EXAMINING SLEEP AND INCIDENT DEMENTIA AND ALL-CAUSE MORTALITY IN A LONGITUDINAL, NATIONALLY REPRESENTATIVE SAMPLE OF OLDER ADULTS IN THE US

EXAMINING SLEEP AND INCIDENT DEMENTIA AND ALL-CAUSE MORTALITY IN A LONGITUDINAL, NATIONALLY REPRESENTATIVE SAMPLE OF OLDER ADULTS IN THE US

By

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A Dissertation Submitted to the Faculty of Harvard Medical School in Partial Fulfillment of the Requirements for the Degree of Master of Medical Sciences in Clinical Investigation (MMSCI)

Harvard University

Boston, Massachusetts

April 2022

Area of Concentration: Sleep and Circadian Disorders
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I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

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ACKNOWLEDGEMENTS

I wish to thank the MMSci course Director, Dr. Ajay Singh, and MMSci Co-Director, Dr. Finnian McCausland. I also wish to thank other members of the MMSCI program leadership, Drs. Rosalyn Adam and Martina McGrath, as well as Ms. Claire Frances, the MMSci Program manager, for all their support and kind efforts on my behalf. I wish to thank my mentor, Dr. Charles Czeisler, and Co-Mentor, Dr. Laura Barger. I sincerely appreciate Dr. Jeanne Duffy for serving as my external content expert. Finally, I am forever grateful to my husband, Andrew Parchman, for supporting me every step of the way, and to my son, Hancock (Hap) Parchman (11 months), for his active participation in a few Zoom lectures on several occasions during the COVID-19 pandemic when courses were virtual.

OVERVIEW OF THESIS PAPERS

According to the Centers for Disease Control, Alzheimer's Disease (AD), the most common cause of dementia among older adults, is currently the 6th leading cause of death in the United States (US) (1). Moreover, in 2019 it was estimated that 5.8 million Americans were living with AD and related dementia and 14 million are expected to be living with the condition by 2050 (2). With the rising threat posed by AD and related dementia, it is vital to identify the precipitating factors to its development and progression; one possible contributing factor is sleep difficulty.

Sleep deficiency and disturbance and cognitive decline

Sleep deficiency, including insufficient sleep duration or the experience of sleep difficulties, such as difficulty initiating sleep or difficulty falling back asleep, are associated with a host of serious, adverse consequences, ranging from poor mental health to diabetes and cardiovascular disease when left untreated (3–5). According to epidemiological research, sleep deficiency and sleep difficulties are significantly more common among older adults (65 years of age and above) compared to younger adults (35 years of age and below). For instance, sleep difficulties are reported by 47% of older adults compared to only 27% of younger adults (6). Sleep difficulties are experienced with greater prevalence among older as compared to younger adults. A nationally representative study found that difficulty initiating sleep is reported by 15% of older adults and only 9% of younger adults, while early morning awakenings are reported by 17% of older adults and 9% of young adults. The most common sleep difficulties according to this study are difficulty falling back asleep, which are reported by 39% of older adults versus 12% of younger adults (6).

Research on a variety of sleep-related measures and cognition among older adults has been the subject of a number of studies. The majority of studies focused on this topic have shown that markers of poor sleep (e.g., insufficient sleep duration, self-reported poor sleep quality and daytime sleepiness) are associated with subsequent cognitive decline, including AD and dementia (7–11). For instance, research has found associations between both long (>9 hours) and short (<7 hours) sleep duration and Alzheimer's disease and dementia. Specifically, in research with data from the Framingham Heart Study, self-reports of longer sleep (>9 hours) were associated with all-cause dementia and clinical Alzheimer disease, but not short sleep (<6 hours) (12). However, according to meta-analysis of 27 studies, both short (< 7 hours) and long sleep duration (> 8 hours) were both associated with approximately 86% greater risk for Alzheimer's disease and dementia (8). With regard to sleep difficulties and dementia, research commonly draws upon summary measures of difficulties. For instance, in a study conducted among older Spanish adults, self-reported "sleep problems" at baseline were associated with a 2-fold greater risk for mild cognitive impairment, dementia, or AD 2 years later (10). In a study conducted among Finnish individuals, poor self-reported sleep quality at baseline was significantly associated with cognitive decline at follow-up 22 years later (11). In a smaller cohort, objectively measured fragmented sleep among older adults was associated with a nearly 1.5 times greater risk for AD at 3-year follow-up (9). However, not all studies have demonstrated a linkage between markers of poor sleep and reduced cognition in older adults (Elwood et al., 2011; Foley et al., 2001; Potvin et al., 2012). For instance, one study conducted among older men did not find self-reported sleep issues relating to an insomnia diagnosis to be associated with either vascular or non-vascular dementia over a 10-year follow-up interval, but authors did find daytime sleepiness associated with vascular dementia over time (15). One study measuring

specific sleep difficulties (i.e., falling asleep and waking too early) at baseline among a sample of older Japanese American individuals did not find either measure to be associated with cognitive decline or dementia at 3-year follow-up Foley et al., 2001).

One limitation of studies focused on sleep deficiency or difficulties and dementia is the use of an aggregate score of sleep difficulties, a clinical insomnia diagnosis, or a sum score of all difficulties. However, each difficulty (e.g., difficulty initiating sleep) has unique challenges and treatment recommendations, and difficulties are reported at varying intensities across the population of older adults, lending support for exploring each difficulty distinctly (6). For instance, difficulty initiating sleep is typically treated with stimulus control therapy, or the instruction to use bed for sleep as opposed to watching television or other activities, and leaving bed when one experiences difficulty initiating sleep (16). Another limitation of the literature examining sleep deficiency and cognitive decline is that studies have relied on a wide range of measures, and few studies have included a comprehensive list of sleep measures in a single study.

Sleep deficiency or disturbance and all-cause mortality

Prospective studies examining sleep deficiency or difficulties and all-cause mortality, on the other hand, have explored the relationships between specific difficulties and all-cause mortality. However, not all studies show a clear relationship between sleep difficulties and mortality. According to a meta-analysis of studies with a median of 10 years of follow-up (17), difficulty initiating sleep was associated with all-cause mortality (e.g., Li et al., 2014), yet nighttime awakenings and early morning awakenings were not (e.g., Foley et al., 1995; Lallukka et al., 2016). According to another meta-analysis of studies with a mean of 11 years of follow-up (20), there was not an association between insomnia and all-cause mortality (e.g., Choi et al.,

2017), yet one study with a 20 year follow-up interval found that, after adjusting for covariates, adult participants (ages 21 to 70) with persistent insomnia (i.e., in most years) were at significantly higher risk for all-cause mortality, while those with transient insomnia (i.e., only some years) were not at greater risk (22). Little attention has been paid to the relationships among sleep difficulties and the competing risks of incident dementia and all-cause mortality in the same population.

Two studies address the limitations in the literature

Research on sleep disturbance and deficiency and all-cause mortality therefore has shown conflicting results. Further, few studies have included a comprehensive set of sleep characteristics in a single examination of incident dementia and all-cause mortality. We address these gaps in the literature with two studies. First, in Study 1 we examine the relationship between sleep disturbance, sleep duration, alertness and incident dementia and all-cause mortality across a five-year time interval using data captured in the National Health and Aging Trends Study (NHATS), a nationally representative study among adults 65 years and above in the US.

In Study 2, we examine specific sleep difficulties, including difficulty initiating sleep and waking from sleep and experiencing difficulty falling back asleep (hereafter termed "difficulty falling back asleep"), both reported annually, and their relationship to incident dementia and all-cause mortality in NHATS over a period of 8 years of follow-up.

PAPER 1

MATERIALS & METHODS

Data from the National Health and Aging Trends Study (NHATS), an annual in-home, computer-assisted, longitudinal, nationally representative survey of community-dwelling Medicare beneficiaries 65 years and older drawn from the Medicare enrollment database, were analyzed. The NHATS data collection began in 2011 with a core interview administered annually. Adults ages 65 and older were sampled from the Medicare enrollment file. NHATS also used proxy respondents for those individuals who were unwilling or unable to complete an interview, a practice which has been shown to reduce attrition bias in longitudinal studies with older adults0 (23). Additional information regarding the study's sampling strategy, design and content are available to the public (24). All respondents provided consent, and the study protocol was approved by the Johns Hopkins University Institutional Review Board (IRB). Our analysis of the publicly available, de-identified data from NHATS was considered exempt from IRB review.

Participants

The comprehensive sleep questionnaire was administered in 2013 and 2014 to a randomly selected subset of the larger NHATS population. In 2013, 27% of the sample was randomly selected to receive the sleep questionnaire (n=1,575) out of a total 5,799 respondents, and in 2014, 26% of the sample was randomly selected to receive the sleep questionnaire (n=1,237) out of a total of 4,737 respondents. Participants with dementia at baseline (year 2013) were excluded (N=202) for a sample of 2,610 with sleep data in either 2013 or 2014. We utilized this sub-sample of NHATS participants that were randomly selected to respond to the sleep supplement in either 2013 or 2014 to understand the relationship between these sleep

characteristics, incident dementia, and all-cause mortality in each year leading up to 2018. A flow diagram can be found in the Supplemental Information section detailing the participants included in this study.

To determine if the NHATS subset analyzed in this manuscript differed from the full cohort, we performed Pearson chi-square tests to examine potential differences in the demographic variables (i.e., gender, age, marital status, and race) and health conditions between the sub-sample that was included in this analysis and the full sample in each year. We found no difference in gender ($p>0.05$), marital status ($p>0.05$) or race ($p>0.05$) between those in the sub-sample analyzed in this manuscript and the full sample, but we did find that age varied between the sub-sample analyzed in this manuscript and the full sample ($p<.05$). We found differences in depression ($p<0,05$), heart attack ($p<0.05$), heart disease ($p<0.05$), high blood pressure ($p<0.05$), arthritis ($p<0.05$), diabetes ($p<0.05$), but neither stroke ($p>0.05$) nor cancer ($p>0.05$).

Measures

We examined several characteristics of sleep. Sleep duration was reported by respondents in hours rounded to the nearest whole number. We created a variable to stratify sleep duration into the following categories: 1), recommended duration (7-8 hours); 2), short sleep duration (6-7 hours); 3, very short sleep duration (≤5 hours); and 4) long sleep duration (≥ 9 hours).

Participants marked their response to sleep latency in minutes. Sleep latency responses were categorized into a three-level variable: 1) <15 minutes; 2) 15-30 minutes; and 3) >30 minutes. Next, a series of sleep characteristics were measured on Likert scales. First, difficulty maintaining alertness was measured with the question “In the last month, how often did you have trouble staying awake at times during the day when you wanted to be awake” on a 5-point Likert

scale from “never” to “every day.” Next, sleep quality was measured with the question “In the last month please rate the quality of your sleep” on a 5-point Likert scale from “very poor” to “very good.” Napping frequency was measured with the question “In the last month, how often did you take naps during the day” on a 5-point Likert scale from “never” to “every day”. Finally, snoring was measured with the question “In the last month, how often did you have trouble staying asleep because you snored loudly, or you woke up gasping or choking” on a 5-point Liker scale from “never” to “every night”. We reverse coded all responses so that higher values indicated greater frequency of the sleep parameter (i.e., sleep quality, snoring, napping) and lower values indicated lower frequency of the parameter. All responses to the questions with 5-point Likert scales were transformed into 3-level variables (e.g., difficulty maintaining alertness responses were recoded: 0 was used to indicate “never” and “rarely” responses, 1 was used to indicate “some days,” and 2 was used to indicate “most days or “every day”).

Screening for incident dementia

To assess cognitive capacity, participants first rated their memory and then performed a memory-related activity (immediate and delayed 10-word recall) (25). Also, as part of the memory assessment, participants were asked to respond to items related to orientation and perform a clock drawing test to assess executive function (26). For proxy interviews, the Ascertain Dementia 8-item (AD8), an informant screener for dementia, was administered (27,28) A score of 2 or higher on the AD8 is indicative of dementia. Scores on the AD8 and performance on orientation, memory and clock drawing tests were used in our study to form a screening result of either negative (no dementia) or positive (risk for probable dementia). Over the follow-up interval, 321 individuals met the criteria for incident dementia.

All-cause mortality

The participant's death was reported to the study personnel by informants during attempts to contact the participant for their annual interview.

Covariates

In adjusted analyses, we controlled for time-varying covariates including marital status, chronic conditions, body weight, and depressive symptoms. Body weight was reported by participants annually in pounds. Depressive symptoms were measured using the Patient Health Questionnaire-2 which was administered as part of the NHATS (29). Chronic conditions reported by the sample included self-reported diagnosis of the following conditions: heart attack, heart disease, hypertension, arthritis, diabetes, stroke, and cancer. We included a single variable indicating the number of chronic conditions reported by each individual in the adjusted models. Covariates which did not change over time, including sex and educational attainment, were entered from the baseline interview. Baseline age was also included as a covariate. In models examining all-cause mortality, dementia was also added as a confounder.

Statistical Analyses

We computed descriptive statistics for demographic factors and for sleep characteristics. Demographic and health condition data were obtained from the annual NHATS questionnaires in 2013 and 2014. We performed Cox proportional hazards modeling to examine the prospective relationship between sleep characteristics reported at baseline (either years 2013 or 2014) and risk of incident dementia (primary aim) and subsequently all-cause mortality (secondary aim) in the 5 or 4 years of follow-up. Using Cox proportional hazards models, we modeled each outcome (primary: incident dementia; secondary: all-cause mortality), entering the sleep variables individually. Analyses were conducted both without confounders (unadjusted) and with

confounders (adjusted). Next, using Cox proportional hazards models, we modeled each outcome, entering all sleep variables simultaneously in the same model, while adjusting for covariates. The distribution of the data was assessed to ensure assumptions for all hypothesis testing were met (i.e., proportional hazards). All tests were two-sided with alpha set at 0.05. All analyses were performed in Stata (Version 16, College Station, TX).

RESULTS

Table 1 displays demographic characteristics of the sample at baseline (Year 2013: n=1,573), average age was 76.9 (s.d.=7.5 years). The sample was comprised of 40% female respondents in both 2013 and 2014 and 72% white respondents, followed by approximately 20% black (2013: 20%; 2014: 19%), 3% Hispanic/Latino (both years), and 6% Asian (both years) respondents. Among respondents, 48% and 44% reported being married in 2013 and 2014, respectively. Nearly 44% and 45% demonstrated clinical depression in 2013 and 2014, respectively. The most common comorbid condition among the sample was cancer (2013: 5%; 2014: 7%), followed by hypertension (2013: 3%; 2014: 3%).

[Insert Table 1]

Table 2 displays descriptive statistics summarizing sleep variables. Approximately 60% of participants reported experiencing difficulty with alertness “never” or “rarely” (2013: 59.63%, 2014: 61.36); nearly one half of participants reported “never” or “rarely” taking naps (2013: 44.09%, 2014: 44.03%). More than half of participants reported taking fewer than 15 minutes to fall asleep (2013: 52.93%, 2014: 52.22%), and more than half reported sleeping 7-8 hours per night (2013: 55.05%, 2014: 54.74%). Nearly 70% of participants reported a sleep quality of good

or very good (2013: 68.74%, 2014: 69.62%), and over 90% of participants reported snoring never or rarely (2013: 91.87%, 2014: 92.84%).

[Insert Table 2]

Examining the relationship between each sleep characteristic and incident dementia

Table 3 summarizes results of Cox proportional hazard models examining each sleep characteristic and incident dementia.

In the unadjusted models, participants who slept both fewer than 5 hours (HR =1.81, 95%CI:1.14-2.86, p<.05) and more than 9 hours per night (HR =1.43, 95%CI:1.04-1.97, p<.05) demonstrated significantly higher risk for incident dementia. Participants who reported taking between 15 and 30 minutes to fall asleep showed a higher risk for incident dementia (HR =1.41, 95%CI:1.06-1.89, p<.05), as did those who took longer than thirty minutes to fall asleep (HR =1.65, 95%CI:1.20-2.27, p<.01).

In fully adjusted models, participants who reported taking 30 minutes or longer to fall asleep demonstrated higher risk for incident dementia (HR =1.45, 95%CI:1.03-2.03, p<.05, see Figure 1 Panel A). Participants who reported sleeping 5 hours or fewer per night demonstrated significantly higher risk for incident dementia (HR =2.04, 95%CI:1.26-3.33, p<.01, see Figure 1 Panel B).

[Insert Figure 1 Panel A]

[Insert Figure 1 Panel B]

[Insert Table 3]

Examining the relationship between each sleep variable and all-cause mortality

Table 4 summarizes results of the Cox proportional hazard models examining each sleep characteristic and all-cause mortality. In the unadjusted models, a greater risk for all-cause mortality was associated with self-reported difficulty with alertness both most/every day (OR=2.23, 95%CI:1.79-2.75, p<.001) and some days (OR=1.50, 95%CI:1.25-1.82, p<.001). Risk for all-cause mortality was increased for participants who slept for longer than eight hours per night (OR=2.14, 95%CI:1.73-2.65, p<.001) and for participants who reported napping some days (OR=1.32, 95%CI:1.06-1.64, p<.05) or most/every day (OR=2.23, 95%CI:1.84-2.79, p<.001). Additionally, increased risk of all-cause mortality was associated with self-reported sleep quality of poor or very poor (OR=1.33, 95%CI:1.00-1.77, p<.05).

In the fully adjusted Cox proportional hazard models, the risk of all-cause mortality was higher for those participants who reported difficulty maintaining alertness "Some Days" (HR =1.49, 95%CI: 1.13-1.94, p<.01) and "Most Days/Every Day" (OR=1.65, 95%CI: 1.17-2.32, p<.01, see Figure 2 Panel A); for those who reported napping "Some Days" (HR=1.38, 95%CI: 1.03-1.85,p<.05) and "Most/Every Day" (HR =1.73, 95%CI: 1.29-2.32, p<.001, see Figure 2 Panel B); those reporting "Poor/Very Poor" sleep quality (HR =1.75, 95%CI: 1.17-2.61, p<.01, see Figure 2 Panel C), and those reporting sleeping 5 or fewer hours per night (HR=2.38, 95%CI:1.44-3.92, p<.01 see Figure 2 Panel D).

[Insert Table 4]

[Insert Figure 2 Panel A]

[Insert Figure 2 Panel B]

[Insert Figure 2 Panel C]

[Insert Figure 2 Panel D]

Relationship between all sleep characteristics and incident dementia and all-cause mortality

Table 5 summarizes results of the Cox proportional hazard models examining all sleep characteristics in a single model and incident dementia (Model A) and all-cause mortality (Model B), after adjusting for confounders. Among the sleep characteristics, only sleep duration ≤5 hours was associated with greater risk of incident dementia (HR=2.62, 95%CI: 1.48-4.64). Among the sleep characteristics, only difficulty maintaining alertness "Some Days" (HR=1.42, 95%CI: 1.05-1.92), difficulty maintaining alertness "Most Days/Every Day" (HR=1.57, 95%CI: 1.05-2.33), and sleeping ≤5 hours (HR=2.07, 95%CI: 1.15-3.74) were associated with risk of all-cause mortality.

PAPER 2

MATERIALS & METHODS

Data for this study were obtained from NHATS, the nationally representative survey of Medicare beneficiaries 65 years and older drawn from the Medicare enrollment database (24). We analyzed eight years of prospectively-collected data (2011 to 2018). A core interview was administered annually to adults, aged 65 and older, randomly sampled from the Medicare enrollment file. NHATS also used proxy respondents for those individuals who were unwilling or unable to complete an interview, which has been shown to reduce attrition bias in longitudinal studies with older adults (23). Previous studies recruiting older adult-proxy pairs have demonstrated high agreement between responses from the older adult and their proxy, and more than 80% sensitivity of proxy responses to those of the older adult (30). Proxy responses in the current study represented a small proportion of participants (Year 1: n=583, 8%; Year 2: n=964, 15%; Year 3: 897, 17%; Year 4: n=722, 16%; Year 5: n=779, 10%; Year 6: n=894, 13%; Year 7: n=759, 13%; Year 8: n=664, 12%).

The baseline sample comprised 8,245 individuals, which represents a 71% response rate. Four hundred sixty-eight nursing home residents who lacked information on sleep difficulties were excluded. Of the 7,777 remaining respondents, 168 were excluded due to missing outcome information. We further excluded those who screened positive for dementia at baseline (1,236), leaving a sample of 6,373 respondents, which was representative of 33,151,098 older adults in the US.

Measures

In each of the 8 years, participants report demographic variables. Specifically, participants are asked to report age in categories from 65-69, 70-74, 75-79, 80-84, 85-89, and 90 years of age and older. Participants were asked to report their race/ethnicity by selecting one of

the following categories: White, Black, American Indian, Hispanic/Latino, or Other. Gender was measured by asking participants to select male or female. Participants reported marital status as married, living w/ partner, separated, divorced, widowed, or never married. Education was reported by participants as their highest degree, ranging from high school, some college, college, or graduate degree. Participants were asked to report clinical diagnosis received, including history of a heart attack, depression, hypertension, stroke, and diabetes.

Difficulty initiating sleep was assessed annually with the question "In the last month, how often has it taken more than 30 minutes to fall asleep at night?" Participants recorded their responses on a scale from "every night: 7 nights a week" (1) to "most nights: 5-6 nights a week" (2), "some nights: 2-4 nights a week" (3), "rarely: once a week or less" (4), and "never" (5). Difficulty falling back asleep were measured with the question "In the last month, on the nights you woke up before you wanted, how often did you have trouble falling back asleep?" Participants recorded their responses on a scale from "every night" (1) to "most nights" (2), "some nights" (3), "rarely" (4), and "never" (5). We reverse-coded all sleep responses so that higher values indicated greater difficulties. In accordance with literature showing that sleep difficulty is most problematic when the difficulty is experienced several nights per week,(31) we dichotomized responses so that a value of 1 indicated responses of "most nights" or "every night" as compared to a value of 0 which indicated responses of "never," "rarely," or "some nights."

Screening for incident dementia

To assess cognitive capacity, participants first rated their memory and then performed a memory-related activity (immediate and delayed 10-word recall) (25). Also, as part of the memory assessment, participants were asked to respond to items related to orientation and

perform a clock drawing test to assess executive function (26). For proxy interviews, the Ascertain Dementia 8-item (AD8), an informant screener for dementia, was administered (27,28) A score of 2 or higher on the AD8 is indicative of dementia. Scores on the AD8 and performance on orientation, memory and clock drawing tests were used in our study to form a screening result of either negative (no dementia) or positive (risk for probable dementia). Over the follow-up interval, 321 individuals met the criteria for incident dementia.

All-cause mortality

The participant's death was reported to the study personnel by informants during attempts to contact the participant for their annual interview.

Statistical Analyses

We computed descriptive statistics to summarize the sleep difficulty variables. Next, in order to explore the stability of sleep difficulties reported by participants across study years, we examined the proportion of participants who either reported no sleep difficulties across the 8 years, those who reported the difficulty in 1 year alone, and those who reported the difficulty in two or more years. Next, we use Cox proportional hazards modeling, the most widely used time to event analysis, to model the relationship between covariates and survival, or censored outcomes, which include incident dementia and all-cause mortality in this study (32,33). A significant strength of this study is the availability of annual reports of sleep difficulties; therefore, we employed a time varying covariance process to model the relationship between time-varying sleep difficulties the outcomes of incident dementia and all-cause mortality. This allowed us to examine the relationship between the survival outcomes (i.e., incident dementia

and all-cause mortality) as a function of the change of the time-varying covariates (i.e., sleep difficulties).

In the model, each participant was included until the first probable dementia screening result, a proxy reported all-cause mortality, or they were censored at the end of study, whichever occurred first. Since sleep difficulties changed over time, we treated the annually reported sleep difficulties as a binary time-varying predictor of time to either incident dementia or all-cause mortality that was updated each year. In the case of all-cause mortality, if death occurred in the survey year prior to survey administration, all variables from the year prior to all-cause mortality (i.e., sleep difficulties, demographic details, health conditions, and dementia diagnoses) were carried forward to the year in which the outcome occurred. We constructed the Cox proportional hazard models using the population weights provided by the original study (24). As participants are followed prospectively, the population weights from the first study year are used in the Cox models.

We performed the aforementioned Cox models to examine the relationships between each time-varying sleep difficulty and either incident dementia or all-cause mortality or both. The Cox proportional hazards models were performed both without ("unadjusted") and with potentially confounding factors ("adjusted"), such as age, sex, and education at baseline. Time varying covariates included marital status and total number of chronic conditions. Each health condition (e.g., myocardial infarction, hypertension) was added for a summary total number of all diagnoses reported (referent=0 for no conditions). Meta-analysis has shown that dementia and cognitive impairment are associated with increased risk of all-cause mortality (34,35). Therefore, in the adjusted models predicting all-cause mortality, incident dementia was included as a time-varying covariate.

Finally, we graphed the non-parametric estimates from each hazard function for those with and without each difficulty, at each point in time, for the outcome in question so that we can visually compare the probability of the event (i.e., incident dementia or all-cause mortality) and time-varying predictors (i.e., sleep difficulties) over time. All tests were two-sided with alpha set at 0.05. All analyses were performed in Stata (Version 16, College Station, TX).

RESULTS

Demographic characteristics of the sample at baseline are outlined in Table 6. The 6373 participants are representative of 31 million older adults living in the US. Among respondents at baseline, 21% were 70-74 years of age; 71% were white non-Hispanic; 59% were female, and 53% were either married or living with a partner.

[Insert Table 6]

Across the 8-year time interval, difficulty initiating sleep was reported by 19% (year 3) to 22% (year 1) of participants. Difficulty falling back asleep were reported each year by approximately 15% of the population. Difficulty initiating sleep was consistently reported by approximately 20% of the sample each year.

Regarding the stability of difficulties across study years, 61% of participants reported no difficulty with initiating sleep in any study year, 19% reported the difficult in 1 study year, and 20% reported the difficulty in 2 or more study years. Regarding difficulty falling back asleep, 68% reported no difficulty in any study year, 18% reported difficulty in 1 study year, and 14% reported the difficulty in 2 or more study years.

Sleep difficulties and incident dementia

Table 7 displays the results of the Cox proportional hazard models examining the relationships between time-varying sleep difficulties and incident dementia. Difficulty initiating

sleep was associated with increased dementia risk (HR=1.49, 95%CI: 1.25-1.77) after adjusting for confounders. Similarly, difficulty falling back asleep were associated with greater risk of dementia (HR=1.39, 95%CI:1.14-1.70) after adjusting for confounders. Estimated survival curves display the results of the covariate-adjusted cox models (Figures 3a-1b).

[Insert Table 7]

[Insert Figures 3a-3b]

Sleep difficulties and all-cause mortality

Table 8 displays the results of the Cox proportional hazard models examining the relationships between time-varying sleep difficulties and all-cause mortality. Difficulty initiating sleep was associated with all-cause mortality (HR=1.44, 95%CI: 1.20-1.72) after adjusting for confounders as were difficulty falling back asleep (HR=1.56, 95%CI:1.29-1.89). Estimated survival curves are shown in Figures 4a-4b.

[Insert Table 8]

[Insert Figures 4a-2b]

SUMMARY OF PAPER 1 AND 2 CONCLUSIONS

These studies offer a contribution to the literature on sleep among aging populations in its assessment of incident dementia and all-cause mortality and a range of sleep characteristics, including sleep deficiency and disturbance among older adults. According to our findings from Study 1, longer time to fall asleep and short sleep duration predicted incident dementia, while short sleep duration, difficulty maintaining alertness, napping, and poor sleep quality predict all-cause mortality. Short sleep duration was a strong predictor of both incident dementia and all-cause mortality, suggesting this may be a sleep characteristic that is important – over and above the other predictors – of adverse outcomes among older adults. Study 2 demonstrated that sleep difficulties are associated with a significantly greater risk of incident dementia and all-cause mortality over the following 8 years.

DISCUSSION AND PERSPECTIVES

We demonstrate, in two studies, a consistent, strong relationship between sleep deficiency and difficulties and both incident dementia and all-cause mortality over a period of up to 8-years of follow-up collected from a national sample representative older adults in the US. Specifically, in Study 1, we demonstrate that, compared to sleeping 7-8 hours per night, those sleeping less than 5 hours per night was associated with two-fold greater risk for dementia, and routinely taking 30 minutes or longer to fall asleep was associated with a 45% greater risk for incident dementia. We also found associations between sleep disturbance and deficiency variables and all-cause mortality. Specifically, an increased risk of all-cause mortality was observed for those routinely experiencing difficulty maintaining alertness, those reporting routinely napping, those with poor sleep quality, and those reporting sleeping 5 or fewer hours per night. In study 2, self-reported difficulty with initiating asleep was associated with a 49% increased risk of incident dementia over an 8-year study interval. Risk of incident dementia was increased 39% in those who reported difficulty falling back asleep. Difficulty initiating sleep concurrent with difficulty falling back asleep was associated with a 58% greater risk of incident dementia. The results from Study 2 also demonstrate a strong association between sleep difficulties and all-cause mortality risk. Specifically, difficulty initiating sleep was associated with a 44% greater risk for all-cause mortality. Difficulty falling back asleep was associated with a 56% greater risk of all-cause mortality, and concurrent sleep difficulties were associated with a 80% greater risk of all-cause mortality after adjustment for variables that could potentially confound this relationship.

Research has demonstrated a long disease trajectory and protracted “pre-clinical” phase for those who ultimately develop dementia (36). The development of dementia likely

commences before – in some cases many years prior to – the presentation of symptoms. In an attempt to control for the directionality of the association between sleep difficulties and dementia, we removed those who screened positive for dementia at baseline. After removing those individuals who screened positive for dementia at baseline and controlling for potentially confounding factors, including demographic and health characteristics, our findings show independent relationships between each sleep difficulty and incident dementia. Nevertheless, it is possible that the association observed in our study between sleep difficulties and all-cause dementia is a symptomatic manifestation of the disease that is not necessarily on the causal pathway. Minimally invasive, cost-effective, plasma biomarkers able to provide pre-clinical markers of neurodegeneration may provide insight into disease mechanisms, such as sleep difficulties, that either predict or protect against dementia (37).

These results contribute to the literature in several ways. First, a large body of evidence (e.g., Blackwell et al., 2006; Lim et al., 2013) and two meta analyses summarizing this literature demonstrate an association between sleep difficulties and cognitive impairment (8,39), however, these studies typically used summary measures of sleep difficulties, when the nature of sleep difficulties can vary widely. We evaluated the frequency of three hallmark symptoms of insomnia (i.e., difficulty initiating sleep, difficulty falling back asleep, and concurrent sleep difficulties) and their relationship to dementia. This is important, for each difficulty has nuanced treatment recommendations (6). Second, while research has examined clinical insomnia diagnoses across similar follow-up periods as we examined in this study, the results have been somewhat mixed. Two studies, one with 3 years of follow-up and one with 10 years of follow-up, did not find an association between sleep difficulties and dementia (14,15). Similarly, in the literature examining sleep difficulties and all-cause mortality, studies have examined individual

sleep difficulties, but results have been mixed. One meta-analysis found a strong association between difficulty initiating sleep and all-cause mortality, but not other sleep difficulties, including nighttime awakenings or falling back asleep after waking (17), yet another meta-analysis that aggregated sleep difficulties did not find a relationship with all-cause mortality (20), whereas other research has found associations between specific sleep difficulties and all-cause mortality (17). Our findings show strong associations between individual and concurrent sleep difficulties and dementia and all-cause mortality across 8 years of data.

There are several plausible mechanisms for our primary findings on the relationship between sleep deficiency and difficulties and both dementia and all-cause mortality. First, previous research has shown that, during sleep, there is increased interstitial fluid volume and greater clearance of toxins implicated in the pathogenesis of dementia and AD (40). Further, extended wakefulness has been associated with the accumulation, as well as possibly the impaired clearance, of toxic metabolites in the brain (41,42). Thus, those reporting sleep difficulties such the ones measured in this study, may not benefit from the sleep-related clearance of toxins and/or wake-related toxic accumulation, thereby increasing their risk for dementia over time. Second, routine sleep difficulties, such as difficulty initiating sleep or waking from sleep, may disrupt sleep architecture leading to a reduction in slow wave sleep (SWS). Lower levels of SWS have been associated with higher levels of cerebral spinal fluid amyloid beta which may lead to brain amyloid plague deposition (43). Also, inflammatory biomarkers have been shown to increase more rapidly among those with insomnia compared to those without (22). It could be that the greater risk for dementia and all-cause mortality are due in part, or perhaps exacerbated, by inflammation.

Due to the literature showing a strong association between sleep apnea (a disorder for which loud snoring is the most common symptom) and cognitive impairment (8,44), we were surprised, however, in Study 1, to not see an association between frequent snoring and either incident dementia or all-cause mortality, it was surprising Several possible explanations may be hypothesized for this lack of a significant relationship between snoring and either incident dementia or all-cause mortality. First, the wording of the snoring question ("In the last month, how often did you have trouble staying asleep because you snored loudly, or you woke up gasping or choking") is problematic as it does not account for hearing impairment, which is common among the sample of older adults. Additionally, the question combines several symptoms which are not necessarily part of the same continuum (i.e., difficulty staying asleep *and* loud snoring). Furthermore, common questionnaire wording asks for participants to consider others and their reports of the participant and their snoring. By way of example, one common snoring questionnaire asks participants "do you snore loudly, loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night?"(45) Finally, there were few individuals who reported snoring "Most Nights" or "Every Night" in the sample. Specifically, 9% of the sample in 2013 reported snoring "Most Nights" or "Every Night" and 7% of the sample in 2014 reported snoring "Most Nights" or "Every Night."

Also, it is important to note that insomnia is a heterogenous condition. For this reason, recent research has called for a broader list of psychometric characteristics of insomnia that potentially extend beyond sleep and include such additional factors as childhood trauma, life events, and coping (46). This view of insomnia also highlights the possibility that there are novel contributing factors to each sleep difficulty measured in Study 2. For instance, it could be that nighttime awakenings are a different phenotype than difficulty falling back asleep, with different

precipitating factors, the study of which may uncover novel treatments for the specific sleep difficulties.

While both studies control for covariates such as gender, age, and chronic medical conditions, the analyses examining all-cause mortality must be interpreted with caution given that participants in geriatric research often die during follow-up without having the event of interest (47). Finally, it is possible that despite controlling for confounding, it is possible that residual confounding persists due to either the study design, data collection methods, or recruitment of participants for the NHATS study.

These studies contribute to the growing body of evidence regarding sleep difficulties and both cognitive decline and all-cause mortality by prospectively documenting the relationship between sleep deficiency, specific sleep difficulties (i.e., difficulty initiating sleep, difficulty falling back asleep) and risk for incident dementia and all-cause mortality prospectively across 8 years among a cohort of nationally representative older adults.

Future Research

These findings illuminate a number of opportunities for future research. First, given the long trajectory of AD (36), future research studies should include older adults not expressing symptoms and examine their sleep and risk for dementia over time. Given the association we found between sleep difficulties and incident dementia and all-cause mortality, education and behavioral change programs targeting specific sleep difficulties in older adults should be developed and evaluated on improvements in sleep and downstream impact on dementia and all-cause mortality risk. Further, as our study identified relationships between specific difficulties and dementia, researchers and practitioners may consider designing targeted interventions for these specific sleep issues and their specific behavioral treatment (6). For instance, an intervention to address difficulty initiating sleep may offer stimulus control therapy, or coaching

to reduce the anxiety or conditioned arousal individuals may feel when attempting to go to bed (48). Further, it would be interesting to examine the potential causes of the different sleep difficulties examined in this study, which may uncover potential contributing mechanisms that resulted in the different rates of incident dementia and all-cause mortality observed for difficulty initiating sleep, difficulty falling back asleep, and concurrent difficulties in this study. Another opportunity for future research is to explore sleep among those demonstrating symptoms of depression.

Limitations

The strengths of our study include the large, nationally representative cohort and the prospective nature of these data across 8 years. Notwithstanding these strengths, there are several limitations. First, the sleep characteristics utilized in Study 1 were only available at baseline, not prospectively. Further, in Study 1, age and several chronic health conditions varied between the sub-sample of NHATS participants that replied to the sleep questionnaire compared to the larger NHATS cohort, which is a limitation. It is possible that the responses to the sleep questionnaires are not representative of the Medicare beneficiary population of older adults in the US. Second, insomnia is traditionally characterized by experience of one or more of the following three sleep difficulties: difficulty initiating sleep, difficulty falling back asleep, and early morning awakenings. Unfortunately, the sleep difficulty variables used in Study 2 did not include reports of difficulties with early morning awakenings, the third characteristic of insomnia. Future research may explore this difficulty and its relationship to incident dementia and mortality. Also, although we identify incident dementia using either reported physician-administered diagnoses or performance on validated memory and cognitive measures of dementia, the sensitivity and specificity of these measures is 66% and 87% respectively, with relation to clinical diagnoses (49,50). Access to actual clinical data on dementia diagnoses would have been beneficial.

Finally, although we attempt to control for the directionality of the association between sleep difficulty and dementia by removing those who screened positive for dementia at baseline, research has shown that the AD disease process commences well before the development of symptoms. Therefore, it is possible that sleep difficulties are a symptomatic manifestation of, as opposed to a risk factor for, cognitive decline.

REFERENCES

1. Centers for Disease Control and Prevention. Leading causes of death and numbers of deaths, by sex, race, and Hispanic origin: United States, 1980 and 2017 [Internet]. 2018. Available from: https://www.cdc.gov/nchs/data/hus/2018/006.pdf

2. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2019;15(3):321–87.

3. Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis. Sleep Med Rev. 2016 Dec;30:11–24.

4. Gangwisch JE, Malaspina D, Posner K, Babiss LA, Heymsfield SB, Turner JB, et al. Insomnia and sleep duration as mediators of the relationship between depression and hypertension incidence. American journal of hypertension. 2010;23(1):62–9.

5. Li Y, Zhang X, Winkelman JW, Redline S, Hu FB, Stampfer M, et al. Association between insomnia symptoms and mortality: a prospective study of U.S. men. Circulation. 2014 Feb 18;129(7):737–46.

6. Ohayon MM, Reynolds CF. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). Sleep Med. 2009 Oct;10(9):952–60.

7. de Almondes K, Costa MV, Malloy-Diniz LF, Diniz BS. Insomnia and risk of dementia in older adults: Systematic review and meta-analysis. J Psychiatr Res. 2016 Jun;77:109–15.

8. Bubu OM, Brannick M, Mortimer J, Umasabor-Bubu O, Sebastião YV, Wen Y, et al. Sleep, Cognitive impairment, and Alzheimer's disease: A Systematic Review and Meta-Analysis. Sleep. 2017 01;40(1).

9. Lim ASP, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. Sleep. 2013 Jul 1;36(7):1027–32.

10. Lobo A, López-Antón R, de-la-Cámara C, Quintanilla MA, Campayo A, Saz P, et al. Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia, Alzheimer's type. Neurotox Res. 2008 Oct;14(2–3):263–72.

11. Virta JJ, Heikkilä K, Perola M, Koskenvuo M, Räihä I, Rinne JO, et al. Midlife sleep characteristics associated with late life cognitive function. Sleep. 2013 Oct 1;36(10):1533–41, 1541A.

12. Westwood AJ, Beiser A, Jain N, Himali JJ, DeCarli C, Auerbach SH, et al. Prolonged sleep duration as a marker of early neurodegeneration predicting incident dementia. Neurology. 2017 Mar 21;88(12):1172–9.

13. Potvin O, Lorrain D, Forget H, Dubé M, Grenier S, Préville M, et al. Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. Sleep. 2012 Apr 1;35(4):491–9.

14. Foley D, Monjan A, Masaki K, Ross W, Havlik R, White L, et al. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. J Am Geriatr Soc. 2001 Dec;49(12):1628–32.

15. Elwood PC, Bayer AJ, Fish M, Pickering J, Mitchell C, Gallacher JEJ. Sleep disturbance and daytime sleepiness predict vascular dementia. Journal of Epidemiology & Community Health. 2011 Sep 1;65(9):820–4.

16. Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia:update of the recent evidence (1998-2004). Sleep. 2006 Nov;29(11):1398–414.

17. Ge L, Guyatt G, Tian J, Pan B, Chang Y, Chen Y, et al. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies. Sleep Med Rev. 2019;48:101215.

18. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep. 1995 Jul;18(6):425–32.

19. Lallukka T, Podlipskytė A, Sivertsen B, Andruškienė J, Varoneckas G, Lahelma E, et al. Insomnia symptoms and mortality: a register-linked study among women and men from Finland, Norway and Lithuania. Journal of Sleep Research. 2016;25(1):96–103.

20. Lovato N, Lack L. Insomnia and mortality: A meta-analysis. Sleep Medicine Reviews. 2019 Feb 1;43:71–83.

21. Choi J-W, Song JS, Lee YJ, Won T-B, Jeong D-U. Increased Mortality in Relation to Insomnia and Obstructive Sleep Apnea in Korean Patients Studied with Nocturnal Polysomnography. J Clin Sleep Med. 2017 Jan 15;13(1):49–56.

22. Parthasarathy S, Vasquez MM, Halonen M, Bootzin R, Quan SF, Martinez FD, et al. Persistent insomnia is associated with mortality risk. Am J Med. 2015 Mar;128(3):268-275.e2.

23. Weir D, Faul J, Langa K. Proxy interviews and bias in the distribution of cognitive abilities due to non-response in longitudinal studies: a comparison of HRS and ELSA. Longitudinal and life course studies. 2011;2(2):170.

24. Montaquila J, Freedman VA, Edwards B, Kasper JD. National Health and Aging Trends Study round 1 sample design and selection [Internet]. 2012 p. 1–8. Available from: www.NHATS.org

25. Morris JC, Heyman A, Mohs RC, Hughes JP, Van Belle G, Fillenbaum G, et al. The consortium to establish a registry for Alzheimer's disease (CERAD): I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 1989;39(9):1159–65.

26. Wolf-Klein GP, Silverstone FA, Levy AP, Brod MS. Screening for Alzheimer's disease by clock drawing. J Am Geriatr Soc. 1989 Aug;37(8):730–4.

27. Wolff JL, Spillman BC, Freedman VA, Kasper JD. A national profile of family and unpaid caregivers who assist older adults with health care activities. JAMA internal medicine. 2016;176(3):372–9.

28. Galvin J, Roe C, Xiong C, Morris J. Validity and reliability of the AD8 informant interview in dementia | Neurology. 2006;67(11):1942–8.

29. Phipps AI, Bhatti P, Neuhouser ML, Chen C, Crane TE, Kroenke CH, et al. Pre-diagnostic sleep duration and sleep quality in relation to subsequent cancer survival. J Clin Sleep Med. 2016;12(4):495–503.

30. Layde PM, Beam CA, Broste SK, Connors AF, Desbiens N, Lynn J, et al. Surrogates' predictions of seriously ill patients' resuscitation preferences. Arch Fam Med. 1995 Jun;4(6):518–23.

31. Edinger JD, Bonnet MH, Bootzin RR, Doghramji K, Dorsey CM, Espie CA, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. Sleep. 2004 Dec 15;27(8):1567–96.

32. Cox DR. Regression models and life-tables. Journal of the Royal Statistical Society: Series B (Methodological). 1972;34(2):187–202.

33. Crowley J, Hu M. Covariance Analysis of Heart Transplant Survival Data. Journal of the American Statistical Association. 1977;72(357):27–36.

34. Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. International Journal of Geriatric Psychiatry. 2001;16(8):751–61.

35. Meller I, Fichter MM, Schröppel H. Mortality risk in the octo- and nonagenerians: longitudinal results of an epidemiological follow-up community study. European Archives of Psychiatry and Clinical Neurosciences. 1999 Aug 1;249(4):180–9.

36. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement. 2016 Mar;12(3):292–323.

37. Bateman RJ, Blennow K, Doody R, Hendrix S, Lovestone S, Salloway S, et al. Plasma Biomarkers of AD Emerging as Essential Tools for Drug Development: An EU/US CTAD Task Force Report. J Prev Alzheimers Dis. 2019;6(3):169–73.

38. Blackwell T, Yaffe K, Ancoli-Israel S, Schneider JL, Cauley JA, Hillier TA, et al. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci. 2006 Apr;61(4):405–10.

39. Shi L, Chen S-J, Ma M-Y, Bao Y-P, Han Y, Wang Y-M, et al. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. Sleep Med Rev. 2018;40:4–16.

40. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. science. 2013;342(6156):373–7.

41. Lucey BP, Mawuenyega KG, Patterson BW, Elbert DL, Ovod V, Kasten T, et al. Associations Between β-Amyloid Kinetics and the β-Amyloid Diurnal Pattern in the Central Nervous System. JAMA Neurol. 2017 Feb 1;74(2):207–15.

42. Lucey BP, Hicks TJ, McLeland JS, Toedebusch CD, Boyd J, Elbert DL, et al. Effect of sleep on overnight CSF amyloid-β kinetics. Ann Neurol. 2018 Jan;83(1):197–204.

43. Varga AW, Wohlleber ME, Giménez S, Romero S, Alonso JF, Ducca EL, et al. Reduced Slow-Wave Sleep Is Associated with High Cerebrospinal Fluid Aβ42 Levels in Cognitively Normal Elderly. Sleep. 2016 Nov 1;39(11):2041–8.

44. Liguori C, Mercuri NB, Nuccetelli M, Izzi F, Cordella A, Bernardini S, et al. Obstructive sleep apnea may induce orexinergic system and cerebral β-amyloid metabolism dysregulation: is it a further proof for Alzheimer's disease risk? Sleep Medicine. 2019 Apr 1;56:171–6.

45. Farney RJ, Walker BS, Farney RM, Snow GL, Walker JM. The STOP-Bang equivalent model and prediction of severity of obstructive sleep apnea: relation to polysomnographic measurements of the apnea/hypopnea index. J Clin Sleep Med. 2011;7(5):459-65B.

46. Benjamins JS, Migliorati F, Dekker K, Wassing R, Moens S, Blanken TF, et al. Insomnia heterogeneity: Characteristics to consider for data-driven multivariate subtyping. Sleep Med Rev. 2017 Dec;36:71–81.

47. Buzkova P. Competing risk of mortality in association studies of non-fatal events. PLOS ONE. 2021 Aug 13;16(8):e0255313.

48. Bootzin RR, Epstein D, Wood JM. Stimulus control instructions. In: Case studies in insomnia [Internet]. Springer; 1991. p. 19–28. Available from: http://link.springer.com/chapter/10.1007/978-1-4757-9586-8_2

49. Hunt LJ, Covinsky KE, Yaffe K, Stephens CE, Miao Y, Boscardin WJ, et al. Pain in Community-Dwelling Older Adults with Dementia: Results from the National Health and Aging Trends Study. J Am Geriatr Soc. 2015 Aug;63(8):1503–11.

50. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study. Neuroepidemiology. 2007 Nov;29(1–2):125–32.

TABLES & FIGURES

Table 1
Study 1 demographic characteristics of the sample that received the comprehensive sleep questionnaire in 2013 and 2014 (N=2,610).

		2013 (N=1,575)		2014 (N=1,237)	
Variables		*%*	*N*	*N*	*%*
Gender					
	Male	613	40.4	496	39.8
	Female	904	59.6	749	60.2
Race					
	White	1,091	71.9	895	71.9
	Black	295	19.5	240	19.3
	Hispanic/Latino	45	3.0	31	2.5
	Asian	86	5.7	79	6.4
Marital Status					
	Married	727	47.9	544	43.7
	Living with partner	25	1.7	21	1.7
	Separated	19	1.3	26	2.1
	Divorced	165	10.9	138	11.1
	Widowed	520	34.3	476	38.2
	Never married	61	4.0	40	3.2
Chronic Conditions					
	Depressed	665	43.8	556	44.7
	Heart Attack	41	2.7	37	3.0
	Heart Disease	29	1.9	28	2.3
	High Blood Pressure	39	2.6	27	2.2
	Arthritis	58	3.8	38	3.1
	Diabetes	17	1.1	8	0.6
	Stroke	40	2.6	37	3.0
	Cancer	71	4.7	85	6.8

Table 2
Descriptive statistics summarizing 2013 and 2014 demographic variables (N=2,610).

		2013 (N=1,575)		2014 (N=1,237)	
Variables		***N***	***%***	***N***	***%***
Difficulty with Alertness					
	Never, rarely	901	59.63%	1,722	61.35%
	Some days	424	28.06%	735	26.18%
	Most, every day	186	12.31%	350	12.47%
Nap Frequency					
	Never, rarely	668	44.09%	1,240	44.03%
	Some days	429	28.32%	775	27.52%
	Most, every day	418	27.59%	801	28.44%
Sleep Latency					
	<15 minutes	695	52.93%	1,269	52.22%
	15-30 minutes	385	29.32%	720	29.63%
	>30 minutes	233	17.75%	441	18.15%
Sleep Quality					
	Good, Very Good	1,040	68.74%	1,957	69.62%
	Fair	349	23.07%	630	22.41%
	Very poor, poor	124	8.20%	224	7.97%
Sleep Duration					
	7-8 hours	818	55.05%	1,508	54.74%
	≤5 hours	60	4.04%	119	4.32%
	6-7 hours	419	28.20%	769	27.91%
	≥ 9 hours	189	12.72%	359	13.03%
Snoring					
	Never, rarely	1,390	91.87%	2,605	92.84%
	Some nights	87	5.75%	143	5.10%
	Most, every night	36	2.38%	58	2.07%

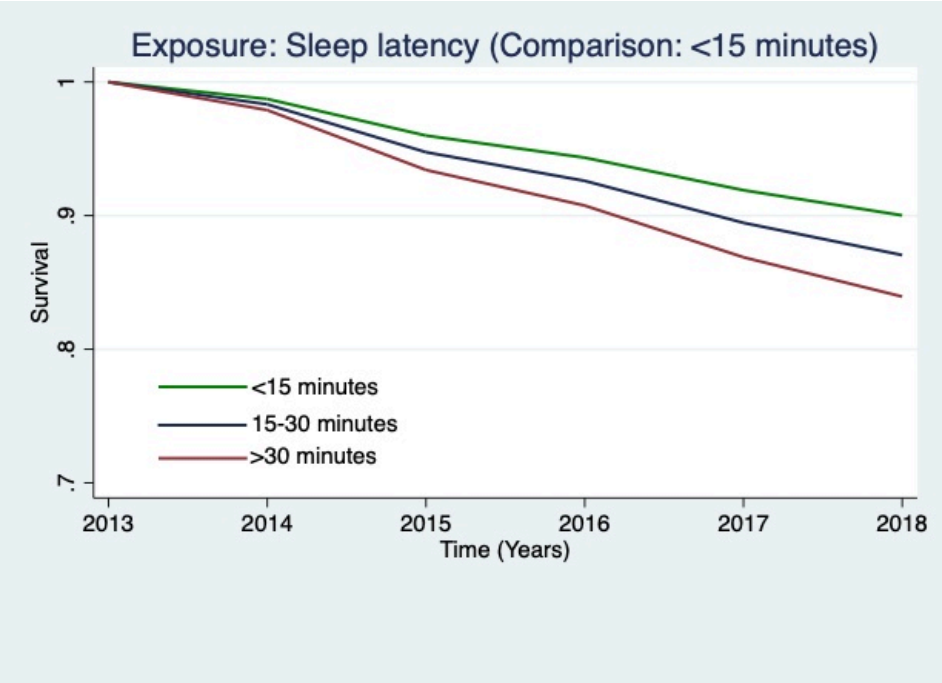
Table 3
Cox models examining each sleep disturbance characteristic and incident dementia (N=2,610).

	Incident Dementia				**Incident Dementia**			
	Unadjusted Models				***Fully Adjusted Models*** [a]			
	HR	*p-value*	*Lower*	*Upper*	*HR*	*p-value*	*Lower*	*Upper*
Difficulty with Alertness								
Never/Rarely	Reference							
Some Days	**1.32**	**.034**	**1.02**	**1.71**	1.13	.392	0.83	1.43
Most Days/Every Day	1.20	.286	0.85	1.71	1.01	.970	0.69	1.46
Nap Frequency								
Never/Rarely	Reference							
Some Days	1.22	.160	0.92	1.61	1.08	.631	0.76	1.45
Most Days/Every Day	1.21	.185	0.94	1.58	0.96	.786	0.71	1.29
Sleep Latency								
<15 minutes	Reference							
15-30 minutes	**1.41**	**.017**	**1.06**	**1.89**	1.22	.192	0.92	1.67
>30 minutes	**1.65**	**.002**	**1.20**	**2.27**	**1.45**	**.032**	**1.03**	**2.03**
Sleep Quality								
Good/Very Good	Reference							
Fair	1.08	.574	0.82	1.43	1.03	.828	0.73	1.31
Poor/Very Poor	1.01	.954	0.65	1.58	1.11	.644	0.65	1.59
Sleep Duration								
7-8 hours	Reference							
≤5 hours	**1.81**	**.011**	**1.14**	**2.86**	**2.04**	**.004**	**1.26**	**3.33**
6-7 hours	0.88	.250	0.62	1.12	0.86	.330	0.63	1.17
≥ 9 hours	**1.43**	**.030**	**1.04**	**1.97**	0.97	.857	0.66	1.39
Snoring								
Never/Rarely	Reference							
Some Nights	**1.62**	**.024**	**1.06**	**2.54**	1.52	.079	0.95	2.44
Most Nights/Every Night	0.70	.479	0.26	1.88	0.39	.184	0.09	1.56

Note.
Bold indicates significance at the p<.05 level.
[a] Adjusted models control for demographic characteristics, including age, marital status, race, education, chronic health conditions, and body weight.

Figure 1
Estimated survival curves displaying the relationships between sleep variables and incident dementia, adjusting for covariates, which were found to be significant in the Cox hazard proportional models.

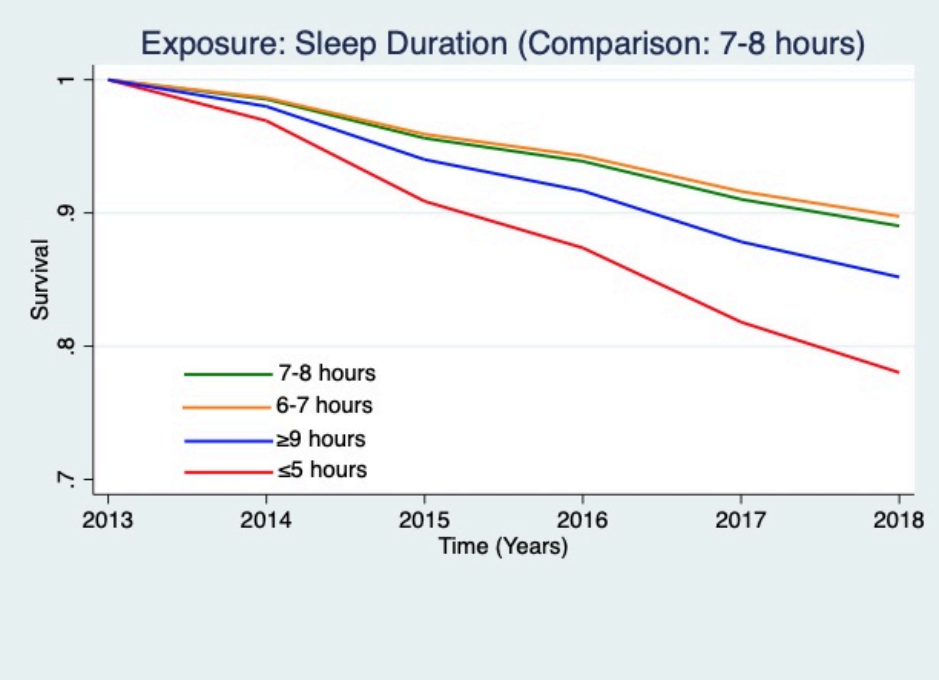
Panel 1A
Survival curve from the Cox model examining incident dementia and sleep latency, adjusting for covariates.



Note.
Sleep latency >30 minutes, as compared to <15 minutes, was associated a greater risk of incident dementia ($p<.05$).

Panel 1B

Survival curve from Cox model examining incident dementia and sleep duration, adjusting for covariates.



Note.

Sleep duration ≤5 hours, compared to 7-8 hours, was associated a greater risk of incident dementia ($p<.01$).

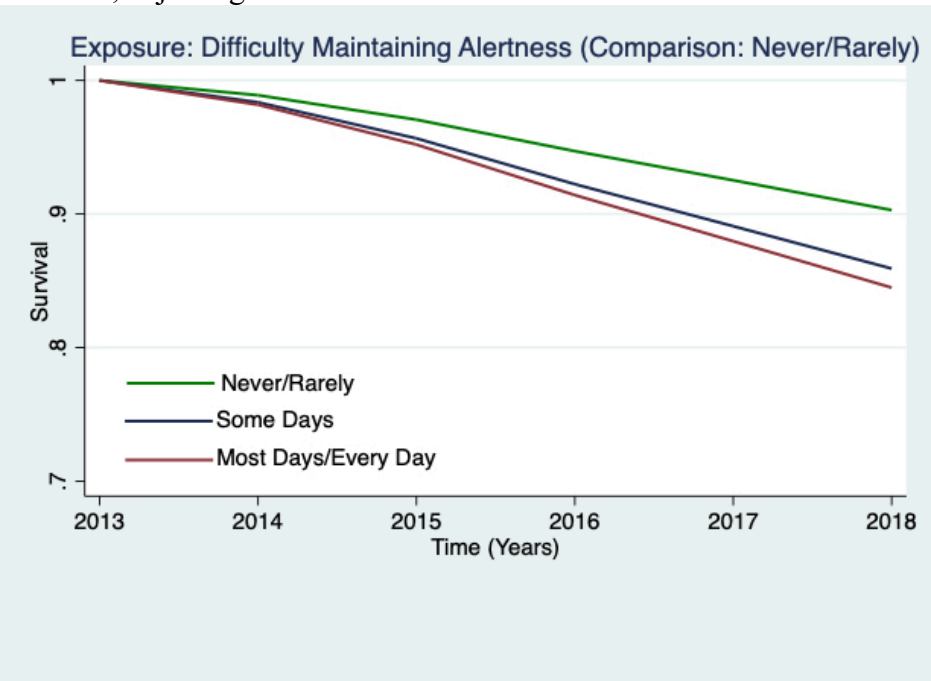
Table 4
Cox models examining each sleep disturbance characteristic and all-cause mortality (N=2,610).

	All-Cause Mortality *Unadjusted Models*				**All-Cause Mortality** *Fully Adjusted Models* [a]			
	HR	*p-value*	*Lower*	*Upper*	*HR*	*p-value*	*Lower*	*Upper*
Difficulty with Alertness								
Never/Rarely				Reference				
Some Days	**1.50**	**.000**	**1.25**	**1.82**	**1.49**	**.004**	**1.13**	**1.94**
Most Days/Every Day	**2.23**	**.000**	**1.79**	**2.75**	**1.65**	**.004**	**1.17**	**2.32**
Nap Frequency								
Never/Rarely				Reference				
Some Days	**1.32**	**.012**	**1.06**	**1.64**	**1.38**	**.032**	**1.03**	**1.85**
Most Days/Every Day	**2.23**	**.000**	**1.84**	**2.79**	**1.73**	**.000**	**1.29**	**2.32**
Sleep Latency								
<15 minutes				Reference				
15-30 minutes	**1.37**	**.012**	**1.06**	**1.64**	1.32	.053	0.99	1.75
>30 minutes	1.20	.140	0.94	1.54	1.14	.444	0.81	1.63
Sleep Quality								
Good/Very Good				Reference				
Fair	1.13	.225	0.93	1.37	1.24	.119	0.94	1.63
Poor/Very Poor	**1.33**	**.043**	**1.00**	**1.77**	**1.75**	**.006**	**1.17**	**2.61**
Sleep Duration								
7-8hours				Reference				
≤5 hours	1.40	.087	0.95	2.07	**2.38**	**.001**	**1.44**	**3.92**
6-7 hours	1.05	.623	0.86	1.29	1.22	.160	0.92	1.61
≥9 hours	**2.14**	**.000**	**1.73**	**2.65**	1.31	.171	0.88	1.94
Snoring								
Never/Rarely				Reference				
Some Nights	**1.41**	**.037**	**1.02**	**1.96**	1.40	.181	0.85	2.29
Most Nights/Every Night	0.98	.959	0.56	1.75	0.71	.506	0.26	1.92

Note.
Bold indicates significance at the p<.05 level.
[a] Adjusted models control for demographic characteristics, including age, marital status, race, education, chronic health conditions, body weight, and incident dementia.

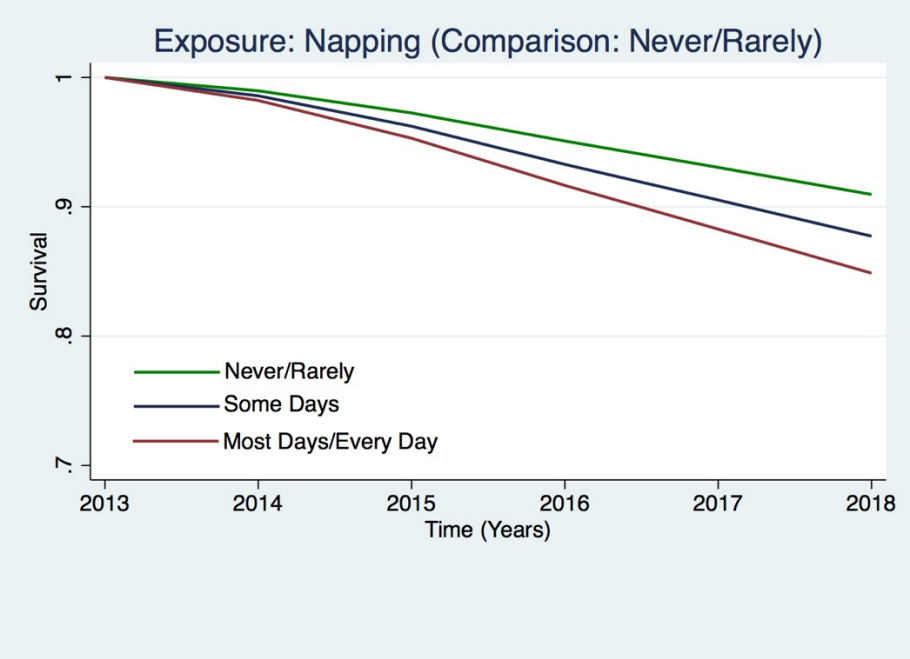
Figure 2
Estimated survival curves displaying the relationships between sleep variables and all-cause mortality, adjusting for covariates, which were found to be significant in the Cox hazard proportional models.

Panel 2A
Survival curve from Cox model examining all-cause mortality and difficulty maintaining alertness, adjusting for covariates.



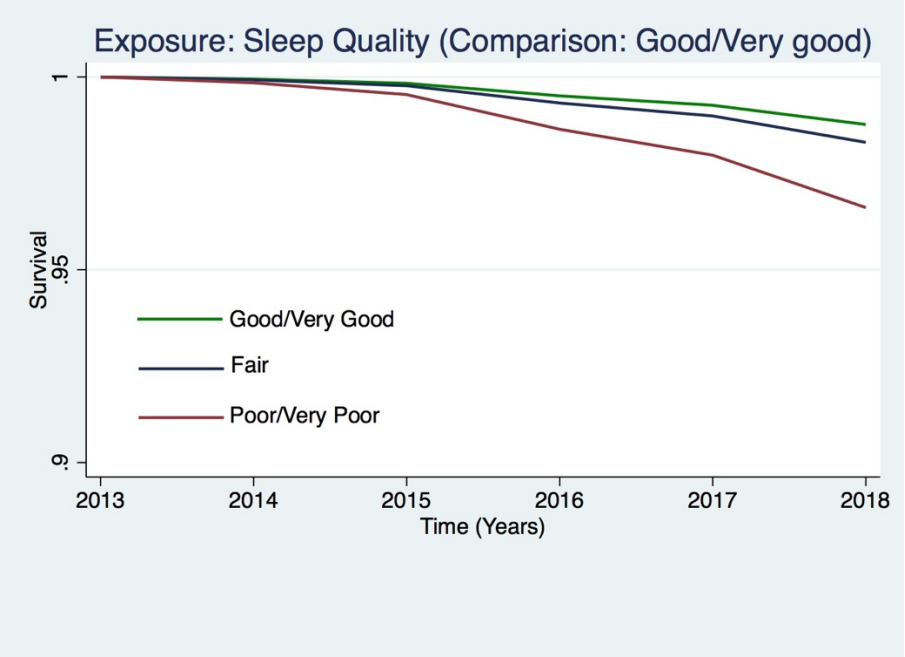
Notes.
Difficulty maintaining alertness "Some Days" and "Most Days/Every Day," as compared to "Never/Rarely, were associated a greater risk of all-cause mortality ($p<.01$ and $p<.01$, respectively).

Panel 2B
Survival curve from the Cox model examining all-cause mortality and napping, adjusting for covariates.



Notes.
Napping "Some Days" and "Most Days/Every Day," as compared to "Never/Rarely," were associated a greater risk of all-cause mortality ($p<.05$ and $p<.01$, respectively).

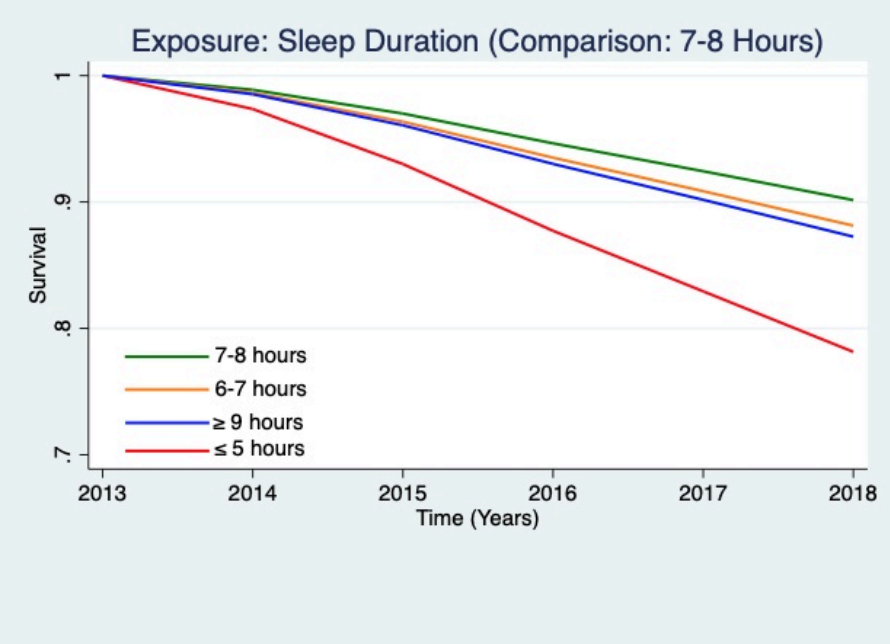
Panel 2C
Survival curve from Cox model examining all-cause mortality and sleep quality, adjusting for covariates.



Note.
Sleep quality reported to be "Poor/Very Poor," as compared to "Good/Very Good," was associated a greater risk of all-cause mortality ($p<.01$).

Panel 2C

Survival curve from Cox model examining all-cause mortality and sleep duration, adjusting for covariates.



Note.

Sleep duration ≤5 hours, as compared to 7-8 hours, was associated a greater risk of all-cause mortality ($p<.01$).

Table 5
Cox model examining all sleep disturbance characteristic and incident dementia (Model A) and all-cause mortality (Model B) (N=2,610), adjusting for covariates.

	Model A **Incident Dementia[a]**				***Model B*** **All-Cause Mortality[b]**			
	HR	*P-Value*	*Lower*	*Upper*	*HR*	*P-value*	*Lower*	*Upper*
Difficulty with Alertness								
Never/Rarely								
Some Days	1.14	.427	0.83	1.57	**1.42**	**.022**	**1.05**	**1.92**
Most Days/Every Day	1.08	.730	0.70	1.67	**1.57**	**.026**	**1.05**	**2.33**
Nap Frequency								
Never/Rarely								
Some Days	1.04	.818	0.75	1.45	1.14	.416	0.83	1.57
Most Days/Every Day	0.99	.954	0.70	1.41	1.34	.080	0.97	1.87
Sleep Latency								
<15 minutes								
15-30 minutes	1.21	.230	0.88	1.66	1.21	.198	0.90	1.63
>30 minutes	1.44	.056	0.99	2.10	0.98	.901	0.67	1.43
Sleep Quality								
Good/Very Good								
Fair	0.76	.148	0.53	1.10	1.05	.766	0.76	1.46
Poor/Very Poor	0.82	.477	0.47	1.42	1.28	.348	0.77	2.13
Sleep Duration								
7-8hours								
≤5 hours	**2.62**	**.001**	**1.48**	**4.64**	**2.07**	**.016**	**1.15**	**3.74**
6-7 hours	0.92	.624	0.65	1.30	1.06	.737	0.77	1.45
≥9 hours	1.06	.779	0.71	1.57	1.23	.330	0.81	1.87
Snoring[c]								
Never/Rarely								
Some /Most /Every Night	1.67	.050	1.00	2.80	1.27	.368	0.75	2.15

Notes.
[a]Adjusted models control for demographic characteristics, including age, marital status, race, education, chronic health conditions, and body weight.
[b]Adjusted models control for demographic characteristics, including age, marital status, race, education, chronic health conditions, body weight, and incident dementia.
[c]Due to a small sample size in "Most/Every Night," the comparison conditions "Some," Most Nights," and "Every Night" were combined as the exposure for snoring.

Table 6
Study 2 demographic characteristics (unweighted N=6,373 respondents; weighted N= 33,151,098).

		Unweighted		*Weighted*	
Variable		***N***	***%***	***N***	***%***
Age	65-69	1,345	19%	9,282,307	28%
	70-74	1,503	21%	9,407,049	28%
	75-79	1,370	20%	6,062,638	18%
	80-84	1,334	19%	4,471,604	14%
	85-89	845	12%	2,571,775	8%
	90+	612	9%	1,178,381	4%
Race	White	4,986	71%	26,404,422	80%
	Black	1,446	21%	2,495,632	8%
	American Indian	169	2%	1,232,367	4%
	Hispanic/Latino	344	1%	1,877,678	6%
	Other	93	12%	940,316	3%
Sex	Male	2,840	41%	4,602,232	42%
	Female	4,169	59%	6,367,287	58%
Marital Status	Married	3,217	51%	17,529,676	57%
	Living w/ partner	138	2%	753,856	2%
	Separated	103	2%	376,053	1%
	Divorced	710	11%	3,536,771	11%
	Widowed	1,980	31%	7,719,918	25%
	Never married	110	3%	1,011,352	3%
Education	High school	31	1%	333,148	1%
	Some college	3,186	53%	16,924,830	53%
	College	2,435	43%	13,698,795	43%
	Grad. degree	669	3%	953,188	3%
Chronic Health Conditions	Heart attack	911	14%	4,110,744	12%
	Depression	2,713	43%	12,658,748	38%
	Hypertension	4,275	67%	19,685,326	59%
	Stroke	616	10%	2,613,432	8%
	Diabetes	1,594	25%	7,181,002	22%

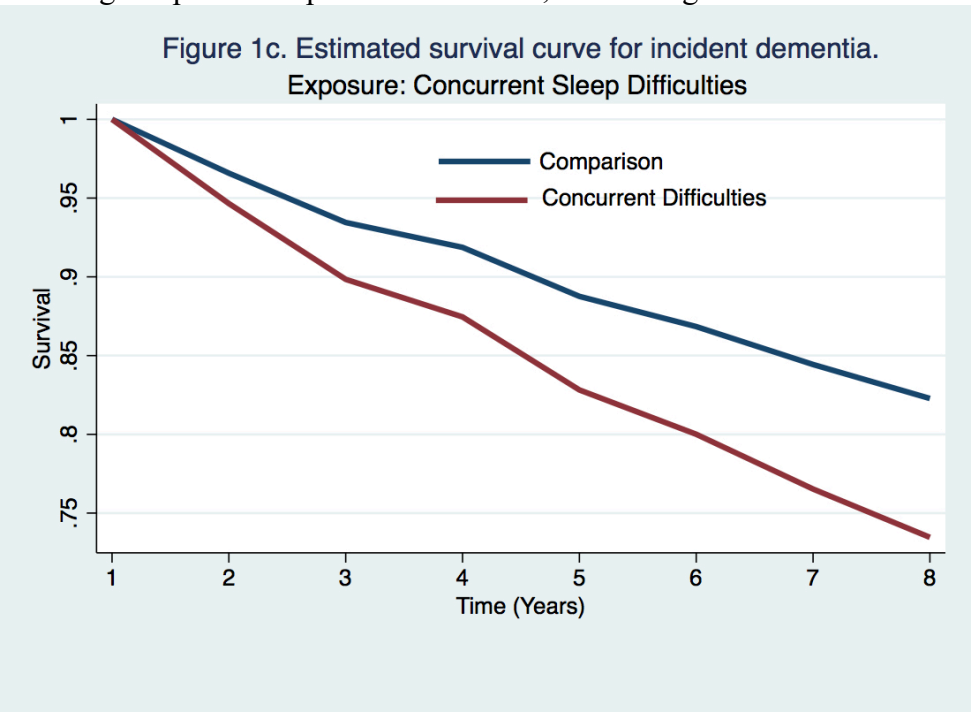
Table 7
Hazard Models Examining the Relationship Between Sleep Difficulties and Risk for Incident Dementia (unweighted N=6,373 respondents; weighted N= 33,151,098).

	Incident Dementia	
	OR (95%CI)	
	Unadjusted[a]	Adjusted[b]
Variable		
Difficulty Initiating Sleep		
Never/rarely/some nights	1 [Reference]	1 [Reference]
Most nights/every night	1.59 (1.34-1.88)	1.49 (1.25-1.77)
Difficulty Falling Back Asleep		
Never/rarely/some nights	1 [Reference]	1 [Reference]
Most nights/every night	1.63 (1.35-1.96)	1.39 (1.14-1.70)

Legend
[a] The unadjusted model includes no covariates.
[b] The adjusted model controls for age, sex, marital status, education, and chronic health conditions.

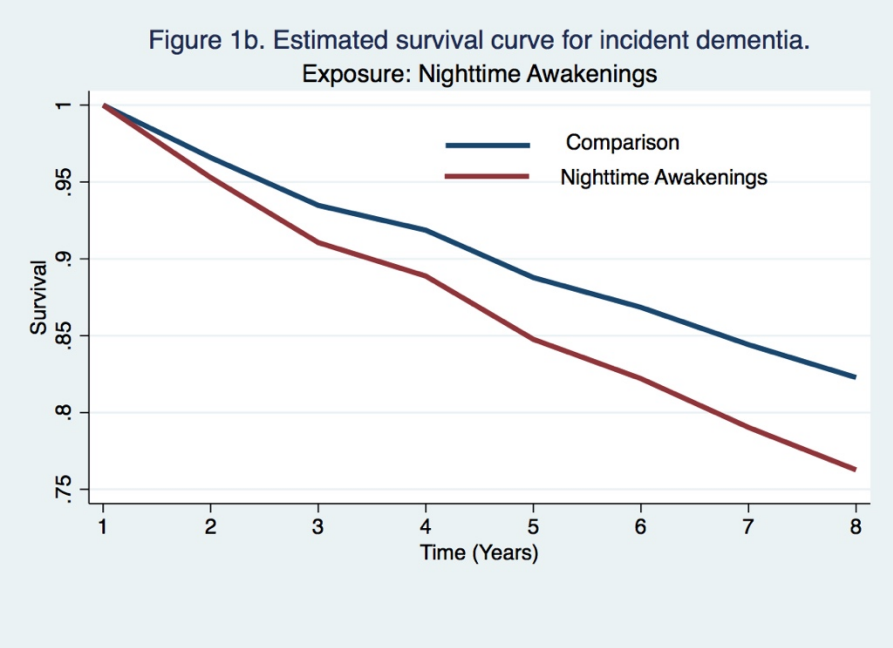
Figure 3
Estimated survival curves from adjusted cox models for incident dementia in the sleep difficulty or comparison conditions, controlling for covariates.

Panel 3A
Estimated survival curve from adjusted cox model for incident dementia in the difficulty initiating sleep and comparison conditions, controlling for covariates.



Panel 3B

Estimated survival curve from adjusted cox model for incident dementia in the nighttime awakening and comparison conditions, controlling for covariates.



Legend

[a] The red line represents the respondents who reported each sleep difficulty "most nights" or "every night."

[b] The blue line represents respondents who did not report difficulty (i.e., reported "never," "rarely," or "some nights").

[c] Respondents who screened positive for dementia at baseline were removed.

[d] The curves represent covariate-adjusted analyses (i.e., age, sex, education, marital status, and chronic health conditions).

Table 8
Hazard models examining the relationship between sleep difficulties and all-cause mortality (unweighted N=6,373 respondents; weighted N= 33,151,098).

	All-cause mortality	
	OR (95%CI)	
	Unadjusted[a]	Adjusted[b]
Variable		
Difficulty Initiating Sleep		
Never/rarely/some nights	1 [Reference]	1 [Reference]
Most nights/every night	1.56 (1.35-1.81)	1.44 (1.20-1.72)
Difficulty Falling Back Asleep		
Never/rarely/some nights	1 [Reference]	1 [Reference]
Most nights/every night	1.65 (1.41-1.95)	1.56 (1.29-1.89)

Legend
[a] The unadjusted model includes no covariates.
[b] The adjusted model controls for age, sex, marital status, education, chronic health conditions, and dementia.

Figure 4
Estimated survival curves from adjusted cox models for all-cause mortality in the sleep difficulty or comparison conditions, controlling for covariates.

Panel 4a
Estimated survival curve from adjusted cox model for all-cause mortality in the difficulty initiating sleep and comparison conditions, controlling for covariates.

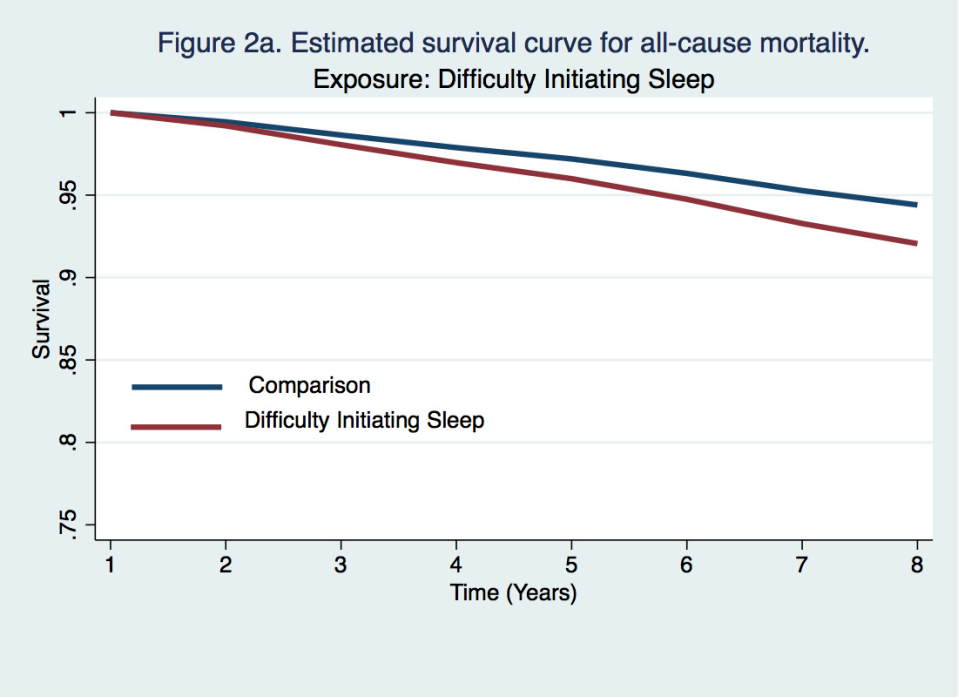
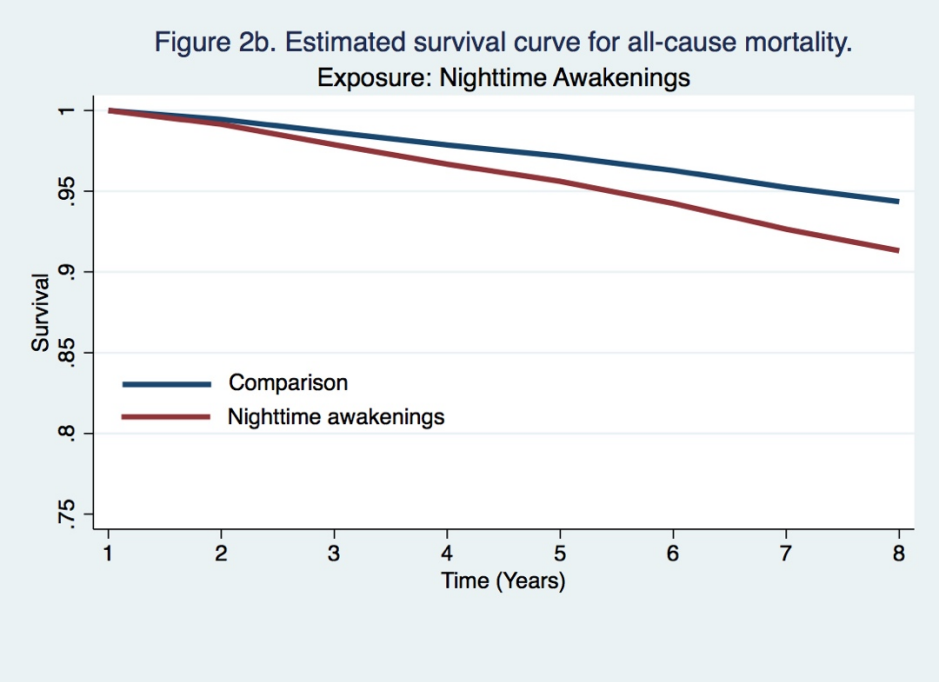


Figure 4b
Estimated survival curve from adjusted cox model for all-cause mortality in the nighttime awakening and comparison conditions, controlling for covariates.



Legend

[a] The red line represents the respondents who reported each sleep difficulty "most nights" or "every night."

[b] The blue line represents respondents who did not report difficulty initiating sleep (i.e., reported "never," "rarely," or "some nights").

[c] Respondents who screened positive for dementia at baseline were removed.

[d] The curves represent covariate-adjusted analyses (i.e., age, sex, marital status, education, chronic health conditions, and dementia).