RESEARCH ARTICLE

Association Between Insomnia Symptoms and Trajectory With the Risk of Stroke in the Health and Retirement Study

Wendemi Sawadogo, MD, MPH, PhD, Tilahun Adera, PhD, MPH, Maha Alattar, MD, Robert Perera, PhD, and James B. Burch, MS, PhD

Correspondence
Dr. Sawadogo
sawadogow@vcu.edu

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Abstract

Background and Objectives

Insomnia is a common condition affecting more than a third of the US population. However, the link between insomnia symptoms and stroke is understudied and the underlying mechanism remains unclear. This study aimed to investigate the relationship between insomnia symptoms and the incidence of stroke.

Methods

The Health and Retirement Study, a survey of Americans older than 50 years and their spouses, from 2002 to 2020 was used as the data source. Only those who were stroke-free at baseline were included in this study. The exposure variable was insomnia symptoms and was derived from self-reported sleep-related factors including difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and nonrestorative sleep. Repeated-measures latent class analysis was used to identify insomnia trajectories over time. To investigate the relationship between insomnia symptoms and stroke events reported during the follow-up period, Cox proportional hazards regression models were used. Mediation analyses of comorbidities were performed using causal mediation within a counterfactual framework.

Results

A total of 31,126 participants were included with a mean follow-up of 9 years. The mean age was 61 years (SD = 11.1) and 57% were females. Insomnia symptom trajectories remained constant over time. Compared with those with no insomnia symptoms, an increased risk of stroke was observed for those with insomnia symptom scores ranging from 1 to 4 and 5 to 8 (hazard ratio (HR) = 1.16, 95% confidence interval (CI) 1.02–1.33) and (HR = 1.51, 95% CI 1.29–1.77), respectively, indicating a dose-response relationship. The association was stronger in participants younger than 50 years (HR = 3.84, 95% CI 1.50–9.85) than in those aged 50 years and older (HR = 1.38, 95% CI 1.18–1.62), comparing those with insomnia symptoms ranging from 5 to 8 with those with no insomnia symptoms. This association was mediated by diabetes, hypertension, heart disease, and depression.

Discussion

Insomnia symptoms were associated with an increased risk of stroke, especially in adults younger than 50 years, and the risk was mediated by certain comorbidities. Increased awareness and management of insomnia symptoms may contribute to the prevention of stroke occurrence.

From the Division of Epidemiology (W.S., T.A., J.B.B.), Department of Family Medicine and Population Health, and Division of Adult Neurology (M.A.), Sleep Medicine, Vascular Neurology, Department of Neurology; and Department of Biostatistics (R.P.), Virginia Commonwealth University, School of Medicine, Richmond.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

BIC = Bayesian Information Criterion; **BIQ** = Brief Insomnia Questionnaire; **CESD** = Centers for Epidemiologic Study of Depression; **CRP** = C-reactive protein; **DBS** = dried blood spot; **EBB** = Early Baby Boomers; **HRS** = Health and Retirement Study; **LBB** = Late Baby Boomers; **MBB** = Mid Baby Boomers; **NDE** = Natural Direct Effects; **NIE** = Natural Indirect Effect; **SDI** = social deprivation index; **TE** = Total Effect; **TIA** = transient ischemic attack.

Sleep disorders, specifically sleep apnea, are increasingly recognized as risk factors of stroke.[1,2] However, uncertainties remain regarding the potential risk of insomnia. A large cohort (0.5 million participants) from China reported that participants with insomnia symptoms (difficulty initiating sleep, difficulty maintaining sleep) were slightly at a higher risk of ischemic stroke (hazard ratio (HR) = 1.05, 95% confidence interval (CI) 1.02–1.08).[3] Another study based on claim data from Taiwan with more than 1 million participants noted that the insomnia group had a higher incidence of stroke (Hazard Ratio: 1.85, 95% CI 1.62–2.12).[4] The incidence decreased with advanced age, and a higher incidence was observed among those with persistent insomnia.[5] On the contrary, a study from Sweden 6 found that insomnia was unrelated to cardiovascular events that included stroke. Similarly, a study from Germany reported that insomnia symptoms (difficulty falling and maintaining sleep) were not associated with stroke in either sex.

These inconsistencies are potentially due to multiple factors including the variability in insomnia definition (studies using diagnostic criteria[4,5] were more likely to find an association than studies using questionnaires[6,8]), the study population (studies conducted in Asia[3-5] were more likely to find an association than studies conducted in Europe[6,8]), the sample size, and the prevalence of stroke in the study population (studies with large sample size were more likely to find association[3]). In addition, insomnia is most of the time measured at baseline only. A one-time measurement may not accurately reflect the association between insomnia symptoms, which could change over time, and the occurrence of the disease.

Furthermore, the role of comorbidities such as diabetes, hypertension, heart disease, and depression in the potential association between insomnia and stroke is unclear. Most studies adjust for these comorbidities.[3-5] While such an approach is conservative, there are reasons to believe that these comorbidities could be acting as mediators in this association. Insomnia has been linked to an increased risk of diabetes,[9] hypertension,[10] heart disease,[11] and depression.[12]

The underlying mechanisms by which sleep disorders increase the risk of stroke are not well understood. One of the proposed physiopathologic mechanisms is through inflammation.[13,14] C-reactive protein (CRP) is a nonspecific marker of acute inflammation, which is mainly released from the hepatocytes in response to IL-6 expression.[15] Evidence suggests that inflammation contributes to atherosclerosis, thrombosis, and cerebral small vessel disease, thus increasing the risk of various stroke types.[15,16] In addition, the relationship between insomnia and elevated inflammatory biomarkers is supported by growing literature.[17,18] In a systematic review and meta-analysis of 72 studies, insomnia symptoms were associated with higher levels of CRP (OR = 1.25, 1.10–1.41) and IL-6 (OR = 1.44, 1.16–1.76).[19]

The purpose of this study was to investigate the relationship between insomnia symptoms and the incidence of stroke. In addition, mediation by inflammation and comorbidities and effect modification by age, sex, race/ethnicity, and social deprivation index were assessed.

Methods

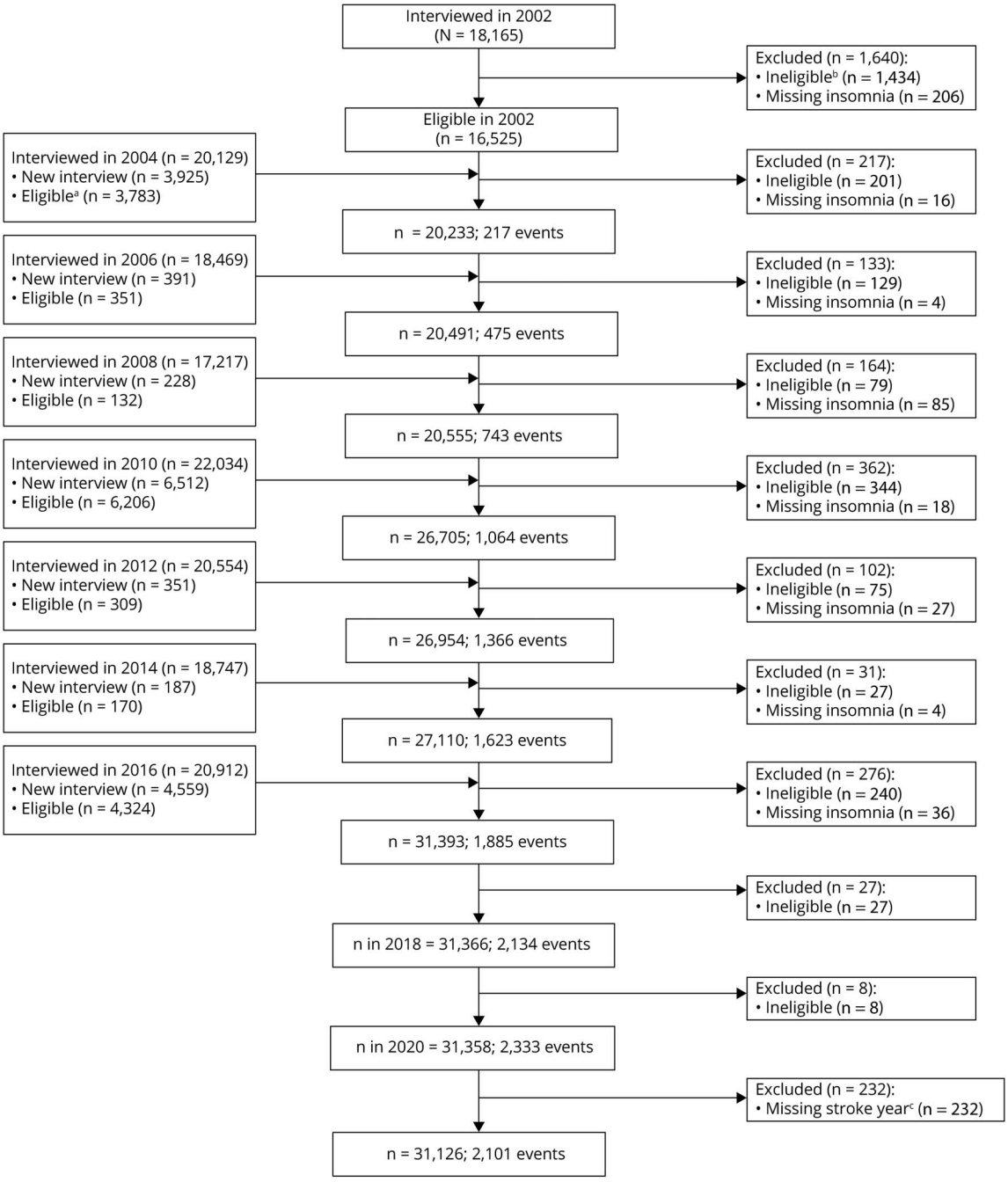
Data Source and Study Population

This prospective cohort study used data from the Health and Retirement Study (HRS). The HRS is an ongoing national longitudinal survey conducted by the University of Michigan and sponsored by the National Institute on Aging (NIA U01AG009740). The study aimed to provide a national data resource on the role of changing health and economic circumstances because they relate to aging at both individual and population levels.[20]

HRS Design and Data Collection

The HRS sample was assembled in several waves of enrollment and data collection. The initial cohort was recruited in 1992 and included individuals born between 1931 and 1941 (then aged 51–61 years) and their spouses of any age. A second study, Asset and Health Dynamics Among the Oldest Old (AHEAD), targeted the cohort that included those born during 1890–1923 (then aged 70 years and older). In 1998, the 2 samples were merged and, to make the sample representative of the US population older than 50 years, they enrolled the Children of the Depression (CODA), born during 1924–1930, and the War Babies, born during 1942–1947. The HRS cohort is replenished every 6 years with younger participants not previously represented. The Early Baby Boomers (EBB, born during 1948–1953) and the Mid Baby Boomers (MBB, born during 1954–1959) were added in 2004 and 2010, respectively.[20] Finally, the Late Baby Boomers (LBB, born during 1960–1965) were added in 2016. At the start of each interview, all respondents gave oral consent to a confidentiality statement. Further details about the survey can be found on the HRS website (hrs.isr.umich.edu).

Figure 1 Flowchart of the Study Inclusion Process



[a]Eligible: provided answer to the insomnia symptoms questions and have never been told that they had a stroke (including TIA). [b]Ineligible: a history of stroke or transient ischemic attack (TIA), unknown stroke status (do not know, refuse). [c]Missing stroke year: did not provide the year of stroke occurrence.

Study Inclusion and Design

The sleep questions of interest were introduced in 2002. Therefore, this study included participants starting from 2002 and followed up until self-report of stroke, loss to follow-up, or the end of the study in 2020, whichever occurred first. Only participants who were stroke-free and completed the sleep questions were included. We excluded respondents with transient ischemic attack (TIA), unknown stroke status, and stroke events with an unknown year of occurrence leading to a final sample of 31,126, as shown in Figure 1.

Exposure: Insomnia Symptoms

Insomnia symptoms were measured using the Adapted Brief Insomnia Questionnaire (BIQ), a validated screening tool assessing self-reported sleep complaints rather than diagnosed insomnia.[21,22] Participants answered 4 questions about how

often they had trouble falling asleep, trouble with waking up during the night, trouble with waking up too early and not being able to return to sleep, and how often they feel rested in the morning (eTable 1, links.lww.com/WNL/C854). The possible response options were "most of the time," "sometimes," or "rarely or never." Those reporting "most of the time" to the first 3 questions were given a score of 2, "sometimes" a score of 1, and "rarely or never" a score of 0. Reverse coding was applied to the last question resulting in a total insomnia symptom severity score that ranges between "0 = no insomnia" and "8 = severe insomnia symptoms."[23]

A second insomnia symptom scale was also used in which individuals were considered as experiencing insomnia symptoms if they answered "most of the time" or "sometimes" to the first 3 questions and "sometimes" or "rarely or never" to the fourth question. The number of symptoms was summed to provide a total insomnia symptom severity score, ranging from "0 = no insomnia symptoms" to "4 = severe insomnia symptoms."[24]

Insomnia Symptom Trajectories

Insomnia symptom trajectories were determined using 3 consecutive assessments of insomnia symptoms. Participants were grouped according to their insomnia symptoms pattern using repeated-measures latent class analysis.[25,26] The analysis was performed for multiple classes, and the model with the best fit was selected based on Bayesian Information Criterion (BIC) and substantive knowledge, as suggested by Jones et al.[26,27]

Outcome: Incident Stroke

Stroke events were self-reported or proxy-reported at biennial interviews. During the interviews, respondents were asked, "Has a doctor ever told you that you had a stroke?" They were also asked for the month and year of stroke events. If a participant died or could not complete the interview, proxy respondents answered questions on stroke events.[28] Based on the responses, new strokes that occurred during the follow-up were identified. The day of stroke occurrence was not collected; therefore, the midpoint of the month was assigned to all stroke events. For respondents missing stroke month, we used the midpoint of the year on which the stroke was reported.[29] Participants who did not report their stroke occurrence year were excluded (Figure 1). If a participant reported multiple strokes, only the first stroke was included in our analyses.

Covariates

Based on previous literature[3-5] and guided by a directed acyclic graph (eFigure 1, links.lww.com/WNL/C854), the below-mentioned covariates were considered.

Demographic factors included age, sex, race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, and Non-Hispanic Other), marital status (divorced, widowed, never-married, currently married), and geographic region (Southern or no). Socioeconomic (SES) factors included education (less than high school, high school, some college, college graduate, and more), household income, employment status, and social deprivation index (SDI). The SDI was produced by the Robert Graham Center, using 7 key neighborhood factors including the percent population with less than 12 years of education, percent of the population with <100% Federal Poverty Level, percent nonemployed, percent of single-parent households, percent of the population living in renter-occupied housing units, percent population living in crowded housing units, and percent population with no car.[30] The index was derived at the level of the census tract, generating values from 0 to 100, applied to each participant with a higher score indicating a more deprived area. Behavioral risk factors included alcohol consumption, smoking, body mass index, and physical activity.

Mediators

CRP: the HRS has used dried blood spot (DBS) in which participants agree to have their fingers pricked and the spots of blood were dripped onto cards. Every 4 years, each participant was asked to provide a blood sample. CRP was obtained by assay of high-sensitivity CRP using a BNII nephelometer (Siemens, Inc., Deerfield, IL).[31]

Comorbidities included self-reported diabetes, hypertension, heart disease (i.e., heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems), and depression. Depressive symptoms were assessed with the 8-item version of the Centers for Epidemiologic Study of Depression (CESD) scale without the sleep item.[32-34] The final score of depressive symptoms was between 0 and 7. Based on previous research indicating that a score of 4 on the 8-item CES-D corresponds to a score of 16 on the 20-item CES-D, which is used for the diagnosis of depression, 4 was used as the cutoff point for the depression variable.[35-37]

Data Analysis

Descriptive Statistics

Descriptive statistics were used to present the distribution of the baseline characteristics by insomnia symptom scores. Mean and standard deviation values were used for continuous variables while frequencies and percentages were used for categorical or ordinal variables. A correlation matrix and phi coefficient were produced to assess the linear relationships between the study variables. Multicollinearity was tested for the covariates using the variance inflation factor, which was considered significant if ≥10.

Time-to-Event Analysis

Cox proportional hazard regression analyses were performed to evaluate the relationship between insomnia symptoms and stroke incidence. The proportional hazard assumption was tested graphically and using the Kolmogorov-type supremum test. The covariates were entered into the model sequentially. Model 1 was adjusted for demographic factors. Model 2 was adjusted for variables included in model 1 and socioeconomic factors. Model 3 was further adjusted for variables included in model 2 and behavioral risk factors.

Several predefined subgroup analyses were performed to determine whether the association of insomnia symptoms with the risk of stroke was modified by age (younger than 50 years vs 50 years or older), sex (male vs female), race/ethnicity (White, Black, Hispanic, Other), and SDI (Fist quartile, second quartile, third quartile, fourth quartile). A p value for interaction was obtained by comparing models with and without multiplicative interaction terms before conducting the abovementioned subgroup analyses.

Mediation

In mediation analyses, CRP and comorbidities were assessed as mediators, and the degree to which they mediate the association between insomnia symptoms and incident stroke were quantified, adjusting for the variables included in model 3. A marginal structural approach that is based on the counterfactual framework was used.[38] In the counterfactual framework, an exposure causal effect on an outcome is defined by the hypothetical contrast between the outcomes that would be observed in the presence and the absence of the exposure of interest in the same individual at the same time.[39] Only one of those outcomes is observed for each individual, the one corresponding to the exposure value experienced by the individual. All other counterfactual outcomes remain unobserved.[40] In this framework, mediation analysis is modeled under the assumption of observed and unobserved potential outcomes. This flexible approach, unlike the traditional approach (causal step, change in coefficient, and path analysis), can accommodate non-normally distributed data such as time-to-event data.[38,41] Furthermore, this approach is suitable for exposure-mediator interactions.[42] The total effect (TE) of insomnia symptoms on incident stroke was decomposed into natural direct effect (NDE) and natural indirect effect (NIE). The NDE is the effect of insomnia symptoms on incident stroke through pathways that do not involve the mediator while the mediator is allowed to vary. The NIE represents the effect of insomnia symptoms on incident stroke due to the effect that insomnia symptoms have on the mediator, that is, estimating the counterfactual outcome, given insomnia symptoms, if the mediator level changed to that it would be, given no insomnia symptoms. The mediated proportion was computed by dividing the natural indirect effect by the total effect. Multiple repeated bootstrapped approaches were used to generate the corresponding 95% CIs. A cross-product term was included to test exposure and mediator interaction. Stroke occurrence within our study population satisfied the rare outcome assumption (<10%); therefore, mediation was measured by Cox proportional hazard models.

Sensitivity Analysis

A series of sensitivity analyses were performed. First, an analysis was conducted using an insomnia symptom scale of 0–4 and further adjusting for comorbidities that were not adjusted in the main analysis because they were considered mediators. Second, an analysis was conducted excluding participants with a proxy reporter. Third, an analysis was conducted excluding participants included in 2016 (due to the shorter follow-up time). Fourth, to assess reverse causation, a lagged analysis was conducted where strokes reported 2 years after insomnia symptom assessment were excluded. Fifth, because participants did not enter the cohort in the same year, an analysis controlling for the cohort entry year was conducted. Sixth, an analysis for model selection and parsimony was conducted in which variables were included in the models if their presence resulted in a greater than 10% change in the estimate for insomnia or if the variable had a p-value <0.05. Another analysis was conducted using the manual backward selection approach. Seventh, physical activity and obesity were tested for mediation. Eighth, an analysis was conducted controlling for obstructive sleep apnea, restless leg syndrome, and narcolepsy. Additional sleep questions were added in 2016 including sleep disorders (have you ever been told by a doctor or other health professional that you have a sleep disorder?) and the type of sleep disorder (what was the sleep disorder?). To account for these variables, a new cohort was constructed using the data for 2016–2020 (N = 18,986). Finally, the E-value for residual unmeasured confounders was computed. The E-value is the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome, conditional on the measured covariates, to fully explain a specific exposure-outcome association.[43] The analyses were conducted using SAS version 9.4 (SAS, Cary, NC) and R (R Foundation, Vienna, Australia).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by Virginia Commonwealth University Institutional Review Bord (HM20023839). Participant consent was waived for this secondary data analysis.

Data Availability

The authors accessed and analyzed the data within the University of Michigan Virtual Data Enclave system upon formal request. Therefore, the data cannot be shared but any qualified investigator may request access.

Results

Descriptive Statistics

Over a mean of 9.2 years of follow-up (q1 = 3.8; q3 = 14.8; max = 19.1) of 31,126 participants, 2,101 incident strokes were recorded (eFigure 2, links.lww.com/WNL/C854). The mean age was 61 years, 92.5% were older than 50 years, 57% were female, and 63% were Non-Hispanic White (Table 1, eTable 2). The mean age and income decreased with increasing insomnia symptom scores, while mean CRP levels increased with increasing insomnia symptom scores. Insomnia symptom scores were higher in female individuals, current smokers, those who were unemployed/disabled, those with low education, conditions of low physical activity, obesity, and any comorbidity, and those living in a socially deprived neighborhood.

Table 1 Baseline Characteristics of Participants by Insomnia Symptom Scores

Variable	Total n (%) (n = 31,126)	Insomnia symptom score								
		0% (n = 6,282)	1% (n = 5,119)	2% (n = 5,638)	3% (n = 4,552)	4% (n = 3,840)	5% (n = 2,275)	6% (n = 1,643)	7% (n = 992)	8% (n = 785)
Age, y										
Mean (SD)	61.0 (11.1)	60.9 (10.9)	61.5 (11.1)	61.5 (11.1)	61.4 (11.4)	60.9 (11.1)	60.4 (10.8)	59.6 (11.0)	58.9 (10.3)	58.9 (10.7)
Median	58.0	58.0	59.0	59.0	58.0	57.0	57.0	56.0	56.0	55.0
Q1, Q3	53.0; 68.0	53.0; 68.0	53.0; 69.0	53.0; 68.0	53.0; 69.0	53.0; 68.0	53.0; 67.0	53.0; 65.0	52.0; 64.0	52.0; 63.0
Age group										
<50	2,343 (7.5)	7.8	7.2	7.3	7.5	7.2	7.4	8.5	8.3	8.5
50–64	18,699 (60.1)	60.0	58.1	57.8	58.0	61.6	62.6	65.0	67.1	68.2
65–74	5,765 (18.5)	18.8	20.3	20.2	19.4	17.1	16.9	14.4	15.0	12.4
75–84	3,258 (10.5)	10.3	10.6	11.2	11.4	10.8	10.3	9.0	6.7	7.0
≥85	1,061 (3.4)	3.0	3.7	3.7	3.8	3.3	2.8	3.0	2.9	4.0
Sex										
Male	13,395 (43.0)	51.2	46.6	45.2	40.4	37.6	36.4	34.0	33.4	32.1
Female	17,731 (57.0)	48.9	53.4	54.8	59.6	62.4	63.6	66.0	66.6	67.9
Race/ethnicity										
Non-Hispanic White	19,575 (63.0)	61.0	64.9	64.2	64.2	62.2	62.0	60.5	62.2	62.3
Non-Hispanic Black	5,890 (18.9)	20.3	19.1	17.8	17.9	18.8	19.5	20.0	18.8	18.2
Hispanic	4,336 (13.9)	14.3	11.9	14.4	14.1	14.3	14.2	15.1	15.0	14.5
Non-Hispanic Other	1,305 (4.2)	4.5	4.2	3.6	3.8	4.7	4.3	4.5	4.0	5.0
Missing	20									
Education										
Lt High school	6,458 (20.8)	17.9	17.6	20.4	22.0	22.8	23.8	25.3	24.5	25.9
HS graduate/GED	10,334 (33.2)	30.7	33.1	33.3	33.4	34.1	35.2	34.4	36.0	36.6
Some college	7,537 (24.2)	24.7	24.4	24.5	23.3	23.7	22.2	24.7	26.9	27.4
College and above	6,787 (21.8)	26.7	24.9	21.8	21.3	19.5	18.7	15.6	12.6	10.2
Missing	10									
Household income ($US)[a]										
Mean	69,011.6	79,991.85	76,698.3	68,075.2	64,897.0	60,314.0	68,530.2	56,331.3	57,021.7	47,232.9
SD	144,552.9	189,598.0	159,541.3	99,638.0	90,226.8	84,610.4	246,277.6	76,974.4	143,163.1	68,196.7
Median	40,982.0	48,600	47,000.0	41,374.0	40,206.0	36,600.0	34,192	33,300.0	29,402.5	26,080.0
Q1	19,225.9	23,784	23,000.0	20,400.0	19,746.2	16,078.0	15,832.3	14,002.0	14,023.1	12,328.0
Q3	81,418.8	93,000	90,036.0	82.000.0	77,950.0	73,964.0	76,016.0	67,230.0	60,798.0	57,000.0
Marital status										
Married/Partnered	21,457 (69.0)	73.9	70.5	71.0	69.1	66.2	65.3	62.3	59.8	54.7
Separate/divorced	4,170 (13.4)	11.8	12.4	11.5	12.3	14.4	15.1	18.0	20.8	24.5
Widowed	3,826 (12.3)	10.0	12.6	12.6	13.4	13.7	12.2	12.5	11.8	14.5
Never married	1,646 (5.3)	4.4	4.5	4.9	5.2	5.8	7.4	7.2	7.6	6.3
Missing	27									

Continued

Table 1 Baseline Characteristics of Participants by Insomnia Symptom Scores *(continued)*

Variable	Total n (%) (n = 31,126)	Insomnia symptom score								
		0% (n = 6,282)	1% (n = 5,119)	2% (n = 5,638)	3% (n = 4,552)	4% (n = 3,840)	5% (n = 2,275)	6% (n = 1,643)	7% (n = 992)	8% (n = 785)
Region of the U.S[b]										
Northeast	4,969 (16.0)	16.9	15.4	15.9	15.4	15.6	16.2	17.2	15.1	16.9
Midwest	6,802 (21.9)	20.1	23.1	22.8	22.7	21.8	22.9	19.1	20.2	21.8
South	12,952 (41.7)	41.5	40.6	40.8	42.4	42.9	41.3	43.3	42.2	41.9
West	6,369 (20.5)	21.4	20.9	20.5	19.6	19.7	19.7	20.4	22.5	19.4
Missing	34									
Labor force										
Works full time	11,760 (37.8)	43.9	41.8	38.3	36.6	34.3	33.1	30.2	28.0	25.0
Works PT/partly retired	4,204 (13.5)	13.4	14.6	14.3	13.5	13.7	13.1	11.6	10.8	9.4
Retired	9,540 (30.7)	28.4	29.4	31.1	31.7	31.2	31.1	32.7	32.2	37.3
Unemployed/disabled	2,428 (7.8)	5.2	5.0	6.0	7.6	8.7	11.8	15.0	17.4	18.0
Not in work force	3,194 (10.3)	9.12	9.3	10.3	10.6	12.1	11.0	10.5	11.6	10.3
Smoking status										
Never	20,697 (71.8)	75.2	75.4	74.1	72.6	70.3	67.4	63.0	58.4	55.0
Former	4,615 (16.0)	15.1	15.1	15.8	15.8	16.5	17.8	17.0	19.7	16.9
Current	3,526 (12.2)	9.6	9.5	10.1	11.6	13.2	14.8	20.0	21.9	28.2
Missing	2,288									
Number of days/wk drink										
0	19,267 (62.0)	61.0	60.0	61.1	61.5	64.0	64.0	64.1	66.0	69.3
1	4,201 (13.5)	14.1	13.8	14.2	13.3	13.0	12.9	12.9	10.6	12.5
2	2,381 (7.7)	7.9	8.1	7.9	7.9	6.6	7.4	7.6	7.1	6.9
3	1,656 (5.3)	5.5	5.5	5.3	5.8	4.8	5.3	5.3	5.0	4.1
4	726 (2.3)	2.1	2.5	2.4	2.2	2.2	3.1	1.8	3.7	0.8
5	679 (2.2)	2.2	2.3	2.2	2.5	2.0	2.2	2.0	2.0	1.3
6	304 (1.0)	1.0	1.1	1.3	0.7	1.0	0.8	0.8	0.8	0.3
7	1,852 (6.0)	6.2	6.7	5.7	6.1	6.4	4.4	5.6	4.9	5.0
Missing	63									
Vigorous physical activity> 1/wk										
No	20,027 (64.4)	55.6	62.2	62.3	65.1	69.1	70.0	74.7	79.2	81.0
Yes	11,073 (35.6)	44.4	37.8	37.7	34.9	30.9	30.0	25.3	20.8	19.0
Missing	26									
BMI group										
Underweight (BMI ≤18.4)	1,167 (3.8)	3.5	3.3	4.2	3.4	3.9	3.9	4.1	4.2	5.0
Healthy weight (18.5–24.9)	8,818 (28.3)	30.1	28.7	28.1	29.4	28.0	26.0	26.1	24.3	25.7
Overweight (25–29.9)	11,453 (36.8)	38.5	38.2	38.0	36.7	36.4	34.0	32.9	33.1	28.9
Obese (BMI ≥30)	9,688 (31.1)	27.9	29.8	29.7	30.5	31.7	36.1	36.9	38.4	40.4
Social deprivation index (SDI)[c]										
First quartile	7,226 (24.5)	26.8	27.8	24.4	24.9	22.0	22.9	20.8	17.9	17.7

Continued

Table 1 Baseline Characteristics of Participants by Insomnia Symptom Scores *(continued)*

Variable	Total n (%) (n = 31,126)	Insomnia symptom score								
		0% (n = 6,282)	1% (n = 5,119)	2% (n = 5,638)	3% (n = 4,552)	4% (n = 3,840)	5% (n = 2,275)	6% (n = 1,643)	7% (n = 992)	8% (n = 785)
Second quartile	7,397 (25.1)	24.9	25.3	25.6	24.7	25.7	24.6	24.3	26.2	23.7
Third quartile	7,345 (24.9)	23.9	23.3	25.4	24.7	25.8	26.4	25.6	28.5	27.4
Forth quartile	7,495 (25.4)	24.5	23.7	24.6	25.7	26.6	26.1	29.3	27.4	31.3
Missing	1,663									
Depression (CESD-7)										
No (0–3)	25,223 (86.9)	96.3	94.6	91.4	87.7	82.8	75.9	69.7	62.8	49.2
Yes (4–7)	3,790 (13.1)	3.7	5.4	8.6	12.4	17.2	24.2	30.3	37.2	50.8
Missing	2,113									
Diabetes										
No	26,102 (83.2)	87.9	84.2	84.4	82.1	81.3	80.3	77.3	77.1	77.1
Yes	5,260 (16.8)	12.1	15.8	15.6	17.9	18.7	19.7	22.7	22.9	22.9
Missing	10									
Hypertension										
No	16,480 (53.0)	60.9	54.1	53.6	51.8	50.0	47.3	44.9	44.7	42.7
Yes	14,629 (47.0)	39.1	45.9	46.4	48.2	50.0	52.7	55.1	55.3	57.3
Missing	17									
Heart disease[d]										
No	25,902 (83.2)	87.8	84.7	85.0	81.8	81.2	80.6	79.3	74.9	69.5
Yes	5,212 (16.8)	12.2	15.3	15.0	18.2	18.8	19.4	20.7	25.1	30.5
Missing	12									
CRP (mg/L)										
Mean (SD)	3.0 (5.4)	2.7 (4.6)	2.6 (4.7)	2.9 (6.0)	2.9 (5.1)	3.4 (6.0)	3.2 (5.4)	3.7 (6.7)	4.0 (6.7)	4.3 (5.7)
Median	1.44	1.3	1.3	1.4	1.5	1.7	1.7	1.8	2.0	2.1
Q1, Q3	0.7, 3.3	0.6; 3.0	0.6; 2.9	0.6; 3.1	0.7; 3.2	0.68; 3.6	0.7; 3.6	0.8; 4.1	0.9; 4.5	0.9; 5.4
Missing	10,688									
CRP										
Low	14,794 (72.4)	74.8	75.7	74.2	73.6	69.9	68.8	65.3	63.0	58.0
High	5,646 (27.6)	25.2	24.3	25.8	26.4	30.1	31.2	34.8	37.0	42.0

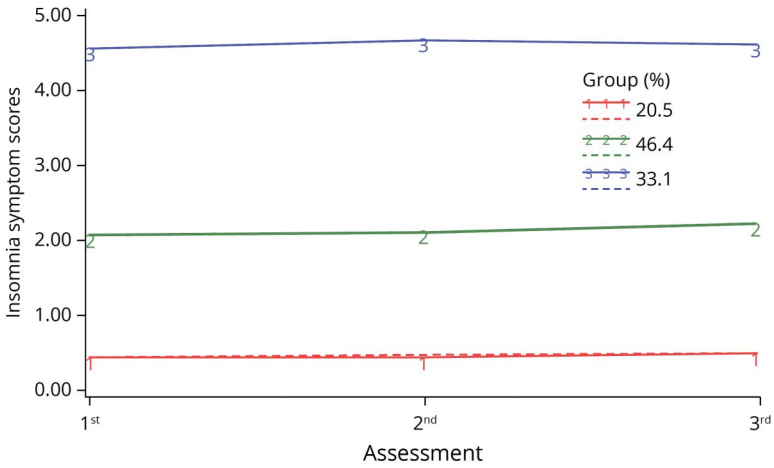
[a] Respondent and Spouse only.
[b] Northeast + Other(N = 22).
[c] The SDI includes 7 measures (percent population with <100% FPL, percent population with less than 12 y of education, percent nonemployed, percent population living in renter-occupied housing units, percent population living in crowded housing units, percent of single-parent households, and percent population with no car). The score ranges from 0-100, the highest score is more deprived.
[d] Heart disease: heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems.

Insomnia Symptom Trajectories

Insomnia symptoms remained constantly reported and did not change over time. The 3-group model was selected based on 2ΔBIC (eTable 3, links.lww.com/WNL/C854). These subgroups of insomnia symptoms were identified based on 3 consecutive measurements of insomnia symptoms at 2-year intervals. The subgroups were named "constantly no symptom," "constantly low symptoms," and "constantly high insomnia symptoms" (Figure 2).

Compared with participants classified as "constantly no symptom," participants classified as "constantly low symptom" had an increased risk of stroke (HR = 1.15, 95% CI 1.00–1.32) (Table 2). Similarly, compared with participants classified as

Figure 2 Insomnia Symptom Trajectories in 3 Consecutive Assessments



"constantly no symptom," participants classified as "constantly high symptom" had an increased risk of stroke (HR = 1.42, 95% CI 1.22, 1.64).

Association of Insomnia Symptoms (Scale 0–8) With the Risk of Stroke

In the continuous insomnia symptom models, every 1-unit increase of insomnia symptom scores was associated with a 7% increased risk of stroke (HR = 1.07, 95% CI 1.04–1.09) after adjusting for demographic factors, socioeconomic factors, and behavioral risk factors (Table 3). The adjustment did not significantly reduce the strength of the association compared with the crude model.

Compared with those with no insomnia symptoms, the hazard ratio of stroke for those with insomnia symptom scores of 1, 2, 3, 4, 5, 6, 7, and 8 were 1.20 (95% CI 1.02–1.41), 1.06 (95% CI 0.90–1.25), 1.18 (95% CI 1.00–1.40), 1.26 (95% CI 1.06–1.51), 1.32 (95% CI 1.07–1.62), 1.69 (95% CI 1.36–2.10), 1.54 (95% CI 1.16–2.03), and 1.80 (95% CI 1.33–2.43), respectively. Overall, compared with individuals with no insomnia symptoms, an increased risk of stroke was observed for those with insomnia symptom scores ranging from 1 to 4 and 5 to 8 (HR = 1.16, 95% CI 1.02–1.33) and (HR = 1.51, 95% CI 1.29–1.77), respectively. A dose-response relationship was observed (p for trend <0.0001, eFigure 2, links.lww.com/WNL/C854).

Differences by age were noticed in the subgroup analyses. A stronger association was noticed in participants younger than 50 years (HR = 3.84, 95% CI 1.50–9.85) than in those 50 years and older (HR = 1.38, 95% CI 1.18–1.62), comparing those with insomnia symptoms scores 5 to 8 with those with no insomnia symptoms (Table 4). Similar trends were observed in participants younger than 50 years (HR = 1.22, 95% CI 1.09–1.37) and those 50 years and older (HR = 1.15, 95% CI 1.01–1.31), comparing those with insomnia symptoms scores 1 to 4 with those with no insomnia symptoms. There was no significant difference by sex, race/ethnicity, and social deprivation index.

The analysis using individual insomnia symptoms showed that difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and, nonrestorative sleep were all associated with an increased risk of stroke (eTable 4, links.lww.com/WNL/C854). The association was stronger for difficulty initiating sleep, followed by difficulty maintaining sleep, waking up too early, and nonrestorative sleep.

Table 2 Association Between Insomnia Symptom Trajectories and Stroke

Insomnia symptom score	Unadjusted HR, 95% CI (n = 31,126)	Model 1 HR, 95% CI (n = 31,046)	Model 2 HR, 95% CI (n = 29,396)	Model 3 HR, 95% CI (n = 27,268)
"Constantly no symptom"	Ref	Ref	Ref	Ref
"Constantly low symptom"	1.20 (1.06–1.36)	1.17 (1.03–1.32)	1.17 (1.03–1.33)	1.15 (1.00–1.32)
"Constantly high symptom"	1.47 (1.29–1.67)	1.56 (1.37–1.78)	1.49 (1.29–1.71)	1.42 (1.22–1.64)

Model 1: adjusted for demographic factors including age, sex, race/ethnicity, marital status, and region.
Model 2: adjusted for model 1 + socioeconomic factors including education, household income, employment status, and social deprivation index.
Model 3: adjusted for model 2 + behavioral risk factors including alcohol consumption, smoking, body mass index, and physical activity.

Table 3 Incidence of Stroke by Insomnia Symptom Scores

Insomnia symptoms score	Unadjusted HR, 95% CI (n = 31,126)	Model 1 HR, 95% CI (n = 31,046)	Model 2 HR, 95% CI (n = 29,396)	Model 3 HR, 95% CI (n = 27,268)	*p* Value for trends[a]
Continuous (1 unit)	1.07 (1.05–1.09)	1.09 (1.07–1.11)	1.07 (1.05–1.10)	1.07 (1.04–1.09)	
0	Ref	Ref	Ref	Ref	<0.0001
1	1.21 (1.04–1.39)	1.17 (1.01–1.36)	1.23 (1.05–1.43)	1.20 (1.02–1.41)	
2	1.12 (0.97–1.30)	1.09 (0.94–1.27)	1.09 (0.91–1.27)	1.06 (0.90–1.25)	
3	1.21 (1.04–1.41)	1.19 (1.02–1.38)	1.21 (1.03–1.42)	1.18 (1.00–1.40)	
4	1.39 (1.19–1.63)	1.42 (1.21–1.66)	1.36 (1.16–1.61)	1.26 (1.06–1.51)	
5	1.42 (1.18–1.70)	1.47 (1.23–1.77)	1.42 (1.17–1.72)	1.32 (1.07–1.62)	
6	1.61 (1.32–1.97)	1.72 (1.41–2.11)	1.72 (1.39–2.12)	1.69 (1.36–2.10)	
7	1.65 (1.29–2.10)	1.87 (1.46–2.39)	1.63 (1.25–2.12)	1.54 (1.16–2.03)	
8	1.82 (1.39–2.39)	2.13 (1.63–2.80)	1.89 (1.42–2.52)	1.80 (1.33–2.43)	
0	Ref	Ref	Ref	Ref	<0.0001
1–4	1.22 (1.08–1.37)	1.20 (1.07–1.35)	1.21 (1.07–1.36)	1.16 (1.02–1.33)	
5–8	1.56 (1.36–1.79)	1.68 (1.46–1.93)	1.59 (1.37–1.84)	1.51 (1.29–1.77)	

Model 1: adjusted for demographic factors (age, sex, race/ethnicity, marital status, and region).
Model 2: adjusted for model 1 + socioeconomic factors (education, household income, employment status, and social deprivation index).
Model 3: adjusted for model 2 + behavioral risk factors (alcohol consumption, smoking, body mass index, and physical activity).
[a] *p* Value for trend, model 3.

Mediation

More than one-third of the participants had missing CRP values. CRP mediated only 0.76% of the effect of insomnia symptoms (5–8 vs 0) on stroke (total effect: HR = 1.64, 95% CI 1.55–2.02); indirect effect: HR = 1.00 (95% CI 0.92–1.10, Table 5). However, diabetes, hypertension, heart disease, and depression mediated 9.75% (indirect effect: HR = 1.04, 95% CI 1.02–1.15), 14.59% (indirect effect: HR = 1.06, 95% CI 1.04–1.19), 14.89% (indirect effect: HR = 1.07, 95% CI 1.05–1.19) and 17.78% (indirect effect: HR = 1.08, 95% CI 1.06–1.22) of the effect of insomnia symptoms (5–8 vs 0) on stroke, respectively. Similarly, diabetes, hypertension, heart disease, and depression mediated 17.07% (indirect effect: HR = 1.02, 95% CI 0.98–1.12), 20.70% (indirect effect: HR = 1.03, 95% CI 1.00–1.13), 15.36% (indirect effect: HR = 1.02, 95% CI 0.98–1.12), and 13.41% (indirect effect: HR = 1.02, 95% CI 0.96–1.11) of the effect of insomnia symptoms (1–4 vs 0) on stroke, respectively. The mediation effects were statistically significant for high insomnia symptom scores (5–8 vs 0) and not for low insomnia symptom scores (1–4 vs 0). The analysis was not further stratified by age because of the low sample size. There was no interaction between insomnia symptoms and CRP, diabetes, hypertension, heart disease, or depression.

Sensitivity Analyses

The analysis using an insomnia symptom scale of 0–4 (eTable 5, links.lww.com/WNL/C854) was consistent with the main analysis. Adjustments for comorbidities that were not adjusted in the main analysis because they were considered mediators reduced the effect estimates, but they remained statistically significant (eTable 5). In analyses in which the proxy reporter was excluded (eTable 6), in which participants included in 2016 were excluded (eTable 7), with 2 years lag (eTable 8), or controlled for cohort entry year (eTable 9), the results were all consistent with results from the main analysis. Furthermore, the analysis using the change in estimate approach (eTable 10A) and the manual backward approach (eTable 10B) did not alter the association between insomnia symptoms and stroke. In the analyses further adjusted for obstructive sleep apnea, restless leg syndrome, and narcolepsy (2016–2020 data), the estimate (HR = 1.02, 95% CI 0.97, 1.07) was comparable with that without the variables mentioned earlier (HR = 1.03, 95% CI 0.97, 1.08, eTable 11). The E-value was estimated at 1.34, which is the minimum strength of association that an unmeasured confounder would need to have with both insomnia symptoms and stroke to fully explain away this association, conditional on the covariates included in the models. The covariate with the strongest association with stroke was smoking (HR = 1.28), meaning that for an unmeasured confounder to fully explain away this association, the association of such an unmeasured confounder with stroke must be stronger than the association between smoking and stroke. Finally, obesity and physical activity did not mediate the association between insomnia symptoms and stroke (eTable 12).

Discussion

In this prospective population-based cohort study, we found that insomnia symptoms did not change over time. Insomnia

Table 4 Incidence of Stroke by Insomnia Symptom Scores (Stratified by Age, Sex, Race/Ethnicity, and SDI)

Stratification variable	Insomnia symptoms	HR, 95% CI[a]	*p* For interaction[b]
Sex			0.6866
Male (N = 11,709)	Continuous (1 unit)	1.08 (1.04–1.12)	
	0	Ref	
	1–4	1.10 (0.92–1.32)	
	5–8	1.51 (1.19–1.90)	
Female (N = 15,559)	Continuous (1 unit)	1.06 (1.02–1.09)	
	0	Ref	
	1–4	1.24 (1.03–1.50)	
	5–8	1.54 (1.24–1.91)	
Age			**0.0003**
Age <50 (N = 2,160)	Continuous (1 unit)	1.22 (1.09–1.37)	
	0	Ref	
	1–4	1.64 (0.67–4.02)	
	5–8	3.84 (1.50–9.85)	
Age ≥50 (N = 25,108)	Continuous (1 unit)	1.05 (1.02–1.07)	
	0	Ref	
	1–4	1.15 (1.01–1.31)	
	5–8	1.38 (1.18–1.62)	
Race			0.2877
White (N = 16,801)	Continuous (1 unit)	1.07 (1.04–1.10)	
	0	Ref	
	1–4	1.28 (1.09–1.51)	
	5–8	1.54 (1.26–1.88)	
Black (N = 5,307)	Continuous (1 unit)	1.07 (1.02–1.12)	
	0	Ref	
	1–4	1.04 (0.79–1.37)	
	5–8	1.39 (1.00–1.94)	
Hispanic (N = 3,968)	Continuous (1 unit)	1.07 (1.00–1.14)	
	0	Ref	
	1–4	1.03 (0.70–1.53)	
	5–8	1.68 (1.07–2.62)	
Other (N = 1,192)	Continuous (1 unit)	1.05 (0.89–1.24)	
	0	Ref	
	1–4	0.40 (0.18–0.90)	
	5–8	0.87 (0.32–2.37)	
Social deprivation Index (SDI)			0.6599
First quartile (N = 6,740)	Continuous (1 unit)	1.05 (0.99–1.10)	
	0	Ref	
	1–4	1.16 (0.89–1.51)	
	5–8	1.34 (0.95–1.90)	
Second quartile (N = 6,859)	Continuous (1 unit)	1.07 (1.03–1.13)	
	0	Ref	
	1–4	1.17 (0.90–1.53)	
	5–8	1.58 (1.15–2.18)	
Third quartile (N = 6,751)	Continuous (1 unit)	1.09 (1.05–1.14)	
	0	Ref	
	1–4	1.53 (1.16–2.01)	
	5–8	1.93 (1.39–2.67)	
Forth quartile (N = 6,918)	Continuous (1 unit)	1.05 (1.00–1.09)	
	0	Ref	
	1–4	0.92 (0.72–1.17)	
	5–8	1.26 (0.95–1.69)	

[a] Model adjusted for variables included in model 3 with the exception of the stratification variable.
[b] The *p* values for interaction were estimated by including an interaction term of insomnia symptom and the stratification variable in the model.

symptoms were associated with an increased risk of stroke in a dose-response manner. Moreover, this association remained after multiple sensitivity analyses were performed. The association was strongest among individuals younger than 50 years and was mediated by diabetes, hypertension, heart disease, and depression. No significant mediation was found for inflammation measured by CRP.

Insomnia symptoms remained constant on 3 consecutive assessments over a period of 4 to 6 years. This suggests that insomnia symptoms tend to be chronic or they were not diagnosed and/or managed in this population. Studies have found that those with insomnia usually fail to discuss their sleep problems with their healthcare providers.[44] This underscores the importance of raising awareness around insomnia symptoms.

Table 5 Mediation of the Association Between Insomnia Symptoms and Incident Stroke

Mediator	Insomnia symptom score	Total effect HR, 95% CI	Direct effect HR, 95% CI	Indirect effect HR, 95% CI	% Mediated
CRP	0	Ref	Ref	Ref	Ref
	1–4	1.23 (1.13–1.45)	1.23 (1.17–1.42)	1.00 (0.90–1.09)	−1.45
	5–8	1.64 (1.55–2.02)	1.63 (1.58–1.96)	1.00 (0.92–1.10)	0.76
Depression	0	Ref	Ref	Ref	Ref
	1–4	1.15 (0.98–1.24)	1.13 (0.97–1.18)	1.02 (0.96–1.11)	13.41
	5–8	1.53 (1.29–1.65)	1.42 (1.10–1.41)	1.08 (1.06–1.22)	17.78
Diabetes	0	Ref	Ref	Ref	Ref
	1–4	1.16 (1.04–1.28)	1.13 (1.00–1.20)	1.02 (0.98–1.12)	17.07
	5–8	1.50 (1.33–1.68)	1.44 (1.25–1.53)	1.04 (1.02–1.15)	9.75
Heart disease	0	Ref	Ref	Ref	Ref
	1–4	1.17 (1.02–1.27)	1.14 (0.99–1.20)	1.02 (0.98–1.12)	15.36
	5–8	1.53 (1.31–1.64)	1.43 (1.16–1.43)	1.07 (1.05–1.19)	14.89
Hypertension	0	Ref	Ref	Ref	Ref
	1–4	1.18 (1.05–1.29)	1.14 (0.99–1.20)	1.03 (1.00–1.13)	20.70
	5–8	1.54 (1.33–1.66)	1.44 (1.19–1.46)	1.06 (1.04–1.19)	14.59

Model adjusted for: age, sex, race/ethnicity, region, marital status, education, income, employment, social deprivation index, alcohol consumption, smoking, body mass index and, physical activity.

Our findings that insomnia symptoms were significantly associated with an increased risk of stroke were consistent with some other investigations. Zheng et al. reported a slight increase in risk associated with difficulty initiating/maintaining sleep (HR = 1.05, 95% CI 1.02–1.08), early morning awakening (HR = 1.05, 95% CI 1.02–1.08), and daytime dysfunction (HR = 1.08, 95% CI 1.02–1.14).[3] In other studies, increased risk were observed for difficulty initiating sleep, difficulty maintaining sleep, and nonrestorative sleep but not early morning awakening.[45,46] In addition, our findings that the association was stronger in the younger adults (younger than 50 years) than the older adults (aged 50 years or older) were consistent with prior studies. These studies found that the effect of insomnia symptoms on stroke incidence decreased as age advanced.[3,5] This could be due to the higher incidence of stroke at an older age and the shared causal effect with additional risk factors in the older individuals. This striking difference suggests that insomnia symptom management may be an effective strategy for stroke prevention, especially in younger adults. Studies that explore the reduction of stroke risk through the management of insomnia symptoms are warranted.

Our study may have lacked the statistical power to detect mediation by CRP. The measured CRP may have been insufficient (35% missing) to detect mediation or CRP was not the best indicator of inflammation in this population. However, we found that CRP levels increased with increasing insomnia symptom scores. While previous studies did not investigate such mediation, evidence suggests that inflammation increases the risk of stroke.[16] Comorbidities that mediated the association between insomnia symptoms and stroke included diabetes, hypertension, heart disease, and depression. Insomnia symptoms may elicit endocrine and metabolic dysregulation,[6,47,48] inflammation, vasoconstriction, and stress, which in turn may increase the risk of diabetes, hypertension, heart diseases, and depression and facilitate a predisposition to the development of stroke.

The sensitivity analyses were consistent with the main analysis indicating that the reported association between insomnia symptoms and stroke is less likely attributable to unmeasured confounders. The association was robust and remained even with overadjustment (i.e., adjusting for mediators such as comorbidities) and adjustment for obstructive sleep apnea and other sleep disorders that may be expressed by insomnia symptoms, especially when undiagnosed.

This study identified insomnia symptoms as a risk factor for stroke and explored mediation and effect measure modification within this complex association. While the diagnosis of insomnia required access to health care, individual insomnia symptoms are easily defined and individual insomnia symptoms are easily defined and can be ascertained by the general population. Therefore, focusing on self-reported insomnia symptoms and identifying them as a risk factor of stroke is a step forward toward early prevention.

This analysis was based on a large sample with more than 18 years of follow-up and high participation and retention rates. Most of the participants were representative of US adults aged 50 years and older. This age group is the population at the greatest risk of developing a stroke. The repeated measures are a unique strength of the HRS, and the results were robust to potential confounding and sensitivity analyses.

This study had several limitations that are worth mentioning. First, the exposure and outcome variables were self-reported. Self-reported data are more likely to be nondifferential regarding exposure (i.e., insomnia symptoms) and given that the exposure and the outcome were measured at different times and participants were unaware of the study hypothesis. Any resulting bias will be toward the null. A study compared the HRS self-reported stroke data with studies with medically verified strokes and concluded that the HRS provides valuable data for stroke incidence, surveillance, and risk factors.[49] Therefore, this limitation is less likely to have biased the results. Second, insomnia symptoms were combined into a linear symptom index with the equal weight assigned to all symptoms. The unscaled analysis indicates that the strength of the association was stronger for trouble initiating sleep. Thus, this unweighted scale likely underestimates the association. Third, the data did not distinguish between ischemic and hemorrhagic strokes. However, in the United States, 87% of all strokes are ischemic and 13% are hemorrhagic.[50] Therefore, the results from this study might not apply to a nonpredominately ischemic stroke population. Furthermore, only the first stroke was modeled; thus, our findings might not be generalizable to recurrent strokes. Fourth, the mediation variables were measured at baseline. In the presence of reverse causation (comorbidities causing insomnia symptoms), there would not be mediation by comorbidities. However, the association between insomnia symptoms and stroke would remain. The effect of insomnia on stroke persisted after adjustment for the comorbidities. This demonstrates that insomnia remains an important risk factor of stroke even if reverse causation by comorbidities existed. Future studies where incident comorbidities can be evaluated are needed to address this issue.

In summary, insomnia symptoms were associated with an increased risk of stroke, especially in adults who are younger than 50 years. This increased risk is mediated through the effect that insomnia symptoms have on comorbidities such as diabetes, hypertension, heart disease, and depression. These findings suggest that increased awareness and management of insomnia symptoms would likely contribute to preventing stroke occurrence.

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Appendix Authors

Name	Location	Contribution
Wendemi Sawadogo, MD, MPH, PhD	Division of Epidemiology, Department of Family Medicine and Population Health, Virginia Commonwealth University, School of Medicine, Richmond	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Tilahun Adera, PhD, MPH	Division of Epidemiology, Department of Family Medicine and Population Health, Virginia Commonwealth University, School of Medicine, Richmond	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Maha Alattar, MD	Division of Adult Neurology, Sleep Medicine, Vascular Neurology, Department of Neurology, Virginia Commonwealth University, School of Medicine, Richmond	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Robert Perera, PhD	Department of Biostatistics, Virginia Commonwealth University, School of Medicine, Richmond	Study concept or design
James B. Burch, MS, PhD	Division of Epidemiology, Department of Family Medicine and Population Health, Virginia Commonwealth University, School of Medicine, Richmond	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data

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