate between ischemic and hemorrhagic stroke events, and the reported association with long sleep did not adjust for the potential confounding by income, physical activity level, and depressive symptoms. We found that income, physical activities, depressive symptoms, and other CVD risk factors were all important correlates of sleep duration in postmenopausal women (Tables 1 and 2). Nonetheless, results of our adjusted analyses (Table 3) suggested that these factors could only account for part of the positive association between ischemic stroke and habitual sleep patterns. Previous analyses of NHANES-I data did not show an increased risk of stroke in short-duration sleepers, although...
there was only a small number of stroke events (n = 26 in 675 subjects with sleep < 6 hours/night) in a likely less vulnerable study population (>50% younger than 52 years), with subjects reporting 6 hours of sleep included in the referent and less rigorous requirements for stroke case ascertainment than the WHI protocols.

We found an association of ischemic stroke (=60% to 70% increase in risk) with long sleep that was stronger than the

Table 3. Differences in the Ischemic Stroke Rate and RR in Relation to Sleep Duration in WHI-OS, 1994–2005

<table>
<thead>
<tr>
<th>Hours of Sleep/Night</th>
<th>≤5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7738</td>
<td>25 077</td>
<td>34 902</td>
<td>21 158</td>
<td>3758</td>
<td>542</td>
</tr>
<tr>
<td>Average length of follow-up, yr</td>
<td>7.3</td>
<td>7.5</td>
<td>7.6</td>
<td>7.6</td>
<td>7.5</td>
<td>7.1</td>
</tr>
<tr>
<td>N of ischemic stroke</td>
<td>99</td>
<td>325</td>
<td>372</td>
<td>286</td>
<td>69</td>
<td>15</td>
</tr>
<tr>
<td>Event rate, cases/10⁵ person-yr</td>
<td>175</td>
<td>173</td>
<td>141</td>
<td>179</td>
<td>246</td>
<td>391</td>
</tr>
</tbody>
</table>

Hazard Ratios or RR (95% CI)

| Crude analysis | 1.24 (1.08, 1.42) | 1.00 | 1.27 (1.09, 1.48) | 1.88 (1.49, 2.39) |
| Adjusted analyses | | | | |
| *Model-I | 1.19 (1.03, 1.37) | 1.00 | 1.23 (1.05, 1.43) | 1.74 (1.38, 2.21) |
| †Model-II | 1.15 (0.99, 1.34) | 1.00 | 1.24 (1.05, 1.47) | 1.66 (1.29, 2.14) |
| ‡Model-III | 1.16 (1.00, 1.36) | 1.00 | 1.26 (1.07, 1.49) | 1.71 (1.33, 2.21) |
| §Model-IV | 1.14 (0.97, 1.33) | 1.00 | 1.24 (1.04, 1.47) | 1.70 (1.32, 2.21) |

*Model-I: adjusted for age and race.
†Model-II: adjusted for Model-I covariates plus socioeconomic status (education, family income, and employment status).
‡Model-III: adjusted Model-II covariates plus depression (5-item CES-D).
§Model-IV: adjusted for Model-III covariates plus smoking, exercise, use of hormone therapy and relevant CVD risk factors (previous CVD, DM, hypertension, high cholesterol level requiring pills, BMI).

Table 4. Associations of Ischemic Stroke Risk With Sleep Duration in WHI-OS, Stratified by Baseline Comorbidities

| | Previous CVD | Previous CHD | Diabetes Mellitus | Hypertension |
| | Yes (N = 5877) | No (N = 85 896) | Yes (N = 3215) | No (N = 88 525) |
| | Yes (N = 3867) | No (N = 89 189) | Yes (N = 35 967) | No (N = 56 122) |

<table>
<thead>
<tr>
<th>Sleep duration</th>
<th>≤6 hours</th>
<th>7 hours</th>
<th>8 hours</th>
<th>≥9 hours</th>
<th>ρ†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (N = 5877)</td>
<td>0.75 (0.53, 1.07)</td>
<td>1.26 (1.06, 1.50)</td>
<td>0.84 (0.52, 1.37)</td>
<td>1.19 (1.00, 1.40)</td>
<td>0.03</td>
<td>0.60</td>
</tr>
<tr>
<td>No (N = 85 896)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (N = 3215)</td>
<td>1.23 (0.84, 1.79)</td>
<td>1.24 (1.02, 1.50)</td>
<td>1.03 (0.58, 1.83)</td>
<td>1.26 (1.05, 1.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (N = 88 525)</td>
<td>1.76 (1.05, 2.95)</td>
<td>1.66 (1.24, 2.24)</td>
<td>1.69 (0.77, 3.68)</td>
<td>1.73 (1.31, 2.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (N = 3867)</td>
<td>0.68 (0.43, 1.07)</td>
<td>1.22 (1.03, 1.44)</td>
<td>1.11 (0.92, 1.36)</td>
<td>1.19 (0.92, 1.54)</td>
<td>0.07</td>
<td>0.29</td>
</tr>
<tr>
<td>No (N = 89 189)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (N = 35 967)</td>
<td>1.13 (0.69, 1.84)</td>
<td>1.25 (1.04, 1.50)</td>
<td>1.34 (1.09, 1.65)</td>
<td>1.05 (0.78, 1.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (N = 56 122)</td>
<td>1.74 (0.90, 3.33)</td>
<td>1.68 (1.27, 2.23)</td>
<td>1.59 (1.14, 2.20)</td>
<td>1.92 (1.27, 2.91)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All effect estimates adjusted for age, race, socioeconomic status (education, family income, employment), depression, smoking, exercise, use of hormone therapy, and relevant CVD risk factors (previous CVD/CHD, DM, hypertension, high cholesterol levels requiring pills, BMI).
†P comparing the RR with potential effect modifier present vs RR with potential effect modifier absent.
association with short sleep (≈10% to 20% increase in risk), and such a difference was present in all our adjusted analyses, regardless of clinical comorbidities predictive of habitual sleep patterns (Table 3). This was consistent with previous studies showing that the effect size of long sleep on mortality was larger than that of short sleep.1,3

With long sleep duration, there was increased CHD risk in the Nurses’ Health study4 and MI risk in the Monitoring Trends and Determinants on Cardiovascular Diseases Augsburg cohort.4 It had been speculated that the increased risks for CHD, stroke, and mortality among long-duration sleepers might be attributable to other sleep disorders, such as sleep-disordered breathing.3,6 We categorized women who reported both frequent snoring and sleepiness as having sleep-disordered breathing-related symptoms and found that women with ≥10 hours of sleep had the highest prevalence of sleep-disordered breathing-related symptoms, and the risk of ischemic stroke was increased in women with frequent snoring/sleepiness. However, our exploratory analysis that jointly modeled the effects of sleep duration and frequent snoring/sleepiness supported the putative effect of long sleep independent of sleep-disordered breathing-related symptoms.

The reported detrimental health effects of long sleep have also been attributed to the potential confounding by depression.7,9 Having previous histories of depression was an important determinant of habitual sleep duration (Table 2), and increased risk of stroke was documented in WHI-OS participants with depressive symptoms or previous depression.18 However, in our sensitivity analyses that included the 6-item CES-D score in the multivariable-adjusted model or accounted for the history of depression, we still observed a statistically significant increase (by ≈60% to 70%) in ischemic stroke risk among long sleepers.

The demonstrated consistent association of increased risk of ischemic stroke with long sleep raises the question of underlying mechanisms. If long sleep duration is part of the prodromal complex of subsequent stroke symptoms, then there would have been an attenuated association in the sensitivity analyses excluding cases accrued in the first 6 months of follow-up. Another possibility is that long sleep duration may also reflect some unmeasured sociobehavioral attributes, environmental factors, or underlying biophysical constructs that are proximate causes of ischemic stroke. Given the strength of association and low prevalence of long-duration sleepers, if such unmeasured confounders exist, they need to be strong predictors of long sleep and increase the risk of ischemic stroke to a large extent not mediated by those CVD risk factors included in our analyses. Because our multivariable models have included a large set of sociodemographic features, lifestyle factors, and clinical characteristics, it is unlikely that the observed consistent increase in ischemic stroke risk in long-duration sleepers is entirely attributable to unmeasured confounding.

Provided that long sleep duration is an independent neurobehavioral risk factor for ischemic stroke, at least in postmenopausal women, what exactly predisposes long-duration sleepers to be more likely to experience ischemic stroke than those with usually 7 hours of sleep? Previous studies have found increased risks of diabetes and hypertension in people who sleep ≥9 hours per night.19,20 These plausible links with diabetes and hypertension, however, could not fully explain the increased risk for ischemic stroke among long sleepers in the WHI-OS, because our analyses have accounted for a large set of conventional CVD risk factors. Are long-duration sleepers more likely to have systemic inflammation, thrombotic abnormalities, and endothelial dysfunction, making them more susceptible to the development and progression of atherosclerosis and subsequent ischemic stroke? Can habitual long sleep duration reset the individual’s circadian pacemaker into a chronobiological state with neurocardio-electrophysiological excitability predisposing to cardiac arrhythmia? Does the longer than average duration of recumbent position increase the period with high intracranial pressure or alter hemodynamics that can compromises the cerebral blood flow? Sound epidemiological and laboratory data are needed to explore these hypotheses to establish the neurobiological basis and identify the mechanistic mediators underlying the detrimental health consequence of long sleep duration.

The modest increase in ischemic stroke risk associated with short sleep (≤6 hours/night), among those without previous CVD, supports the growing evidence of long-term adverse effects of sleep deprivation. If we considered short sleep duration ≤5 hours per night equivalent to sleep <6 hour as often classified and reported by others, the prevalence (8.3%) of having short sleep duration among older women aged 50 to 79 years in 1994 to 1998 was much less than the estimated prevalence (14%) of having weekday sleep <6 hours per night for women aged 55 to 84 included in the 2003 Sleep in America poll, conforming to the notion of a downward trend in sleep duration over time.8 Population-based data have previously shown that insufficient sleep increases the risks for mortality, obesity, DM, hypertension, and CHD. Clinical laboratory studies have found that sleep deprivation causes neuroendocrine disturbance, metabolic abnormalities, and systemic inflammation, all indicative of increased risk of atherosclerosis.8 Given these congruent lines of evidence all pointing to the adverse health consequence of sleep deprivation, appropriate behavioral intervention should be considered.

We recognized several limitations in our study. First, the WHI-OS is restricted to postmenopausal women. Although there is suggested evidence that women may be more susceptible to the detrimental health effects of sleep deprivation,4 there remains uncertainty in the speculated gender-specific difference. Whether the risks of ischemic stroke in younger women and in men also depend on sleep duration needs to be investigated. Second, no objective measures of sleep duration were available in the WHI-OS, and our classification of habitual sleep duration is based on self-reports at baseline. However, it has been shown that objective sleep measures have a much larger nightly variability of sleep duration than its corresponding yearly variability,21 suggesting that sleep behavior changes little in 1 year, despite large daily fluctuations. Good reproducibility of exposure classification of self-reported habitual sleep duration has also been documented in large cohort studies.2,3 Given our prospective study design, it is more likely that the subjective measure of sleep...
duration will lead to nondifferential misclassification, which tends to bias the association toward the null. Third, although we have included a large set of potential confounders in our analyses, we could not completely rule out the possibility of any residual or unmeasured confounding. This is a more legitimate concern regarding the modest association with short sleep, because its estimated effect size was gradually attenuated in the adjusted analyses. For instance, short sleep duration could result from occupational stressors or concurrent stressful life events, and these psychosocial stressors may lead to ischemic stroke by alternative pathways other than through the mediation of conventional CVD risk factors or associated lifestyle modification.

Summary
In postmenopausal women, long sleep duration (≥9 hours/night) increases the risk for ischemic stroke. This association is not confounded by socioeconomic status, depressive symptoms, or other conventional CVD risk factors, and is likely independent of the effect of frequent snoring and sleepiness. The underlying neurobiology and mechanistic mediators linking habitual long sleep with increased risk of ischemic stroke need to be investigated. Our data also suggest short sleep duration (≤6 hours/night) as a neurobehavioral risk factor for ischemic stroke in postmenopausal women without clinically overt CVD.

Acknowledgments
The authors are grateful for the dedicated efforts of all investigators and staff at the WHI clinical centers and the WHI clinical coordinating center (listed in the Supplemental Appendix, available online at http://stroke.ahajournals.org), and acknowledge Dr Wayne Rosamond for providing the references on stroke statistics used in this study.

Sources of Funding
The Women’s Health Initiative Observation Study was funded by the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), Department of Health and Human Services. Drs Chen and Levine are supported in part by the NIH grant R21HL89422.

Disclosure
None.

References
Sleep Duration and Risk of Ischemic Stroke in Postmenopausal Women

Stroke. 2008;39:3185-3192; originally published online July 17, 2008;
doi: 10.1161/STROKEAHA.108.521773
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/12/3185

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/