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Prospective Investigation of Insomnia Symptoms and Sleep Duration as Risk Factors for Stroke Incidence and All-Cause Mortality in U.S Adult

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Prospective Investigation of Insomnia Symptoms and Sleep Duration as Risk Factors for Stroke Incidence and All-Cause Mortality in U.S Adult

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List of Abbreviations

BIQ: Brief Insomnia Questionnaire

CESD: Centers for Epidemiologic Study of Depression

CI: Confidence Interval

CIE: Change in Estimate

CRP: C-Reactive Protein

CPAP: Continuous Positive Airway Pressure

HR: Hazard Ratio

HRS: Health and Retirement Study

NIH: National Institute of Health

NSES: Neighborhood Socio Economic Status

OR: Odd Ratio

OSA: Obstructive Sleep Apnea

REGARDS: REasons for Geographic And Racial Differences in Stroke

SD: Standard Deviation

SDI: Social Deprivation Index

SES: Socio Economic Status

TIA: Transient Ischemic Attack

US: United States

VIF: Variance Inflation Factor

Overall Abstract

Background and Objectives: Stroke is the second leading cause of death in the world. In the United States, on average, someone has a stroke every 40 seconds and someone dies as a result of stroke every 3.5 minutes. Identifying modifiable risk factors of stroke is therefore a public health priority. The purpose of this study was to investigate the extent to which insomnia symptoms and sleep duration contribute to stroke incidence, all-cause mortality, and explore potential causal pathways.

Methods: The Health and Retirement Study (HRS) and the REasons for Geographic And Racial Differences in Stroke (REGARDS) study were used as the data sources. While the exposure variables were insomnia symptoms and sleep duration, the outcome variables were stroke incidence and all-cause mortality. Insomnia symptoms were derived from self-reported sleep-related factors including difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and nonrestorative sleep. Sleep duration was categorized into short sleep (≤6 hours), adequate sleep (7.0-8.9 hours), and long sleep (≥9 hours). Cox proportional hazards regression models were employed to investigate the association between insomnia symptoms, sleep duration and the risk of stroke incidence and all-cause mortality.

Results: Compared to subjects with no insomnia symptoms, those with insomnia symptom scores ranging from 1 to 4 and 5 to 8 were associated with increased risk of stroke (hazard ratio (HR) = 1.16, 95% confidence interval (CI): 1.02, 1.33) and (HR =1.51, 95% CI: 1.29, 1.77), respectively, suggesting a dose-response relationship. In stroke survivors, insomnia symptom scores ranging from 5 to 8 were associated with increased risk of all-cause mortality among males less than 65 years old and males 65 years and over (HR=2.24, 95% CI: 1.09, 4.58 and HR=1.26, 95%: 0.97, 1.65, respectively) compared to those with no insomnia symptoms. Stroke survivors with long sleep (≥9 hours) were at increased risk of all-cause mortality (HR=1.53, 95% CI=1.03, 2.29) compared to stroke survivors with adequate sleep (7.0-8.9 hours). However, short sleep (≤6 hours) was not associated with an increased risk of all-cause mortality (HR=1.36, 95% CI=0.93, 2.02).

Discussion: Insomnia symptoms were associated with an increased risk of first ever stroke in the general population and an increased risk of all-cause mortality among stroke survivors while long sleep duration was associated with increased risk of all-cause mortality among stroke survivors. Increased awareness and better management of insomnia symptoms may contribute to the prevention of stroke occurrence and premature death.

Chapter 1: Background

Stroke Epidemiology

Stroke or cerebrovascular accident occurs when a blood vessel, which carries oxygen and nutrients to the brain tissue, is either blocked by a clot and therefore leading to an ischemic stroke or rupture (hemorrhagic stroke). [1] As a result of this injury, part of the brain is deprived of blood (oxygen and nutrients) which it requires to sustain viability, and thus, brain cells began to die. Stroke is a medical emergency, the earlier it is diagnosed and treated, the better the chances of reducing death and long-term disability.

In 2019, the reported new cases of stroke worldwide was 12.2 million, 101 million were stroke survivors and, an estimated 6.55 million death were due to a stroke. [2] Globally, stroke remains the second-leading cause of death (11.6% of total deaths) behind ischemic heart disease. Stroke is a leading cause of serious long term disability. [2]

In the United States (U.S), stroke ranks number five among all-cause mortality, with an estimated 150,005 deaths in 2019.[3] Each year, approximately 795,000 people experience a new or recurrent stroke with 77% being first attacks and 23% recurrent. Recurrent stroke is gaining increased importance and stroke prevention is as crucial in the general population as in stroke survivors. Of all strokes in the U.S, 87% are ischemic, while 10% are due to intracerebral hemorrhage, and 3% to subarachnoid hemorrhage. It is projected that between 2012 to 2030, an additional 3.4 million U.S adults (18 years and older), will have had a stroke. [4] The total annual cost of stroke in the U.S was projected to increase to $240.67 billion, a 129% increase from 2012. [4] These estimates excluded costs associated with other cardiovascular diseases linked to stroke.

The risk factors of stroke include nonmodifiable risk factors (age, low birth weight, genetic factors), well documented and modifiable risk factors (hypertension, smoking, diabetes, atrial fibrillation and other cardiac conditions, dyslipidemia, asymptomatic carotid stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, obesity and low physical activity), and less well documented and or potentially modifiable risk factors (metabolic syndrome, alcohol abuse, drug abuse, oral contraceptive use, sleep disorder breathing, migraine, hyperhomocysteinemia, elevated lipoprotein (a), hypercoagulability, inflammation, infection, and aspirin use). [5] Symptoms of stroke include trouble walking, speaking, and understanding, as well as paralysis or numbness of the face, arm, or leg.

Sleep Epidemiology

Adequate and healthy sleep is an essential biological function. As with any other biological system, its disruption leads to adverse health outcomes. Humans spend about one-third of their life sleeping. [6] This significant portion of life spent sleeping is due to the role that sleep plays in the function of the body and brain, specifically by forming new neural pathways and processing information so the induvial is prepared for optimal cognition during wake. Research has shown that adequate sleep improves memory and learning, increases attention and creativity, and aids in decision-making. [7] Sleep is essential for memory consolidation and the processing of relevant information and stimuli that is received throughout the day. Furthermore, sleep plays a so-called housekeeping role in that during sleep, harmful proteins (toxins) that build-up in the brain during wake, are removed. [6] Sleep is also essential for the maintenance of the physical health of the body, particularly in the healing and repair of cells, including immune system, but also the cardiovascular and skeletomuscular. Research shows that a chronic lack of adequate sleep, increases the risk of multiple disorders including type 2 diabetes, [8] cardiovascular

disease,[9,10] obesity,[11,12] and depression. [11,12] It also increases the risk of accidents, injuries,[13] and all-cause mortality.[14]

Millions of people, however, suffer from not getting adequate and good quality of sleep. According to the Global Sleep Survey, 62% of adults around the world reported that they don't sleep as well as they would like to and, 44% said that the quality of their sleep has gotten worse over the past five years. [15] In the U.S, over one-third of adults do not get the recommended seven to eight hours of sleep daily. [16]

Association between sleep disorders and stroke, literature gap

Sleep disorders are classified according to major categories that include insomnia, sleep-related breathing disorders, central disorder of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders, and other sleep disorders (International Classification of Sleep Disorders, 3rd Edition). [17]

Obstructive sleep apnea (OSA) is the best-studied and most established as a risk factor for stroke. [18] In a systematic review including 10 studies, OSA was associated with a two-fold increased risk of incident stroke [Relative Risk (RR) 2.10; 95% CI 1.50–2.93]. [19] However, the role of continuous positive airway pressure (CPAP) use in stroke prevention is unclear. [20,21] Optimal adherence to CPAP treatment (≥4h CPAP use per night) is often lacking and could reduce the potential benefit of CPAP in stroke prevention, and the ability to detect differences between users and non-users is limited.

Hypersomnia is reported in 20% to 40% of stroke patients [22] and several post-stroke hypersomnia cases have been reported. [23,24] However, studies linking hypersomnia or narcolepsy to an increased risk of stroke are rare. Likewise, restless leg syndrome and periodic limb

movement have been reported in stroke patients, [25,26,27] but being risk factors for stroke remains to be elucidated.

Parasomnias are undesirable nocturnal movements that occur during entry into sleep, within sleep, or during arousals from sleep. Stroke-induced parasomnia has been reported. [28] More typically, parasomnias may arise in stroke patients due to other underlying sleep disorders that fragment sleep. [29]

A study found that stroke onset rate was higher in the morning and evening hours. [30] More specifically, stroke onset was significantly higher in the morning compared to the afternoon both in the hemorrhagic and in the ischemic type. [31]Another study found that 20% to 40% of ischemic strokes occur during sleep. [32] Theses findings suggest that the time before, during, or after sleep may represent a vulnerable period for stroke occurrence. In addition, the timing of sleep could be also important. In the Nurses' Health Study, rotating night shift work was associated with a 4% increased risk of ischemic stroke (Hazard Ratio (HR)=1.04, 95% CI: 1.01, 1.07). [33]

Insomnia marginally increases the risk for cardiovascular events, but data on insomnia and stroke risk is conflicting. [34] The systematic review by He et al. [35] showed that insomnia increases the risk of future cardiovascular or cerebrovascular events with relative risks below 1.3. However, when considering only studies with stroke as an outcome, data were insufficient to support a link between insomnia and stroke. Only two studies in this meta-analysis assessed the relationship between insomnia and stroke. [36,37] In the study by Helbig et al, [36] there were 917 strokes observed in a cohort of 17604 subjects followed for a mean period of 14 years. After adjusting for other risk factors, symptoms of insomnia and short sleep duration were not predictive of stroke in either sex. In the study by Westerlund et al.,[37] 41192 adults were followed

for 13.2 years, 1685 strokes were observed. The authors found that insomnia was unrelated to the risk of cardiovascular events. In addition, the systematic review by Kwok et al. did not find an association between poor sleep quality and stroke outcome. [38] In a more recent study, however, participants with insomnia symptoms were at increased risk of ischemic stroke but not hemorrhagic stroke**.**[39] Two other studies based on claim data, both from Taiwan [40,41] reported a higher risk for stroke in patients diagnosed to have insomnia according to International Classification of Diseases codes (adjusted HR ranging from 1.54 to 1.85, statistically significant). These inconsistencies in the literature are potentially due to multiples factors including the variability in insomnia definition (studies using diagnostic criteria[40,41] were more likely to find association than studies using questionnaire [37,38]), the study population (studies conducted in Asia [39,40,41] were more likely to find association than studies conducted in Europe [37,38]), the sample size and prevalence of stroke in the study population (studies with large sample size were more likely to find association [39]). In addition, potential changes in sleep pattern may not be captured by a single measurement and reserve causality is probable.

Differences by age, sex, race/ethnicity, and socio-economic status (SES) are reported in stroke incidence and mortality studies. [3] While there is an increasing trend of stroke incidence in the younger population, stroke occurs mostly in older people and the burden of stroke is expected to increase within aging populations. [42] Racial and ethnic minorities bear the highest burden of stroke mortality. For example, the age adjusted stroke mortality is higher among Black men, followed by Black women, White men, and White female.[5] Poor understanding of the drivers of these differences hinders the development of effective interventions to reduce health disparities. Assessing the role of sleep disturbances in stroke incidence and mortality; and identifying differences among subpopulation is essential for proper primary and secondary prevention of

stroke. The overall objective of this research was to investigate the extent to which sleep disturbances contribute to stroke morbimortality and shed light on the mechanism by which sleep disturbances increase the risk of stroke. This objective was accomplished by addressing the following specific aims:

1) assess the association between insomnia symptoms and stroke incidence and whether inflammation and comorbidities mediate that association,

2) examine the association between insomnia symptoms and all-cause mortality among stroke survivors, and

3) evaluate the association between sleep duration and all-cause mortality among stroke survivors.

Chapter 2: Insomnia Symptoms and Stroke Incidence

Abstract

Background and Objectives: Insomnia is a frequent disorder affecting over one-third of the United States population. However, the association between insomnia symptoms and stroke is less studied and the underlying mechanism remains unclear. The purpose of this study was to investigate the association between insomnia symptoms and the risk 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 the present 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. Cox proportional hazards regression models were employed to investigate the association between insomnia symptoms and stroke events reported during the follow-up period. Mediation analyses of comorbidities were performed utilizing 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 female. Insomnia symptom trajectories remained constant over time. Compared to subjects with no insomnia symptoms, those with insomnia symptoms score ranging from 1 to 4 and 5 to 8 were respectively associated with increased risk of stroke (hazard ratio (HR) = 1.16, 95% confidence interval (CI): 1.02, 1.33) and (HR =1.51, 95% CI: 1.29, 1.77) indicating a dose-response relationship. There were differences by age as the association was stronger in participants less than 50 years of age (HR=3.84, 95% CI: 1.50, 9.85) than in those 50 years and above (HR=1.38, 95% CI: 1.18, 1.62) for insomnia symptoms ranging from 5-8 compared to no insomnia symptoms. Comorbidities including diabetes, hypertension, heart diseases, and depression mediate that association.

Conclusion: 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.

Key terms: stroke, insomnia symptoms, insomnia symptom trajectories, mediation, effect modification.

Introduction

Sleep disorders, specifically sleep apnea, are increasingly recognized as risk factors for stroke. [19,18] However, uncertainties remain regarding the potential risk of insomnia. A large cohort (0.5 million participants) from China reported that participants with insomnia symptoms (trouble falling asleep, trouble staying asleep) were slightly at increased risk of ischemic stroke (Hazard Ratio:1.05, 95% CI: 1.02-1.08)**.** [39] Another study which included one million participants from the Taiwan National Health Insurance Research Database noted that the insomnia group had a higher incidence of stroke (HR: 1.85, 95% CI: 1.62-2.12). [41] The incidence decreased with advanced age and a higher incidence was observed among those with persistent insomnia. [40] On the contrary, in a study by Westerlund et al., the authors found that insomnia was unrelated to the risk of overall cardiovascular events which included stroke. [37] Similarly, in the study by Helbig et al., insomnia symptoms (difficulty falling and maintaining sleep) were not predictive of stroke in either sex. [36]

These inconsistencies in the literature are potentially due to multiples factors including the variability in insomnia definition (studies using diagnostic criteria[40,41] were more likely to find association than studies using questionnaires [37,38]), the study population (studies conducted in Asia [39,40,41] were more likely to find association than studies conducted in Europe [37,38]), the sample size and prevalence of stroke in the study population (studies with large sample size were more likely to find association [39]) and the adjustment variables (studies that find association failed to adjust for important variables such as socioeconomic status, physical activity, smoking, body mass index). Also, insomnia is most of the time measured at baseline only. A single

measurement may fail to adequately reflect the association between insomnia symptoms and disease development, given that the symptoms could have changed over the follow-up period. In addition, 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. [39,41,40] 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,[43] hypertension,[44] heart disease,[45] and depression.[46]

The underlying mechanisms by which sleep disorders increase the risk of stroke are not well understood. One of the proposed physiopathological mechanisms is through inflammation. [47,48] C-Reactive Protein (CRP) is a nonspecific acute-phase protein released mainly from hepatocytes in response to IL-6 expression and is an established marker of inflammation. [49] Evidence suggests that inflammation is an important contributor to atherosclerosis, thrombosis, and cerebral small vessel disease, all key mechanisms contributing to the risk of various stroke types. [49,50] In addition, the relationship between insomnia symptoms and elevated inflammatory biomarkers is supported by growing literature. [51,52] In a systematic review and meta-analysis of 72 studies, insomnia symptoms were associated with higher levels of CRP (Odd Ratio(OR)=1.25, 1.10-1.41) and IL-6 (OR=1.44, 1.16-1.76)[53]

The purpose of this study was to investigate the association between insomnia symptoms and stroke incidence. Additionally, mediation by inflammation and comorbidities, 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). HRS is an ongoing national longitudinal study of Americans older than 50 years and their spouses, conducted by the University of Michigan and sponsored by the National Institute on Aging (NIA U01AG009740). The survey was established to provide a national resource for data on the changing health and economic circumstances associated with aging at both individual and population levels. [54]

HRS design and data collection

The HRS sample was constructed over time. The initial HRS cohort, recruited in 1992, consisted of persons born 1931- 41 (then aged 51- 61) and their spouses of any age. A second study, Asset and Health Dynamics Among the Oldest Old (AHEAD), was fielded the next year to capture the cohort born 1890 -1923 (then aged 70 and above). In 1998, the two studies merged and, to make the sample fully representative of the USA population over age 50, two new cohorts were enrolled: the Children of the Depression (CODA), born 1924 - 30, and the War Babies, born 1942 - 47. HRS now employs a steady-state design, replenishing the sample every 6 years with younger cohorts not previously represented. In 2004, Early Baby Boomers (EBB, born 1948 - 53) were added, and in 2010, Mid Baby Boomers (MBB, born 1954 - 59) were added. [54] Finally, in 2016, the Late Baby Boomers (LBB, born 1960 - 65) were added. 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 (https://hrs.isr.umich.edu).

Study design and inclusion criteria

The sleep questions of interest were introduced in 2002. Therefore, the present study included participants starting from 2002 and followed 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 2.1.

Exposure: Insomnia symptoms

Insomnia symptoms were assessed using the Adapted Brief Insomnia Questionnaire (BIQ), a validated screening tool that measures self-reported sleep complaints rather than diagnosed insomnia. [55,56] Participants answered four 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 (Supplemental Table 2.1). 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 symptoms severity score that ranges between "0=no insomnia" and "8=severe insomnia symptoms". [57]

A second insomnia symptoms scale was also used in which, answers were recorded so that individuals were considered as experiencing insomnia symptoms if they answered "most of the time" or "sometimes" to the first three questions and "sometimes" or "rarely or never" felt rested to the fourth. The number of symptoms was summed to give an overall insomnia symptoms severity score, ranging from "0 =no insomnia symptoms" to "4=severe insomnia symptoms". [58]

Insomnia symptom trajectories:

Insomnia symptoms trajectories were assessed using 3 consecutive assessments of insomnia symptoms. Participants were categorized into groups according to their insomnia

symptoms pattern using Repeated Measure Latent Class Analysis.[59,60] 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. [60,61]

Outcome: Incident stroke

Stroke events were self- 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. [62] 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. [63] 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, [39,40,41] and guided by a directed acyclic graph (Supplemental Figure 2.1) the following 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 region (Southern or no).

Socio-economic (SES) factors: included education (less than high school, high school, some college, college graduate, and more), household income and wealth, employment status, and social deprivation index (SDI). The SDI index was produced by the Robert Graham Center, using 7 key neighborhood factors including the percent population with <100% Federal Poverty

Level, percent population with less than 12 years of education, percent non-employed, percent population living in renter-occupied housing units, percent population living in crowded housing units, percent single-parent households, and percent population with no car.[64] The index was derived at the level of the census tract, generating values from 0 to 100 that are 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 utilized the dried blood spot (DBS) in which participants agree to have their fingers pricked and have spots of blood dripped onto cards. Every four years, each participant was asked to provide a blood sample. CRP was obtained by assay of high-sensitivity CRP using BNII nephelometer (Siemens, Inc., Deerfield, IL). [65]

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 an 8-item version of the Centers for Epidemiologic Study of Depression (CESD) scale. The sleep item was excluded from the total score due to the issue of shared variance with insomnia symptoms. [66,67,68] The final score of depressive symptoms ranged from 0 to 7. Based on previous research showing that scoring 4 on the eight-item CES-D corresponds to scoring 16 on the 20-item CES-D, which indicates a diagnosis of depression; 4 was used as the cut-off point to create a depression variable. [69, 70,71]

Data Analysis

Descriptive statistics

Descriptive statistics were generated to assess the distribution of the study characteristics by insomnia symptom scores. All baseline characteristics were summarized using mean and standard deviation for continuous variables and frequencies and percentages for the categorical or ordinal variables. Chi-square was used to compare participants based on insomnia symptoms. 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 (VIF). A VIF of 10 or greater was used to signify multicollinearity.

Time to event analysis

Cox proportional hazard regression analyses were performed to evaluate the association between insomnia symptoms and incident stroke. 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 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 (<50 vs. ≥50 years), 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 above subgroup analyses.

Mediation

In mediation analyses, CRP and comorbidities were assessed as a mediator, 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 based on the counterfactual framework was used. [72] In a counterfactual framework, the individual causal effect of the exposure on the outcome is defined as the hypothetical contrast between the outcomes that would be observed in the same individual at the same time with and without the exposure of interest. [73] Only one of those outcomes is observed for each individual, the one corresponding to the treatment(exposure) value actually experienced by the individual. All other counterfactual outcomes remain unobserved. [74] 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, path analysis) can accommodate non-normally distributed data such as time-to-event data. [72,75] Furthermore, the counterfactual framework allows for exposure-mediator interactions. [76] The Total Effect (TE) of insomnia symptoms on incident stroke was decomposed into Natural Indirect Effect (NIE) and Natural Direct Effects (NDE). The Natural Direct Effect (NDE) is the effect of insomnia symptoms on incident stroke via pathways that do not involve the mediator while the mediator is allowed to vary. The Natural Indirect Effect (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 as the natural indirect effect divided by the total effect and 95% CIs were estimated by repeating 100 bootstrapped computations. 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 two years after insomnia symptoms assessment were excluded. Fifth, since 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 was statistically significant ($p<0.05$). 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, E-value for residual unmeasured confounders was computed. The E-value is defined as the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates. [77]

Protocol Approvals and Participants Consents

The study was approved by VCU IRB (HM20023839). This is a de-identified secondary data analysis, therefore the IRB waived participant consent. The data was accessed and analyzed within the University of Michigan Virtual Data Enclave. The analyses were conducted using SAS version 9.4 (SAS, Cary, NC) and R (R Foundation, Vienna, Australia).

Results

Descriptive statistics

Over a median of 9.2 years follow-up (q1=3.8; q3=14.8; max=19.1) of 31,126 participants; 2,101 incident stroke were recorded. The mean age was 61 years, 92.5 % were over the age of 50, 57% were female, and 63% were Non-Hispanic White (Table 2.1). 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 females, current smokers, those who were unemployed/disabled, those with low education, low physical activity, obesity, any comorbidity, and living in a socially deprived neighborhood.

Insomnia symptom trajectories

Insomnia symptoms remained constantly reported and did not change over time. The 3-group model was selected based on *2ΔBIC* (Supplemental Table 2.3). These subgroups of insomnia symptoms were identified based on 3 consecutive measurements of insomnia symptoms at 2 years intervals. The subgroups were named “constantly no symptom”, “constantly low symptoms”, and “constantly high insomnia symptoms” (Figure 2.2).

Compared to participants classified as “constantly no symptom”, participants classified as “constantly low symptom” had an increased risk of stroke (hazard ratio (HR) = 1.15, 95% confidence interval (CI): 1.00, 1.32) (Table 2.2). Similarly, compared to participants classified as

"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 one unit increase of insomnia symptom scores was associated with a 7% increased risk of stroke (hazard ratio (HR) = 1.07, 95% confidence interval (CI): 1.04, 1.09) after adjusting for demographic factors, socioeconomic factors, and behavioral risk factors (Table 2.3). The adjustment did not significantly reduce the strength of the association compared to the crude model.

Compared to those with no insomnia symptoms, the hazard ratio of stroke for those with insomnia symptom scores of 1, 2, 3, 4, 5, 6, 7, 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), 1.80 (95% CI: 1.33, 2.43), respectively. Overall, insomnia symptom scores ranging from 1 to 4 and 5 to 8 were respectively associated with an increased risk of stroke (HR= 1.16, 95% CI: 1.02, 1.33) and (HR =1.51, 95% CI: 1.29, 1.77) in comparison with no insomnia symptoms. A dose-response relationship was observed (p for trend <.0001).

Differences by age were noticed in the subgroup analyses. The association was stronger in participants less than 50 years of age (HR=3.84, 95% CI: 1.50, 9.85) than in those 50 years and above (HR=1.38, 95% CI: 1.18, 1.62) for insomnia symptoms ranging from 5-8 compared to no insomnia symptoms (Table 4). Similarly, the association was stronger in participants less than 50 years of age (HR=1.22, 95% CI: 1.09, 1.37) than in those 50 years and above (HR=1.15, 95% CI: 1.01, 1.31) for insomnia symptoms ranging from 1-4 compared to 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 (Supplemental Table 2.4). The association was stronger for difficulty initiating sleep followed by difficulty maintaining sleep, waking up too early, and nonrestorative sleep.

Mediation

Over 1/3 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 2.5). However, diabetes, hypertension, heart disease, and depression mediated respectively 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. Similarly, diabetes, hypertension, heart disease, and depression mediated respectively 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. 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 due to 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 symptoms scale of 0-4 (Supplemental Table 2.5) 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 (Supplemental Table 2.5). In analyses in which the proxy reporter was excluded (Supplemental Table 2.6), participants included in 2016 were excluded (Supplemental Table 2.7), with 2 years lag (Supplemental Table 2.8), or controlled for cohort entry year (Supplemental Table 2.9) were all consistent with results from the main analysis. Furthermore, the analysis using the change in estimate approach (Supplemental Table 2.10) and the manual backward approach (Supplemental Table 2.11) 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 to that without the variables mentioned above (HR=1.03, 95%CI: 0.97, 1.08, Supplemental Table 2.12). 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 the treatment and the outcome to fully explain away this association, conditional on the measured. 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 (Supplemental Table 2.13).

Discussion

In this prospective population-based cohort study, we found that insomnia symptoms did not change over time. Insomnia 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 aged<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 three consecutive assessments over a period of four 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.[78] This underscores the importance of raising awareness around insomnia symptoms.

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 for 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). [39] However, in other studies, positive associations were observed for difficulty initiating sleep, difficulty maintaining sleep, and non-restorative sleep but not early morning awakening. [35,79] In addition, our findings that the association was stronger in the younger adults (age<50) than the older adults (age≥50) were consistent with prior studies. These studies found that the effect of insomnia symptoms on stroke incidence decreased as age advanced. [39,40] 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 elderly. This striking difference suggests that insomnia symptoms 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. However, we found that CRP level increased with increasing insomnia symptom scores. While previous studies did not investigate such mediation, evidence suggests that inflammation increases the risk of stroke. [50] 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 [37,80,81], 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 remains even with over-adjustment (i.e., adjusting for mediators such as comorbidities) and control for obstructive sleep apnea and other sleep disorders that may be expressed by insomnia symptoms, especially when undiagnosed.

Strengths

To the best of our knowledge, this is the first study that identified insomnia symptoms as a risk factor for stroke in the US population. In addition, this is the first study that explored mediation within this complex association. While the diagnosis of insomnia requires access to health care, individual insomnia symptoms are easily defined and accessible to the general population. Therefore, focusing on self-reported insomnia symptoms and identifying them rather as a risk factor for stroke is a step forward toward early prevention.

The current analysis was based on a large sample with over 18 years of follow-up and high participation, and retention rates. The majority of the participants were representative of U.S. adults 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.

Limitations

First, the exposure and outcome variables were self-reported. Self-reported data is more likely to be non-differential with regard to 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. [82] Therefore, this limitation is less likely to have biased the results. Second, insomnia symptoms were compiled into an unweighted linear symptoms index assuming equal weighting of 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 stroke. However, in the U.S., 87% of all strokes are ischemic and 13 % are hemorrhagic. [4] Therefore, the results from this study might not apply to a non-predominately ischemic stroke population. Furthermore, only the first stroke was modeled; thus, our findings might not be generalizable to recurrent stroke. Fourth, the mediation variables were measured at baseline. In the presence of reverse causation (comorbidities causing insomnia symptoms), there wouldn't 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 for 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 of age. 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.

Chapter 3: Insomnia Symptoms and all-cause mortality among Stroke Survivors

Abstract

Background: Insomnia is more frequently reported in stroke survivors but the independent role of insomnia in mortality in this vulnerable group is unknown. The purpose of this study was to investigate the association of insomnia symptoms with all-cause mortality among stroke survivors.

Methods: The Health and Retirement Study from 2002 to 2018 was used as the data source. Only participants with a history of stroke were included. The exposure variable of interest was insomnia symptoms and was derived from sleep-related factors including difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and nonrestorative sleep. The outcome was all-cause mortality and was assessed by linking the HRS data with the National Death Index and determining the exact date of death. Cox proportional hazards regression models were employed to investigate the association between insomnia symptoms and all-cause mortality.

Results: A total of 3,501 males and females were included in this analysis. Over a mean follow-up of 6 years, 1,782 deaths occurred. Difficulty initiating sleep and difficulty maintaining sleep were associated with all-cause mortality only among males less than 65 years old (HR=2.19, 95% CI=1.31, 3.65 and HR=2.13, 95% CI: 1.27, 3.60, respectively), while waking up too early and nonrestorative sleep were associated with all-cause mortality only among males 65 years and over (HR=1.30, 95% CI=1.04, 1.63 and HR=1.28, 95% CI: 1.03, 1.59, respectively), compared to those without symptoms. Compared to stroke survivors with no insomnia symptoms, stroke survivors with insomnia symptom scores ranging from 5 to 8 were associated with increased risk of all-cause mortality among males less than 65 years old and males 65 years and over (HR=2.24, 95% CI: 1.09, 4.58 and HR=1.26, 95%: 0.97, 1.65, respectively).

Conclusion: Insomnia symptoms were associated with an increased risk of death among stroke survivors, especially in males younger than 65 years. Increased awareness and management of insomnia symptoms may contribute to the prevention of premature death among stroke survivors.

Key terms: insomnia symptoms, all-cause mortality, stroke survivors.

Introduction

Sleep is essential for human health and its disruption could increase mortality. In a recent study linking a national survey to death records, being diagnosed with sleep disorder (e.i. sleep apnea, insomnia, restless leg syndrome,…) was associated with 50% increased risk of death. [83] A systematic review reported higher risk of mortality in patients with insomnia disorder when compared to those without insomnia (HR = 1.66, 95% CI = 1.25–2.19) [84]. Another one find more specifically, that difficulty initiating sleep and non-restorative sleep were associated with an increased risk of all-cause mortality.[85]

Several studies noticed differences by sex in the association between insomnia and death. Difficulty initiating sleep was found to be associated with increased mortality in men (HR=1.25, 95% CI 1.04-1.50), [86] but not in women (HR=0.89, 95% CI 0.79, 1.00) [87] while being an "early waker" was not associated with increase mortality in both men (HR=1.04, 95% CI 0.88-1.22) [87] and women (HR=0.81, 95% CI 0.75, 0.91). [86] Furthermore, in the Atherosclerosis Risk in Communities Study, insomnia was not associated with an increased risk for death (OR 1.01, CI 0.85–1.21) in both sex. [88]

Insomnia has been linked to multiple adverse health outcome and chronic condition (increased inflammation, glucose intolerance, dysregulation of the hypothalamic-pituitary axis, increase sympathetic nervous system activity).[58,89,90,91] However, studies suggest that these chronic conditions cannot totally explain the observed association between insomnia symptoms and total mortality. [86] The mechanism by which insomnia increases the risk of death may also include the daytime impairments, such as depressed mood, anxiety, and fatigue.[84]

Insomnia is highly prevalent, affecting approximately 32 to 41% of stroke survivors.[92] Both insomnia and insomnia symptoms are higher in stroke survivors compared to the general population. Insomnia could negatively affect stroke rehabilitation including post stroke

depression, recurrent stroke and death but less attention has been given to identifying the independent role of insomnia in mortality in this vulnerable group. [93] Most of the previous studies were conducted on the general population. The objective of this study was to determine the independent role of insomnia in mortality within community-dwelling stroke survivors and whether this association is modified by age, sex, race/ethnicity, or social deprivation index.

Methods

Data source and study population

This study used data from the Health and Retirement Study (HRS), which is an ongoing national longitudinal study of Americans older than 50 years and their spouses, conducted by the University of Michigan and sponsored by the National Institute on Aging (NIA U01AG009740). The study was established to provide a national data resource on the role of changing health and economic circumstances as they relate to aging at both individual and population levels. [54]

HRS design and data collection

The HRS sample was assembled in several waves of enrollment and data collection. The initial HRS cohort, recruited in 1992, consisted of persons born between 1931 and 1941 (then aged 51- 61) and their spouses of any age. A second study, Asset and Health Dynamics Among the Oldest Old (AHEAD), targeted the cohort born 1890 -1923 (then aged 70 and above). In 1998, the two samples were merged and, to make the sample fully representative of the USA population over age 50, two new cohorts were enrolled: the Children of the Depression (CODA), born 1924 - 30, and the War Babies, born 1942 - 47. HRS now employs a steady-state design, replenishing the sample every 6 years with younger cohorts not previously represented. In 2004, Early Baby Boomers (EBB, born 1948 - 53) were added, and in 2010, Mid Baby Boomers (MBB, born 1954 - 59) were added. [54] Finally, in 2016, the Late Baby Boomers (LBB, born 1960

- 65) were added. Further details about the survey can be found on the HRS website (https://hrs.isr.umich.edu).

Study design and inclusion criteria

The sleep questions of interest were introduced in 2002. Therefore, the present study included participants starting in 2002 and followed until death, loss to follow-up, or the end of the study in 2018, whichever occurred first. Only participants who selft-reported a history of stroke and completed the sleep questions were included. If a participant reported multiple strokes, only the first stroke was considered. Respondents with Transient Ischemic Attack (TIA) and unknown stroke status were excluded. Among those interviewed in 2002, 1,222 met the inclusion criteria. In the subsequent years, new participants were added to the cohort if they reported a history of stroke resulting in a final sample of 3,501 (Figure 3.1).

Exposure: Insomnia symptoms

Self-reported insomnia symptoms were assessed using the Adapted Brief Insomnia Questionnaire (BIQ), a validated screening tool that measures self-reported sleep complaints rather than diagnosed insomnia. [55,56] Participants answered four 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 (Supplemental Table 2.1). 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 symptoms severity score that ranges between “0=no insomnia” and “8=severe insomnia symptoms”. [57] For each participant, insomnia symptoms were assessed at the time of their inclusion to the present study (cohort entry).

A second insomnia symptoms scale was also used that reduced the range from 0-8 to 0-4. Answers to the above questions reflected individuals experiencing insomnia symptoms if they answered, “most of the time” or “sometimes” to the first three questions on the BIQ and “sometimes” or “rarely or never” to the fourth question (i.e., “how often do you feel really rested when you wake up in the morning?”). The number of symptoms was summed to give an overall insomnia symptoms severity score, ranging from “0 =no insomnia symptoms” to “4=severe insomnia symptoms”. [58]

Outcome: All-cause mortality

Mortality event that occurred during the follow up was obtained by linking the HRS data to the National Death Index which contain the exact date of death.

Covariates

Based on previous literature [58,93] and guided by a directed acyclic graph (Supplemental Figure 3.1), the following covariates were considered. First, demographic factors include 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 other). Second, socio-economic status (SES) factors include education (less than high school, high school, some college, college graduates, and more), household income and wealth, employment status, and the social deprivation index (SDI). The SDI index was produced by the Robert Graham Center, using 7 key neighborhood factors derived from the 2011-2015 American Community Survey (ACS) including the percent population with <100% Federal Poverty Level, percent population with less than 12 years of education, percent non-employed, percent population living in renter-occupied housing units, percent population living in crowded housing units, percent single-parent households, and percent population with no

car.[64] The index was derived at the level of the census tract, generating values from 0 to 100 that is applied to each participant with a higher score indicating a more deprived area. Third, behavioral risk factors include alcohol consumption, smoking, body mass index, and physical activity. Finally, lung disease and time since stroke occurrence were included as covariates.

Comorbidities were considered mediators and were therefore not used as covariates in the main analysis. These included self-reported diabetes, hypertension, heart disease (i.e., heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems), depression, and cancer. Depressive symptoms were assessed with an 8-item version of the Centers for Epidemiologic Study of Depression (CESD) scale. [94] The sleep item was excluded from the total score due to the issue of shared variance with insomnia symptoms. [66,67,68] The final score of depressive symptoms ranged from 0 to 7. A score of 4 on the eight-item CES-D corresponds to a score of 16 on the 20-item CES-D scale, which indicates a diagnosis of depression. [69, 70,71] Therefore, 4 was used as the cut-off point to create a dichotomous depression variable.

Data Analysis

The study was approved by VCU IRB (HM20023839). The data was accessed and analyzed within the University of Michigan Virtual Data Enclave. The analysis was conducted using SAS version 9.4 (SAS, Cary, NC).

Descriptive statistics

Descriptive statistics were generated to assess the distribution of the study characteristics by insomnia symptoms score. All baseline characteristics were summarized using mean and standard deviation for continuous variables and frequencies and percentages for the categorical

or ordinal variables. Multicollinearity was tested for the covariates using the variance inflation factor (VIF). A VIF of 10 or greater was used to signify multicollinearity.

Time to event analysis

Cox proportional hazard regression analyses were performed to evaluate the association between insomnia symptoms and all-cause mortality. The proportional hazard assumption was tested graphically and using the Kolmogorov-type supremum test. Time independent covariates were entered into the model sequentially. Model 1 was adjusted for demographic factors. Model 2 was adjusted for model 1 variables and socioeconomic factors. Model 3 was adjusted for model 2 variables, behavioral risk factors, lung disease, and time since stroke diagnosis (time from stroke diagnosis to insomnia symptoms assessment).

Predefined stratified analyses were performed to determine whether the association of insomnia symptoms with all-cause mortality was modified by age (<65 vs. ≥65 years, sex (male vs female), age and sex, race/ethnicity (White, Black, Hispanic, Other), or SDI (first 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 stratified analyses.

Sensitivity analysis

A series of sensitivity analyses were performed on the unstratified models. First, an analysis was conducted using an insomnia symptom scale of 0-4. Second, an analysis was conducted excluding participants that reported a stroke event without a year of occurrence. Third, an analysis was conducted excluding participants with a proxy reporter. Fourth, an analysis was conducted excluding participants included in 2016 (due to the shorter follow-up time). Fifth, to further assess reverse causation, a lagged analysis was conducted where deaths that occurred within two years

of insomnia symptoms assessment were excluded. Analysis were also conducted by: further adjusting for comorbidities that were not adjusted in the main analysis because they were considered mediators; by controlling for the cohort entry year; and by performing analysis for model selection and parsimony 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 was statistically significant ($p<0.05$), and manual backward selection approach . Another analysis was conducted restricted to death due to cardiovascular diseases. Finally, an E-value for residual unmeasured confounders was computed.

Results

Descriptive statistics

The study participants' mean age was 71 years, 66.7 % were over the age of 65, 55% were female, and 64.6% were Non-Hispanic White (Table 3.1). Mean age and income decreased with increasing insomnia symptoms score. Insomnia symptom scores were higher in females, current smokers, those who were unemployed/disabled, those with low education, low physical activity, obesity, any comorbidity, and living in a socially deprived neighborhood. Over a mean of 6 years of follow-up (SD=4.4; q1=2.0; q3=8.2; max=16.9) of 3501 stroke survivors; 1782 (50.9%) death were recorded. More males (52%) than females (50%) died. The leading cause of death were cardiovascular disease (39 %), cancer (14%), allergies and infectious disease (11.5%). Majority of the death (61.8%) were expected and 64% resulted from an illness that lasted more than a week (Supplemental Table 3.1)

Association of insomnia symptoms with all-cause mortality

In the continuous insomnia symptoms models, one unit increase in the of insomnia symptom score was associated with a 2% increased risk of all-cause mortality (hazard ratio (HR)

= 1.02, 95% confidence interval (CI): 1.00, 1.04) after adjusting for demographic factors, socioeconomic factors, and behavioral risk factors (Table 3.2). Models adjusted for demographic factors (Model 1) and further adjusted for socioeconomic factors (Model 2) shifted the direction of the association away from the null, compared to the unadjusted model.

Differences by age and sex were noticed in the stratified analyses. The association of insomnia symptoms with all-cause mortality was statistically significant among those less than 65 years old (HR=1.07, 95% CI: 1.01, 1.13) and males (HR=1.05, 95 % CI: 1.01, 1.09, Table 3.3). Compared to those with no insomnia symptoms, insomnia symptom scores ranging from 5 to 8 were associated with increased risk of all-cause mortality among males aged <65 years and males aged ≥ 65 years (HR=2.24, 95% CI: 1.09, 4.58 and HR=1.26, 95%: 0.97, 1.65, respectively). Similar trends were observed comparing males aged <65 years and males aged ≥ 65 years with insomnia symptom scores ranging from 1 to 4 to those with no insomnia symptoms, but the associations were not statistically significant (HR=1.55, 95% CI: 0.82, 2.91, and HR=1.14, 95%CI: 0.92, 1.43 respectively). There was no association between insomnia symptoms and death in females. Furthermore, there was no notable effect modification by race/ethnicity or social deprivation index.

The analysis using individual insomnia symptoms (Table 3.4) showed that difficulty initiating sleep and difficulty maintaining sleep were associated with all-cause mortality only among males less than 65 years old (HR=2.19, 95% CI=1.31, 3.65 and HR=2.13, 95% CI: 1.27, 3.60, respectively) comparing those reporting the symptom most of the time to those without symptoms. Similarly, waking up too early and nonrestorative sleep were associated with all-cause mortality only among males 65 years and over (HR=1.30, 95% CI=1.04, 1.63 and

HR=1.28, 95% CI: 1.03, 1.59, respectively) comparing those reporting the symptom most of the time to those without symptoms.

Sensitivity analyses

The analysis using insomnia symptom scales 0-4 (Supplemental Table 3.4) was consistent with the main analysis. Analyses in which missing stroke occurrence year was excluded, a proxy reporter was excluded, participants included in 2016 were excluded, with 2 years lag were all consistent with results from the main analysis (Supplemental Table 3.5 and 3.6). Adjustments for comorbidities that were not adjusted in the main analysis because they were considered mediators slightly reduced the effect estimates but they remain in the same direction (Supplemental Table 3.7). The analysis controlled for cohort entry year was similar to the main analysis (Supplemental Table 3.7). Furthermore, the analysis using the change in estimate approach and the manual backward approach (Supplemental Table 3.8) were comparable to the main analysis. The analysis restricted to the leading cause of death; cardiovascular disease did not change the result (Supplemental Table 3. 1**).** The E-value was estimated at 1.52 for males less than 65 years and 1.24 for males 65 years and older. The E- value is the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away this association, conditional on the measured. The covariate with the strongest association with all-cause mortality was lung disease (HR=1.40) meaning that for an unmeasured confounder to fully explain away this association, the association of such an unmeasured confounder with death must be stronger than the association between lung disease and death. In addition, such an unmeasured confounder must be associated with insomnia symptoms with at least the among of the E-value (i.e., 1.52 for males less than 65 years and 1.24 for males 65 years and older.) after controlling for the variables included in model 3.

Discussion

In this study, insomnia symptoms were associated with an increased risk of death among stroke survivors, especially in males and those who are younger than 65 years of age. To our knowledge, this population-based prospective cohort study is the first to investigate the relationship between insomnia symptoms and mortality among stroke survivors in the US. Recent improvement in acute stroke management has contributed to a decrease in stroke-related mortality and increasing number of stroke survivors. Therefore, improving post-stroke life expectancy has become a public health priority.

The association between insomnia symptoms and all-cause mortality differed by age and sex. The association was stronger in younger adults (age<65) than older adults (age≥65), which is similar to results from previous studies. Insomnia symptoms such as difficulty falling asleep were found to be associated with increased mortality in men (HR=1.25, 95% CI 1.04-1.50), [86] but not in women (HR=0.89, 95% CI 0.79, 1.00) [87] in the general population from the USA and Australia, respectively. In a study from China, restricted to stroke patients at the early stage of recovery, insomnia symptoms were associated with death but the study did not report a stratified analysis by age and sex. [93] The difference by age could be due to the higher risk of death at an older age and the competing causes of death as age increased. Potential sex differences in the association between insomnia symptoms and risk of death have not been reported previously. However, some studies suggest that females have a better quantity (total sleep time) and quality (Slow Wave Sleep and Rapid Eye Movement sleep) of sleep than males.[95] Furthermore, females may cope better with sleep loss in terms of inflammation makers which in part may contribute to females' lower risk of death in association with insomnia symptoms. [96]

The association between insomnia symptoms and all-cause mortality seems to be stronger in stroke survivors compared to the general population. In a study restricted to male health

professionals in the USA, Li et al found that the mortality HR was 1.25 (95% CI:1.04-1.50) for difficulty initiating sleep, 1.09 (95%CI: 0.97-1.24) for difficulty maintaining sleep, 1.04 (95%CI: 0.88-1.22) for waking up too early, and 1.24 (95%CI:1.05-1.46) for non-restorative sleep. [86] In the present study among stroke survivors, mortality HRs were 1.28 (95% CI: 1.04, 1.57), 1.09 (95% CI: 0.90-1.31), 1.27 (95% CI: 1.04, 1.56) and 1.31 (95%CI: 1.09, 1.57) for males reporting the same insomnia symptoms, respectively. Future studies comparing stroke survivors to individuals without a history of stroke are needed.

The current analysis was based on a representative sample of U.S. adults 50 years and older. Strengths of this study include its prospective design, large sample size and the valid assessment of the outcome, which was drawn from the National Death Index. There are several limitations to the present study that should be noted. First, most of the study variables were self-reported. Misclassification that could result would likely be non-differential given that the outcome was measured at different times and participants were unaware of the study hypothesis. Therefore, any resulting bias will be toward the null hypothesis. Second, insomnia symptoms were compiled into an unweighted linear symptoms index assuming equal weighting of all symptoms. Third, we cannot rule out the possibility of residual confounding such as obstructive sleep apnea and the use of hypnotics. However, the E-value of unmeasured confounders appeared high meaning that the effect of a potential unmeasured confounding would likely be negligible.

In summary, insomnia symptoms increased the risk of death among stroke survivors, especially in males younger than 65 years of age. These findings suggest that increased awareness and management of insomnia symptoms may contribute to improving post-stroke life expectancy.

Chapter 4: Sleep Duration and All-Cause Mortality Among Stroke Survivors

Abstract

Background and Objectives: Sleep complaints are commonly reported among stroke survivors. Sleep duration could change after a person has experienced a stroke. This study tested the hypothesis that inadequate sleep duration is associated with increased mortality among stroke survivors.

Methods: The REasons for Geographic And Racial Differences in Stroke (REGARDS), a national population-based, longitudinal study, was used as a data source. Sleep duration was estimated as the difference between wake-up time and bedtime to which was subtracted the time spent in bed without sleep. Sleep duration was ascertained between 2013 and 2016 among stroke survivors who were subsequently follow up until death or the end of the study in 2022. Cox proportional hazards regression models were employed to investigate the association between sleep duration and all-cause mortality.

Results: A total of 468 non-Hispanic Black and White stroke survivors were included in this analysis. The mean age was 76.3 years, 52.6% were female and 56.0% were Non-Hispanic White. The distribution of short (≤6 hours), adequate (7.0-8.9 hours), and long sleep (≥9 hours) was 30.3%, 44.7%, and 25% of the cohort, respectively. Over a mean follow-up of 5.4 years, 190 deaths occurred. Compared to stroke survivors with adequate sleep (7.0-8.9 hours), stroke survivors with long sleep (≥9 hours) were at increased risk of all-cause mortality (HR=1.53, 95% CI=1.03, 2.29). However, short sleep (≤6 hours) was not associated with an increased risk of all-cause mortality (HR=1.36, 95% CI=0.93, 2.02). Subgroup analyses indicated higher risk in the age <75 years group and Non-Hispanic Blacks but those differences were not statistically significant.

Conclusion: In this study of stroke survivors, 9 hours or more of sleep per day was associated with an increased risk of all-cause mortality. This finding suggests that excessive sleep duration maybe a warning sign of an underlying problem associated with poor life expectancy.

Key terms: stroke survivors, sleep duration, all-cause mortality, death.

Introduction

Sleep duration has declined in contemporary society over the past decades. In the United States for example, the mean sleep duration (age-adjusted) has decreased from 7.40h to 7.18h between 1985 and 2012 while the percentage of adults sleeping ≤ 6 h has increased by 31%. [97,98] This could be the result of changes in sleep patterns to accommodate work requirements, or sleep disturbances due to stress, depression, or other factors such as chronic disease including stroke.[99,100,101]

Stroke is the second leading cause of death globally after ischemic heart disease. [2] To reduce the risk of premature death, it is important to identify modifiable lifestyle factors, such as sleep duration, that may be associated with increased mortality risk. Sleep duration has been linked to adverse health outcomes and mortality in the general population.[102] A systematic review and meta-analysis reported that long sleep duration was associated with increased mortality in the general population.[103] Several prospective studies found that both short (≤6 hours/night) and long (> 8 hours/night) sleep duration were predicting mortality risk. [14, 38,104,105] A 'J' or 'U-shaped' curve describing the relationship has often been reported, with the lowest risk for those who slept 7-8 hours per night. Stratified analyses revealed little variation by sex, [105] with a modestly higher risk in women.[106] The mechanisms behind the association between inadequate sleep duration and adverse health outcomes are not fully understood. Short sleep duration could increase inflammation, impaired glucose tolerance, evening cortisol levels, alterations in sympathetic nervous system activity, or other pathological processes which could directly or indirectly lead to death. [107] Long sleep duration may be associated with a poor health condition and underlying co-morbidities which increases the risk of death. [14]

There is sufficient evidence to suggest that stroke survivors might be different from the general population. However, few studies have examined whether sleep duration has an

independent role in mortality among stroke survivors. Biological and psychological consequences of having a stroke including potential brain cell death due to blood disruption and the experience of a sudden and disabling disease could have lasting consequences on sleep. [108,109,110] The objective of this study is to determine the association between sleep duration and all-cause mortality within community-dwelling stroke survivors and assess effect measure modification by age, sex, race/ethnicity, neighborhood socioeconomic status, and geographic region.

Methods

Data Source

This study utilized data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) which is an ongoing national prospective cohort study sponsored by the NIH focusing on the factors that increase the risk of stroke. [111] The study recruited participants by initially obtaining a list (Genesys, Inc.) of residents aged ≥45, and then by random enumeration of households that were approached to solicit participation. The exclusion criteria included race other than non-Hispanic Black or White, active treatment for cancer, other medical conditions that would prevent long-term participation, cognitive impairment judged by the telephone interviewer, residence in or inclusion on a waiting list for a nursing home, or inability to communicate in English. [111] A total of 30,239 participants were recruited from January 2003 to October 2007. Residents from the Stroke Belt (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee) and non-Hispanic Blacks were oversampled due to excess stroke mortality. As a result, 56% of the sample consisted of residents from the Stroke Belt and 42% consisted of non-Hispanic Blacks. [111] At baseline, participants answered demographic and medical history questions during a computer-assisted telephone

interview. During a home visit, participants provided appropriate written informed consent, anthropometric measurements, blood pressure, blood and urine, medication inventory, and an electrocardiogram. Self-administered questionnaires were left with the participant to gather information on additional demographic characteristics and stroke risk factor. These measurements were repeated during a second in-home exam that occurred between 2013 and 2016. [111] All participants were contacted by telephone twice per year. If a participant reported a suspected stroke, his/her medical record was obtained and adjudicated by study physicians to confirm or refute stroke incidence.

Study design and inclusion

The prospective cohort study used the second in-home visit as the baseline and included only participants diagnosed with stroke between the first and second in-home visit (n=468) who were followed until death, loss to follow-up, or the end of the study (2022), whichever occurred first.

Exposure: Sleep duration

Several sleep-related questions were asked during the second in home visit: a) "thinking about a typical day for you, what time do you usually start trying to fall asleep?" b) "thinking about a typical day, what time do you usually wake up?" c) "how many minutes does it usually take you to fall asleep, after you start trying to fall asleep?" and d) "how much time, in minutes, do you usually spend awake in between the time you first fall asleep and the time you wake up and start your day?". Sleep duration was computed as the difference in hours between b and a minus the sum of c and d to obtain sleep duration as the time spent in bed sleeping. Sleep duration was further categorized into ≤ 6 hours (short sleep), 7.0-8.9 hours (adequate sleep), and ≥9 hours (long sleep). The sleep duration categories were chosen based on the American

Academy of Sleep Medicine and National Sleep Foundation guidelines for recommended and appropriate sleep durations among adults thus, facilitating the interpretation.[112,113]

Outcome: all-cause mortality was reported during the follow-up (from the second in-home visit to the end of the study in 2022). REGARDS participants or their next of kin were contracted by telephone twice a year. REGARDS study also received letters from proxy informing of a study participant death. Deaths were also identified through search on the Social Security Death Index. Once a death was identified, an exit interview was conducted with the next of kin and medical records was obtained and assessed.

Covariates

The following covariates were considered based on previous literature. [58,93] Demographic factors included age, sex, race/ethnicity (Non-Hispanic White, Non-Hispanic Black), marital status (divorced, widowed, never-married, currently married), and region (southern US region or other). Socioeconomic factors included education (less than high school, high school, some college, college graduates, and more), household income and wealth, employment status, and neighborhood socioeconomic status (NSES). A summary NSES index variable was created in REGARDS including 6 variables representing wealth/income, education, and occupation: (1) log of median household income, (2) log of the median value of owner-occupied housing units, (3) proportion of households receiving interest, dividend, or net rental income, (4) proportion of adults aged ≥25 years with a high school diploma, (5) proportion of adults aged ≥25 years with a college degree, and (6) proportion of people employed in executive, managerial, or professional occupations. [114] Higher values indicate higher NSES. [114] Behavioral risk factors included alcohol consumption, smoking, body mass index, and physical activity. Comorbidities included diabetes (self-reported), hypertension (systolic blood pressure ≥140 or

diastolic blood pressure ≥90 or self-reported current medication use to control blood pressure), dyslipidemia (total cholesterol≥240 or low-density lipoprotein≥160 or high-density lipoprotein≤40 or on medication), heart disease (self-reported myocardial infarction, coronary artery bypass, angioplasty, or stenting or evidence of myocardial infarction via electrocardiogram), atrial fibrillation (self-report or electrocardiogram evidence), history of sleep apnea (self-reported), history of cancer (self-reported), depression symptoms, and time since stroke diagnostic**.** Depressive symptoms were assessed with the 10-item version of the Centers for Epidemiologic Study of Depression (CESD) scale without the sleep question. [70]

Data Analysis

Descriptive statistics

Descriptive statistics were generated to assess the distribution of the study characteristics by sleep duration. Mean and standard deviation was used for continuous variables and frequencies and percentages for the categorical or ordinal variables. To compare the participants based on the sleep duration group, a chi-squared test (categorical variables) and t-test (continuous variables) was used. A variance inflation factor of 10 or greater was used to indicate multicollinearity among the variables.

Time to event analysis

To evaluate the association between sleep duration and all-cause mortality, multiple Cox proportional hazard regression models were developed. The proportional hazard assumption was initially tested using graphic, time-varying, and the Kolmogorov-type supremum tests. Covariates were entered sequentially into each model. Model 1 was adjusted for demographic factors. Model 2 was adjusted for variables included in model 1 plus socioeconomic factors. Model 3 was adjusted for variables included in model 2 plus behavioral risk factors and time

since stroke diagnosis. Model 4 was adjusted for variables included in Model 3 plus comorbidities.

Several predefined subgroup analyses were performed to determine whether the association of sleep duration with all-cause mortality was modified by age (<75 vs. ≥75 years), sex (male vs female), race/ethnicity (White vs Black), NSES (low: first and second quartile vs high: third and fourth quartile) and region (stroke belt vs non-stroke belt). A p-value for interaction was obtained by comparing models with and without multiplicative interaction terms before conducting the above subgroup analyses.

Multiple imputations

Three approaches were used to perform the main analysis. The initial analysis was conducted using a complete case analysis approach in which any observation with missing data was deleted. Then, an analysis was performed in which covariates with more than 10% missing observations were not included in the models. Finally, due to the attrition of the sample size in the multivariable analysis which excluded observation with missing values, multiple imputations of covariates were performed. Only missing covariates were imputed, the outcome and exposure variables were not inputted. The subgroup and sensitivity analyses were based solely on the imputed data.

Sensitivity analysis

Several sensitivity analyses were conducted. First, an analysis was conducted using the change in estimate approach in which variables were included in the models as confounders if their presence resulted in a greater than 10% change in the estimate, or if the variable was statistically significant ($p<0.05$). Second, to assess reverse causation, a one-year lagged analysis was conducted where deaths reported one year after sleep duration assessment were excluded.

Third, an analysis was conducted with further adjustment for sleep medication use, which was assessed at the REGARDS baseline visit but not at the second visit. Fourth, an E-value for residual unmeasured confounders was computed.

Results

A total of 468 non-Hispanic Black and White stroke survivors were included in this analysis. The mean age was 76.3 years, 52.6% were female and 56.0% were Non-Hispanic White (Table 4.1). Short sleep (≤6 h), adequate sleep (7.0-8.9 h), and long sleep (≥9 h) were reported by 30.3%, 44.7%, and 25%, respectively. Mean age increased with increasing sleep duration. The mean age of short sleepers was significantly different from the mean age of long sleepers (74.7 and 76.5 years, respectively). Males and Non-Hispanic Black reported shorter sleep duration compared to their counterparts. Short sleepers were more likely from to be younger, Non-Hispanic Black, employed, high NSES, depression symptoms and less likely to have diabetes, cancer than adequate sleepers. Long sleepers were more likely to be females, Non-Hispanic Black, less educated, heavy alcohol users, have higher depression symptoms, diabetes, and less likely to be working than adequate sleepers. Over a mean follow-up of 5.0 years (Standard deviation=2.4), 190 deaths occurred.

In the unadjusted model, the HR for death was 1.08 (CI=0.76, 1.53) for a short sleep and 1.76 (CI=1.26, 2.47) for a long sleep (Table 4.2). After adjusting for demographic factors, socioeconomic factors, behavioral risk factors, and time since stroke, the HR for death was 1.26 (CI=0.74, 2.11) for a short sleep and 1.93 (CI=1.10, 3.38). In the model further adjusted for comorbidities (diabetes, hypertension, heart disease, atrial fibrillation, depression symptoms, dyslipidemia, cancer, sleep apnea), short sleep was not associated with all-cause mortality

(HR=0.99, CI=0.42, 2.34) while long sleep was associated with all-cause mortality (HR=5.20, CI=2.04, 13.25) compared to adequate sleep.

Similar trends with reduced variance were observed after excluding variables with high number of missing observation and after performing multiple imputations of missing covariates (Table 4.2). The following covariates were imputed: household income (n=97), occupation (n=74), NSES (n=43), smoking (n=1), exercise (n=4), BMI (n=52), depression symptoms (n=42), diabetes (n=4), hypertension (n=11), heart disease(n=55), atrial fibrillation (n=75), dyslipidemia (n=52), cancer (n=163), and sleep apnea (n=7) (Supplemental Table 4.2). Compared to stroke survivors with adequate sleep (7.0-8.9 h), stroke survivors with long sleep (≥9 h) were at increased risk of death (HR=1.73, 95% CI=1.19, 2.53) but short sleep (≤6 h) was not associated with increased risk of death (HR=1.30, 95% CI=0.89, 1.90) after adjusting for demographic factors, socioeconomic factors, behavioral risk factors and time since stroke. In the model further adjusted for comorbidities, short sleep was not associated with all-cause mortality (HR=1.36, CI=0.93, 2.02) while long sleep was associated with all-cause mortality (HR=1.53, CI=1.03, 2.29) compared to adequate sleep.

Subgroup analysis indicates a higher risk associated with long sleep (≥9 h) in the age <75 (HR=3.17, CI=1.11, 8.33) and Non-Hispanic Black (HR=2.38, CI=0.99, 5.72) compared to the counterpart (HR=1.55, CI=0.91, 2.65 and HR=1.31, CI=0.74, 2.32, respectively, Table 4.3). However, these differences were not statistically significant.

The sensitivity analysis showed no significant difference from the main analysis (Supplemental Table 4.3). The association between long sleep and all-cause mortality was still stronger than the association between short sleep and all-cause mortality after removing death that occurred one year after the baseline. In addition, the analysis using the change in estimate

approach or p-value<.05 was comparable to the main analysis. The association between long sleep and all-cause mortality remained after further adjustment for sleep medication. Sleep medication use was neither associated with short sleep nor long sleep. The E-value of the association between long sleep and all-cause mortality was estimated at 2.85 based on Model 3 and 2.52 based on Model 4. The E- value is the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away this association, conditional on the measured covariates.

Discussion

In this population of stroke survivors, we found that compared to those with adequate sleep duration (7.0-8.9 h), those with long sleep duration(≥9h) had an increased risk of all-cause mortality. Short sleep duration (≤6h) was also associated with an increased risk of all-cause mortality but this association did not reach a statistical significance. To the best of the author's knowledge, no previous study investigated the association between sleep duration and mortality in the population of stroke survivors. Others have reported that both short and long sleep was linked to mortality among people with coronary heart disease and type 2 diabetes. [115,116] However, multiple studies have looked at the association between sleep duration and stroke mortality in the general population. Two studies conducted in China found that both short and long sleep durations were associated with an increased risk of stroke mortality. [117, 118] These findings were confirmed in a recent meta-analysis, and the association was stronger for long sleepers than for short sleepers. [119]

One study, the study from the Sleep Apnea Cardiovascular Endpoints trial, which included patients with moderate to severe obstructive sleep apnea and a history of coronary or cerebrovascular disease found that long sleep(≥8h) but not short sleep (<6h) was associated with

increased cerebral events (HR 1.67, CI=1.17–2.39) and stroke alone (HR 1.79, CI=1.22–2.63).[120] This suggests that cerebrovascular events could contribute to explaining the association between long sleep duration and increased mortality.

The reason why long sleep but not short sleep duration was associated with increased risk of mortality in stroke survivors in the current study is not clear. This study may have lacked power to reach a statistical significance. Furthermore, it is possible that long sleepers could be at the early stage of stroke recovery or have experienced a more severe form of stroke. A treatment of such severe stroke is more likely to involve multiple drugs with their respective side effects. In addition, the social profile of long sleeper (more likely to be females, Non-Hispanic Black, less educated, heavy alcohol users, and less likely to be working) and the health profile (more likely to have higher depression symptoms, and diabetes) suggest that social determinant of health and underlying poor health play a role in long sleep. Long sleep could reflect disrupted sleep quality and poor sleep efficiency which is associated with increased risk of death.[121] Furthermore, underlying conditions including excessive daytime sleepiness and reverse Robin Hood syndrome could increase both sleep duration and mortality among stroke survivors. [122] Lastly, long sleep could reduce the time for hobbies, the time spent socializing or being active which is associated with better quality of life and life expectancy. [123,124]

The association between sleep duration and all-cause mortality was relatively similar across different subgroups (age, sex, race, NSES, geographic region). However, a higher risk was observed in those <75 years of age and among Non-Hispanic Blacks. This study may have lacked the power to detect significant subgroup differences, the apparent age and sex differences should therefore be interpreted with caution. Future studies with larger sample sizes are warranted.

This study has several limitations that should be mentioned. First, the REGARDS cohort is biracial (Black and White) and is therefore not generalizable to other race/ethnicity groups. Second, sleep duration was self-reported and a single time point measurement which could have resulted in non-differential misclassification and likely an underestimation of the mortality risk. However, studies suggest that sleep disturbances are most likely to persist over time. [125,126] Third, the small sample size limited the ability to ability to analyze others sleep categories, assess dose-response trends or mediation analysis. Comorbidities could be acting as mediators but since it was not possible to test those hypotheses, results from models with (model 4) and without comorbidities (model 3) were reported. Both results were in the same direction. Finally, some variables (occupation, region, NSES, cancer, sleep apnea, prescribed and non-prescribed sleep medication) were assessed before the present study baseline and may not have reflected the subsequent baseline value. One of the strengths of this study was it prospective design drawn from the REGARDS cohort, which was representative of the US population. In addition, the study consisted of stroke survivors in which the diagnosis was physician adjudicated.

In conclusion, the results of this study indicate that long sleep duration was associated with an increased risk of all-cause mortality among stroke survivors. Long sleepers were characterized by a poor health profile. These finding suggests that excessive sleep could be an indicator of poor life expectancy among stroke survivors.

Chapter 5: Summary

Stroke is the fifth leading cause of death in the US. This research sought to investigation sleep quality and quantity as potentially modifiable risk factor of stroke and all-cause mortality. Three specific Aims were developed. All three specific Aims were addressed using a prospective cohort study design. Specific aim 1 focused on the association between insomnia symptoms and the occurrence of first ever stroke in the general population while specific Aim 2 and 3 investigated the risk of all-cause mortality among stroke survivors. Specific Aim 3 complemented specific Aim 2 by looking at another aspect of sleep (i.e., sleep duration) within another data set. Two databases, both representative of the US population, were used, the Health and Retirement Study and the REasons for Geographic And Regional Differences in Stroke. Altogether, this research contributed to establishing relationships between sleep quality (insomnia symptoms), sleep quantity (sleep duration) and stroke incidence or all-cause mortality. This research found that insomnia symptoms were associated with an increased risk of stroke, especially in younger adults. In addition, insomnia symptoms and long sleep were associated with increased mortality among stroke survivors. The association between insomnia symptoms and all-cause mortality was stronger in males aged less than 65 years.

These studies are significant timely in a global context given the increasing trend of stroke incidence globally. The knowledge gained from sleep studies have recently led the American Heart Association to add sleep health in their key measures for improving and maintaining cardiovascular health, known as Life's Essential 8.

Public Health implications

These studies have several public implications. The result can help raise awareness and guide healthcare providers towards primary prevention of stroke and post-stroke rehabilitation,

specifically by addressing insomnia symptoms, by making appropriate diagnoses of sleep disorders, and by eventually targeting appropriate sleep management to improve health and longevity. Sleep disturbances are sometimes unnoticed by the patient and subsequently not treated by healthcare providers. Systematic screening of sleep disturbances in the routine care could be appropriate. However, insomnia treatment is not always accessible as some healthcare plans do not cover, for example the cost of cognitive behavioral therapy, which is a treatment option for insomnia.

Future research

This research could be a ground for future studies to evaluate the contribution of insomnia treatment to stroke prevention and mortality reduction. In addition, further investigations assessing the co-occurrence of poor sleep quality (insomnia symptoms) and inadequate sleep duration are warranted. Furthermore, studies utilizing objective sleep measures including for example electronic matches and actigraphy are needed. Finally, the growing population of stroke survivors should be a source of future studies to address the need of this vulnerable population.

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) at Virginia Commonwealth University (HM20023839).

Chapter 6: References

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Chapter 7: Appendices

Appendix A. Chapter 2: Insomnia Symptoms and Stroke Incidence

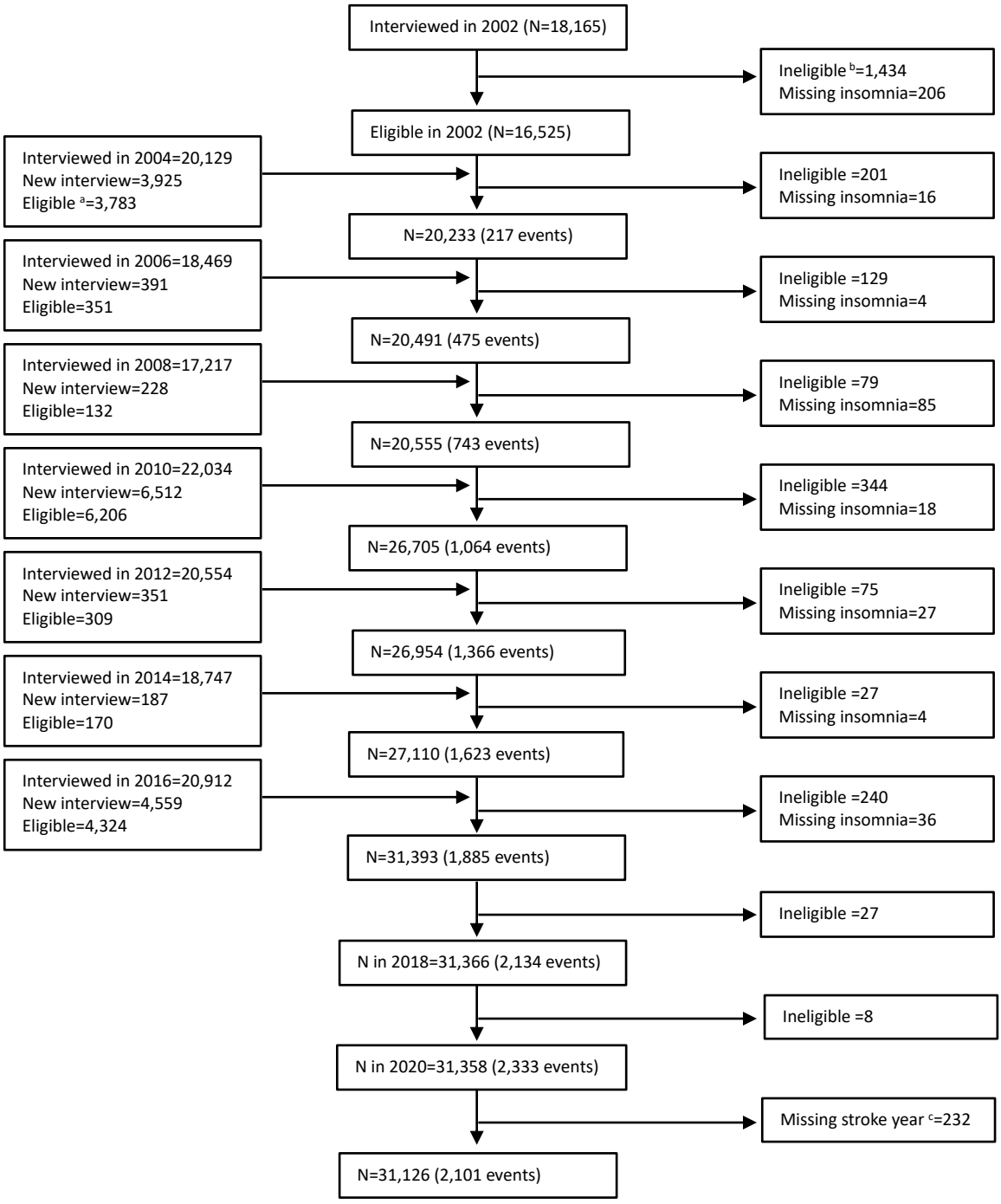


Figure 2. 1. Flowchart of the study inclusion process.

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

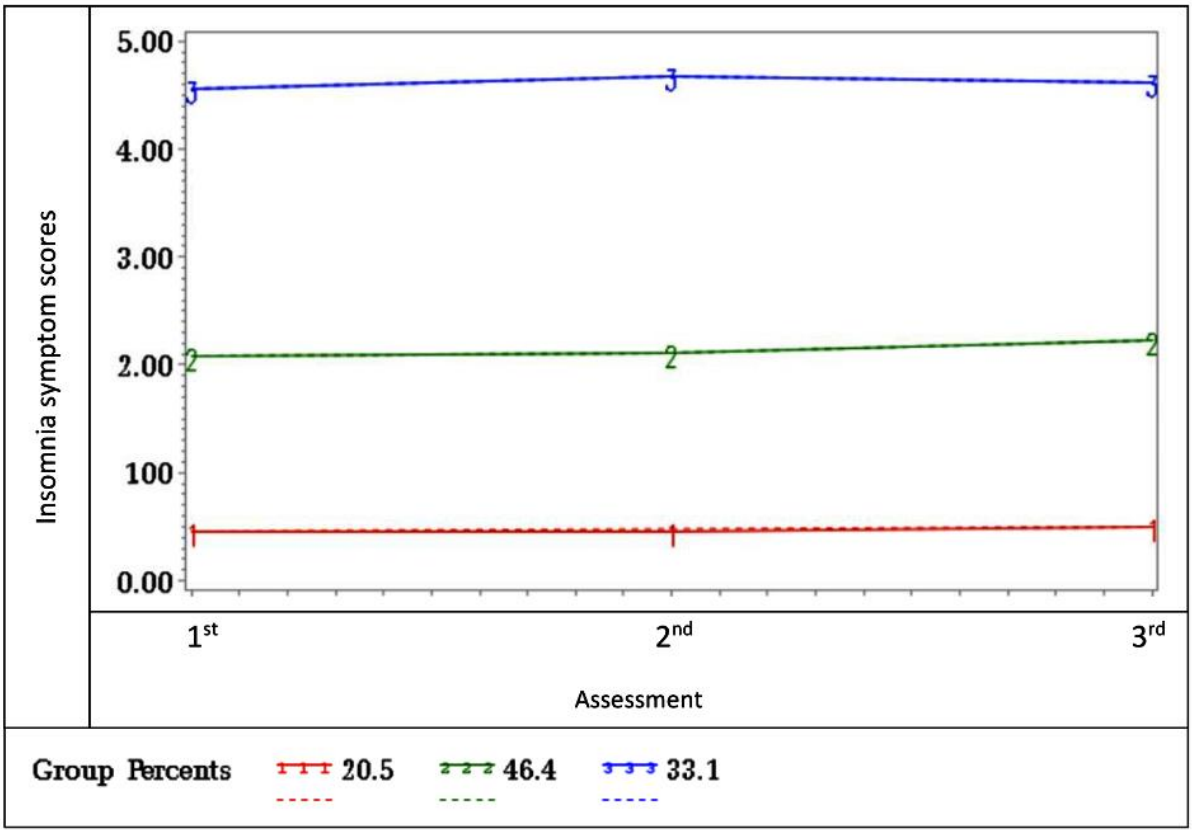


Figure 2. 2. Insomnia symptom trajectories in three consecutive assessments.

Table 2. 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 (in Years)										
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	144552.9	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	40982.0	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	19225.9	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	81418.8	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									
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/week 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/week										
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
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	26102 (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] SDI index include 7 measures (percent population with <100% FPL, percent population with less than 12 years of education, percent non-employed, percent population living in renter-occupied housing units, percent population living in crowded housing units, percent 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

Table 2. 2. Association between insomnia symptom trajectories and stroke

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)
"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, 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, physical activity

Table 2. 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]
1 unit increase	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	<.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	<.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, 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, physical activity)
- [a] p value for trend, Model 3

Table 2. 4. Incidence of stroke by insomnia symptom scores (stratified by age, sex, race/ethnicity, and SDI)

Stratification variable		Insomnia symptom scores	HR, 95 % CI [a]	p for interaction [b]
Sex	Male (N=11,709)	1 unit increase	1.08 (1.04, 1.12)	0.6866
		0	Ref	
		1-4	1.10 (0.92, 1.32)	
		5-8	1.51 (1.19, 1.90)	
	Female (N=15,559)	1 unit increase	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	Age < 50 (N=2,160)	1 unit increase	1.22 (1.09, 1.37)	**0.0003**
		0	Ref	
		1-4	1.64 (0.67, 4.02)	
		5-8	3.84 (1.50, 9.85)	
	Age ≥50 (N=25,108)	1 unit increase	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	White (N=16,801)	1 unit increase	1.07 (1.04, 1.10)	0.2877
		0	Ref	
		1-4	1.28 (1.09, 1.51)	
		5-8	1.54 (1.26, 1.88)	
	Black (N=5,307)	1 unit increase	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)	1 unit increase	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)	1 unit increase	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)	First quartile (N=6,740)	1 unit increase	1.05 (0.99, 1.10)	0.6599
		0	Ref	
		1-4	1.16 (0.89, 1.51)	
		5-8	1.34 (0.95, 1.90)	
	Second quartile (N=6,859)	1 unit increase	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)	1 unit increase	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)	1 unit increase	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 (age, sex, race/ethnicity, marital status, region, education, household income, employment status, social deprivation index, alcohol consumption, smoking, body mass index, physical activity) with the exception of the stratification variable.

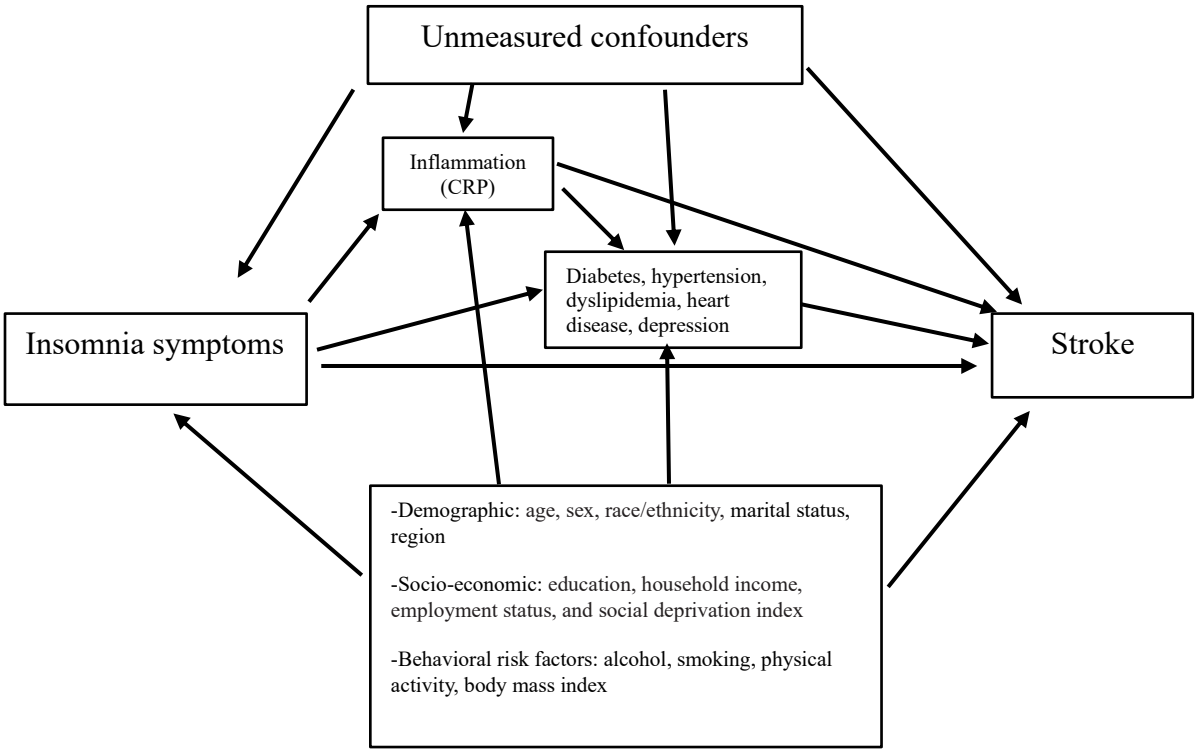
[b] The p-value for interaction were estimated by including an interaction term of insomnia symptom and the stratification variable in the model.

Table 2. 5. Mediation of the association between insomnia symptoms and incident stroke

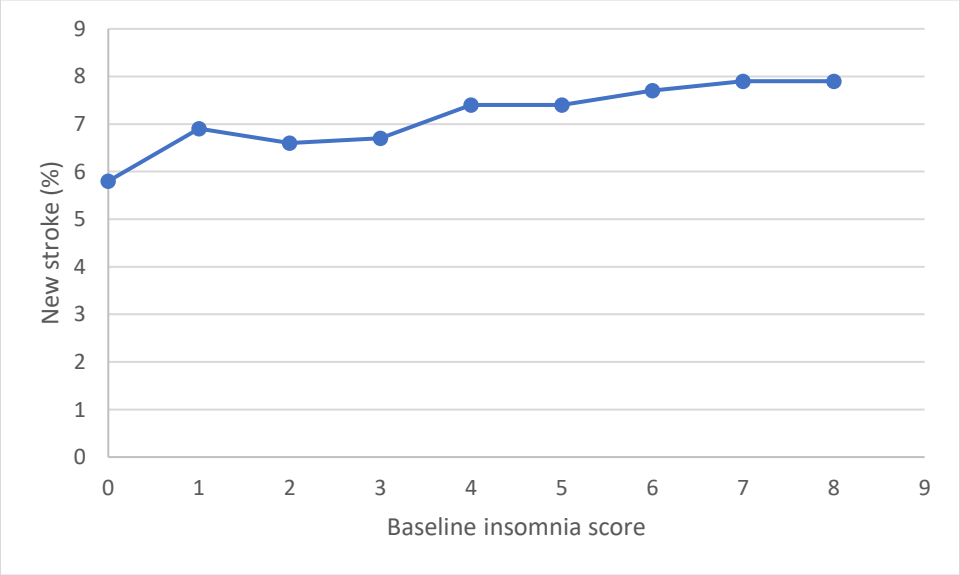
Mediator	Insomnia symptom scores	Total Effect HR, 95% CI	Direct Effect HR, 95% CI	Indirect Effect HR, 95% CI	% Mediated
CRP	0	Ref	Ref	Ref	Ref
	1-4	1.23 (1.13, 1.45)	1.23 (1.17, 1.42)	1.00 (0.90, 1.09)	-1.45
	5-8	1.64 (1.55, 2.02)	1.63 (1.58, 1.96)	1.00 (0.92, 1.10)	0.76
Depression	0	Ref	Ref	Ref	Ref
	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.

Supplemental Materials



Supplemental Figure 2. 1. Directed Acyclic Graph illustrating the pathways on the association between insomnia symptoms and stroke



Supplemental Figure 2. 2. Incidence of stroke by baseline insomnia symptom scores

Supplemental Table 2. 1. Insomnia symptoms questions and scaling

Individual insomnia symptoms	Insomnia symptoms Scale 0-4	Insomnia symptoms Scale 0-8
Difficulty initiating sleep		
"How often do you have trouble falling asleep?"		
1-Most of the time	1	2
2-Sometimes	1	1
3-Rarely or never	0	0
Difficulty maintaining sleep		
"How often do you have trouble with waking up during the night?"		
1-Most of the time	1	2
2-Sometimes	1	1
3-Rarely or never	0	0
Waking up too early		
"How often do you have trouble with waking up too early and not being able to fall asleep again?"		
1-Most of the time	1	2
2-Sometimes	1	1
3-Rarely or never	0	0
Nonrestorative sleep		
How often do you feel really rested when you wake up in the morning?		
1-Most of the time	0	0
2-Sometimes	1	1
3-Rarely or never	1	2
Total	0-4	0-8

Supplemental Table 2. 2. Variance inflation factor (VIF)

Variable	**Variance inflation factor (VIF)**
Age	1.83
Sex	1.14
race	1.33
Marital status	1.14
Region	1.04
Education	1.27
Income	1.09
Labor	1.46
Social deprivation index	1.29
Drink	1.11
Smoking	1.27
Active	1.09
Bmi	1.13
Diabetes	1.12
Hypertension	1.15
Heart disease	1.12
Depression	1.15

Supplemental Table 2. 3. Insomnia symptom trajectories model selection

Group	Model	BIC (N=74,671)	BIC (N=31,126)	*2ΔBIC*	Group %	Trajectory
1	Zero Inflated Poisson	-143145.8	-143139.7		100%	Cubic
2	Zero Inflated Poisson	-143023.8	-143015.5	248.4	44.8-55.2	Cubic
3	Zero Inflated Poisson	-143051.8	-143041.3	51.6	20.5-46.4-33.1	Cubic
4	Zero Inflated Poisson	-143038.3	-143025.7	-31.2	7.8-40.5-25.9-25.8	Cubic

Supplemental Table 2. 4. Incidence of stroke by individual insomnia symptoms

	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)
Difficulty initiating sleep				
Most of the time	1.56 (1.38, 1.76)	1.68 (1.49, 1.90)	1.53 (1.34, 1.74)	1.52 (1.32, 1.74)
Sometimes	1.16 (1.05, 1.27)	1.22 (1.11, 1.35)	1.18 (1.07, 1.31)	1.17 (1.05, 1.31)
Rarely or never	Ref	Ref	Ref	Ref
Difficulty maintaining sleep				
Most of the time	1.41 (1.26, 1.57)	1.32 (1.18, 1.48)	1.31 (1.17, 1.47)	1.26 (1.12, 1.42)
Sometimes	1.15 (1.04, 1.27)	1.07 (0.97, 1.19)	1.09 (0.98, 1.21)	1.04 (0.93, 1.16)
Rarely or never	Ref	Ref	Ref	Ref
Waking up too early				
Most of the time	1.41 (1.24, 1.59)	1.42 (1.26, 1.61)	1.31 (1.15, 1.50)	1.26 (1.10, 1.46)
Sometimes	1.12 (1.02, 1.23)	1.11 (1.00, 1.22)	1.11 (1.00, 1.22)	1.09 (0.98, 1.22)
Rarely or never	Ref	Ref	Ref	Ref
Restorative sleep				
Most of the time	Ref	Ref	Ref	Ref
Sometimes	0.97 (0.88, 1.07)	1.12 (1.01, 1.24)	1.09 (0.98, 1.21)	1.01 (0.90, 1.13)
Rarely or never	1.09 (0.97, 1.24)	1.36 (1.20, 1.53)	1.25 (1.10, 1.43)	1.22 (1.07, 1.40)

- Model 1: adjusted for demographic factors (age, sex, race/ethnicity, marital status, 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, physical activity)

Supplemental Table 2. 5. Incidence of stroke by insomnia symptom scores (scale 4 and scale 8)

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)	**Model 4 HR, 95% CI** (n=27,235)	**Model 5 HR, 95% CI** (n=25,541)
Insomnia symptom scale 0-8						
1 unit increase	1.07 (1.05, 1.09)	1.09 (1.07, 1.11)	1.07 (1.05, 1.10)	1.07 (1.04, 1.09)	1.05 (1.03, 1.08)	1.04 (1.01, 1.07)
0	Ref	Ref	Ref	Ref	Ref	Ref
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)	1.15 (0.98, 1.35)	1.16 (0.98, 1.37)
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)	1.02 (0.87, 1.20)	1.02 (0.86, 1.21)
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)	1.10 (0.93, 1.30)	1.07 (0.90, 1.27)
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)	1.19 (1.00, 1.42)	1.18 (0.98, 1.41)
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)	1.22 (0.99, 1.50)	1.18 (0.95, 1.46)
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)	1.51 (1.21, 1.87)	1.39 (1.11, 1.75)
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)	1.40 (1.06, 1.85)	1.34 (1.01, 1.80)
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)	1.58 (1.17, 2.14)	1.44 (1.05, 1.99)
0	Ref	Ref	Ref	Ref	Ref	Ref
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)	1.11 (0.97, 1.26)	1.10 (0.96, 1.26)
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)	1.37 (1.17, 1.60)	1.29 (1.09, 1.53)
Insomnia symptom scale 0-4						
1 unit increase	1.09 (1.06, 1.12)	1.11 (1.08, 1.15)	1.10 (1.06, 1.13)	1.08 (1.04, 1.12)	1.06 (1.02, 1.09)	1.04 (1.00, 1.08)
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.20 (1.05, 1.38)	1.16 (1.01, 1.33)	1.19 (1.04, 1.37)	1.17 (1.01, 1.36)	1.13 (0.97, 1.31)	1.14 (0.98, 1.33)
2	1.17 (1.01, 1.34)	1.14 (0.99, 1.32)	1.14 (0.98, 1.32)	1.10 (0.94, 1.29)	1.04 (0.89, 1.22)	1.02 (0.86, 1.20)
3	1.42 (1.24, 1.63)	1.44 (1.26, 1.66)	1.42 (1.23, 1.64)	1.36 (1.16, 1.58)	1.27 (1.08, 1.48)	1.21 (1.03, 1.42)
4	1.41 (1.22, 1.63)	1.54 (1.33, 1.78)	1.45 (1.25, 1.69)	1.36 (1.15, 1.60)	1.24 (1.05, 1.46)	1.19 (1.00, 1.42)
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	1.19 (1.05, 1.34)	1.15 (1.02, 1.30)	1.17 (1.03, 1.33)	1.14 (1.00, 1.31)	1.09 (0.95, 1.25)	1.08 (0.94, 1.25)
3-4	1.42 (1.25, 1.60)	1.48 (1.31, 1.68)	1.43 (1.26, 1.63)	1.36 (1.18, 1.56)	1.25 (1.09, 1.44)	1.20 (1.04, 1.40)

- Model 1: adjusted for demographic factors (age, sex, race/ethnicity, marital status, 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, physical activity)
- Model 4: adjusted for model 3 + diabetes, hypertension, heart disease.
- Model 5: adjusted for model 4 + depression

Supplemental Table 2. 6. Incidence of stroke by insomnia symptoms excluding proxy report

Insomnia symptoms score	**Unadjusted HR, 95% CI** (n=29,045)	**Model 1 HR, 95% CI** (n=31,046)	**Model 2 HR, 95% CI** (n=27,512)	**Model 3 HR, 95% CI** (n= 25,589)
1 unit increase	1.07 (1.05, 1.10)	1.09 (1.07, 1.12)	1.08 (1.05, 1.10)	1.07 (1.04, 1.09)
0	Ref	Ref	Ref	Ref
1	1.20 (1.03, 1.40)	1.16 (1.00, 1.36)	1.21 (1.04, 1.42)	1.21 (1.02, 1.43)
2	1.12 (0.96, 1.31)	1.09 (0.94, 1.27)	1.08 (0.92, 1.26)	1.07 (0.90, 1.28)
3	1.21 (1.03, 1.41)	1.17 (1.00, 1.38)	1.19 (1.01, 1.40)	1.17 (0.98, 1.40)
4	1.39 (1.19, 1.64)	1.41 (1.20, 1.66)	1.36 (1.14, 1.61)	1.28 (1.07, 1.54)
5	1.44 (1.19, 1.74)	1.48 (1.23, 1.79)	1.42 (1.16, 1.73)	1.33 (1.08, 1.64)
6	1.62 (1.31, 1.99)	1.71 (1.39, 2.11)	1.69 (1.36, 2.10)	1.67 (1.33, 2.10)
7	1.71 (1.33, 2.20)	1.95 (1.52, 2.50)	1.66 (1.27, 2.18)	1.58 (1.19, 2.10)
8	1.82 (1.37, 2.41)	2.16 (1.63, 2.87)	1.88 (1.39, 2.54)	1.80 (1.32, 2.47)
0	Ref	Ref	Ref	Ref
1-4	1.22 (1.08, 1.37)	1.19 (1.05, 1.34)	1.19 (1.05, 1.36)	1.17 (1.02, 1.34)
5-8	1.58 (1.37, 1.83)	1.69 (1.46, 1.96)	1.58 (1.36, 1.84)	1.52 (1.29, 1.79)

- Model 1: adjusted for demographic factors (age, sex, race/ethnicity, marital status, 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, physical activity)

Supplemental Table 2. 7. Incidence of stroke by insomnia symptoms excluding participants included in 2016

Insomnia symptoms score	**Unadjusted HR, 95% CI** (n=26,811)	**Model 1 HR, 95% CI** (n=26,746)	**Model 2 HR, 95% CI** (n=25,184)	**Model 3 HR, 95% CI** (n= 23,081)
1 unit increase	1.07 (1.05, 1.09)	1.09 (1.06, 1.11)	1.07 (1.05, 1.09)	1.06 (1.04, 1.09)
0	Ref	Ref	Ref	Ref
1	1.20 (1.04, 1.39)	1.17 (1.01, 1.36)	1.23 (1.05, 1.43)	1.20 (1.02, 1.41)
2	1.11 (0.96, 1.29)	1.09 (0.94, 1.26)	1.08 (0.92, 1.26)	1.05 (0.89, 1.24)
3	1.20 (1.03, 1.40)	1.18 (1.01, 1.37)	1.20 (1.02, 1.41)	1.17 (0.99, 1.39)
4	1.39 (1.19, 1.63)	1.41 (1.21, 1.65)	1.36 (1.15, 1.60)	1.26 (1.05, 1.50)
5	1.41 (1.17, 1.70)	1.46 (1.21, 1.75)	1.41 (1.16, 1.71)	1.30 (1.06, 1.60)
6	1.64 (1.34, 2.01)	1.74 (1.42, 2.13)	1.74 (1.41, 2.15)	1.72 (1.38, 2.15)
7	1.67 (1.30, 2.14)	1.86 (1.45, 2.39)	1.63 (1.24, 2.13)	1.54 (1.16, 2.05)
8	1.65 (1.24, 2.20)	1.90 (1.42, 2.54)	1.67 (1.23, 2.27)	1.57 (1.13, 2.17)
0	Ref	Ref	Ref	Ref
1-4	1.21 (1.08, 1.36)	1.19 (1.06, 1.34)	1.20 (1.06, 1.36)	1.16 (1.02, 1.32)
5-8	1.55 (1.34, 1.78)	1.65 (1.43, 1.90)	1.56 (1.34, 1.81)	1.48 (1.26, 1.74)

- Model 1: adjusted for demographic factors (age, sex, race/ethnicity, marital status, 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, physical activity)

Supplemental Table 2. 8. Incidence of stroke by insomnia symptoms excluding participants with less than 2 years of follow-up (reverse causation)

Insomnia symptoms score	**Unadjusted HR, 95% CI** (n=26,932)	**Model 1 HR, 95% CI** (n=26,868)	**Model 2 HR, 95% CI** (n=25,431)	**Model 3 HR, 95% CI** (n= 23,595)
1 unit increase	1.07 (1.0**4**, 1.09)	1.09 (1.0**6**, 1.11)	1.07 (1.05, 1.10)	1.07 (1.04, 1.09)
0	Ref	Ref	Ref	Ref
1	1.24 (1.06, 1.45)	1.21 (1.03, 1.41)	1.27 (1.07, 1.49)	1.24 (1.04, 1.48)
2	1.09 (0.93, 1.28)	1.06 (0.90, 1.25)	1.06 (0.90, 1.26)	1.06 (0.89, 1.27)
3	1.20 (1.01, 1.41)	1.17 (0.99, 1.39)	1.21 (1.02, 1.44)	1.21 (1.00, 1.45)
4	1.39 (1.18, 1.65)	1.42 (1.20, 1.68)	1.39 (1.16, 1.66)	1.30 (1.07, 1.57)
5	1.43 (1.17, 1.74)	1.48 (1.21, 1.81)	1.47 (1.19, 1.80)	1.39 (1.12, 1.74)
6	1.49 (1.18, 1.87)	1.59 (1.26, 2.00)	1.61 (1.27, 2.05)	1.61 (1.25, 2.06)
7	1.66 (1.27, 2.17)	1.88 (1.43, 2.46)	1.66 (1.24, 2.22)	1.59 (1.16, 2.16)
8	1.77 (1.31, 2.40)	2.09 (1.54, 2.84)	1.89 (1.36, 2.61)	1.81 (1.28, 2.55)
0	Ref	Ref	Ref	Ref
1-4	1.21 (1.07, 1.38)	1.19 (1.05, 1.35)	1.21 (1.06, 1.39)	1.19 (1.03, 1.37)
5-8	1.52 (1.31, 1.78)	1.64 (1.40, 1.91)	1.58 (1.34, 1.86)	1.52 (1.28, 1.81)

- Model 1: adjusted for demographic factors (age, sex, race/ethnicity, marital status, 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, physical activity)

Supplemental Table 2. 9. Incidence of stroke by insomnia symptoms controlled for cohort entry year

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)
1 unit increase	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
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, 1.28)	1.09 (0.93, 1.27)	1.06 (0.90, 1.25)
3	1.21 (1.04, 1.41)	1.19 (1.02, 1.39)	1.21 (1.03, 1.42)	1.19 (1.00, 1.40)
4	1.39 (1.19, 1.63)	1.42 (1.22, 1.66)	1.37 (1.16, 1.61)	1.27 (1.07, 1.51)
5	1.42 (1.18, 1.70)	1.48 (1.23, 1.78)	1.42 (1.18, 1.72)	1.32 (1.08, 1.62)
6	1.61 (1.32, 1.97)	1.73 (1.41, 2.12)	1.72 (1.40, 2.13)	1.70 (1.37, 2.12)
7	1.65 (1.29, 2.10)	1.88 (1.50, 2.40)	1.64 (1.26, 2.13)	1.55 (1.17, 2.05)
8	1.82 (1.39, 2.39)	2.15 (1.64, 2.82)	1.90 (1.43, 2.53)	1.81 (1.34, 2.45)
0	Ref	Ref	Ref	Ref
1-4	1.22 (1.08, 1.37)	1.20 (1.07, 1.35)	1.21 (1.07, 1.36)	1.17 (1.02, 1.33)
5-8	1.56 (1.36, 1.79)	1.68 (1.46, 1.94)	1.59 (1.37, 1.85)	1.52 (1.30, 1.77)

- Model 1': adjusted for demographic factors (age, sex, race/ethnicity, marital status, region) and cohort entry year
- 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, physical activity.

Supplemental Table 2. 10. Incidence of stroke by insomnia symptoms controlled for variable with p<.05 or Change In Estimate ≥10

Insomnia symptoms score	**Model 3''** **HR, 95% CI** (n= 27,268)	**Model 4''** **HR, 95% CI** (n= 27,235)	**Model 5''** **HR, 95% CI** (n= 25,541)
1 unit increase	1.07 (1.04, 1.09)	1.05 (1.03, 1.08)	1.04 (1.01, 1.07)
0	Ref	Ref	Ref
1	1.20 (1.02, 1.41)	1.15 (0.98, 1.35)	1.16 (0.98, 1.37)
2	1.06 (0.90, 1.25)	1.02 (0.87, 1.20)	1.02 (0.86, 1.21)
3	1.18 (1.00, 1.40)	1.10 (0.93, 1.30)	1.07 (0.90, 1.27)
4	1.27 (1.06, 1.51)	1.19 (1.00, 1.42)	1.18 (0.98, 1.41)
5	1.33 (1.08, 1.63)	1.22 (0.99, 1.50)	1.18 (0.95, 1.46)
6	1.70 (1.37, 2.11)	1.51 (1.21, 1.87)	1.39 (1.11, 1.75)
7	1.55 (1.17, 2.04)	1.39 (1.05, 1.85)	1.34 (1.01, 1.80)
8	1.82 (1.34, 2.46)	1.59 (1.17, 2.15)	1.45 (1.05, 2.00)
0	Ref	Ref	Ref
1-4	1.17 (1.03, 1.33)	1.11 (0.97, 1.26)	1.10 (0.96, 1.26)
5-8	1.52 (1.30, 1.78)	1.37 (1.17, 1.60)	1.29 (1.09, 1.53)

- Model 3'': adjusted for age, sex, race/ethnicity, marital status, region, education, household income, employment status, social deprivation index, alcohol consumption, smoking, physical activity.
- Model 4'': adjusted for model 3'' + diabetes, hypertension, cardiovascular disease.
- Model 5'': adjusted for model 4'' + depression.

Supplemental Table 2. 11. Incidence of stroke by insomnia symptoms controlled for variables significant in the presence of others (manual backward selection)

Insomnia symptoms score	Considering only confounders	Considering all variables
	Model 6 **HR, 95%** (n= 27,368)	**Model 7** **HR, 95% CI** (n= 25,655)
1 unit increase	1.07 (1.04, 1.09)	1.04 (1.02, 1.07)
0	Ref	Ref
1	1.19 (1.01, 1.39)	1.15 (0.98, 1.37)
2	1.06 (0.90, 1.25)	1.03 (0.87, 1.22)
3	1.19 (1.01, 1.41)	1.09 (0.91, 1.29)
4	1.25 (1.05, 1.50)	1.18 (0.99, 1.42)
5	1.30 (1.06, 1.59)	1.18 (0.95, 1.46)
6	1.68 (1.35, 2.09)	1.40 (1.11, 1.76)
7	1.53 (1.15, 2.02)	1.35 (1.01, 1.81)
8	1.80 (1.33, 2.43)	1.46 (1.06, 2.01)
0	Ref	Ref
1-4	1.16 (1.02, 1.32)	1.11 (0.96, 1.27)
5-8	1.50 (1.28, 1.75)	1.30 (1.10, 1.54)

- Model 6: adjusted for age, sex, race/ethnicity, income, employment status, social deprivation index, smoking, BMI, physical activity.
- Model 7: adjusted for age, sex, race/ethnicity, employment status, social deprivation index, smoking, diabetes, Hypertension, heart disease, depression.

Supplemental Table 2. 12. Incidence of stroke by insomnia symptoms controlled for sleep disorder other than insomnia (obstructive sleep apnea, restless leg syndrome and narcolepsy, 2016-2020 cohort)

Insomnia symptoms score	Unadjusted HR, 95 % CI (n=18,986)	Adjusted for sleep disorder other than insomnia HR, 95 % CI (n=18,917)	Adjusted for demographic, SES, and behavioral risk factors HR, 95 % CI (n=17,910)	Adjusted for demographic, SES, and behavioral risk factors + sleep disorder other than insomnia HR, 95 % CI (n=17,910)
1 unit increase	1.02 (0.98, 1.07)	1.02 (0.97, 1.07)	1.03 (0.97, 1.08)	1.02 (0.97, 1.07)
0	Ref	Ref	Ref	Ref
1-4	1.00 (0.75, 1.33)	0.99 (0.74, 1.31)	0.99 (0.73, 1.35)	0.96 (0.71, 1.30)
5-8	1.11 (0.80, 1.54)	1.06 (0.76, 1.48)	1.17 (0.82, 1.66)	1.10 (0.77, 1.58)

Insomnia symptoms score	Adjusted for demographic, SES, behavioral risk factors and comorbidities HR, 95 % CI (n=17,210)	Adjusted for demographic, SES, behavioral risk factors and comorbidities + sleep disorder other than insomnia HR, 95 % CI (n=17,210)	Adjusted for demographic, SES, behavioral risk factors after excluding participants with sleep disorders other than insomnia HR, 95 % CI (n=15,590)	Adjusted for demographic, SES, behavioral risk factors and comorbidities after excluding participants with sleep disorders other than insomnia HR, 95 % CI (n=14,974)
1 unit increase	1.00 (0.95, 1.06)	1.00 (0.94, 1.05)	1.00 (0.95, 1.06)	0.97 (0.91, 1.04)
0	Ref	Ref	Ref	Ref
1-4	0.96 (0.70, 1.32)	0.93 (0.68, 1.28)	0.87 (0.63, 1.19)	0.79 (0.57, 1.11)
5-8	1.02 (0.70, 1.49)	0.97 (0.66, 1.43)	1.03 (0.70, 1.52)	0.85 (0.56, 1.29)

Comorbidities: diabetes, hypertension, heart disease, depression.

Supplemental Table 2. 13. Mediation of the association between insomnia symptoms and incident stroke (obesity and physical activity)

Mediator	Insomnia symptom score	Total Effect	Direct Effect	Indirect Effect	% Mediated
Obesity (BMI≥30)	0	Ref	Ref	Ref	Ref
	1-4	1.16 (1.06, 1.31)	1.16 (1.05, 1.26)	1.00 (0.95, 1.09)	2.90
	5-8	1.52 (1.35, 1.70)	1.50 (1.31, 1.60)	1.01 (0.98, 1.11)	3.31
Physical activity	0	Ref	Ref	Ref	Ref
	1-4	1.18(1.06, 1.31)	1.16(1.05, 1.26)	1.01 (0.95, 1.09)	5.24
	5-8	1.53(1.35, 1.70)	1.50(1.31, 1.60)	1.02 (0.98, 1.11)	6.85

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

Appendix B. Chapter 3: Insomnia symptoms and all-cause mortality among stroke survivors.

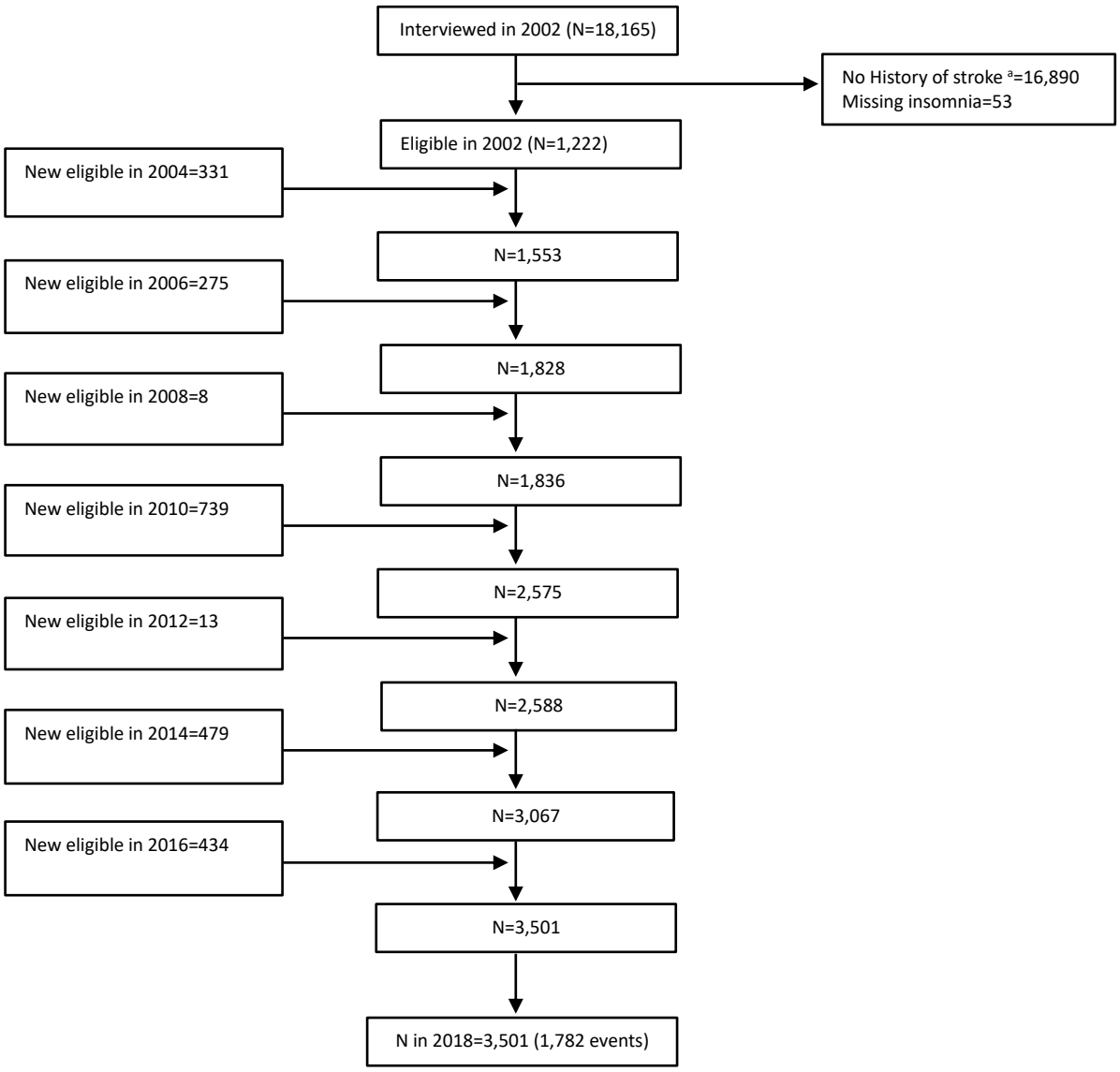


Figure 3. 1. Flowchart of stroke survivors' inclusion process.

[a] Transient ischemic attack (TIA), unknown stroke status (don't know, refuse), have never been told that they had a stroke.
[b] Missing stroke year: did not provide the year of stroke occurrence.
New eligible are participants who were not in the initial interview of 2002 or participants who developed a stroke later and became eligible.
Insomnia symptoms were assessed at the participant study entry period.

Table 3. 1. Baseline characteristics of stroke survivors by insomnia symptom scores

		Insomnia symptom scores		
Variable	Total n (%) (n=3,501)	0 n (%) 517 (14.8)	1-4 n (%) 2003 (57.2)	5-8 n (%) 981 (28.0)
Age (in Years)				
Mean (SD)	**71.0 (12.1)**	72.6 (11.6)	71.9 (12.0)	67.7 (12.3)
Median	**72.0**	73.0	73.0	67.0
Q1, Q3	**61.0, 80.0**	64.0, 82.0	62.0, 81.0	57.0, 78.0
Age group				
<50	**66 (1.9)**	7 (1.3)	30 (1.5)	29 (2.9)
50-64	**1100 (31.4)**	121 (23.4)	564 (28.2)	415 (42.3)
65-74	**875 (25.0)**	158 (30.6)	493 (24.6)	224 (22.8)
75-84	**933 (26.7)**	142 (27.5)	580 (28.9)	211 (21.5)
>=85	**527 (15.0)**	89 (17.2)	336 (16.8)	102 (10.4)
Sex				
Male	**1576 (45.0)**	284 (54.9)	933 (46.6)	359 (36.6)
Female	**1925 (55.0)**	233 (45.3)	1070 (53.4)	622 (63.4)
Race/ethnicity				
Non-Hispanic White	**2263 (64.6)**	349 (67.5)	1312 (65.5)	602 (61.4)
Non-Hispanic Black	**784 (22.4)**	112 (21.7)	438 (21.9)	234 (23.9)
Hispanic	**353 (10.1)**	41 (7.9)	203 (10.1)	109 (11.0)
Non-Hispanic Other	**100 (2.9)**	15 (2.9)	49 (2.5)	36 (3.7)
Missing	**1**			
Education				
Lt High school	**1064 (30.4)**	136 (26.4)	607 (30.3)	321 (32.7)
HS graduate/GED	**1226 (35.0)**	170 (33.0)	724 (36.1)	332 (33.8)
Some college	**741 (21.2)**	119 (23.0)	396 (19.8)	226 (23.0)
College and above	**469 (13.4)**	91 (17.6)	276 (13.8)	102 (10.4)
Missing	**1**			
Household income ($US) [a]				
Mean	**38986.8**	46,474.1	39,088.7	36,085.4
SD	**72106.0**	78,795.5	86,868.9	77,377.9
Median	**23448.0**	28,090.5	23,894.0	20,628.0
Q1	**12500.0**	14,544.0	13,080.0	11,310.0
Q3	**43800.0**	54,467.1	43,798.0	37,622.0
Marital status				
Married/Partnered	**1885 (53.9)**	289 (56.0)	1104 (55.1)	492 (50.3)
Separate/divorced	**467 (13.4)**	58 (11.2)	218 (10.9)	191 (19.5)
Widowed	**987 (28.2)**	152 (29.5)	591 (29.5)	244 (24.5)
Never married	**158 (4.5)**	17 (3.3)	90 (4.5)	51 (5.2)
Missing	**4**			
Region of the U.S [b]				
Northeast	**521 (14.9)**	83 (16.1)	296 (14.8)	142 (14.5)
Midwest	**776 (22.2)**	116 (22.4)	463 (23.1)	197 (20.1)
South	**1607 (45.9)**	230 (44.5)	901 (45.0)	476 (48.5)
West	**596 (17.0)**	88 (17.0)	342 (17.1)	166 (16.9)
Missing	**1**			
Labor Force				
Works full time	**279 (8.0)**	51 (9.9)	165 (8.2)	63 (6.4)
Works PT/partly retired	**221 (6.3)**	35 (6.8)	128 (6.4)	58 (5.9)
Retired	**2300 (65.7)**	350 (66.7)	1327 (66.3)	623 (63.5)
Unemployed/disabled	**393 (11.2)**	41 (7.9)	209 (10.4)	143 (14.6)
Not in work force	**308 (8.8)**	40 (7.7)	174 (8.7)	94 (9.6)
Smoking status				
Never	**1888 (56.8)**	306 (61.7)	1114 (58.4)	468 (50.7)
Former	**980 (29.5)**	140 (28.2)	570 (29.9)	270 (29.2)
Current	**459 (13.8)**	50 (10.1)	223 (11.7)	186 (20.1)
Missing	**174**			

Number of days/week drink				
0	2734 (78.3)	391 (76.1)	1557 (77.9)	786 (80.3)
1-3	509 (14.6)	87 (16.9)	296 (14.8)	126 (12.9)
4-7	248 (7.1)	36 (7.0)	145 (7.3)	67 (6.8)
Missing	10			
Vigorous physical activity >1/week				
No	2945 (84.3)	406 (79.0)	1672 (83.6)	867 (88.6)
Yes	548 (16.7)	108 (21.0)	328 (16.4)	112 (11.4)
Missing	8			
BMI group				
Underweight (BMI≤18.4)	157 (4.5)	19 (3.7)	99 (4.9)	39 (4.0)
Healthy weight (18.5-24.9)	1127 (32.2)	192 (37.1)	659 (32.9)	276 (28.1)
Overweight (25-29.9)	1222 (34.9)	197 (38.1)	707 (35.3)	318 (32.4)
Obese (BMI≥30)	995 (28.4)	109 (21.1)	538 (27.0)	348 (35.5)
Social deprivation Index (SDI)[c]				
First quartile	795 (24.5)	138 (28.8)	473 (25.6)	184 (20.2)
Second quartile	812 (25.1)	116 (24.2)	476 (25.7)	220 (24.2)
Third quartile	816 (25.2)	112 (23.4)	448 (24.2)	256 (28.1)
Forth quartile	818 (25.2)	113 (23.6)	454 (24.5)	251 (27.5)
Missing	260			
Depression (CESD-7)				
No (0-3)	2192 (75.8)	365 (92.9)	1354 (82.0)	473 (55.9)
Yes (4-7)	699 (24.2)	28 (7.1)	298 (18.0)	373 (44.1)
Missing	610			
Diabetes				
No	2347 (67.1)	357 (69.1)	1382 (69.0)	608 (62.0)
Yes	1153 (32.9)	160 (30.9)	620 (31.0)	373 (38.0)
Missing	1			
Hypertension				
No	729 (20.9)	135 (26.3)	416 (20.8)	178 (18.2)
Yes	2759 (79.1)	378 (73.7)	1580 (79.2)	801 (81.8)
Missing	13			
Heart disease [d]				
No	1816 (52.0)	313 (60.7)	1069 (53.5)	434 (44.4)
Yes	1677 (48.0)	203 (39.3)	930 (46.5)	544 (55.6)
Missing	8			
Cancer				
No	2885 (82.4)	438 (84.7)	1663 (83.1)	774 (79.9)
Yes	615 (17.6)	79 (15.3)	339 (16.9)	197 (20.1)
Missing	1			
Lung disease				
No	2934 (83.8)	466 (90.3)	1736 (86.7)	732 (74.7)
Yes	565 (16.2)	50 (9.7)	267 (13.3)	248 (25.3)
Missing	2			

[a] Respondent and Spouse only; [b] Northeast + Other(N=6); [c] SDI index include 7 measures (percent population with <100% FPL, percent population with less than 12 years of education, percent non-employed, percent population living in renter-occupied housing units, percent population living in crowded housing units, percent 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

Table 3. 2. Association of insomnia symptom scores with all-cause mortality among stroke survivors

Insomnia symptoms score	**Unadjusted HR, 95% CI** (n=3,501)	**Model 1 HR, 95% CI** (n=3,495)	**Model 2 HR, 95% CI** (n=3,235)	**Model 3 HR, 95% CI** (n= 3,067)
1 unit increase	0.98 (0.96, 1.00)	1.03 (1.01, 1.05)	1.02 (1.00, 1.05)	1.02 (1.00, 1.04)
0	Ref	Ref	Ref	Ref
1	1.05 (0.89, 1.24)	1.04 (0.88, 1.23)	1.08 (0.91, 1.29)	1.08 (0.90, 1.30)
2	0.95 (0.80, 1.11)	0.93 (0.79, 1.10)	0.95 (0.80, 1.13)	0.88 (0.74, 1.06)
3	0.89 (0.75, 1.05)	0.92 (0.77, 1.09)	0.87 (0.73, 1.05)	0.86 (0.71, 1.04)
4	1.00 (0.84, 1.19)	1.06 (0.89, 1.26)	1.09 (0.91, 1.31)	1.02 (0.85, 1.24)
5	0.85 (0.69, 1.03)	1.02 (0.84, 1.25)	0.93 (0.75, 1.16)	0.93 (0.75, 1.16)
6	0.93 (0.76, 1.13)	1.22 (1.00, 1.49)	1.01 (0.82, 1.24)	1.15 (0.92, 1.44)
7	1.01 (0.80, 1.29)	1.23 (0.96, 1.56)	1.17 (0.95, 1.45)	1.14 (0.88, 1.48)
8	0.79 (0.61, 1.03)	1.23 (0.94, 1.60)	1.21 (0.91, 1.59)	1.22 (0.91, 1.63)
0	Ref	Ref	Ref	Ref
1-4	0.97 (0.85, 1.10)	0.98 (0.86, 1.12)	0.99 (0.86, 1.14)	0.95 (0.83, 1.10)
5-8	0.89 (0.77, 1.03)	1.15 (0.99, 1.33)	1.12 (0.96, 1.31)	1.07 (0.91, 1.27)

- Model 1: adjusted for demographic factors (age, sex, race/ethnicity, marital status, 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, physical activity) and lung disease and time since stroke occurrence.

Table 3. 3. Association of insomnia symptom scores with all-cause mortality among stroke survivors stratified by age and sex.

		History of Stroke	**p-value of interaction**
Stratification variable	Insomnia symptom scales	HR, 95 % CI	
Age < 65	n 1 unit increase 0 1-4 5-8	1,024 1.07 (1.01, 1.13) Ref 1.16 (0.74, 1.83) 1.35 (0.83, 2.18)	0.0439
Age ≥65	n 1 unit increase 0 1-4 5-8	2,043 1.00 (0.97, 1.02) Ref 1.01 (0.87, 1.18) 1.01 (0.85, 1.21)	
Male	n 1 unit increase 0 1-4 5-8	1,383 1.05 (1.01, 1.09) Ref 1.01 (0.82, 1.25) 1.28 (1.01, 1.63)	0.0996
Female	N 1 unit increase 0 1-4 5-8	1,684 1.00 (0.97, 1.03) Ref 0.89 (0.73, 1.09) 0.94 (0.75, 1.18)	
Male < 65	n 1 unit increase 0 1-4 5-8	478 1.12 (1.02, 1.23) Ref 1.55 (0.82, 2.91) 2.24 (1.09, 4.58)	0.0995
Male ≥ 65	n 1 unit increase 0 1-4 5-8	905 1.04 (1.00, 1.08) Ref 1.14 (0.92, 1.43) 1.26 (0.97, 1.65)	
Female < 65	n 1 unit increase 0 1-4 5-8	546 1.06 (0.97, 1.16) Ref 0.89 (0.43, 1.84) 0.93 (0.44, 1.98)	
Female ≥ 65	n 1 unit increase 0 1-4 5-8	1138 0.97 (0.93, 1.00) Ref 0.89 (0.72, 1.11) 0.84 (0.66, 1.08)	

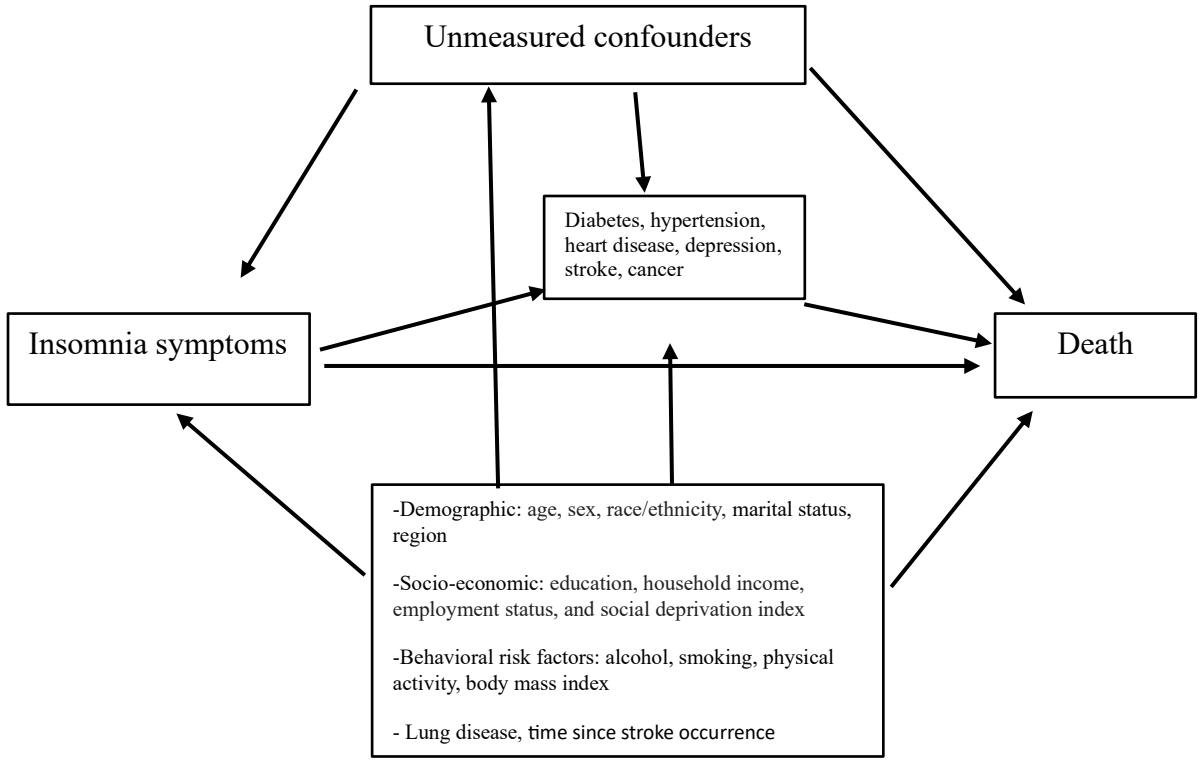
Model adjusted for: race/ethnicity, region, marital status, education, income, employment, social deprivation index, alcohol consumption, smoking, body mass index, physical activity, lung disease, and time since stroke occurrence.

Table 3. 4. Association of individual insomnia symptom with all-cause mortality among stroke survivors stratified by age and sex.

	Male < 65 HR, 95% CI (n= 478)	**Male ≥ 65** HR, 95% CI (n= 905)	**Female < 65** HR, 95% CI (n= 546)	**Female ≥ 65** HR, 95% CI (n= 1,138)
Difficulty initiating sleep				
Most of the time	2.19 (1.31, 3.65)	1.10 (0.87, 1.40)	1.32 (0.81, 2.14)	0.92 (0.76, 1.12)
Sometimes	1.01 (0.57, 1.77)	1.05 (0.86, 1.29)	1.26 (0.77, 2.05)	0.76 (0.64, 0.91)
Rarely or never	Ref	Ref	Ref	Ref
Difficulty maintaining sleep				
Most of the time	2.13 (1.27, 3.60)	1.00 (0.82, 1.23)	1.32 (0.80, 2.20)	0.80 (0.66, 0.98)
Sometimes	1.39 (0.83, 2.31)	0.98 (0.80, 1.19)	1.53 (0.94, 2.50)	0.80 (0.67, 0.95)
Rarely or never	Ref	Ref	Ref	Ref
Waking up too early				
Most of the time	1.21 (0.71, 2.04)	1.30 (1.04, 1.63)	1.24 (0.77, 2.00)	0.96 (0.78, 1.18)
Sometimes	0.84 (0.52, 1.37)	0.96 (0.79, 1.17)	0.95 (0.59, 1.55)	0.76 (0.63, 0.90)
Rarely or never	Ref	Ref	Ref	Ref
Restorative sleep				
Most of the time	Ref	Ref	Ref	Ref
Sometimes	0.98 (0.61, 1.58)	1.38 (1.13, 1.69)	1.07 (0.67, 1.73)	1.07 (0.89, 1.28)
Rarely or never	1.25 (0.71, 2.18)	1.28 (1.03, 1.59)	1.41 (0.87, 2.29)	0.99 (0.81, 1.21)

Model adjusted for: race/ethnicity, region, marital status, education, income, employment, social deprivation index, alcohol consumption, smoking, body mass index, physical activity, lung disease and time since stroke occurrence.

Supplemental material



Supplemental Figure 3. 1. Directed Acyclic Graph illustrating the pathways on the association between insomnia symptoms and all-cause mortality.

Supplemental Table 3. 2. Cause of death

Cause of death	N (%)
Death was expected	
Yes	1107 (61.8)
No	624 (34.8)
Other	48 (2.7)
Don't know	12 (0.7)
Missing	1710
Duration of final illness/death	
One or two hours	137 (7.7)
Less than a day	136 (7.6)
Less than a week	335 (18.7)
Less than a month	350 (19.7)
Less than a year	409 (22.8)
More than a year	385 (21.5)
Don't know	38 (2.1)
Refuse	1 (0.1)
Missing	1710
Cause of death (major illness that led to death)	
Cancers and tumors; skin condition	251 (14.0)
Musculoskeletal system and connective tissue	30 (1.7)
Heart, circulatory and blood conditions	699 (39.0)
Allergies; hay fever; sinusitis; tonsillitis	206 (11.5)
Endocrine, metabolic and nutritional conditions	60 (3.4)
Digestive system (stomach, liver, gallbladder, kidney, bladder)	132 (7.4)
Neurological and sensory conditions	53 (3.0)
Reproductive system and prostate conditions	3 (0.2)
Emotional and psychological conditions	4 (0.2)
Miscellaneous	11 (0.6)
Other symptoms	115 (6.4)
Not A Health Condition	10 (0.6)
None	2 (0.1)
Other health condition	166 (9.3)
(Don't Know); NA (Not Ascertained)	47 (2.6)
RF (Refused)	2 (0.1)
Missing	1710

Supplemental Table 3. 3. Variance inflation factor (VIF)

Variable	**Variance inflation factor (VIF)**
Age	1.73
Sex	1.20
race	1.29
Marital status	1.22
Region	1.03
Education	1.15
Income	1.14
Labor	1.32
Social deprivation index	1.28
Drink	1.10
Smoking	1.22
Active	1.07
Bmi	1.18
Diabetes	1.13
Hypertension	1.06
Heart disease	1.07
Depression	1.12
Cancer	1.04
Lung disease	1.09

Supplemental Table 3. 4. Association of individual insomnia symptoms with all-cause mortality among stroke survivors.

	Unadjusted HR, 95% CI (n=3,501)	**Model 1 HR, 95% CI** (n=3,495)	**Model 2 HR, 95% CI** (n=3,235)	**Model 3 HR, 95% CI** (n= 3,067)
Difficulty initiating sleep				
Most of the time	0.90 (0.80, 1.01)	1.16 (1.03, 1.31)	1.14 (1.00, 1.29)	1.10 (0.96, 1.25)
Sometimes	0.87 (0.78, 0.98)	0.93 (0.83, 1.04)	0.92 (0.81, 1.03)	0.89 (0.78, 1.00)
Rarely or never	Ref	Ref	Ref	Ref
Difficulty maintaining sleep				
Most of the time	0.93 (0.83, 1.05)	0.98 (0.88, 1.11)	0.99 (0.87, 1.11)	0.99 (0.87, 1.13)
Sometimes	1.01 (0.90, 1.12)	0.93 (0.84, 1.04)	0.90 (0.80, 1.01)	0.92 (0.82, 1.04)
Rarely or never	Ref	Ref	Ref	Ref
Waking up too early				
Most of the time	0.94 (0.83, 1.06)	1.13 (1.00, 1.28)	1.11 (0.97, 1.26)	1.11 (0.97, 1.27)
Sometimes	0.89 (0.80, 0.99)	0.91 (0.81, 1.01)	0.89 (0.79, 0.99)	0.87 (0.77, 0.98)
Rarely or never	Ref	Ref	Ref	Ref
Restorative sleep				
Most of the time	Ref	Ref	Ref	Ref
Sometimes	1.00 (0.90, 1.12)	1.21 (1.09, 1.36)	1.21 (1.07, 1.36)	1.19 (1.05, 1.34)
Rarely or never	0.98 (0.87, 1.10)	1.30 (1.15, 1.46)	1.25 (1.10, 1.41)	1.20 (1.05, 1.37)

- Model 1: adjusted for demographic factors (age, sex, race/ethnicity, marital status, 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, physical activity) + lung disease and, time since stroke occurrence

Supplemental Table 3. 5. Association of insomnia symptoms scale 0-4 with all-cause mortality among stroke survivors.

Insomnia symptoms score	**Unadjusted HR, 95% CI** (n=3,501)	**Model 1 HR, 95% CI** (n=3,495)	**Model 2 HR, 95% CI** (n=3,235)	**Model 3 HR, 95% CI** (n= 3,067)
0	Ref	Ref	Ref	Ref
1	1.04 (0.90, 1.22)	1.03 (0.89, 1.20)	1.07 (0.92, 1.26)	1.03 (0.88, 1.22)
2	0.93 (0.79, 1.08)	0.95 (0.81, 1.11)	0.95 (0.80, 1.12)	0.91 (0.77, 1.08)
3	0.88 (0.75, 1.03)	0.99 (0.84, 1.16)	0.98 (0.83, 1.16)	0.93 (0.78, 1.10)
4	0.92 (0.79, 1.08)	1.15 (0.98, 1.34)	1.12 (0.94, 1.31)	1.08 (0.91, 1.28)

Supplemental Table 3. 6. Association of insomnia symptom scores with all-cause mortality among stroke survivors (restricted sample)

	Excluding missing stroke year		Excluding proxy	
Insomnia symptoms score	**Unadjusted HR, 95% CI** (n= 2,472)	**Model 3 HR, 95% CI** (n= 2,224)	**Unadjusted HR, 95% CI** (n= 2,900)	**Model 3 HR, 95% CI** (n= 2,550)
1 unit increase	0.98 (0.96, 1.01)	1.03 (1.00, 1.06)	0.99 (0.97, 1.02)	1.02 (1.00, 1.06)
0	Ref	Ref	Ref	Ref
1	1.05 (0.84, 1.32)	1.05 (0.82, 1.34)	1.08 (0.88, 1.32)	1.17 (0.94, 1.46)
2	1.03 (0.83, 1.27)	0.93 (0.73, 1.18)	0.96 (0.78, 1.17)	0.90 (0.73, 1.12)
3	0.91 (0.72, 1.14)	0.88 (0.68, 1.13)	0.95 (0.78, 1.17)	0.92 (0.73, 1.15)
4	1.05 (0.84, 1.32)	1.11 (0.87, 1.42)	1.08 (0.88, 1.32)	1.10 (0.88, 1.37)
5	0.87 (0.67, 1.13)	1.01 (0.76, 1.34)	0.90 (0.71, 1.14)	0.98 (0.76, 1.26)
6	0.98 (0.77, 1.26)	1.15 (0.87, 1.52)	1.04 (0.83, 1.31)	1.32 (1.02, 1.70)
7	1.04 (0.76, 1.41)	1.26 (0.91, 1.76)	1.05 (0.79, 1.39)	1.17 (0.86, 1.60)
8	0.76 (0.55, 1.06)	1.22 (0.85, 1.75)	0.88 (0.65, 1.18)	1.30 (0.94, 1.81)
0	Ref	Ref	Ref	Ref
1-4	1.01 (0.84, 1.20)	0.99 (0.81, 1.20)	1.01 (0.87, 1.19)	1.01 (0.85, 1.20)
5-8	0.92 (0.75, 1.11)	1.13 (0.91, 1.40)	0.96 (0.81, 1.15)	1.16 (0.96, 1.41)

Supplemental Table 3. 7. Association of insomnia symptom scores with all-cause mortality among stroke survivors (restricted sample)

	Excluding 2016 baseline		Reverse causation	
Insomnia symptoms score	**Unadjusted HR, 95% CI** (n= 3,066)	**Model 3 HR, 95% CI** (n= 2,659)	**Unadjusted HR, 95% CI** (n= 2,609)	**Model 3 HR, 95% CI** (n= 2,268)
1 unit increase	0.98 (0.96, 1.00)	1.01 (1.00, 1.04)	0.99 (0.96, 1.01)	1.02 (1.00, 1.05)
0	Ref	Ref	Ref	Ref
1	1.05 (0.89, 1.24)	1.07 (0.89, 1.29)	0.97 (0.80, 1.18)	1.02 (0.83, 1.27)
2	0.96 (0.81, 1.13)	0.89 (0.74, 1.07)	0.88 (0.74, 1.08)	0.83 (0.67, 1.02)
3	0.88 (0.74, 1.05)	0.84 (0.70, 1.02)	0.83 (0.68, 1.01)	0.78 (0.62, 0.97)
4	1.01 (0.85, 1.21)	1.03 (0.85, 1.25)	0.96 (0.78, 1.18)	0.96 (0.77, 1.20)
5	0.83 (0.68, 1.02)	0.91 (0.73, 1.14)	0.83 (0.66, 1.04)	0.90 (0.70, 1.15)
6	0.92 (0.75, 1.13)	1.11 (0.89, 1.40)	0.93 (0.74, 1.17)	1.15 (0.89, 1.48)
7	1.01 (0.80, 1.29)	1.13 (0.86, 1.47)	0.96 (0.72, 1.27)	1.03 (0.75, 1.42)
8	0.80 (0.61, 1.04)	1.20 (0.89, 1.62)	0.82 (0.61, 1.10)	1.25 (0.90, 1.73)
0	Ref	Ref	Ref	Ref
1-4	0.97 (0.85, 1.11)	0.95 (0.82, 1.10)	0.91 (0.78, 1.06)	0.89 (0.75, 1.05)
5-8	0.88 (0.76, 1.03)	1.05 (0.89, 1.24)	0.88 (0.74, 1.04)	1.04 (0.86, 1.26)

Supplemental Table 3. 8. Association of insomnia symptom scores with all-cause mortality among stroke survivors (further adjustment)

Insomnia symptoms score	**Model 4 HR, 95% CI** (n= 2,535)	**Model 5 HR, 95% CI** (n= 2,528)	**Unadjusted HR, 95% CI** (n=3,501)	**Model 3 + cohort entry HR, 95% CI** (n= 3,067)
1 unit increase	1.01 (0.99, 1.04)	1.01 (0.99, 1.03)	0.98 (0.96, 1.00)	1.02 (1.00, 1.04)
0	Ref	Ref	Ref	Ref
1	1.16 (0.93, 1.44)	1.14 (0.91, 1.42)	1.02 (0.86, 1.20)	1.08 (0.90, 1.29)
2	0.87 (0.70, 1.08)	0.85 (0.69, 1.06)	0.93 (0.79, 1.09)	0.88 (0.74, 1.06)
3	0.88 (0.70, 1.10)	0.85 (0.68, 1.06)	0.87 (0.73, 1.04)	0.86 (0.71, 1.04)
4	1.05 (0.84, 1.31)	1.04 (0.83, 1.30)	1.00 (0.83, 1.18)	1.03 (0.85, 1.24)
5	0.92 (0.71, 1.20)	0.92 (0.71, 1.19)	0.86 (0.71, 1.05)	0.93 (0.75, 1.16)
6	1.16 (0.89, 1.50)	1.14 (0.88, 1.48)	0.91 (0.75, 1.11)	1.16 (0.93, 1.45)
7	1.03 (0.75, 1.40)	0.97 (0.70, 1.33)	1.00 (0.78, 1.26)	1.14 (0.87, 1.47)
8	1.14 (0.81, 1.59)	1.07 (0.70, 1.51)	0.78 (0.60, 1.01)	1.22 (0.91, 1.63)
0	Ref	Ref	Ref	Ref
1-4	0.98 (0.82, 1.16)	0.96 (0.80, 1.14)	0.97 (0.84, 1.10)	0.95 (0.83, 1.10)
5-8	1.04 (0.85, 1.28)	1.03 (0.84, 1.26)	0.89 (0.77, 1.03)	1.08 (0.91, 1.27)

Model 4: adjusted for Model 3 + diabetes, heart disease, hypertension, depression
Model 5: adjusted for Model 4 + cancer, lung disease.

Supplemental Table 3. 9. Association of insomnia symptoms score with all-cause mortality among stroke survivors (model selection)

	controlled for variable with p<.05 or Change In Estimate≥10		Manual backward selection	
Insomnia symptoms score	**Model 3a HR, 95% CI** (n= 3,306)	**Model 3b HR, 95% CI** (n= 3,287)	**Model 3c HR, 95% CI** (n= 3,073)	**Model 3d HR, 95% CI** (n= 2,536)
1 unit increase	1.01 (1.00, 1.04)	1.00 (0.98, 1.02)	1.02 (1.00, 1.04)	1.01 (0.98, 1.03)
0	Ref	Ref	Ref	Ref
1	1.00 (0.84, 1.19)	1.01 (0.85, 1.21)	1.06 (0.87, 1.28)	1.14 (0.92, 1.42)
2	0.85 (0.72, 1.01)	0.84 (0.71, 1.00)	0.89 (0.75, 1.06)	0.86 (0.69, 1.06)
3	0.85 (0.71, 1.00)	0.83 (0.69, 0.99)	0.86 (0.71, 1.04)	0.85 (0.68, 1.07)
4	0.96 (0.80, 1.15)	0.94 (0.78, 1.12)	1.04 (0.86, 1.25)	1.04 (0.83, 1.30)
5	0.88 (0.72, 1.08)	0.86 (0.70, 1.07)	0.94 (0.76, 1.17)	0.92 (0.71, 1.18)
6	1.11 (0.90, 1.37)	1.05 (0.85, 1.29)	1.16 (0.93, 1.44)	1.14 (0.88, 1.47)
7	1.02 (0.86, 1.41)	0.99 (0.75, 1.28)	1.16 (0.90, 1.51)	0.98 (0.72, 1.34)
8	1.14 (0.86, 1.50)	1.01 (0.76, 1.35)	1.21 (0.90, 1.61)	1.08 (0.77, 1.51)
0	Ref	Ref	Ref	Ref
1-4	0.89 (0.78, 1.02)	0.89 (0.78, 1.03)	0.95 (0.83, 1.10)	0.96 (0.81, 1.14)
5-8	1.02 (0.87, 1.19)	0.96 (0.82, 1.13)	1.08 (0.92, 1.27)	1.02 (0.83, 1.24)

- Model 3a: adjusted for age, race/ethnicity, marital status, education, household income, employment status, alcohol consumption, smoking, body mass index, physical activity, time since last stroke
- Model 3b: adjusted for age, race/ethnicity, marital status, education, household income, employment status, alcohol consumption, smoking, body mass index, physical activity, diabetes, heart disease, cancer, lung disease, and time since last stroke.
- Model 3c: adjusted for age, sex, employment status, social deprivation index, alcohol consumption, smoking, body mass index, physical activity.
- Model 3d: adjusted for age, sex, race/ethnicity, employment status, social deprivation index, alcohol consumption, smoking, body mass index, physical activity, diabetes, heart disease, depression, cancer, lung disease.

Supplemental Table 3. 10. Association of insomnia symptom scores with heart disease* mortality among stroke survivors

Insomnia symptoms score	**Unadjusted HR, 95% CI** (n=699)	**Model 1 HR, 95% CI** (n=697)	**Model 2 HR, 95% CI** (n=635)	**Model 3 HR, 95% CI** (n= 591)
1 unit increase	1.00 (0.97, 1.04)	1.02 (0.99, 1.06)	1.02 (0.99, 1.06)	1.02 (0.98, 1.06)
0	Ref	Ref	Ref	Ref
1-4	1.03 (0.84, 1.28)	1.04 (0.84, 1.29)	1.04 (0.82, 1.31)	0.97 (0.75, 1.25)
5-8	1.06 (0.84, 1.34)	1.18 (0.93, 1.50)	1.18 (0.91, 1.53)	1.08 (0.81, 1.43)

*Heart, circulatory and blood conditions

Appendix C. Chapter 4: Sleep duration and all-cause mortality among stroke survivors

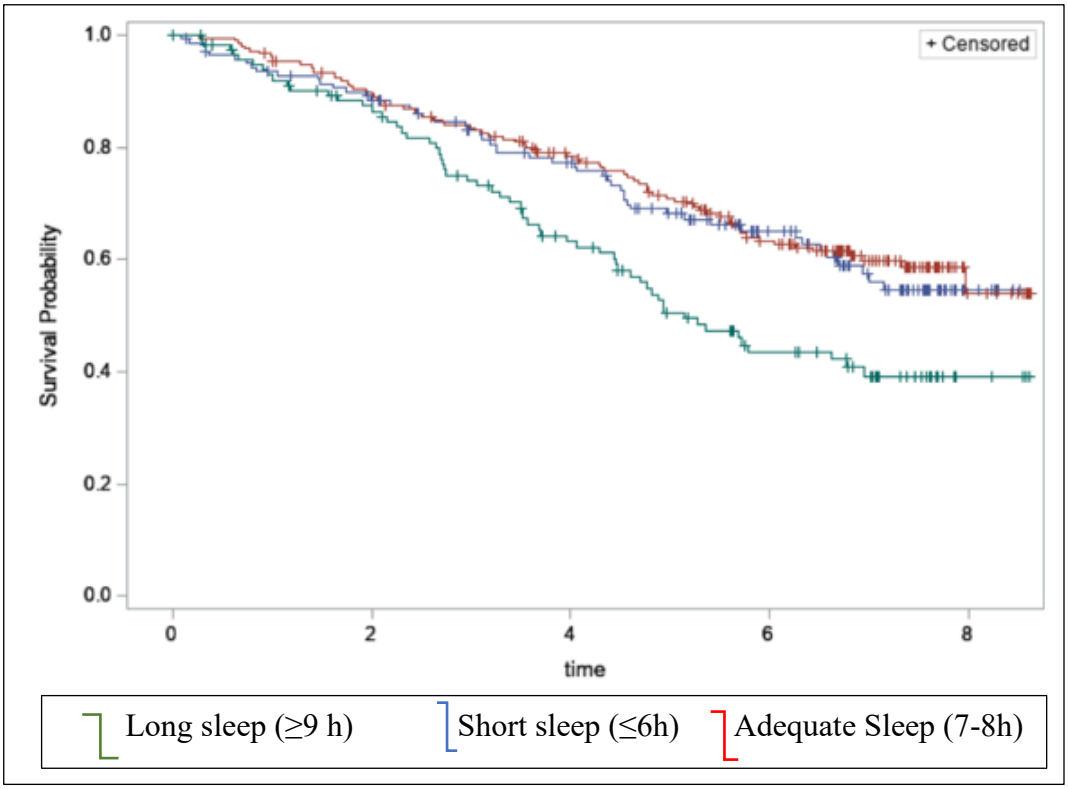


Figure 4. 1. Kaplan-Meir curves for all-cause mortality by sleep duration

Table 4. 1. Baseline characteristics of participants by sleep duration categories

Characteristics	**Total** (n=468)	**Short sleep** (≤ 6 hours) (n=142, 30.3%)	**Adequate sleep** (7.0-8.9 hours) (n=209, 44.7%)	**Long sleep** (≥9 hours) (n=117, 25%)	p-value short sleep vs adequate sleep	p-value long sleep vs adequate sleep
Age (in Years)					0.0335	0.1726
Mean (SD)	76.3 (7.9)	74.7 (7.7)	76.5 (7.8)	77.8 (8.2)		
Median	76.5	74.0	77.0	79.0		
Q1, Q3	70.0, 82.0	70.0, 79.0	70.0, 82.0	72.0, 83.0		
Age group (n, %)					0.0589	0.5600
<50	0	0	0	0		
50-64	27 (5.8)	11 (7.8)	10 (4.8)	6 (5.1)		
65-74	166 (35.5)	63 (44.4)	69 (33.0)	34 (29.1)		
75-84	199 (42.5)	49 (35.5)	98 (46.9)	52 (44.4)		
>=85	76 (16.2)	19 (13.4)	32 (15.3)	25 (21.4)		
Sex (n, %)					0.9510	0.0006
Male	246 (52.6)	82 (57.8)	120 (57.4)	44 (37.6)		
Female	222 (47.4)	60 (42.3)	89 (42.6)	73 (62.4)		
Race/ethnicity (n, %)					0.0002	0.0005
Non-Hispanic White	276 (56.0)	71 (50.0)	146 (69.9)	59 (50.4)		
Non-Hispanic Black	192 (41.0)	71 (50.0)	63 (30.1)	58 (49.6)		
Relationship status (n, %)					0.1810	0.0156
Married	237 (50.6)	77 (54.2)	113 (54.1)	47 (40.2)		
Divorced	65 (13.9)	24 (16.9)	26 (12.4)	15 (12.8)		
Widowed	145 (31.0)	37 (26.1)	62 (29.7)	46 (39.3)		
Other	21 (4.5)	4 (2.8)	8 (3.8)	9 (7.7)		
Region (n, %)					0.9787	0.8888
Belt	165 (35.3)	51 (35.9)	74 (35.4)	40 (34.2)		
Buckle	93 (19.9)	28 (19.7)	40 (19.1)	25 (21.4)		
Non Belt	210 (44.9)	63 (44.4)	95 (45.5)	52 (44.4)		
Education (n, %)					0.1948	0.0002
Lt High school	54 (11.5)	10 (7.0)	21 (10.1)	23 (19.7)		
HS graduate	126 (26.9)	43 (30.3)	43 (20.6)	40 (34.2)		
Some college	126 (26.9)	37 (26.1)	59 (28.2)	30 (25.6)		
College and above	162 (34.6)	52 (36.6)	86 (41.2)	24 (20.5)		
Household income ($US) **(n, %)**					0.8823	<.0001
Less than 20k	86 (23.2)	24 (20.0)	27 (16.6)	35 (39.8)		
20k-34k	114 (30.7)	35 (29.2)	50 (30.7)	29 (33.0)		
35k-74K	119 (32.1)	42 (35.0)	57 (35.0)	20 (22.7)		
75k and above	52 (14.0)	19 (15.8)	29 (17.8)	4 (4.6)		
Missing	97					
Occupation (n, %)					0.0385	0.0770
Employed	71 (18.0)	29 (24.8)	26 (14.4)	16 (16.7)		
Retired	279 (70.8)	75 (64.1)	140 (77.4)	64 (66.7)		
Not working	44 (11.2)	13 (11.1)	15 (8.3)	16 (16.7)		
Missing	74					
Neighborhood Socio economic status (n, %)					0.0309	<.0001
First quartile	108 (25.4)	36 (27.9)	34 (17.6)	38 (36.9)		
Second quartile	104 (24.5)	33 (25.6)	41 (21.2)	30 (29.1)		
Third quartile	107 (25.2)	35 (27.1)	57 (29.5)	15 (14.6)		
Forth quartile	106 (24.9)	25 (19.4)	61 (31.6)	20 (19.4)		
Missing	43					
Alcohol use [a] **(n, %)**					0.0260	0.0053
None	301 (64.3)	93 (65.5)	121 (57.9)	87 (74.4)		
Moderate	154 (32.9)	42 (29.6)	85 (40.7)	27 (23.1)		
Heavy	13 (2.8)	7 (4.9)	3 (1.4)	3 (2.6)		
Smoking status (n, %)					0.7112	0.1794
Never	45 (9.6)	16 (11.3)	19 (9.1)	10 (8.6)		
Former	221 (47.3)	65 (45.7)	92 (44.2)	64 (54.7)		
Current	201 (43.0)	61 (43.0)	97 (46.6)	43 (36.8)		
Missing	1					
Number of Exercise per week (n, %)					0.4834	0.8694
None	242 (52.2)	75 (53.2)	105 (50.7)	62 (53.5)		
1-3	139 (30.0)	37 (26.2)	66 (31.9)	36 (31.0)		
≥ 4	83 (17.9)	29 (20.6)	36 (17.4)	18 (15.5)		

Missing	4					
BMI category (n, %)					0.1187	0.0757
Underweight (BMI≤18.4)	4 (0.96)	1 (0.8)	1 (0.5)	2 (2.0)		
Healthy weight (18.5-24.9)	109 (26.2)	29 (22.5)	54 (29.0)	26 (25.7)		
Overweight (25-29.9)	162 (38.9)	48 (37.2)	81 (43.6)	33 (32.7)		
Obese (BMI≥30)	141 (33.9)	51 (39.5)	50 (26.9)	40 (39.6)		
Missing	52					
Time since stroke					0.5951	0.1199
Mean (SD)	4.2 (2.8)	4.2 (2.9)	4.4 (2.7)	3.9 (2.7)		
Median	3.9	3.8	4.0	3.7		
Q1, Q3	1.9, 6.3	1.8, 6.2	2.2, 6.6	1.5, 5.8		
Depression symptoms (CESD-09)					0.7047	<.0001
Mean (SD)	4.7 (4.8)	4.3 (4.8)	4.1 (4.5)	6.4 (5.0)		
Median	3.0	3.0	3.0	3.0		
Q1, Q3	1.0; 7.0	0.0; 6.0	1.0; 6.0	3.0; 9.0		
Missing	42					
Diabetes (n, %)					0.1087	0.0035
No	293 (63.2)	86 (61.4)	145 (69.7)	62 (53.5)		
Yes	171 (36.9)	54 (38.6)	63 (30.3)	54 (46.5)		
Missing	4					
Hypertension (n, %)					0.0731	0.6474
No	104 (22.8)	23 (16.5)	50 (24.6)	31 (27.0)		
Yes	353 (77.2)	116 (83.5)	153 (75.4)	84 (73.0)		
Missing	11					
Heart disease [b] (n, %)					0.5410	0.7671
No	262 (63.4)	83 (65.4)	114 (62.0)	65 (63.7)		
Yes	151 (36.6)	44 (34.7)	70 (38.0)	37 (36.3)		
Missing	55					
Atrial Fibrillation (n, %)					0.7752	0.9129
No	301 (76.6)	96 (77.4)	133 (76.0)	72 (76.6)		
Yes	92 (23.4)	28 (22.6)	42 (24.0)	22 (23.4)		
Missing	75					
Dyslipidemia (n, %)					0.5862	0.3666
No	111 (26.7)	34 (25.9)	54 (28.7)	23 (23.7)		
Yes	305 (73.3)	97 (74.1)	134 (71.3)	74 (76.3)		
Missing	52					
Cancer (n, %)					0.0830	0.0916
No	261 (85.6)	78 (82.1)	125 (89.9)	58 (81.7)		
Yes	44 (14.4)	17 (17.9)	14 (10.1)	13 (18.3)		
Missing	163					
Stroke type (n, %)					0.1747	0.2691
Ischemic	429 (89.7)	133 (92.4)	187 (87.8)	109 (90.1)		
Hemorrhagic	49 (10.3)	11 (7.6)	26 (12.2)	12 (9.9)		
Both	10					
Sleep apnea (n, %)					0.2646	0.6803
No	397 (86.1)	117 (83.6)	180 (87.8)	100 (86.2)		
Yes	64 (13.9)	23 (16.4)	25 (12.2)	16 (13.8)		
Missing	7					
Prescribed sleep medication[c]					0.0830	0.3437
Mean (SD)	2.1 (7.4)	2.9 (8.6)	1.5 (6.0)	2.3 (7.8)		
Missing	12					
Non-prescribed sleep medication [d]					0.6942	0.6162
Mean (SD)	2.2 (10.4)	2.7 (11.9)	2.2 (11.2)	1.7 (6.4)		
Missing	6					

[a] Alcohol use (none; moderate: up to 7 times per week for women and 14 times for men; heavy)

[b] Heart disease (self-reported myocardial infarction, CABG, bypass, angioplasty, or stenting or evidence of myocardial infarction via ECG.

[c] Number of days/nights in the last month prescription sleeping pills were used

[d] Number of days/nights in the last month non-prescribed sleeping pills were used

Table 4. 2. Association between sleep duration and all-cause mortality

Exposure	**Non-imputed data (complete case analysis: missing observation deleted)**				
	Unadjusted HR, 95% CI (n=468)	Model 1 HR, 95% CI (n=468)	Model 2 HR, 95% CI (n=269)	Model 3 HR, 95% CI (n=269)	Model 4 HR, 95% CI (n=144)
Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	 Ref 1.08 (0.76, 1.53) 1.76 (1.26, 2.47)	 Ref 1.29 (0.90, 1.84) 1.78 (1.26, 2.54)	 Ref 1.27 (0.79, 2.05) 1.62 (0.99, 2.65)	 Ref 1.26 (0.74, 2.11) 1.93 (1.10, 3.38)	 Ref 0.99 (0.42, 2.34) 5.20 (2.04, 13.25)
	Non-imputed data (variable with more than 15 observations missing were not included in the model)				
	Unadjusted HR, 95% CI (n=468)	Model 1 HR, 95% CI (n=468)	Model 2a HR, 95% CI (n=468)	Model 3a HR, 95% CI (n=463)	Model 4a HR, 95% CI (n=443)
Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	 Ref 1.08 (0.76, 1.53) 1.76 (1.26, 2.47)	 Ref 1.29 (0.90, 1.84) 1.78 (1.26, 2.54)	 Ref 1.57 (0.98, 2.51) 1.68 (1.21, 2.31)	 Ref 1.27 (0.88, 1.84) 1.81 (1.26, 2.61)	 Ref 1.31 (0.89, 1.92) 1.82 (1.24, 2.65)
	Multiple imputations (100) of missing covariates*				
	Unadjusted (n=468)	Model 1 (n=468)	Model 2 (n=468)	Model 3 (n=468)	Model 4 (n=468)
Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	 Ref 1.08 (0.76, 1.53) 1.76 (1.26, 2.47)	 Ref 1.22 (0.86, 1.74) 1.77 (1.25, 2.51)	 Ref 1.31 (0.91, 1.89) 1.62 (1.12, 2.34)	 Ref 1.30 (0.89, 1.90) 1.73 (1.19, 2.53)	 Ref 1.36 (0.93, 2.02) 1.53 (1.03, 2.29)

Model 1: adjusted for demographic factors (including age, sex, race, relationship status, and region)
Model 2: Model 1 + socioeconomic factors (including education, income, occupation, NSES)
Model 3: Model 2 + behavioral risk factors (including alcohol, smoking, exercise, body mass index) + time since stroke.
Model 4: Model 3 + comorbidities (diabetes, hypertension, heart disease, atrial fibrillation, depression symptoms, dyslipidemia, history of cancer, history of sleep apnea)
Model 2a: age, sex, race, relationship status, region, education
Model 3a: age, sex, race, relationship status, region, education, alcohol, smoking, exercise, time since stroke.
Model 4a: age, sex, race, relationship status, region, education, alcohol, smoking, exercise, time since stroke, diabetes, hypertension, sleep apnea.
*Variables imputed: household income(n=97), occupation (n=74), NSES (n=43), smoking (n=1), exercise (n=4), BMI (n=52), depression symptoms (n=42), diabetes (n=4), hypertension (n=11), heart disease(n=55), atrial fibrillation (n=75), dyslipidemia (n=52), cancer (n=163), sleep apnea (n=7)

Table 4. 3. Association between sleep duration and all-cause mortality stratified by age, sex, race, NSES, and geographic region.

Stratification variable		Model 3 HR, 95% CI (n=468)	p-value of interaction term	Model 4 HR, 95% CI (n=468)	p-value of interaction term
Age <75 (n=212)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.91 (0.90, 4.08) 2.90 (1.27, 6.60)	0.1690	Ref 2.03 (0.85, 4.85) 3.17 (1.11, 8.33)	0.2431
Age ≥ 75 (n=256)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.14 (0.69, 1.86) 1.68 (1.03, 2.74)		Ref 1.33 (0.79, 2.22) 1.55 (0.91, 2.65)	
Male (n=246)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.06 (0.62, 1.81) 1.91 (1.05, 3.45)	0.2242	Ref 1.38 (0.76, 2.48) 2.09 (1.10, 3.98)	0.4398
Female (n=222)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.14 (0.69, 1.86) 1.68 (1.03, 2.74)		Ref 2.06 (1.05, 4.10) 2.10 (1.08, 4.16)	
White (n=276)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.06 (0.64, 1.74) 1.50 (0.87, 2.59)	0.4428	Ref 1.17 (0.69, 2.02) 1.31 (0.74, 2.32)	0.6955
Black (n=192)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.55 (0.77, 3.14) 2.32 (1.11, 4.86)		Ref 1.26 (0.57, 2.80) 2.38 (0.99, 5.72)	
High NSES (n=237)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.27 (0.86, 1.87) 1.51 (1.01, 2.25)	0.7857	Ref 1.47 (0.81, 2.69) 1.50 (0.75, 3.02)	0.8829
Low NSES (n=231)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.22 (0.69, 2.16) 1.76 (0.93, 3.35)		Ref 1.25 (0.65, 2.41) 1.62 (0.85, 3.05)	
Belt + Buckle Region (n=258)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.27 (0.86, 1.87) 1.51 (1.01, 2.25)	0.8839	Ref 1.07 (0.59, 1.94) 1.98 (1.10, 3.58)	0.5339
Non-Belt Region (n=210)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.27 (0.86, 1.87) 1.51 (1.01, 2.25)		Ref 2.20 (1.15, 4.21) 1.93 (0.93, 4.00)	

NSES: neighborhood socioeconomic status

Model 3: Model adjusted for (age, sex, race, NSES, geographic region, relationship status, education, income, occupation, alcohol, smoking, exercise, body mass index and time since stroke) with the exception of the stratification variable.

Model 4: Model 3 + diabetes, hypertension, heart disease, atrial fibrillation, depression symptoms, dyslipidemia, history of cancer, history of sleep apnea.

Supplemental data

Supplemental Table 4. 1. Variance inflation factor

Age	1.6
Sex	1.7
Race/ethnicity	1.4
Relationship status	1.6
Region	1.3
Education	1.6
Household income	2.2
Occupation	1.5
NSES	1.6
Alcohol use	1.4
Smoking	1.3
Exercise	1.1
BMI	1.3
Time since stroke	1.2
Depression symptoms	1.3
Diabetes	1.6
Hypertension	1.3
Heart disease	1.4
Atrial fibrillation	1.3
Dyslipidemia	1.3
Cancer	1.2
Sleep apnea	1.4
Sleep medication use	1.1

Supplemental Table 4. 2. Percentage of missing data

Variables imputed	**n**	**%**
Household income	97	**20.7**
Occupation	74	**15.8**
NSES	43	9.2
Smoking	1	0.2
Exercise	4	0.9
BMI	52	**11.1**
Diabetes	4	0.9
Hypertension	11	2.4
Heart disease	55	**11.8**
Atrial fibrillation	75	16.0
Dyslipidemia	52	**11.1**
Cancer	163	**34.8**
Sleep apnea	7	1.5

Supplemental Table 4. 3. Sensitivity analysis: Association between sleep duration and all-cause mortality

		Model 3 (n=430)	Model 4 (n=430)
	Sensitivity analysis assessing reverse causation		
1 year lagged.	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.10 (0.73, 1.65) 1.63 (1.09, 2.44)	Ref 1.15 (0.76, 1.74) 1.49 (0.97, 2.29)
	Sensitivity analysis for model selection		
		Model 3a (n=468)	Model 4a (n=468)
Change In Estimate>10 or p-value< 0.05	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.25 (0.87, 1.81) 1.70 (1.18, 2.44)	Ref 1.30 (0.90, 1.88) 1.62 (1.12, 2.34)
	Sensitivity analysis controlling for potential additional confounder		
		Model 3b (n=457)	Model 4b (n=457)
Further adjusted for sleep medication use (prescribed and non-prescribed)	Adequate Sleep (7-8h) Short sleep (≤6h) Long sleep (≥9h)	Ref 1.25 (0.85, 1.85) 1.72 (1.17, 2.54)	Ref 1.33 (0.89, 1.99) 1.55 (1.03, 2.33)

Model 3: adjusted for demographic factors (including age, sex, race, relationship status, and region) socioeconomic factors (including education, income, occupation, NSES)+ behavioral risk factors (including alcohol, smoking, exercise, body mass index) + time since stroke.
Model 4: Model 3 + comorbidities (diabetes, hypertension, heart disease, depression symptoms, dyslipidemia, cancer)
Model 3a: adjusted for age, income, occupation, alcohol use, smoking, exercise, and body mass index.
Model 4a: adjusted for age, income, occupation, body mass index, depression symptoms, atrial fibrillation, and heart disease.
Model 3b: adjusted for Model 3 + sleep medication use (prescribed and non-prescribed)
Model 4b: adjusted for Model 4 + sleep medication use (prescribed and non-prescribed).

Vita

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EDUCATION

Ph.D. in Epidemiology
Virginia Commonwealth University August 2019-May 2023

Master of Public Health, concentration Epidemiology
Louisiana State University Health Sciences Center, New Orleans August 2017- May 2019

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University of Ouagadougou**,** Burkina Faso October 2005- July 2013

WORK EXPERIENCE

Graduate Assistant
Virginia Commonwealth University 2019 - 2023
Research Assistant
Comprehensive Alcohol Research Center, New Orleans, LA 2018- 2019
Internship
Louisiana Tumor Registry, New Orleans, LA 2018- 2019
General practitioner and manager
Centre Medical AGIR, Ouagadougou, Burkina Faso 2013-2014

TEACHING EXPERIENCE

Teaching Assistant

- EPID 571: Principle of Epidemiology Fall 2019, Fall 2020, Fall 2022
- EPID 606: Epidemiologic methods Spring 2021, Spring 2022, Spring 2023
- EPID 650: Epidemiology methods for research Fall 2020, Fall 2022

Courses Taught

- Systematic review and meta-analysis Spring 2022, Spring2023
- Introduction to SAS Spring 2021, Spring 2022, Spring 2023
- Case-control studies design Fall 2022
- Measures of disease occurrence and association in cohort, case-control, and cross-sectional studies Spring 2023

HONORS AND AWARDS

- Inducted member of the Alpha Psi chapter of the Delta Omega Society 2019
- Best poster, Delta Omega Honors Day Poster Presentation 2019
- Society of Epidemiologic Research 2021 Conference Scholarship 2021
- Inducted member of the Honor Society of Phi Kappa Phi 2021
- Dr. Saba W. Masho Endowed Scholarship in Epidemiology recipient 2022
- VCU School of Medicine Charles C. Clayton awardee 2023

CONFERENCE PRESENTATIONS (as Presenting Author)

- **Sawadogo W,** Ferguson TF, Molina PE, Welsh DA. Differences in Hypertension Prevalence and Control by Alcohol Use Severity Among People Living with HIV. Delta Omega honor day, LSUHSC, April 2019
- **Sawadogo W**, Adera T, Lu J. History of stroke as a risk factor for sleep disturbances in U.S adults. APHA annual meeting October 2020.
- **Sawadogo W**, Adera T. The effect of sleep duration on the association between food insecurity and childhood obesity. Society of Epidemiologic Research (SER) annual meeting, July 2021
- **Sawadogo W**, Adera T. The effect of sleep duration on the association between food insecurity and childhood obesity. Society of pediatric perinatal epidemiologic research (SPER) annual meeting, July 2021
- **Sawadogo W**, Chapman D, Taylor DDH, Adera T. The Mediating Effect of Sleep Duration on the Association between Food Insecurity and Childhood Obesity. Virginia Public Health Association Conference, Mars 2022.
- **Sawadogo W,** Adera T, Alattar M, Perera R, Burch J. Age and sex differences in the association of insomnia symptoms with all-cause mortality among community-dwelling stroke survivors: a prospective cohort study. Society for Epidemiologic Research Mid-Year Meeting 2023.
- **Sawadogo W,** Adera T, Alattar M, Perera R, Burch J**.** Age disparities in the association between insomnia symptoms and incidence of stroke: A prospective cohort study. [Accepted 2023 Annual Scientific Session of the American College of Cardiology Together With World Congress of Cardiology]
- **Sawadogo W,** Adera T, Alattar M, Perera R, Burch J. Insomnia Symptoms Trajectories and increased risk of Stroke: A Prospective Cohort Study. [Accepted American Academy of Neurology 2023 Annual Meeting]
- **Sawadogo W,** Adera T, Alattar M, Perera R, Burch J. Age and sex differences in the association of insomnia symptoms with all-cause mortality among community-dwelling stroke survivors: a prospective cohort study. [Accepted Society for Epidemiologic Research Annual Meeting 2023]

CONFERENCE PRESENTATIONS (as co-author)

- Maniscalco L, Rosales C, Zhang L, Poynter J, **Sawadogo W**, Wu XC. An assessment of selection bias in the Cancer Incidence in Louisiana by Census Tract report. North American Association of Central Cancer Registries, Annual Conference 2019.

INVITED PRESENTATION

- Obesity and COVID-19: current evidence. Lowcountry Epidemiology Seminar, South Carolina Department of Health, and Environmental Control. Feb 2022.

PUBLICATIONS

- **Sawadogo W**, Tsegaye M, Gizaw A, Adera T. Overweight and obesity as risk factors for COVID-19-associated hospitalizations and death: systematic review and meta-analysis. *BMJ Nutrition, Prevention & Health* 2022; 0:e000375. doi:10.1136/bmjnph-2021-000375, 2022.
- Iness A, Abaricia J, **Sawadogo W**, Iness C, Duesenburg M, Cyrus J, Prasad V. The effect of hospital visitor policies on patients, their visitors, and healthcare providers during the COVID-19 pandemic: a systematic review. *The American Journal of Medicine*. doi :10.1016/j.amjmed.2022.04.005
- **Sawadogo W**, Chapman DA, Taylor DDH, Adera T. The Mediating Effect of Sleep Duration on the Association between Food Insecurity and Childhood Obesity. Child Obes. 2022 Jun 7. doi: 10.1089/chi.2022.0070. Epub ahead of print. PMID: 35671522.
- **Sawadogo W**, Adera T (2022) Physical Activity Mediates the Association between Food Insecurity and Childhood Obesity. J Clin Nutr Diet Vol. 8 No. S1:01
- **Sawadogo W**, Adera T, Lu J. Association between history of stroke and sleep disturbances in U.S. adults, Cogent Public Health, 9:1, 2022. DOI: 10.1080/27707571.2022.2146300
- **Sawadogo W**, Adera T, Alattar M, Perera R, Burch J. A Prospective Study of Insomnia Symptoms and Risk of Stroke: Exploring Symptom Trajectories, Effect Modification by Age, and Mediation by Comorbidities. Neurology [Forthcoming]
- **Sawadogo W**, Burch J, Alattar M, Perera R, Adera T. Age and Sex differences in the Association of Insomnia Symptoms with All-Cause Mortality among Community-dwelling Stroke Survivors: A Prospective Cohort Study. Stroke [Forthcoming]

MASTER'S RESEARCH MENTORED

- A Systematic Review and Meta-analysis of the Safety and Efficacy of SARS-CoV-2 Vaccines Currently Available for Use. Alyssa Simon, 2022

- Effectiveness of Intimate Partner Violence Prevention Programs on College Campuses: A Systematic Review. Jamie Simpkins, 2023

PROFESSIONAL SERVICE

Invited Peer Reviewer

- 2021- Present: Cochrane
- 2021- Present: Braishideng Publishing Group Inc
- 2023- Present: Childhood Obesity
- 2023- Present: Public Health

2021-Present: Master of Public Health curriculum committee. Member. Virginia Commonwealth University. Richmond, VA
August-September 2022: Promotion and Tenure committee. Member. Virginia Commonwealth University. Richmond, VA

PROFESSIONAL AFFILIATIONS

- 2013-Present: National Order of Physicians, Burkina Faso
- 2019-Present: American Public Health Association
- 2020-Present: Society of Epidemiologic Research
- 2020-Present: Society of Pediatric Perinatal Epidemiologic Research
- 2022-Present: American Academy of Neurology
- 2022-Present: American College of Cardiology