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Insomnia as a predictor of diagnosed memory problems: 2006–2016 Health and Retirement Study

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Abstract

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Objective: To evaluate the longitudinal relationship in insomnia symptoms over time with incident memory problems and dementia diagnoses among U.S. adults aged 65 years and older.

Methods: Secondary analyses were performed on 9,518 elderly participants (≥ 65 years) who completed the 2006 wave of the Health and Retirement Study (HRS) and were followed-up to determine if insomnia symptom scores (2006–2014) were associated with time-to-onset of [1] physician-diagnosed "memory-related disease", "Alzheimer's disease" and/or "dementia, senility or any other serious memory impairment" and [2] diagnosis of dementia based on HRS-specific criteria. Cox proportional hazards models were constructed adjusting for socio-demographic, lifestyle, and health characteristics.

Results: In fully adjusted models, severe insomnia symptoms were associated with increased risk of physician-diagnosed memory problems. Individuals reporting any change (increase or decrease) in insomnia symptoms during the 2006–2010 period were more likely to be diagnosed with dementia based on HRS criteria. Finally, those who experienced an increase in the severity of insomnia symptoms over time exhibited 41–72% increased risks of physician-diagnosed memory problems and 45–58% increased risks of dementia diagnosis based on HRS criteria.

Conclusions: When severe insomnia symptoms increased over time, physician-diagnosed memory problems and dementia diagnoses also increased among U.S. elderly people over a 10-year follow-up period. More studies are required to confirm these findings using large prospective cohort designs and validated tools.

Keywords

Aging; Alzheimer's disease; Insomnia; Dementia; Neurodegenerative; Sleep

1. INTRODUCTION:

Poor sleep is recognized as a modifiable behavioral characteristic that is implicated in the onset, progression and exacerbation of a wide range of chronic conditions, including diabetes[1–3], cardiovascular diseases[4–6], cancers[7–9], injuries[10–12] and cognitive disorders.[13–15] Research also suggests that sleep may affect immune, metabolic, thermoregulatory as well as cardio-respiratory functioning.[16] A recent survey by the National Sleep Foundation indicated that nearly 53% of U.S. adults reported less than seven hours of sleep on workdays and that 37% of them reported their sleep quality as fair or poor.[17] Although evidence remains inconclusive, population-based studies have found that suboptimal sleep duration (≤ 6 h or ≥ 9 h) may increase cardiovascular-, cancer- and all-cause mortality rates[18, 19] whereas cardio-metabolic risk, social functioning and life expectancy may be influenced by indicators of sleep quality.[20] Furthermore, a wide range of sleep disturbances that could impact sleep quality, including insomnia and obstructive sleep apnea, has been previously linked to detrimental physical, mental and cognitive health outcomes.[16, 21] Although frequently undetected, symptoms of insomnia have been reported in 40–70% of older adults whereas the prevalence of moderate-to-severe obstructive sleep apnea (OSA) has been estimated at 9% among middle-aged men and at 4% among middle-aged women.[22, 23]

Aging is often accompanied by a decline in sleep duration and quality with nearly half of older adults experiencing long-term sleep disturbances.[24] In particular, the tendency to

wake up repeatedly during the night, to remain awake for longer periods of time, and to experience fewer hours of sleep increases with age.[24] The burden of chronic disease attributable to poor sleep is expected to rise in response to changes in the age structure of the population, which will feature a near doubling of the number of adults aged 65 years and older in developed countries by 2050.[16] Population aging is also expected to increase the burden of neurodegenerative disorders such Alzheimer's (AD)[25] and Parkinson's[26, 27] diseases. Together, these demographic and epidemiological trends underscore the importance of understanding sleep as a modifiable pathway to neurodegenerative disorders. To date, a limited number of prospective cohort studies have attempted to evaluate the temporal relationship between sleep and broadly defined neurodegenerative disorders[28, 29], and fewer have assessed insomnia symptoms as a risk factor for diagnosed memory problems.[30] Accordingly, we performed secondary analyses of existing data from the Health and Retirement Study (HRS) to evaluate the longitudinal relationship between insomnia symptoms and incident memory problems as diagnosed by a physician or HRS-specific criteria among U.S. elderly people, 65 years and older at baseline.

2. MATERIALS AND METHODS:

2.1. Data source:

Initiated in 1992, the HRS is an ongoing, nationally representative longitudinal study of community-dwelling U.S. adults over the age of 50 and their spouses of any age. The HRS was designed to study economic well-being, labor force participation, health and family composition among older adults through biennial surveys administered by telephone or face-to-face interviews. Although the HRS only interviews community-dwelling adults in their baseline surveys, respondents who enter long-term care facilities are also retained. Multistage probability sampling of U.S. households within geographical strata was performed whereby African Americans, Hispanics and residents of Florida were over-sampled. Response rates at baseline and follow-up waves were >80% for all HRS interviews. Written informed consent was provided by all participants and the University of Michigan's Institutional Review Board approved study protocols. The HRS is sponsored by the National Institute on Aging (grant number U01AG009740) and the Social Security Administration. Because our study relied on de-identified, public-use data, it was considered research not involving human subjects by our institution. Details of HRS procedures were reported elsewhere.[31, 32]

2.2. Study population:

The original HRS study consists of participants from whom data were collected in 1992, 1994 and 1996, and the Study of Asset and Health Dynamics of the Oldest Old (AHEAD) consists of those from whom data were collected in 1993 and 1995. The two studies were merged and two new cohorts (the Children of the Depression (born 1924–1930) and the War Babies (1942–1947)) were added in 1998. Subsequently, the Early Baby Boomers (1948–1953) cohort was added in 2004, the Mid Baby Boomers (1954–1959) cohort was added in 2010 and the Late Baby Boomers (1960–1965) cohort was added in 2016. We restricted our analyses to a baseline cohort of 2006 HRS wave participants, 65 years and older, who were followed-up for up to 10 years (2006–2016) until they developed the outcome

of interest, were lost to follow-up or were deceased. Mid Baby Boomers and Late Baby Boomers cohorts were enrolled after 2006 and therefore automatically excluded from this study. Starting in 2006, HRS began collecting data on psychosocial factors, whereby half of the sample completed detailed face-to-face interviews that included physical, biological and psychosocial measures, and the other half completed a core interview by telephone. To reduce study-related costs and burden on participants, enhanced interviewing was alternated between half-samples at each subsequent wave. Specifically, interviewers left behind a self-report psychological questionnaire at the end of each interview, and respondents were asked to return the completed questionnaire by mail to the University of Michigan. The response rate for the leave-behind questionnaire among interviewees was ~90%. Since psychosocial data were collected every 4 years, our sample was restricted to HRS participants with complete exposure data in 2006, 2010 and/or 2014 and complete follow-up wave data in 2008, 2010, 2012, 2014 and/or 2016. We further excluded participants with a history of physician-diagnosed "emotional, nervous or psychiatric problems" and/or "memory-related disease" by the 2006 HRS wave (when examining physician-diagnosed memory problems or HRS-specific dementia diagnosis) and additionally those diagnosed with dementia during the 2006 HRS wave using HRS-specific criteria (when examining HRS-specific dementia diagnosis). Finally, we excluded participants with missing data on key socio-demographic, lifestyle and health characteristics, the main exposure (insomnia symptoms) and/or outcome variables of interest.

2.3. Variable definitions:

2.3.1. Insomnia symptoms: Key symptoms of insomnia comprise difficulty initiating sleep, difficulty maintaining sleep, early morning awakening and nonrestorative sleep. As such, the HRS applied a modified version of the Jenkins Sleep Questionnaire, a validated and widely used screening tool that measures self-reported sleep complaints rather than diagnosed sleep disorders. Frequency of insomnia symptoms was determined among HRS participants at 2006, 2010 and 2014 waves using four questionnaire items ("How often do you have trouble falling asleep?"; "How often do you have trouble with waking up during the night?"; "How often do you have trouble with waking up too early and not being able to fall asleep again?"; "How often do you feel really rested when you wake up in the morning?") with possible responses being "most of the time", "sometimes" or "rarely or never". Those reporting "most of the time" to any of the first three symptoms and those reporting "sometimes" or "rarely or never" to the fourth symptom were considered as having insomnia symptoms. Total insomnia symptoms score was computed that ranges between "0=no insomnia" and "8=severe insomnia" after reverse-coding responses to the first three items. We also evaluated insomnia symptoms severity at each wave (2006, 2010 and 2014) by identifying a symptom as positive among participants indicating having it "most of the time" for the first three items and "rarely or never" for the fourth item, and subsequently created an index for the number of insomnia symptoms ranging between 0 and 4. We used these insomnia symptom scores to create variables indicating between-wave (2006 to 2010, 2010 to 2014, 2006 to 2014) changes in insomnia symptoms whereby a positive number suggested an increase, a negative number suggested a decrease and a zero suggested no change over time.[33, 34]

2.3.2. Physician-diagnosed memory problems: Cumulative incidence of self-reported physician-diagnosed memory problems was defined among participants using questionnaire items pertaining to "memory-related disease" (2008 HRS wave), "Alzheimer's disease" (2010–2016 HRS waves) and/or "dementia, senility or any other serious memory impairment" (2010–2016 HRS waves). [35, 36]

2.3.3. Health and Retirement Study Dementia diagnosis: The Langa-Weir classification of cognitive function (1 = "Normal", 2 = "Cognitively Impaired but not Demented", 3 = "Demented") is available at each HRS wave since 1995, with imputation of missing data. For self-responding HRS participants ≥ 65 years, a 35-point scale was used that combines immediate and delayed 10-noun free recall test to measure memory (0–20), a serial sevens subtraction test to measure working memory (0–5), a counting backwards test to measure speed of mental processing (0–2) and three mental status questions (date naming (0–4); object naming (0–2); naming the president and the vice president of the United States (0–2)). Since 2000, for proxy-responding HRS participants ≥ 65 years, an 11-point cognition scale (0–11) was generated based on proxy assessment of memory (0 = "excellent", 1 = "very good", 2 = "good", 3 = "fair", 4 = "poor"), Instrumental Activities of Daily Living limitations (0–5), and interviewer's assessment of cognitive impairment (0 = "none", 1 = "may have impairment", 2 = "has impairment"). HRS-specific dementia diagnosis was defined as a dichotomous variable (0 = "Normal/Cognitively Impaired but not Demented", 1 = "Demented").[37–41]

2.3.4. Socio-demographic characteristics: Baseline HRS data were extracted on sex (male, female), age (65–69, 70–74, 75–79, 80+ years), race (White/Caucasian, Black/African American, Other), ethnicity (Hispanic, non-Hispanic), marital status (married, not married), education (no degree, GED or high school diploma, college degree or higher), and total wealth (<25,000; 25,000–124,999; 125,000–299,999; 300,000–649,999; 650,000+).[42]

2.3.5. Lifestyle characteristics: Baseline HRS data were extracted from the 2006 wave on smoking status (never, ever), frequency of alcohol consumption (abstinent, 1–3 days per month, 1–2 days per week, ≥3 days per week) and frequency of moderate and vigorous exercise reported as never, 1–4 times per month, or >1 times per week.[16, 36]

2.3.6. Health characteristics: Baseline HRS data were extracted from the 2006 HRS on body mass index (BMI), presence of cardiovascular risk factors, self-rated health and depressive symptoms. BMI was defined as a continuous variable and categorized as <25, 25–29.9, ≥30 kg/m^2. Cardiovascular risk factors were determined through physician-diagnosed hypertension, diabetes, stroke, heart attack, coronary heart disease, angina, congestive heart failure and/or other heart problems. Self-rated health was evaluated using a single item ("would you say your health is excellent, very good, good, fair, or poor?") and dichotomized as "excellent/very good/good" versus "fair/poor". Depressive symptoms were assessed using the modified 8-item Center for Epidemiological Studies Depression Scale (CES-D) and total CES-D score was calculated with higher scores indicating worse symptoms of depression.[16, 32]

2.4. Statistical analysis:

All statistical analyses were conducted using STATA version 15 (College Station, TX), taking complex sampling design into consideration. Cox proportional hazards regression models were constructed to examine longitudinal relationships between key exposure and outcome variables, as described in similarly conducted HRS-based studies.[33, 43, 44] We used age at each follow-up time and calculated time-to-event by subtracting the age at baseline from the age at occurrence of an event. Specifically, we examined each insomnia indicator (insomnia status, insomnia score, severe insomnia status, severe insomnia score, change in insomnia score over time, change in insomnia severity over time) as a predictor of cumulative incidence or time-to-onset of memory problems or dementia diagnosis while sequentially controlling for socio-demographic, lifestyle and health characteristics. Model I controlled for socio-demographic characteristics alone, Model II controlled for socio-demographic and lifestyle characteristics and Model III controlled for socio-demographic, lifestyle and health characteristics. Complete subject analysis was performed using available data on variables of interest and two-tailed statistical tests were evaluated at an alpha level of 0.05.

Data Availability Statement:

The authors have access to de-identified HRS raw data through online registration on study's website. Therefore, data are restricted and cannot be publicly shared for legal and ethical reasons.

3. RESULTS:

A total of 11,401 participants were ≥65 years at baseline and, of those, 9,550 did not report a history of "emotional, nervous or psychiatric problems" and/or "memory-related disease" as of the 2006 wave of HRS data collection. Furthermore, 9,518 participants remained after excluding missing data on smoking status (n=94), frequency of alcohol drinking (n=2), frequency of moderate exercise (n= 9), frequency of vigorous exercise (n=14), self-rated health (n=12) and CES-D (n=535). Of those, 9,469 had complete data on insomnia symptoms during the 2006 wave, 7,392 had complete data on insomnia symptoms during the 2010 wave and 5,679 had complete data on insomnia symptoms during the 2014 wave of data collection. After accounting for losses to follow-up and deaths, 4,548 had complete self-reported data on memory problems during the 2006–2016 HRS waves. The baseline sample of 9,518 HRS participants contributed 99,176 person-years of follow-up and a total of 1,146 failures in terms of physician-diagnosed memory problems at the end of the follow-up period (Figure 1). Sub-analyses involving a maximum of 6,907 HRS participants with no dementia diagnosed based on HRS criteria in 2006 and with complete data thereafter were performed to assess insomnia symptoms in relation to HRS-based dementia diagnosis.

Table 1 presents the socio-demographic, lifestyle and health characteristics of the study population, which consists of 9,518 HRS participants (55% female) with mean age of 75 years at baseline. Eighty-nine percent of participants were of non-Hispanic white race, 6% self-reported Hispanic origin, 58% were married, 39% had ≥ college degree, and 24%

reported total wealth ≥ $650,000. Furthermore, 57% were ever smokers, 50% abstained from alcohol consumption, 55% performed moderate exercise >1 time/week, and 66% did not perform any vigorous exercise. Nearly 72% had one or more cardiovascular risk factor and 28% reported self-rated health as fair or poor. The mean BMI of participants was 28.3 kg/m^2, and their mean CES-D score was 1.2.

Table 2 presents summary statistics for key exposure and outcome variables over the 2006–2016 HRS waves. The rate of insomnia symptoms appeared to be stable over three data waves (2006, 2010, 2014), with nearly 40% having insomnia symptoms. By contrast, the rate of having at least one severe insomnia symptom decreased from 81.5% in 2006 to 75.4% in 2014. Whereas the average of insomnia symptom scores increased from 2.4 in 2006 to 2.7 in 2014, there was no substantial change in the average score for severe insomnia symptoms. Change over time (2006–2010, 2010–2014, 2006–2014) suggested a nearly equal proportion of HRS participants who experienced no change, an increase or a decrease in prevalent insomnia symptoms. Finally, cumulative incidence of physician-diagnosed memory problems increased from 3.5% in 2008 to 11.0% in 2016 and cumulative incidence of HRS-based dementia diagnosis among 6,907 study-eligible subjects increased from 1.6% in 2008 to 10.8% in 2016.

Table 3 presents Cox proportional hazards models for any or severe insomnia symptoms as a predictor of time-to-onset of physician-diagnosed memory problems, before and after adjustment for baseline characteristics. In fully adjusted models, there was no significant association between insomnia symptoms and physician-diagnosed memory problems (hazard ratio (HR) = 0.96, 95% confidence interval (CI): 0.84, 1.12) whereas severe insomnia symptoms were associated with increased risk of physician-diagnosed memory problems (HR=1.21, 95% CI: 1.02, 1.44). Results also suggested that a unit increase in insomnia symptoms was associated with a slight decrease (HR=0.95, 95% CI: 0.92, 0.99) whereas a unit increase in severe insomnia symptoms was associated with a slight increase (HR=1.10, 95% CI: 1.04, 1.18) in the risk of physician-diagnosed memory problems, after controlling for socio-demographic, lifestyle and health characteristics. Participants who experienced decreased insomnia symptoms (any or severe) between different time periods had similar risks of physician-diagnosed memory problems when compared to those who did not experience a change in their insomnia symptoms, after controlling for confounders. By contrast, those who experienced an increase in the severity of insomnia symptoms over time (2006–2010, 2010–2014, 2006–2014) exhibited 41%–72% increased risks of physician-diagnosed memory problems in fully adjusted models.

Table 4 presents Cox proportional hazards models for any or severe insomnia symptoms as a predictor of time-to-onset of HRS-based dementia diagnosis, before and after adjustment for baseline characteristics. In fully-adjusted models, HRS-based dementia diagnosis was associated with any change in insomnia symptoms between 2006 and 2010 (Increase: HR=1.27, 95% CI: 1.03, 1.55; Decrease: HR=1.36, 95% CI: 1.09, 1.69). By contrast, HRS-based dementia diagnosis was only associated with increase in severity of insomnia symptoms between time periods (2006–2010: HR=1.58, 95% CI: 1.31, 1.90; 2010–2014: HR=1.47, 95% CI: 1.21, 1.80; 2006–2014: HR=1.45, 95% CI: 1.18, 1.79).

4. DISCUSSION:

In this prospective cohort study of HRS participants aged ≥65 years at baseline, we evaluated distinct ways of defining insomnia symptoms as predictors of future diagnosis of memory problems or dementia over a 10-year period. Our results indicated that severe rather than any insomnia symptoms was positively associated with future physician-diagnosed memory problems, including AD and dementias, after adjusting for socio-demographic, lifestyle and health confounders. We also observed that in fully adjusted models an increase in insomnia symptom severity over time was predictive of physician-diagnosed memory problems as well as dementia diagnosis based on HRS criteria. These findings are consistent with a previously published study.[45]

The primary focus of recent studies has been on sleep duration rather than insomnia symptoms in relation to neurodegenerative disorders. Several of these studies found that longer rather than shorter sleep duration was associated with worse cognitive function and increased risks of AD and dementias. For instance, Gildner and colleagues conducted a longitudinal study of Mexican adults from the World Health Organization's Study on global AGEing, who were 50 years and older and healthy sleepers at baseline, to examine if changes in sleep duration may impact rate of cognitive decline as determined by immediate and delayed verbal recall, forward and backward digit span, and verbal fluency.[46] Their study suggested that declines in overall cognitive function, attention/working memory and executive function were associated with longer sleep duration among individuals who slept 6–9 hours at baseline.[46] Low and colleagues analyzed cross-sectional data on 1,496 adults aged ≥60 years who participated in the 2013–2014 National Health and Nutrition Examination Surveys to evaluate weekday (or workday) nighttime sleep duration in relation to Consortium to Establish a Registry for AD Word Learning (CERAD-WL) immediate recall, CERAD-WL delayed recall, Animal Fluency Test (AFT), Digital Symbol Substitution Test (DSST) and subjective cognitive problems (SCP).[47] Their study indicated no significant association of shorter sleep duration with cognition.[47] By contrast, individuals who slept 10 hours or longer had lower scores on CERAD-WL immediate recall, CERAD-WL delayed recall, AFT, and DSST, and were more likely to report SCP and those who slept ≥8 hours had lower scores on CERAD-WL delayed recall.[47] A longitudinal study involving 214 Swedish adults, ≥75 years, who were dementia-free at baseline and had three years of follow-up, was conducted by Hahn and colleagues[48] whereby self-reported (reduced duration and/or depth) in sleep pattern was evaluated in relation to incident all-cause dementia and AD over 9 years of follow-up. After controlling for age, gender and education, reduced sleep duration was associated with increased all-cause dementia (HR=1.75; 95% CI: 1.04–2.93) and AD (HR=2.01; 95% CI: 1.12–3.61).[48] These results persisted after controlling for lifestyle and vascular factors but not after controlling for depressive symptoms, implying that depressive symptoms may explain these observed relationships.[48] In this study, adjustment for health-related characteristics, including depressive symptoms, did not alter the direction or magnitude of the hypothesized relationships between changes in insomnia symptoms over time and memory problems, despite established comorbidity of sleep disorders with psychiatric conditions.[49]

Classified as insomnia, circadian rhythm (sleep-wake schedule) disorders, hypersomnia, sleep-related breathing disorders (SBD), motor disturbances in sleep, and parasomnias, sleep disorders are associated with a wide range of neurologic conditions, including neurodegenerative disorders such as AD and dementias.[50] However, it remains unclear whether memory problems resulting from AD and/or dementias may be associated with specific types of sleep disorders but not others. Whereas evidence that links insomnia to memory problems has been scarce, several studies have assessed SBD, especially OSA, as a potential marker of AD and/or dementias. In a cross-sectional study of 127 community-dwelling older adults from the Age-Well randomized clinical trial who were cognitively unimpaired at baseline and had completed detailed neuropsychological assessment, polysomnography, magnetic resonance imaging, florbetapir and fluorodeoxyglucose positron emission tomography scans, Andre and colleagues examined polysomnography-based SBD parameters as risk factors for brain changes (amyloid deposition, gray matter volume, perfusion, and glucose metabolism).[25] Although participants with SBD showed greater amyloid burden (Cohen d=0.83), gray matter volume (Cohen d=0.75), perfusion (Cohen d=0.86), and metabolism (Cohen d=1.04), no association was found with cognition, self-reported cognitive and sleep difficulties, or excessive daytime sleepiness symptoms.[25] Gronewold and colleagues examined the relationship between SBD severity measured using a portable sleep apnea examination device with severity of cognitive, emotional, and mobility impairment using a clinical sample of 82 geriatric patients with mild dementia.[51] Investigators found low to moderate associations between SBD and dementia severities.[51] In a systematic review of the literature, Bubu and colleagues highlighted evidence linking OSA and Continuous Positive Airway Pressure treatment to mild cognitive impairment and AD across different age groups.[13]

Our finding that increasingly severe insomnia symptoms may lead to worse cognition and subsequently a diagnosis of dementia is biologically plausible. Based on animal studies, sleep may be critical for metabolic homeostasis with evidence for increased β-amyloid clearance during sleep.[52] Spira and colleagues analyzed data on 70 Baltimore Longitudinal Study on Aging participants and found that shorter sleep duration as well as lower quality of sleep was associated with greater β-amyloid burden in specific brain regions.[53] Nevertheless, the temporal relationship between sleep disorders and memory problems remains inconclusive.[25, 51, 54] In fact, evidence suggests that this relationship may be bi-directional and that distinct outcomes may occur when evaluating individuals who experienced sleep disorders across distinct time windows. According to Ju and colleagues, experimental evidence indicates that sleep deprivation may increase soluble beta-amyloid concentrations with chronic accumulation of beta-amyloids potentially leading to more wakefulness and altered sleep patterns, whereas early deposition of beta-amyloid in the context of normal cognition, mild dementia, and AD is associated with sleep abnormalities, and as such sleep and neurodegenerative disease may influence each other.[55] According to Musiek and colleagues sleep-wake cycle and circadian rhythm disruption is frequently observed in the context of AD and has been considered as a late outcome of neurodegeneration, although recent evidence suggests it can occur earlier and could precede onset of cognitive symptoms, affecting disease process through biological mechanisms involving beta-amyloid deposition among others.[56] A study by Choe and colleagues

involving 202 cognitively normal older adults who participated in the Korean Brain Aging Study for the Early Diagnosis and Prediction of AD examined the relationship between sleep experiences during the young adulthood, midlife, and late-life periods with in vivo beta-amyloid deposition and AD signature regional neurodegeneration.[57] Sleep duration and quality were repeatedly evaluated (20–30s, 40–50s, and most recent month), and outcomes were determined using comprehensive clinical assessment, Pittsburgh Compound B positron emission tomography, Fluorodeoxyglucose-PET, and magnetic resonance imaging.[57] After controlling for age, gender, education, APOE epsilon 4 status, vascular risk score, Hamilton Depression Rating Scale score, and use of sleep medication, poor sleep quality, and short sleep duration during midlife were significantly associated with increased beta-amyloid deposition and AD signature regional hypometabolism.[57] Although current poor sleep quality appeared to be associated with increased beta-amyloid deposition, this association disappeared after controlling for the effects of mid-life sleep quality.[57] Neither quality nor duration of sleep during young adulthood was found to be related to beta-amyloid deposition or neurodegeneration.[57]

To our knowledge, this study is among the largest population-based, longitudinal studies to have examined the hypothesized relationships of interest. Whereas numerous studies have analyzed sleep indicators from the HRS[33, 58], none of them have evaluated their association with diagnosed memory problems, AD, and/or dementias among elderly participants over a 10-year period of time. Nevertheless, study findings should be interpreted with caution in light of several limitations. First, a substantial proportion of HRS subjects identified at baseline had died or were lost to follow-up over the 10-year follow-up period potentially leading to selection bias. Second, measures of insomnia symptoms, memory problems and dementia were self- or proxy-reported, and memory problems were determined based on interactions with medical professionals. In addition to differences in criteria used to establish AD and/or dementia among medical professionals, there is notable variation in the frequency with which HRS respondents may seek medical care and with potential for disparities by race, ethnicity and socioeconomic status. Ascertainment bias may be an issue since HRS participants with sleep difficulties may be diagnosed with dementia because they are more likely to seek healthcare services. Unlike previously conducted studies based on the Study of Osteoporotic Fractures or the MrOS sleep study[59–67], insomnia symptoms were evaluated using a validated 4-item questionnaire instead of well-established tools such as the Epworth sleepiness scale or Pittsburgh Sleep Quality Index, and no objective measurements such as polysomnography or actigraphy were available from the selected HRS respondents. Self-reported data are frequently obtained in large studies, and given the longitudinal HRS design, it is unlikely that misclassification of insomnia symptoms is dependent on diagnosis with memory problems or dementia. Therefore, it is safe to assume that non-differential misclassification may have occurred with measures of association biased towards the null value. Third, sleep duration was not evaluated in the 2006–2016 HRS waves, precluding our ability to simultaneously evaluate it with insomnia symptoms. Fourth, residual confounding may be a concern given that several risk or protective factors for AD and/or dementia were either not measured or inadequately measured. For comparability with previously conducted HRS studies, we controlled for baseline socio-demographic, lifestyle and health characteristics, although repeated measures for some of these characteristics were

available for the generation of time-dependent covariates. Fifth, reverse causality could not be eliminated as a potential explanation for the observed associations, since sub-clinical neurodegenerative disease may have been responsible for patterns of insomnia symptoms. Finally, our study findings are only generalizable to adults ≥ 65 years in the United States, and should, therefore, be replicated in a wider range of populations.

In conclusion, more severe insomnia symptoms over time may be predictive of physician-diagnosed memory problems as well as dementia diagnosis based on pre-specified criteria over a 10-year follow-up period among U.S. elderly people. Additional studies are required to confirm these findings using large prospective cohort designs as well as validated tools for measuring insomnia symptoms, AD and dementias.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AD	Alzheimer's disease
AHEAD	Study of Asset and Health Dynamics of the Oldest Old
AFT	Animal Fluency Test
BMI	Body mass index
CERAD-WL	Consortium to Establish a Registry for AD Word Learning
CES-D	Center for Epidemiological Studies Depression Scale
CI	Confidence interval
DSST	Digital Symbol Substitution Test
HR	Hazard ratio
HRS	Health and Retirement Study
OSA	Obstructive sleep apnea
SCP	Subjective cognitive problems
SBD	Sleep-related breathing disorders

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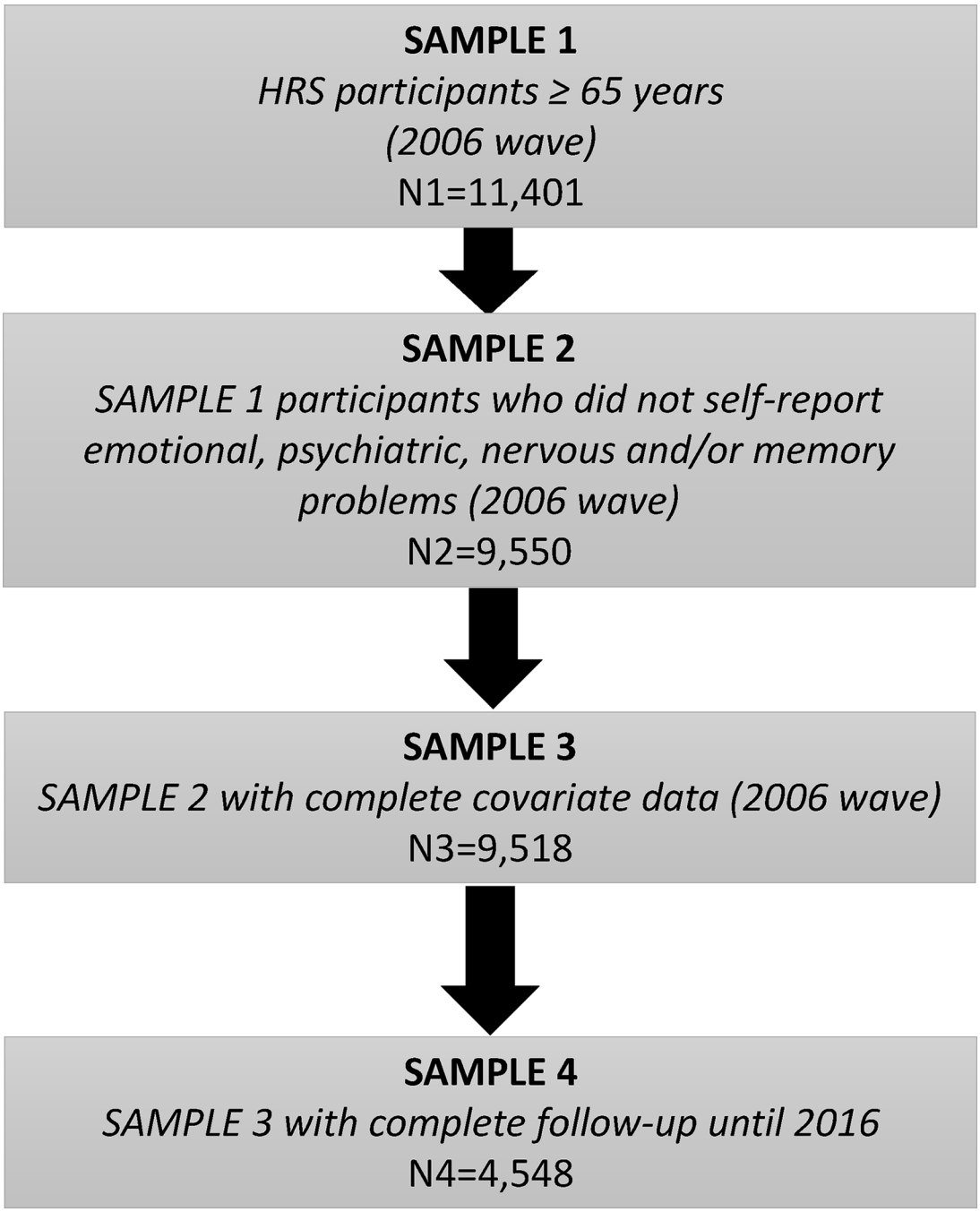

Figure 1.
Study flowchart – 2006–2016 Health and Retirement Study

Table 1.

Socio-demographic, lifestyle and health characteristics of study sample at baseline – 2006–2016 Health and Retirement Study (n=9,518)

	%	Mean ± SEM
SOCIO-DEMOGRAPHIC CHARACTERISTICS:		
Sex:		
Male	44.9	
Female	55.1	
Age (years):		
Continuous		74.9 ± .08
65–69	28.9	
70–74	24.4	
75–79	20.2	
80+	26.6	
Race:		
White/Caucasian	88.6	
Black/African American	8.3	
Other	3.2	
Ethnicity:		
Hispanic	93.6	
Non-Hispanic	6.4	
Marital status:		
Married	58.4	
Not married	41.6	
Education:		
No degree	24.6	
GED or high school diploma	36.0	
College degree or higher	39.4	
Total wealth ($):		
<25,000	14.9	
25,000–124,999	17.7	
125,000–299,999	21.8	
300,000–649,999	21.4	
650,000+	24.1	
LIFESTYLE CHARACTERISTICS:		
Smoking status:		
Never	43.2	
Ever	56.8	
Frequency of alcohol consumption:		
Abstinent	49.7	

	%	Mean ± SEM
1–3 days per month	17.6	
1–2 days per week	14.2	
≥ 3 days per week	18.5	
Frequency of moderate exercise:		
Never	23.5	
1–4 times per month	21.6	
>1 times per week	54.9	
Frequency of vigorous exercise:		
Never	65.9	
1–4 times per month	12.0	
>1 times per week	22.1	
HEALTH CHARACTERISTICS:		
Body mass index (kg/m^2):		
Continuous		28.3 ± 0.09
< 25	11.3	
25–29.9	15.7	
≥30	73.1	
Cardiovascular risk factors:		
Yes	72.1	
No	27.9	
Self-rated health:		
Continuous		2.8 ± 0.01
Excellent/Very good/Good	72.5	
Fair/Poor	27.5	
Center for Epidemiological Studies Depression score:		
Continuous		1.2 ± 0.02

Abbreviations: SEM=Standard error of the mean.

Table 2.

Summary statistics for the key exposure and outcome variables over the 2006–2016 Health and Retirement Study waves (n=9,518)

	2006	2008	2010	2012	2014	2016
Insomnia symptoms:						
N	9,518		7,509		5,803	
% Yes	40.3	--	41.4	--	41.8	--
Mean ± SEM	2.4 ± 0.02	--	2.6 ± 0.02		2.7 ± 0.03	
2006–2010:						
% No change	25.8					
% Increase	41.1					
% Decrease	33.0					
2010–2014:						
% No change			28.2			
% Increase			37.8			
%Decrease			34.0			
2006–2014:						
% No change	28.2					
% Increase	37.8					
%Decrease	34.0					
Severe insomnia symptoms:						
% Yes	81.5		76.4		75.4	
Mean ± SEM	1.6 ± 0.01	--	1.5 ± 0.01	--	1.5 ± 0.02	--
2006–2010:						
% No change	38.6					
% Increase	26.8					
%Decrease	34.7					
2010–2014:						
% No change			41.3			
% Increase			29.5			
%Decrease			29.2			

	2006	2008	2010	2012	2014	2016
2006–2014:						
% No change			37.1			
% Increase			27.1			
%Decrease			35.8			
Physician-diagnosed memory problems:						
% Memory problems	--	3.5	--	--	--	--
% Dementia	--	--	2.2	3.9	5.5	6.9
% Alzheimer's disease	--	--	1.9	3.1	4.2	5.1
% Any	--	3.5	4.2	6.7	9.0	11.0
Dementia diagnosis:						
% Yes	--	1.6	4.3	7.1	9.7	10.8

Table 3.

Cox proportional hazards model for insomnia symptoms as a predictor of time-to-onset of physician-diagnosed memory problems – 2006–2016 Health and Retirement Study (n=9,518)

	Unadjusted		Model I [a]		Model II [b]		Model III [c]	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Insomnia symptoms:								
Any:								
Yes	1.08	0.95, 1.23	1.03	0.90, 1.17	1.04	0.91, 1.19	0.96	0.84, 1.12
No	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Continuous	1.00	0.97, 1.03	0.98	0.95, 1.02	0.98	0.95, 1.02	0.95	0.92, 0.99
Severe:								
Yes	1.06	0.89, 1.26	1.12	0.95, 1.33	1.12	0.95, 1.33	1.21	1.02, 1.44
No	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Continuous	1.04	0.98, 1.11	1.07	1.00, 1.13	1.06	1.00, 1.13	1.10	1.04, 1.18
Change in insomnia symptoms (Any):								
2006–2010:								
Increase	1.13	0.93, 1.36	1.04	0.87, 1.26	1.04	0.86, 1.26	1.02	0.84, 1.23
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.32	1.08, 1.61	1.23	1.01, 1.50	1.22	0.99, 1.48	1.16	0.95, 1.42
2010–2014:								
Increase	1.06	0.84, 1.36	1.00	0.79, 1.26	0.99	0.79, 1.26	0.98	0.77, 1.24
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.23	0.97, 1.56	1.12	0.89, 1.41	1.12	0.88, 1.41	1.05	0.83, 1.33
2006–2014:								
Increase	1.06	0.84, 1.36	1.00	0.79, 1.27	0.99	0.79, 1.26	0.97	0.77, 1.24
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.23	0.97, 1.56	1.12	0.89, 1.41	1.12	0.88, 1.41	1.05	0.83, 1.33
Change in insomnia symptoms (Severe):								
2006–2010:								

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	Unadjusted		Model I [a]		Model II [b]		Model III [c]	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Increase	1.51	1.27, 1.79	1.39	1.17, 1.65	1.38	1.16, 1.64	1.41	1.18, 1.68
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.18	0.99, 1.39	1.12	0.95, 1.33	1.12	0.94, 1.32	1.14	0.96, 1.36
2010–2014:								
Increase	1.42	1.16, 1.74	1.34	1.09, 1.64	1.34	1.09, 1.64	1.34	1.09, 1.64
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.19	0.96, 1.48	1.13	0.91, 1.39	1.14	0.92, 1.41	1.13	0.91, 1.39
2006–2014:								
Increase	1.87	1.53, 2.29	1.73	1.41, 2.10	1.70	1.39, 2.08	1.72	1.40, 2.11
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.22	0.99, 1.50	1.22	0.99, 1.49	1.20	0.98, 1.48	1.24	0.99, 1.54

Abbreviations: HR=hazard ratio; CI: confidence interval.

[a]Model I was adjusted for socio-demographic characteristics;

[b]Model II was adjusted for socio-demographic and lifestyle characteristics;

[c]Model III was adjusted for socio-demographic, lifestyle and health characteristics.

Table 4.

Cox proportional hazards model for insomnia symptoms as a predictor of time-to-onset of dementia diagnosis – 2006–2016 Health and Retirement Study (n=6,907)

	Unadjusted		Model I [a]		Model II [b]		Model III [c]	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Insomnia symptoms:								
Any:								
Yes	1.12	0.97, 1.30	1.06	0.91, 1.24	1.04	0.90, 1.22	0.98	0.83, 1.15
No	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Continuous	1.04	1.00, 1.08	1.01	0.98, 1.05	1.01	0.98, 1.05	0.99	0.95, 1.03
Severe:								
Yes	0.92	0.77, 1.09	0.98	0.82, 1.19	0.98	0.81, 1.17	0.99	0.83, 1.20
No	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Continuous	0.95	0.88, 1.02	0.98	0.92, 1.05	0.98	0.92, 1.05	0.99	0.93, 1.07
Change in insomnia symptoms (Any):								
2006–2010:								
Increase	1.34	1.10, 1,64	1.24	1.01, 1.52	1.26	1.03, 1.54	1.27	1.03, 1.55
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.51	1.23, 1.86	1.41	1,14, 1.74	1.41	1.14, 1.74	1.36	1.09, 1.69
2010–2014:								
Increase	0.86	0.68, 1.10	0.82	0.64, 1.04	0.81	0.64, 1.04	0.78	0.61, 1.00
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.38	1.11, 1.73	1.25	1.00, 1.56	1.25	0.99, 1.57	1.20	0.96, 1.52
2006–2014:								
Increase	0.86	0.67, 1.10	0.82	0.64, 1.04	0.81	0.64, 1.04	0.78	0.61, 1.00
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.38	1.11, 1.72	1.25	1.00, 1.56	1.25	0.99, 1.57	1.21	0.96, 1.52
Change in insomnia symptoms (Severe):								
2006–2010:								

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	Unadjusted		Model I [a]		Model II [b]		Model III [c]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Increase	1.65	1.38, 1.99	1.59	1.33, 1.92	1.58	1.31, 1.90	1.58	1.31, 1.90
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	1.22	1.02, 1.46	1.16	0.97, 1.39	1.15	0.96, 1.37	1.15	0.95, 1.38
2010–2014:								
Increase	1.54	1.27, 1.88	1.47	1.22, 1.79	1.48	1.21, 1.80	1.47	1.21, 1.80
No change	0.97	0.76, 1.22	Ref.	--	Ref.	--	Ref.	--
Decrease			0.97	0.76, 1.22	0.96	0.75, 1.21	0.95	0.74, 1.21
2006–2014:								
Increase	1.59	1.31, 1.96	1.48	1.21, 1.82	1.47	1.19, 1.80	1.45	1.18, 1.79
No change	Ref.	--	Ref.	--	Ref.	--	Ref.	--
Decrease	0.88	0.71, 1.09	0.88	0.70, 1.82	0.86	0.68, 1.07	0.85	0.68, 1.07

Abbreviations: HR=hazard ratio; CI: confidence interval.

[a] Model I was adjusted for socio-demographic characteristics;

[b] Model II was adjusted for socio-demographic and lifestyle characteristics;

[c] Model III was adjusted for socio-demographic, lifestyle and health characteristics.