Sleep Duration and Risk of Ischemic Stroke in Postmenopausal Women

Jiu-Chiuan Chen, MD., MPH, Sc.D.[1], **Robert L. Brunner, PhD.**[2], **Hong Ren, MS.**[3], **Sylvia Wassertheil-Smoller, PhD.**[4], **Joseph C. Larson, MS.**[3], **Douglas W. Levine, PhD.**[5], **Matthew Allison, MD, MPH.**[6], **Michelle J. Naughton, PhD.**[7], and **Marcia L. Stefanick, PhD.**[8]

[1]*Department of Epidemiology, University of North Carolina School of Public Health, Chapel Hill, NC.*

[2]*Department of Family and Community Medicine, University of Nevada School of Medicine, Reno, NV.*

[3]*Fred Hutchinson Cancer Research Center, Seattle, WA.*

[4]*Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY.*

[5]*Department of Psychology, University of North Carolina at Greensboro, Greensboro, NC.*

[6]*Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA.*

[7]*Wake Forest University School of Medicine, Winston-Salem, NC.*

[8]*Department of Medicine, Stanford University, Stanford, CA.*

Abstract

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

Methods—We conducted a prospective study on 93175 older women (aged 50–79 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 CVD-related clinical characteristics.

Results—At baseline, 8.3% of subjects had their reported sleep duration ≤5h/night and 4.6% with long sleep (≥9h/night). After an average of 7.5 years of follow-up, 1166 cases of ischemic stroke had occurred. Multivariable-adjusted relative risks (RR; 95% confidence intervals) for ischemic stroke (using a sleep time of 7h/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 or less, 8, and 9 or more hours of sleep. A modestly stronger

Address for Correspondence: Jiu-Chiuan Chen, MD., MPH, Sc.D., Department of Epidemiology, University of North Carolina School of Public Health, 2104G, McGavran-Greenberg, CB#7435, Chapel Hill, NC 27599-7435, U.S.A., TEL: (919) 962-2756; FAX: (919) 966-2089; Email: jcchen@unc.edu.

association with sleep duration ≤ 6h/night (RR=1.22; 1.03, 1.44) was noted among women without prevalent CVD 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 (≥9h/night) need further elucidation.

Keywords

cerebral infarction; cohort studies; sleep disorders; risk factors

INTRODUCTION

Increases in mortality associated with either shortened sleep (sleep duration ≤6 h/night) or long sleep duration (sleep duration ≥9 h/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 (NHS), and the Monitoring Trends and Determinants on Cardiovascular Diseases (MONICA) 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 NHS and NHANES-I follow-up study reported an increased CHD risk associated with habitual sleep duration less than 6 hours, which also increased the MI risk among middle-aged women in the MONICA Augsburg cohort. Long sleep duration (≥9 h/night) was associated with increased CHD risk in the NHS, but it was associated with statistically non-significant increase in MI risk among women in the recent MONICA 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 sleepers (>8h), but not in short sleepers (<6h).[6] Causal inference cannot be drawn from theses 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 symptoms.[7,8] Although some studies on mortality[1, 3] 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 (e.g., unemployment status).[9] 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 above-mentioned 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 (1994–2005) prospective cohort study designed to identify and assess the relationships of biological, lifestyle, biochemical, and genetic factors to the risks of heart disease, cancer, osteoporosis, and other major health problems of older women.

METHODS

Study Population

Detailed information about the study population, recruitment methods, and measurement protocols of the WHI-OS has been published previously.[10, 11] Briefly, the WHI-OS

population is a multiethnic cohort (0.5% American Indian–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 50–79 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 (WHI-CT) 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 of 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 and colleagues 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.[12] 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 8–14 days).

Ascertainment of Health Outcome

The diagnosis of ischemic stroke followed the established protocols that have been published elsewhere.[13,14] In brief, potential stroke outcomes in WHI-OS, including fatal and non-fatal 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 more than 24 hours (unless death supervenes) without evidence for other cause, such as brain trauma, tumor, or infection, etc. Stroke outcomes were classified as ischemic stroke, if the clinical diagnosis revealed the occlusion of cerebral or pre-cerebral 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 non-ischemic 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 (e.g., surgical evidence) or did not have neuroimaging studies available (e.g., 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 (e.g., smoking, physical activity), and relevant clinical characteristics, including use of menopausal hormone therapy (HT), prior 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 body mass index (BMI, in kg/m^2) categories: Underweight (<18.5), Normal (18.5–24.9),

Overweight (25.0– 29.9), Obesity I (30.0–34.9), Obesity II (35.0–39.9), 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 prior MI, coronary angioplasty, or coronary artery bypass graft (CABG). Histories of CVD include having previous CHD, stroke, or transient ischemic attack (TIA). Good reliability and validity of these self-reported clinical characteristics and physical measures have been documented.[11, 15] Depressive symptoms were assessed with a scale that used 6 items from the 20-item Center for Epidemiological Studies Depression Scale (CES-D).[16] The 6-item CES-D included one item about poor sleep (*"Your sleep was restless"*). To avoid colinearity between measures of sleep measures and depressive symptoms, we excluded one 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[17] were used to assess feelings of sadness or depression for 2 or more weeks in the past year and feelings of sadness on most days for 2 or more years. 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 sleepiness (*"falling asleep during quiet activities like reading, watching TV, or riding in a car"*), based on a 5-point scale (0, <1, 1–2, 3–4, ≥5 times per 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 8–14 days).

Statistical Analyses

We compared the distributions of sleep duration across different population characteristics, using chi-square 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. Accordingly to the WHI protocol, women who had developed non-ischemic stroke during the follow-up would not enter adjudication again. Although non-ischemic stroke is not the outcome of interest in the present analyses, these women were also censored at the time of non-ischemic 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, HT usage, and other clinical characteristics (prior 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 prior comorbid conditions (CVD/CHD, DM, hypertension) predisposing to sleep disturbance and the study endpoint.

Several sensitivity analyses were carried out to evaluate whether the observed associations were sensitive to excluding ischemic stroke events which incurred 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, Cary, NC).

RESULTS

Table 1 presents the population distribution of sleep duration in relation to selected baseline (1994–1998) sociodemographics and lifestyle factors. Approximately 8.3% reported short sleep duration ≤5h/night, while 4.6% were long sleepers (≥9h/night). A higher proportion of minority 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 ≤5h/night. Prevalence of short sleep duration ≤5h/night was much higher in women who were physically inactive, when compared to their counter parts. The prevalence of being long sleepers (≥9h/night) also differed by individual socioeconomic status. There was also a graded increase in the prevalence of being long 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 current smokers or less physically active was associated with a slightly higher prevalence of being long sleepers.

As shown in Table 2, clinical characteristics were important determinants of sleep duration. Increasing BMI, up above normal (18.5–24.9 kg/m^2), was associated with increased prevalence of short sleep duration ≤5h/night. Current HT users were less likely to have short sleep than non-current users. Participants with existing CHD/CVD, treated DM, hypertension, hypercholesterolemia, or depression were more likely to report short sleep duration ≤5h/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 seen in the prevalence of having short sleep duration ≤5h/night.

We noted that self-reported sleep duration had a non-linear 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 8–9h of sleep were the least likely to have frequent sleepiness (42–44% *vs.* 48–61%) and women with 7h of sleep were the least likely to report frequent snoring (20% *vs.* 21–30%). Higher prevalence of having both "frequent snoring and sleepiness" was found in participants with 5 hours or less of sleep (15%) or 10 hours or more of sleep (17%), compared to the others (11–14%).

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=7h/night had the lowest risk for ischemic stroke; the risk was higher in women with sleep≤6h/night and a graded increase in risk was noted for women with increasing sleep duration beyond 7h/night. Given the relatively small number of cases among those with longest (n=15 in those with sleep≥10h/night) or shortest sleep (n=99 in those with short sleep duration ≤5h/night), we combined these two 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=7h/ night as the referent, we found a 19% (95% confidence interval [CI]: 3–37%) increase in relative risk (RR) in women with sleep ≤ 6h/night, after adjustment for age and race. However, the increased RR associated with sleep duration ≤ 6h/night was slightly diminished and became statistically non-significant (Model-IV: RR=1.14, 95%CI: 0.97, 1.33) after additionally accounting for socioeconomic status, depressive symptoms, HT use, and conventional CVD risk factors. In contrast, there was a consistent and graded increase in RR observed for women with sleep=8h/night and for those with sleep≥9h/night. These elevated RRs among women with sleep duration above 7h/night remained fairly stable in all the adjusted models, with the RR increased approximately by 25% among women with sleep duration=8h/night and by 70% in those with sleep≥9h/night. We also noted the increase in ischemic stroke risk among women

with frequent snoring and sleepiness. Compared to those reporting no or <1/week in both snoring and sleepiness, women with both "frequent snoring and sleepiness" had an elevated but statistically non-significant risk for ischemic stroke (RR=1.28, 95%CI: 0.98–1.68), 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-sleepers to those with sleep=7hrs/night) and the U-shape relationship between habitual sleep patterns and ischemic stroke remained in the sensitivity analyses. After we excluded the events which occurred within the first 6 months of follow-up, an increased risk for ischemic stroke was observed among participants reporting 6-h or less (RR=1.15, 95%CI: 0.98–1.35), 8-h (RR=1.22, 95%CI: 1.03–1.45), and 9-h or more (RR=1.71, 95%CI: 1.32–2.23), 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 sleepers (RR=1.15, 95%CI: 0.98–1.36) and in those with sleep duration=8h (RR=1.21, 95%CI: 1.02–1.44) or ≥9h (RR=1.71, 95%CI: 1.32–2.22).

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-h or less (RR=1.11, 95%CI: 0.95–1.30), 8-h (RR=1.22, 95%CI: 1.03–1.45), and 9-h or more (RR=1.60, 95%CI: 1.23–2.08). In our exploratory analysis which jointly modeled the presumably independent effects of "frequent snoring/sleepiness" and habitual sleep duration, the modest increase in risk was still noted in short sleepers (RR=1.14, 95%CI: 0.97–1.35), 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).

In Table 4, the estimated associations with habitual sleep patterns were furthered stratified by the presence of prior CVD/CHD, DM, or hypertension. The increased RRs for ischemic stroke in women with sleep≥9h/night were very consistent and did not depend upon these clinical comorbidities. The positive association with sleep ≤ 6h/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 and colleagues in the NHANES-I follow-up study.[6] In their 10-year longitudinal analyses of the national cohort of 7844 adults (aged 25–74 at baseline), long sleepers (>8 h/night) had increased stroke risk (RR=1.5, 95% CI: 1.1–2.0), compared to those with sleep 6–8 h/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. Indeed, we found that income, physical activities, depressive symptoms, and other CVD risk factors were all important correlates of sleep duration in postmenopausal women (Table 1 & 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 sleepers, although there were only a small number of stroke events (n=26 in 675 subjects with sleep <6 h/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 (~60–70% increase in risk) with long sleep that was stronger than the association with short sleep (~10–20% 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 NHS[5] and MI risk in the MONICA Augsburg cohort.[4] It had been speculated that the increased risks for CHD, stroke, and mortality among long sleepers might be due to other sleep disorders, such as sleep-disordered breathing (SDB).[3,6] We categorized women who reported both frequent snoring and sleepiness as having SDB-related symptoms and found that women with 10 or more hours of sleep had the highest prevalence of SDB-related symptoms, and the risk of ischemic stroke was increased in women with frequent snoring/sleepiness. However, our exploratory analysis which jointly modeled the effects of sleep duration and frequent snoring/sleepiness supported the putative effect of long sleep independent of SDB-related symptoms.

The reported detrimental health effects of long sleep have also been attributed to the potential confounding by depression.[7,9] Having prior 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 prior depression.[18] However, in our sensitivity analyses which 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 ~60–70%) 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, 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 socio-behavioral attributes, environmental factors, or underlying biophysical constructs that are proximate causes of ischemic stroke. Given the strength of association and low prevalence of long 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 multi-variable 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 sleepers is entirely due 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 sleepers to be more likely to develop ischemic stroke than those usually with 7 hours of sleep? Previous studies have found increased risks of diabetes and hypertension in people sleep ≥9h/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, since our analyses have accounted for a large set of conventional CVD risk factors. Are long sleepers more likely to have systemic inflammation, thrombostatic 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-electrophysiologic excitability predisposing to cardiac arrhythmia? Does the longer than average duration of recumbent position increase the period with high intracranial pressure and/ or alter hemodynamics that can compromises the cerebral blood flow? Sound epidemiologic and laboratory data are needed to explore these hypotheses in order 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 (≤6h/night), among those without previous CVD, supports the growing evidence of long-term adverse effects of sleep deprivation. If we considered short sleep duration≤5h/night equivalent to sleep <6h as often classified and reported by others, the prevalence (8.3%) of having short sleep duration among older women aged 50–79 years in 1994–1998 was much less than the estimated prevalence (14%) of having weekday sleep <6h/night for women aged 55–84 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 one 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 non-differential misclassification, which tends to bias the association towards 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, as 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 (≥9h/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 (≤6h/night) as a neurobehavioral risk factor for ischemic stroke in postmenopausal women without clinically overt CVD.

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SHORT LIST OF WHI INVESTIGATORS

Program Office

(National Heart, Lung, and Blood Institute, Bethesda, Maryland) Elizabeth Nabel, Jacques Rossouw, Shari Ludlam, Linda Pottern, Joan McGowan, Leslie Ford, and Nancy Geller.

Clinical Coordinating Center

(Fred Hutchinson Cancer Research Center, Seattle, WA) Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, Anne McTiernan; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (Medical Research Labs, Highland Heights, KY) Evan Stein; (University of California at San Francisco, San Francisco, CA) Steven Cummings.

Clinical Centers

(Albert Einstein College of Medicine, Bronx, NY) Sylvia Wassertheil-Smoller; (Baylor College of Medicine, Houston, TX) Jennifer Hays; (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn Manson; (Brown University, Providence, RI) Annlouise R. Assaf; (Emory University, Atlanta, GA) Lawrence Phillips; (Fred Hutchinson Cancer Research Center, Seattle, WA) Shirley Beresford; (George Washington University Medical Center, Washington, DC) Judith Hsia; (Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA) Rowan Chlebowski; (Kaiser Permanente Center for Health Research, Portland, OR) Evelyn Whitlock; (Kaiser Permanente Division of Research, Oakland, CA) Bette Caan; (Medical College of Wisconsin, Milwaukee, WI) Jane Morley Kotchen; (MedStar Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Northwestern University, Chicago/Evanston, IL) Linda Van Horn; (Rush Medical Center, Chicago, IL) Henry Black; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (State University of New York at Stony Brook, Stony Brook, NY) Dorothy Lane; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Alabama at Birmingham, Birmingham, AL) Cora E. Lewis; (University of Arizona, Tucson/Phoenix, AZ) Tamsen Bassford; (University at Buffalo, Buffalo, NY) Jean Wactawski- Wende; (University of California at Davis, Sacramento, CA) John Robbins; (University of California at Irvine, CA) F. Allan Hubbell; (University of California at Los Angeles, Los Angeles, CA) Howard Judd; (University of California at San Diego, LaJolla/Chula Vista, CA) Robert D. Langer; (University of Cincinnati, Cincinnati, OH) Margery Gass; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Hawaii, Honolulu, HI) David Curb; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Massachusetts/Fallon Clinic, Worcester, MA) Judith Ockene; (University of Medicine and Dentistry of New Jersey, Newark, NJ) Norman Lasser; (University of Miami, Miami, FL) Mary Jo O'Sullivan; (University of Minnesota, Minneapolis, MN) Karen Margolis; (University of Nevada, Reno, NV) Robert Brunner; (University of North Carolina, Chapel Hill, NC) Gerardo Heiss; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (University of Tennessee, Memphis, TN) Karen C. Johnson; (University of Texas Health Science Center, San Antonio, TX) Robert Brzyski; (University of Wisconsin, Madison, WI) Gloria E. Sarto; (Wake Forest University School of Medicine, Winston-Salem, NC) Denise Bonds; (Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI) Susan Hendrix.

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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.

	N†	Hours of sleep per night					
		≤5	6	7	8	9	≥10
All subjects	**93175**	**7738 (8.3%)**	**25077 (26.9%)**	**34902 (37.5%)**	**21158 (22.7%)**	**3758 (4.0%)**	**542 (0.6%)**
Age (years)							
50–59	29559	2503 (8.5%)	8268 (27.6%)	11506 (38.9%)	6128 (20.9%)	1029 (3.5%)	171 (0.6%)
60–69	40984	3177 (7.8%)	10660 (26.0%)	15298 (37.3%)	9907 (24.2%)	1704 (4.2%)	238 (0.6%)
70–79	22632	2058 (9.1%)	6249 (27.6%)	8089 (35.8%)	5069 (22.4%)	1025 (4.5%)	133 (0.6%)
Ethnicity							
White	77712	5189 (6.7%)	19814 (25.6%)	30241 (38.9%)	18792 (24.2%)	3315 (4.3%)	361 (0.5%)
Black	7558	1438 (19.0%)	2668 (35.3%)	2060 (27.3%)	1065 (14.1%)	234 (3.1%)	93 (1.2%)
Hispanic	3527	485 (13.8%)	1032 (29.3%)	1156 (32.8%)	663 (18.8%)	115 (3.3%)	76 (2.2%)
American Indian	412	61 (14.8%)	113 (27.4%)	132 (32.0%)	86 (20.9%)	17 (4.1%)	3 (0.7%)
Asian/Pacific Islander	2663	397 (14.9%)	1035 (38.9%)	876 (32.9%)	310 (11.6%)	39 (1.5%)	6 (0.2%)
Unknown	1303	168 (12.9%)	415 (31.9%)	437 (33.5%)	242 (18.6%)	38 (2.9%)	3 (0.2%)
Education							
0–8 years	1522	246 (16.2%)	413 (27.1%)	425 (27.9%)	320 (21.0%)	68 (4.5%)	50 (3.3%)
Some high school	3247	515 (15.9%)	971 (29.9%)	939 (28.9%)	644 (19.8%)	131 (4.0%)	47 (1.5%)
High school diploma/GED	15036	1499 (10.0%)	4239 (28.2%)	5325 (35.4%)	3276 (21.8%)	618 (4.1%)	79 (0.5%)
School after high school	33772	3105 (9.2%)	9371 (27.8%)	12259 (36.3%)	7513 (22.3%)	1339 (4.0%)	185 (0.6%)
College degree or higher	38839	2299 (5.9%)	9857 (25.4%)	15687 (40.4%)	9244 (23.8%)	1578 (4.1%)	174 (0.5%)
Family income ($)							
<10,000	3860	677 (17.5%)	1105 (28.6%)	1069 (27.7%)	768 (19.9%)	154 (4.0%)	87 (2.3%)
10,000–19,999	10012	1247 (12.5%)	2975 (29.7%)	3273 (32.7%)	2016 (20.1%)	403 (4.0%)	98 (1.0%)
20,000–34,999	20122	1828 (9.1%)	5647 (28.1%)	7239 (36.0%)	4456 (22.1%)	846 (4.2%)	106 (0.5%)
35,000–49,999	17365	1242 (7.2%)	4717 (27.2%)	6688 (38.5%)	3939 (22.7%)	722 (4.2%)	57 (0.3%)
50,000–74,999	17423	1146 (6.6%)	4447 (25.5%)	6939 (39.8%)	4147 (23.8%)	671 (3.9%)	73 (0.4%)
≥75,000	17547	946 (5.4%)	4347 (24.8%)	7324 (41.7%)	4200 (23.9%)	674 (3.8%)	56 (0.3%)
Employment status							
Currently employed	32314	2637 (8.2%)	9638 (29.8%)	12812 (39.7%)	6251 (19.3%)	889 (2.8%)	87 (0.3%)
Not working	14272	1322 (9.3%)	3679 (25.8%)	5122 (35.9%)	3328 (23.3%)	673 (4.7%)	148 (1.0%)
Retired	43884	3540 (8.1%)	11057 (25.2%)	15934 (36.3%)	10990 (25.0%)	2086 (4.8%)	277 (0.6%)
Smoking							
Never smoked	46826	4057 (8.7%)	12550 (26.8%)	17663 (37.7%)	10557 (22.6%)	1757 (3.8%)	242 (0.5%)
Past smoker	39392	2981 (7.6%)	10546 (26.8%)	14785 (37.5%)	9147 (23.2%)	1690 (4.3%)	243 (0.6%)
Current smoker	5764	596 (10.3%)	1662 (28.8%)	2027 (35.2%)	1168 (20.3%)	258 (4.5%)	53 (0.9%)
Moderate or strenuous activities ≥ 20min							
No activity	12574	1468 (11.7%)	3631 (28.9%)	4175 (33.2%)	2604 (20.7%)	572 (1.0%)	124 (1.0%)
Some activity	35534	3222 (9.1%)	9813 (27.6%)	12811 (36.1%)	7977 (22.5%)	1473 (4.2%)	238 (0.7%)
2–4 episodes/wk	17054	1179 (6.9%)	4393 (25.8%)	6733 (39.5%)	4010 (23.5%)	668 (3.9%)	71 (0.4%)
>4 episodes/wk	27168	1797 (6.6%)	7027 (25.9%)	10865 (40.0%)	6372 (23.5%)	1005 (3.7%)	102 (0.4%)

*
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.

Table 2

Population Distribution(*) of Sleep Duration in Relation to Clinical Characteristics in the Women's Health Initiative Observational Study Cohort, 1994–2005.

	N†	Hours of sleep per night					
		≤5	6	7	8	9	≥10
Body mass index (kg/m²)							
Underweight (<18.5)	1101	102 (9.3%)	291 (26.4%)	413 (37.5%)	240 (21.8%)	50 (4.5%)	5 (0.5%)
Normal (18.5–24.9)	36529	2420 (6.6%)	9349 (25.6%)	14724 (40.3%)	8493 (23.3%)	1402 (3.8%)	141 (0.4%)
Overweight (25.0–29.9)	31284	2532 (8.1%)	8463 (27.1%)	11639 (37.2%)	7152 (22.9%)	1309 (4.2%)	189 (0.6%)
Obesity-I (30.0–34.9)	14493	1498 (10.3%)	4141 (28.6%)	4915 (33.9%)	3228 (22.3%)	600 (4.1%)	111 (0.8%)
Obesity-II (35.0–39.9)	5415	647 (12.0%)	1570 (29.0%)	1747 (32.3%)	1168 (21.6%)	231 (4.3%)	52 (1.0%)
Extreme obesity (≥40)	3256	446 (13.7%)	980 (30.1%)	1033 (31.7%)	634 (19.5%)	126 (3.9%)	37 (1.1%)
Use of hormone therapy							
Never	37746	3614 (9.6%)	10389 (27.5%)	13673 (36.2%)	8284 (22.0%)	1524 (4.0%)	262 (0.7%)
Past	13840	1249 (9.0%)	3797 (27.4%)	5001 (36.1%)	3130 (22.6%)	585 (4.2%)	78 (0.6%)
Current	41508	2869 (6.9%)	10863 (26.2%)	16194 (39.0%)	9735 (23.5%)	1645 (4.0%)	202 (0.5%)
History of depression							
No	81188	5896 (7.3%)	21338 (26.3%)	31218 (38.5%)	19103 (25.3%)	3227 (4.0%)	406 (0.5%)
Yes	11459	1726 (15.4%)	3589 (31.3%)	3504 (30.6%)	1952 (17.0%)	518 (4.5%)	134 (1.2%)
History of high cholesterol requiring pills							
No	77542	6228 (8.0%)	20687 (26.7%)	29366 (37.9%)	17765 (22.9%)	3076 (4.0%)	420 (0.5%)
Yes	13708	1327 (9.7%)	3889 (28.4%)	4824 (35.2%)	2965 (21.6%)	594 (4.3%)	109 (0.8%)
Hypertension status							
No	56122	4186 (7.5%)	14832 (26.4%)	21847 (38.9%)	12798 (22.8%)	2180 (3.9%)	279 (0.5%)
Yes	35976	3459 (9.6%)	9971 (27.7%)	12640 (35.1%)	8117 (22.6%)	1532 (4.3%)	257 (0.7%)
Treated for diabetes							
No	89189	7138 (8.0%)	23917 (26.8%)	33660 (37.7%)	20381 (22.3%)	3586 (4.0%)	507 (0.6%)
Yes	3867	589 (15.2%)	1130 (29.2%)	1200 (31.0%)	746 (19.3%)	167 (4.3%)	35 (0.9%)
History of CVD‡							
No	85896	6863 (8.0%)	23068 (26.9%)	32473 (37.8%)	19596 (22.8%)	3423 (4.0%)	473 (0.6%)
Yes	5877	717 (12.2%)	1616 (27.5%)	1938 (33.0%)	1269 (21.6%)	277 (4.7%)	60 (1.0%)
History of CHD§							
No	88525	7169 (8.1%)	23782 (26.9%)	33338 (37.7%)	20175 (22.8%)	3555 (4.0%)	506 (0.6%)
Yes	3215	406 (12.6%)	891 (27.7%)	1062 (33.0%)	683 (21.2%)	145 (4.5%)	28 (0.9%)

*
The data represented the number of subjects (%) belonging to each level of sleep duration, given for each subcategory of clinical characteristics (all p<0.001).

†
The total number of subjects summed up across each subcategory varies slightly because of missing values.

‡
CVD: cardiovascular disease defined as having prior MI, coronary angioplasty, CABG, stroke, or transient ischemic attack

§
CHD: coronary heart disease defined as having prior MI, coronary angioplasty, or CABG.

Table 3

Differences in the Ischemic Stroke Rate and Relative Risk in Relation to Sleep Duration in WHI-OS, 1994–2005

| | Hours of sleep per night | | | | | |
	≤5	6	7	8	9	≥10
N	7738	25077	34902	21158	3758	542
Average length of follow-up (years)	7.3	7.5	7.6	7.6	7.5	7.1
Number of ischemic stroke	99	325	372	286	69	15
Event rate (cases/10^5 person-years)	175	173	141	179	246	391
	Hazard Ratios or Relative Risks (95% confidence interval)					
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 (prior CVD, DM, hypertension, high cholesterol level requiring pills, BMI)

Table 4

The Associations of Ischemic Stroke Risk with Sleep Duration in WHI-OS, Stratified by Baseline Comorbidities.

	Prior CVD		Prior CHD	
	Yes (N=5877)	No (N=85896)	Yes (N=3215)	No (N=88525)
Sleep duration	Hazard Ratios or Relative Risks (95% confidence interval)[*]			
≤ 6 hrs	0.75 (0.53, 1.07)	1.26 (1.06, 1.50)	0.84 (0.52, 1.37)	1.19 (1.00, 1.40)
7 hrs	1.00	1.00	1.00	1.00
8 hrs	1.23 (0.84, 1.79)	1.24 (1.02, 1.50)	1.03 (0.58, 1.83)	1.26 (1.05, 1.51)
≥ 9 hrs	1.76 (1.05, 2.95)	1.66 (1.24, 2.24)	1.69 (0.77, 3.68)	1.73 (1.31, 2.27)
p-value[†]		0.03		0.60

	Diabetes Mellitus		Hypertension	
	Yes (N=3867)	No (N=89189)	Yes (N=35967)	No (N=56122)
Sleep duration	Hazard Ratios or Relative Risks (95% confidence interval)[*]			
≤ 6 hrs	0.68 (0.43, 1.07)	1.22 (1.03, 1.44)	1.11 (0.92, 1.36)	1.19 (0.92, 1.54)
7 hrs	1.00	1.00	1.00	1.00
8 hrs	1.13 (0.69, 1.84)	1.25 (1.04, 1.50)	1.34 (1.09, 1.65)	1.05 (0.78, 1.41)
≥ 9 hrs	1.74 (0.90, 3.33)	1.68 (1.27, 2.23)	1.59 (1.14, 2.20)	1.92 (1.27, 2.91)
p-value[†]		0.07		0.29

[*] 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 (prior CVD/CHD, DM, hypertension, high cholesterol levels requiring pills, BMI). CVD/CHD: defined in Table 2

[†] p-value comparing the RR with potential effect modifier present vs. RR with potential effect modifier absent