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Sleep and affective disorders in relation to Parkinson's disease risk among older women from the Women's Health Initiative

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Abstract

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Hind A. Beydoun conceived the research study, performed data management and statistical analyses and drafted the manuscript.
Jiu-Chiuan Chen participated in protocol writing and revised the manuscript for intellectual content.
Nazmus Saquib revised the manuscript for intellectual content.
Michelle J. Naughton participated in protocol writing and revised the manuscript for intellectual content.
May A. Beydoun participated in protocol writing and revised the manuscript for intellectual content.
Aladdin H. Shadyab revised the manuscript for intellectual content.
Lauren Hale revised the manuscript for intellectual content.
Alan B. Zonderman participated in protocol writing, oversaw the research study and revised the manuscript for intellectual content.

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Objectives: To evaluate sleep and affective (mood/anxiety) disorders as clinical predictors of incident Parkinson's disease (PD) among women ≥ 65 years of age.

Methods: We performed secondary analyses with available data from the Women's Health Initiative Clinical Trials and Observational Study linked to Medicare claims. Sleep, mood and anxiety disorders at baseline were defined using diagnostic codes. Incident PD was defined using self-reported PD, first PD diagnosis, use of PD medications, and/or deaths attributed to PD. Cox regression was applied to estimate hazard ratios (HR) with 95% confidence intervals (CI), controlling for socio-demographic/lifestyle/health characteristics. Time-to-event was calculated from baseline (1993–1998) to year of PD event, loss to follow-up, death, or December 31, 2018, whichever came first.

Results: A total of 53996 study-eligible WHI participants yielded 1756 (3.25%) PD cases over ~14.39 (± 6.18) years of follow-up. The relative risk for PD doubled among women with affective disorders (HR=2.05, 95% CI: 1.84, 2.27), mood disorders (HR=2.18, 95% CI: 1.97, 2.42) and anxiety disorders (HR=1.97, 95% CI: 1.75, 2.22). Sleep disorders alone (without affective) were not significantly associated with PD risk (HR=0.85, 95% CI: 0.69, 1.04), whereas affective disorders alone (without sleep) (HR=1.93, 95% CI: 1.72, 2.17) or in combination with sleep disorders (HR=2.18, 95% CI: 1.85, 2.56) were associated with twice the PD risk relative to no sleep/affective disorders.

Limitations: Observational design; Selection bias; Information bias; Generalizability.

Conclusions: Among older women, joint sleep/affective disorders and affective disorders alone are strong clinical predictors of incident PD over 14 years.

Keywords

Affective; Anxiety; Depression; Sleep; Parkinson's disease

INTRODUCTION:

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD) and the most frequently diagnosed movement disorder affecting 1–2% of the older U.S. population (Bomasang-Layno, Fadlon, Murray, & Himelhoch, 2015; Dalle & Mabandla, 2018; Ossowska & Lorenc-Koci, 2013; Shamim, Warriach, Tariq, Rana, & Malik, 2019). Although most PD cases are of unknown etiology, there is evidence that genetic mutations, environmental toxins and their interactions may contribute to PD development (Dalle & Mabandla, 2018; Dick et al., 2007). PD is the outcome of progressive degeneration of dopaminergic neurons in the nigrostriatal pathway leading to dopamine deficiency in the substantia nigra pars compacta (Dalle & Mabandla, 2018; Dick et al., 2007). Established PD motor symptoms include resting tremor, rigidity, akinesia, bradykinesia, hyperkinesia and postural instability (Dalle & Mabandla, 2018; Diederich & McIntyre, 2012; Frandsen, Baandrup, Kjellberg, Ibsen, & Jennum, 2014; Ossowska & Lorenc-Koci, 2013). In recent years, research focus has shifted to understanding non-motor symptoms (NMS) or comorbid conditions, which may precede or co-occur with motor symptoms (Bomasang-Layno et al., 2015; Dalle & Mabandla, 2018; Dissanayaka et al., 2019; Haasum, Fastbom, & Johnell, 2016; Martinez-Ramirez et al., 2016; Shamim et al.,

2019). These symptoms or comorbid conditions are highly prevalent but often unrecognized or under-treated and may adversely affect the quality of life of PD patients and their caregivers. Available studies suggest that among PD patients nearly 62% have NMS or comorbid conditions, including those resulting from neuropsychiatric and autonomic dysfunctions (Dalle & Mabandla, 2018). The most frequently reported NMS include fatigue (58%), anxiety (56%), leg pain (38%), insomnia (37%), urinary urgency and nocturia (35%), excessive salivation (31%), difficulty maintaining concentration (31%) and depression (22.5%), with an average of 7.8 NMS per patient and psychiatry (67%) as a field being the most impacted (Costa, Rosso, Maultasch, Nicaretta, & Vincent, 2012).

Three broadly defined PD NMS that are frequently comorbid are depression, anxiety and sleep disorders (Dissanayaka et al., 2019; Djamshidian & Friedman, 2014; Lin et al., 2017; Ossowska & Lorenc-Koci, 2013). In particular, depression has been shown to have the greatest impact on quality of life, with estimated prevalence rates among PD-affected individuals that vary considerably among published studies (2.5%−90%) (Bomasang-Layno et al., 2015), whereas prevalence rates of anxiety disorders among PD-affected individuals have been estimated to range between 20% and 49% (Gallagher & Schrag, 2012). Finally, large percentages of PD-affected individuals may experience sleep disturbances (~88%) (Menza et al., 2010) or sleep disorders (~60%) including insomnia, circadian rhythm (sleep-wake schedule) disorders, hypersomnia, sleep-related breathing disorders, motor disturbances in sleep, and parasomnias (Mayer, Jennum, Riemann, & Dauvilliers, 2011; Sateia, Greenough, & Nowell, 2000), which may be attributable, in part, to psychiatric disorders such as depression and anxiety, and have been associated with the pathophysiology of PD (Albers, Chand, & Anch, 2017).

Recent studies have also indicated that past experience with stressful life events as well as chronic stress may increase the likelihood of psychiatric disorders, such as depression and anxiety, which in turn can promote neurodegeneration and the development of PD through a variety of mechanisms which include repeated catecholamine release and reuptake and the formation of toxic dopamine metabolites (Dalle & Mabandla, 2018; Goldstein & Kopin, 2018; Jacob, Gatto, Thompson, Bordelon, & Ritz, 2010). Limited evidence suggests that psychiatric disorders, such as depression and anxiety, as well as psychotropic medications used to treat these disorders may be prodromal to the onset of PD motor symptoms (Andrade, 2015; Huang et al., 2015; Shadfar et al., 2018; Shamim et al., 2019; Zenesini et al., 2019). For instance, a meta-analysis of 15 studies indicated that prodromal depression might be associated with twice the risk of subsequent PD (Bareeqa et al., 2022). Although sleep disorders, particularly insomnia, have been linked to neurodegeneration (Shamim et al., 2019) and frequently co-occur with psychiatric disorders such as depression and anxiety (Qiu, Gu, Liu, & Li, 2022), the bulk of evidence linking sleep disorders to PD has originated from small clinical studies that often emphasized the role played by Rapid Eye Movement Behavior Disorder (RBD) – also known as parasomnia – as a prodromal disorder useful for the early detection of PD prior to onset of motor symptoms (Kim et al., 2016; Liu et al., 2018; C. J. Mao et al., 2018; Z. J. Mao et al., 2017; Pushpanathan, Loftus, Thomas, Gasson, & Bucks, 2016; Salawu & Olokoba, 2015; Wang, Yang, Lan, Wu, & Zhao, 2017; Wu, Mu, Yang, Zang, & Zheng, 2016) as well as for predicting PD progression (Figorilli et al., 2020). A meta-analysis involving 12 studies found that PD occurrence was more frequent among

patients diagnosed with obstructive sleep apnea (OSA) whereas OSA did not increase in PD patients (Sun, Liu, Zhang, Zhao, & Liu, 2020). A limited number of studies have attempted to link PD to sleep disturbance (Beydoun et al., 2022; Chen, Schernhammer, Schwarzschild, & Ascherio, 2006; Lysen, Darweesh, Ikram, Luik, & Ikram, 2019) or disorders (Beydoun et al., 2021) besides RBD (Shrestha et al., 2021), yielding inconsistent findings.

Although several epidemiologic studies have examined the independent and joint roles of sleep and affective (mood/anxiety) disorders on PD risk, many of these studies were of small sample size and could not establish a temporal relationship between variables of interest, and those that have examined the joint roles of sleep and affective disorders on PD risk remain scarce (Andrade, 2015; Huang et al., 2015; Sarwar, 2018; Yang et al., 2014; Zenesini et al., 2019). Examination of the joint roles of sleep and affective disorders enables the disentangling of their respective roles given their frequent co-occurrence, while allowing the evaluation of interactions between these two types of disorders. To date, no studies have specifically focused on older women (≥ 65 years) which account for a larger proportion of late-onset PD cases having characteristically more severe motor symptoms, more frequent NMS, a faster course and shorter survival than early-onset PD (Virameteekul, Phokaewvarangkul, & Bhidayasiri, 2021; Yuan et al., 2021) along with a higher risk for sleep and/or affective disorders (Girgus, Yang, & Ferri, 2017; Hader, Schroeder, Hinz, Micklefield, & Rasche, 2005; Lampert & Rosso, 2015; Schimmel-Spreeuw, Linssen, & Heeren, 2000; Thomas, Redd, Wright, & Hartos, 2017). In this retrospective cohort study, we performed secondary analyses of the Women's Health Initiative (WHI) linked to Medicare claims to evaluate the independent and joint roles of sleep and affective (mood/anxiety) disorders in incident PD among women ≥ 65 years of age. Although the minimum age for late-onset and old-age onset PD are 50 years and 80 years, respectively, we selected 65 years of age as a cut-point because it coincides with Medicare eligibility, thereby facilitating the identification of baseline diagnoses with sleep and/or affective disorders. The linkage between WHI and Medicare data provides a unique opportunity to examine these associations, while controlling for a wide range of socio-demographic, lifestyle and health characteristics.

METHODS:

Women's Health Initiative:

WHI collected longitudinal data on a multiethnic sample of postmenopausal women who were recruited and enrolled between 1993 and 1998 at 40 geographically diverse clinical centers (24 states and the District of Columbia) in the United States. The WHI study received institutional review board approval with informed consent from all participating clinical centers. The WHI study design, eligibility criteria, recruitment methods and measurement protocols are described elsewhere (Anderson et al., 2003; Hays et al., 2003). Briefly, the WHI clinical trials (WHI-CTs) (n=68132) and the WHI Observational Study (WHI-OS) (n=93676) are two components of the WHI (n=161808). Within the clinical trials component, four overlapping WHI-CTs evaluated outcomes of menopausal hormone therapy (Hormone Therapy [HT] Trials), calcium and vitamin D supplementation ([CaD] Trial) and a low-fat eating pattern (Dietary Modification Trial). The WHI-OS evaluated

causes of morbidity and mortality in postmenopausal women, as well as healthy aging. The CT and OS components of WHI occurred between 1993 and 2005. Of 150076 participants who were in active follow-up at the end of these studies, 76.9% participated in Extension Study 1 (2005–2010) and 86.9% of those eligible participated in Extension Study 2 (2010 to 2020) (Carroll et al., 2017; Cauley et al., 2019; Grieshober et al., 2019; Koo, McCool, Hale, Stone, & Eaton, 2016). At baseline, WHI participants, 50–79 years of age, completed the same self-administered questionnaire covering demographics, general health, clinical and anthropometric characteristics, medical history, personal habits and medications, with many of these characteristics assessed at multiple follow-up times. In this study, we followed WHI participants using linked WHI-Medicare data. The research was conducted in accordance with the Helsinki Declaration as revised in 1989. This study received an exempt determination from the institutional review board at Walter Reed National Military Medical Center.

Participants: WHI-CT and WHI-OS participants, ≥ 65 years of age at baseline, who had available WHI-Medicare (Part A and/or Part B) linked data and were followed until censoring or December 31, 2018 to determine incident PD diagnosis, were included in this study. We excluded participants with self-reported PD or ICD-9-CM primary or secondary codes from Medicare data that reflect a PD diagnosis at baseline (Supplemental Table S.1.). Furthermore, we excluded participants with ICD-9-CM Clinical Classification Software (CCS) codes indicating other mental health problems besides affective disorders, with the exception of those having ICD-9-CM codes for sleep disorders (Supplemental Table S.1.). We also excluded WHI participants who reported using medications with Assigned Therapeutic Classes of “Antipsychotic/Antimanic”, “Attention deficit hyperactivity disorder (ADHD)/Anti-narcoplepsy/Anti-obesity/Anorexiants” and “psychotherapeutic and neurological agents (miscellaneous)” at baseline or follow-up (Supplemental Table S.2.). Additional exclusions were WHI participants with a comorbidity of delirium, dementia, amnestic and other cognitive disorders based on Medicare data, which can influence later PD diagnosis (Supplemental Table S.1.). Finally, we excluded women who had < 12 months of WHI-Medicare linked data after the WHI baseline visit and those with missing data on key variables. As shown in Figure 1, 71010 of 161808 WHI participants reported age ≥ 65 years at baseline and of those 53996 remained after applying all eligibility criteria.

Linkage of Women’s Health Initiative to Medicare data:

The U.S. Centers for Medicare & Medicaid Services (CMS) Medicare is the federal health insurance program for individuals ≥ 65 years and those < 65 years who have disabilities or end stage renal disease. The WHI and CMS Medicare data were linked together among consenting participants using social security number, date of birth and, if needed, date of death and residential zip code. Nearly 97% of Medicare-eligible participants were successfully linked. WHI-Medicare data linkage occurred during the time where WHI participants were enrolled in Medicare traditional fee-for-service (80%) but not simultaneously in Medicare Health Management Organization (20%). The linkage between WHI and CMS data was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. In these analyses, we considered WHI participants ≥ 65 years

who were enrolled in fee-for-service Medicare Parts A and B at baseline. Details regarding CMS Medicare files can be obtained from the Research Data Assistance Center (http://www.resdac.org/cms-data).

Study variables:

Sleep disorders: ICD-9-CM primary and secondary diagnostic codes were used to classify sleep disorders as insomnia, sleep-related breathing disorders, hypersomnia, circadian rhythm sleep disorder, parasomnia, sleep-related movement disorder, and other sleep disorders (Keenan et al., 2020; Vin-Raviv, Akinyemiju, Galea, & Bovbjerg, 2018) (Supplemental Table S.1.). Accordingly, we used available Medicare (Medicare Provider Analysis and Review (MEDPAR), outpatient, and carrier) data to define presence of at least one sleep disorder at baseline as a dichotomous ('yes' or 'no') variable.

Affective disorders: ICD-9-CM CCS codes are generally used to classify mental health problems as follows: (1) adjustment disorders; (2) anxiety disorders; (3) attention-deficit, conduct, and disruptive behavior disorders; (4) disorders usually diagnosed in infancy, childhood, or adolescence, including pervasive development disorders, tic disorders, and elimination disorders; (5) impulse control disorders, not elsewhere classified; (6) mood disorders; (7) personality disorders; (8) schizophrenia and other psychotic disorders; (9) alcohol-related disorders; (10) drug-related disorders; (11) intentional self-harm/suicide and intentional self-inflicted injury; (12) miscellaneous disorders, including eating disorders, mental disorders in pregnancy, dissociative disorders, factitious disorders, sleep disorders, and somatoform disorders (Beydoun, Williams, Beydoun, Eid, & Zonderman, 2017). Accordingly, we used available Medicare (MEDPAR, outpatient, and carrier) data to define affective disorders (CCS codes for "mood disorders" or "anxiety disorders") at baseline as a dichotomous ('yes' or 'no') variable (Supplemental Table S.1.).

Joint roles of sleep and affective disorders: We defined a composite variable of all disorders as follows: 0 = "no sleep disorders or affective disorders" (referent); 1 = "sleep disorders only"; 2 = "affective disorders only"; 3 = "sleep disorders and affective disorders". This variable was used as the main exposure variable.

Parkinson's Disease: Incident PD was defined at each available year of follow-up, including self-reported PD, Medicare (MEDPAR, outpatient, and carrier) diagnostic codes that reflect a first occurrence of PD primary or secondary diagnosis using the International Classification of Diseases (9th Revision, Clinical Modification [ICD-9-CM]) or 10th Revision [ICD-10] systems), use of medications consistent with PD diagnosis and/or deaths attributed to PD (Supplemental Tables S.1. and S.2.) (Burstyn, LaCroix, Litvan, Wallace, & Checkoway, 2019). The level of agreement between PD definitions with and without ICD-9-CM/ICD-10 diagnostic codes was estimated among study-eligible subjects (κ=0.44, 95% CI: 0.42, 0.47). Time-to-event was calculated from baseline to index year of PD event, loss to-follow-up, death, or December 31, 2018, whichever came first.

Socio-demographic, lifestyle and health characteristics: Besides WHI component, socio-demographic (age, race/ethnicity, marital status, education, household income),

lifestyle (smoking status, alcohol use, physical activity) and health (body mass index (BMI), history of cardiovascular disease, history of hypertension, history of diabetes, history of hyperlipidemia, self-rated health) characteristics were collected at baseline as part of the WHI questionnaires. Frequency and duration of walking, mild, moderate and strenuous physical activities over the past week were assessed and total weekly kilocalories of energy expenditure were calculated in metabolic equivalents. History of cardiovascular disease was defined in terms of previous coronary heart disease, angina, aortic aneurysm, carotid endarterectomy or angioplasty, atrial fibrillation, congestive heart failure, cardiac arrest, stroke, or transient ischemic attack. History of diabetes was defined as physician-diagnosed diabetes or use of diabetes medications. History of hyperlipidemia was defined as using lipid-lowering medications or having been told of high cholesterol by a physician. Self-rated health was assessed using one questionnaire item: “In general would you say your health is excellent, very good, good, fair or poor?” These risk/protective factors for sleep, affective and neurodegenerative disorders were evaluated as potential confounders of the hypothesized relationships (Cauley et al., 2019; Creasy et al., 2019; Kling et al., 2017; Soucise et al., 2017; Zaslavsky, LaCroix, Hale, Tindle, & Shochat, 2015).

Statistical analysis:

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Summary statistics included means with standard deviations for continuous variables and frequencies with percentages for categorical variables. Bivariate associations were examined using Chi-square, independent samples t-tests and one-way Analysis of Variance, as appropriate. Kaplan-Meier curves were constructed and log-rank tests used to compare cumulative PD incidence according to history of sleep and/or affective disorders at baseline. Cox proportional hazards models were used to calculate hazard ratios (HR) with their 95% confidence intervals (CI) and to examine associations of history of sleep and/or affective disorders at baseline with incident PD, before and after sequentially controlling socio-demographic, lifestyle and health characteristics (Models I-III) as well as WHI component. Stratified analyses by (1) time-to-event (< 5 years vs. ≥ 5 years), (2) age at baseline (<70 vs. ≥ 70) and (3) WHI component (CT vs. OS) were performed to explore the temporality and design differences between WHI components. The proportional hazards assumption was examined in fully adjusted models with an exposure-by-time interaction term. Finally, we performed sensitivity analyses, in fully adjusted models, to assess: (1) the potential for reverse causality by repeating key analyses after exclusion of PD cases that occurred within 2 years of follow-up and (2) the validity of PD definition by repeating key analyses without ICD-9-CM/ICD-10 diagnostic codes, (3) the statistical methodology by repeating key analyses using competing risk models, whereby censored observations were distinguished from deaths attributed to non-PD causes. Since <5% of potentially eligible subjects had missing data on covariates, complete subject analyses were performed. Two-tailed statistical tests were assessed at α=0.05 and α=0.01, before and after familywise Bonferroni correction, respectively.

Data Availability Statement:

The authors have access to the de-identified WHI and Medicare raw data through a data use agreement between Fred Hutchinson Cancer Research Center and Fort Belvoir Community

Hospital. Therefore, these raw data are restricted and cannot be publicly shared for legal and ethical reasons.

RESULTS:

Of 53996 study-eligible WHI participants, 1756 (3.25%) developed PD over an average follow-up time of 14.39 (± 6.18) years. Furthermore, 10% were diagnosed with sleep disorders only, 33% were diagnosed with affective disorders only and 8% were diagnosed with both sleep and affective disorders at baseline. The remaining 49% of study-eligible WHI participants were not diagnosed with sleep, mood or anxiety disorders at baseline. Table 1 presents sleep and/or affective disorders by socio-demographic, lifestyle and health characteristics of the study sample at baseline. Women with relatively high prevalence rates of these disorders encompassed those < 70 years of age, those of White race, past smokers, past alcohol users, those classified as obese or having histories of cardio-metabolic risk factors as well as those with worse self-rated health.

Figure 2 presents Kaplan-Meier curves for sleep disorders (Panel A), affective disorders (Panel B), mood disorders (Panel C), anxiety disorders (Panel D) as well as sleep and/or affective disorders (Panel E). Log-rank tests suggest that study participants having an affective disorder experienced significantly higher PD incidence as compared to those without affective disorders (Panels B-D, P<0.0001). Moreover, study participants having sleep and/or affective disorders experienced significantly higher PD incidence as compared to those without sleep and/or affective disorders (Panel E, P < 0.0001). Interestingly, PD incidence was significantly less among those having at least one type of sleep disorders (Panel A, P < 0.0001).

Table 2 presents sleep disorders and/or affective disorders as a risk factor for PD. There was no significant association of sleep disorders at baseline with increased PD risk (HR=1.03, 95% CI: 0.91, 1.17, P=0.64) after controlling for socio-demographic, lifestyle and health characteristics at baseline. Given the heterogeneity of sleep disorders, we further evaluated each type of sleep disorders in relation to PD risk and found that sleep-related breathing disorders were inversely related (HR=0.42, 95% CI: 0.27, 0.65) and sleep-related movement disorders were directly related (HR=2.01, 95% CI: 1.56, 2.57) to PD risk in fully-adjusted models, while other sleep disorder types were not significantly related to PD risk. Similar results were obtained after stratifying according to diagnosis with affective disorders (Supplemental Table S.3.). By contrast, affective disorders (HR=2.05, 95% CI: 1.84, 2.27, P<0.0001), mood disorders (HR=2.18, 95% CI: 1.97, 2.42, P<0.0001) and anxiety disorders (HR=1.97, 95% CI: 1.75, 2.22, P<0.0001) at baseline were associated with nearly two-fold higher risks of PD. The presence of sleep disorders alone was not significantly associated with PD risk (HR=0.85, 95% CI: 0.69, 1.04, P=0.11), whereas affective disorders alone (HR=1.93, 95% CI: 1.72, 2.17, P<0.0001) as well as the combination of sleep and affective disorders (HR=2.18, 95% CI: 1.85, 2.56, P<0.0001) were associated with nearly twice the risk of PD compared to the absence of sleep and affective disorders. The association of affective disorders (alone or in combination with sleep disorders) was evident for the time-to-event ≥ 5 years subgroup but not for the time-to-event < 5 years subgroup. A diagnosis with mood disorders was associated with increased PD risk among study-eligible WHI

participants with ≥ 5 years of follow-up, but not among those with < 5 years of follow-up. Anxiety disorders were associated with increased PD risk, irrespective of follow-up time. By contrast, we observed consistent patterns of association when stratified analyses were performed according to age group and WHI component. We also obtained similar results in fully adjusted models after PD cases occurring within 2 years of follow-up were excluded to reduce the potential for reverse causality (Supplemental Table S.4.), with a PD definition that did not cover ICD-9-CM/ICD-10 diagnostic codes (Supplemental Table S.5), and using competing risk models (Supplemental Table S.6).

DISCUSSION:

Previous studies have identified a wide range of environmental, biological, physiological and genetic factors as well as cellular and molecular mechanisms such as oxidative stress and neuroinflammation, that can lead to protein misfolding, neuronal damage and the onset of neurodegenerative disorders currently affecting the quality of life of millions of individuals worldwide with limited availability of safe and effective treatments (Argueti-Ostrovsky, Alfahel, Kahn, & Israelson, 2021; Behl et al., 2021). Sleep is a key player in maintaining physiological homeostasis including the clearance of misfolded proteins (α-synuclein, amyloid-β, tau) that can lead to neurodegeneration (Bishir et al., 2020). Furthermore, stress and immune responses have been implicated in neurodegenerative as well as neuropsychiatric conditions (Correia, Cardoso, & Vale, 2021). Four pathognomonic hallmarks of PD include: (1) motor and non-motor deficits; (2) neuroinflammation and oxidative stress; (3) pathological aggregates of the α-synuclein protein; and (4) neurodegeneration of the nigrostriatal system (Goldstein & Kopin, 2018).

Among older women (≥ 65 years) in this prospective cohort study, we observed that sleep disorders diagnosed at baseline were not associated with future risk of PD. By contrast, those diagnosed with affective, mood or anxiety disorders at baseline experienced nearly twice the risk of PD onset as compared to those not diagnosed with these disorders, after controlling for socio-demographic, lifestyle and health characteristics. The role played by sleep in PD risk remains controversial. To date, epidemiological evidence has been mostly limited to small case-control studies focused on PD NMS and to longitudinal studies that examined self-reported sleep-related symptoms rather than diagnosed sleep disorders (Liu et al., 2018; C. J. Mao et al., 2018; Z. J. Mao et al., 2017; Pushpanathan et al., 2016; Wang et al., 2017; Wu et al., 2016). According to Vallee and colleagues, the main risk factor for PD is aging which can be detrimental to cellular homeostasis and lead to metabolic abnormalities such as neuroinflammation and oxidative stress which are in turn driven by circadian rhythms (Vallee, Lecarpentier, Guillevin, & Vallee, 2020).

Evidence supporting a role in PD onset, progression and outcomes for psychological stress and its manifestations through affective (mood/anxiety) disorders, originates from a wide range of studies. For instance, psychological stress as a determinant of PD trajectory in animal and human studies has been recently evaluated in a systematic review of the literature by Austin and colleagues, which identified 11 published articles (Austin, Ameringer, & Cloud, 2016). These studies suggested that psychological stress could exacerbate motor symptoms as well as loss of dopamine-producing neurons in animal models of PD and that

it could adversely affect symptom severity and health outcomes in human subjects diagnosed with PD (Austin et al., 2016).

A strong relationship between affective disorders and PD has been previously reported by two epidemiological studies. Jacob and colleagues conducted a population-based case-control study (371 incident PD cases, 402 population controls and 115 sibling controls) from three counties in California to examine self-reported lifetime depression/anxiety diagnoses and use of psychotropic medications as potential risk factors or prodromal characteristics that precede onset of PD motor symptoms (Jacob et al., 2010). They controlled for age, race, sex, pack-years of smoking, and education after excluding diagnoses and medication use first occurring within 2, 5, 10, and 20 years of the index/diagnosis date. PD patients were more likely to have received a depression/anxiety diagnosis at any time prior to the index date (OR=1.42, 95% CI: 1.01, 2.00), but were not more likely to have been diagnosed and treated with psychotropic medications (OR=1.11, 95% CI: 0.77, 1.60). Male, but not female, PD patients received diagnoses combined with psychotropic medication treatments more often than population controls within 5 years of PD diagnosis (OR=2.21, 95% CI: 1.21, 4.04; 2 year lag: OR=2.44, 95% CI: 1.29, 4.61; 5 year lag: OR=1.67, 95% CI: 0.80, 3.49). Results for PD patients compared to sibling controls were similar to those for population controls (Jacob et al., 2010). In a retrospective cohort study, Zenesini and colleagues evaluated the use of antidepressants between 2006 and 2017, as an indirect measure of depression, and subsequent clinically diagnosed PD in the Local Health Trust of Bologna, Italy (Zenesini et al., 2019). The investigators identified 51 subjects with PD in the exposed group (199093 person-years) and 556 subjects with PD in the non-exposed group (4286470 person-years), reporting an adjusted HR of 1.70 with 95% CI: 1.30, 2.30. Interestingly, the association was significant for males (HR=2.20, 95% CI: 1.50, 3.20) but not for females (HR=1.20, 95% CI: 0.80, 1.90), and for subjects ≤ 65 years of age (HR=2.40, 95% CI: 1.60, 3.60) but not for subjects > 65 years (HR=1.30, 95% CI: 0.80, 1.90) (Zenesini et al., 2019). Whereas interpretation of the case-control study should take into account the potential for recall bias, findings from the retrospective cohort study should be cautiously interpreted given that antidepressants were used as a proxy for depression potentially leading to confounding by indication.

This study has many strengths. First, the WHI database has a large baseline sample coupled with multiple follow-up assessments. The scope of the data collected by the WHI enables the evaluation of hypothesized relationships, taking into account key potential confounders. Second, findings from WHI analyses could potentially be generalized to postmenopausal women of diverse racial and ethnic backgrounds living in various geographical areas within the U.S. Third, the longitudinal study design of WHI allowed us to establish temporal relationships between exposure and outcome measurements. However, there are several limitations of our study. First, selection bias may be a concern given that only fee-for-service Medicare claims data were linked to WHI participant data. Second, several study variables relied on self-report or on ICD-9-CM/ICD-10 codes potentially causing measurement error. Specifically, PD was defined based on multiple data sources and was not among WHI's adjudicated health outcomes. However, sensitivity analyses whereby PD definition did not include ICD-9-CM/ICD-10 codes yielded similar findings with respect to hypothesized relationships. By the same token, previous studies have suggested that the validity of

using ICD-9-CM/ICD-10 diagnostic codes for depression may depend on population and clinical context (Fiest et al., 2014; Hwang et al., 2015; Noyes, Liu, Lyness, & Friedman, 2011). Also, sleep disorders are under-reported and under-diagnosed, and as such, sleep disorders recorded using ICD-9-CM codes are likely more severe than those that were not recorded using ICD-9-CM codes. Future studies may need to supplement ICD-9-CM/ICD-10 codes for sleep disorders with information on prescription drugs used to treat these conditions. On the other hand, for most analyses, we used a single variable to define sleep disorders, which combines heterogeneous conditions that have distinct etiologies and clinical presentations. Of note, REM sleep behavior which was rarely diagnosed in this population is likely the most specific prodromal stage of PD. Third, this study only examined sleep disorders, affective disorders, mood disorders, anxiety disorders and the combination of sleep and/or affective disorders at WHI baseline and did not use any repeated measures, given that Medicare data are largely dependent on healthcare seeking behavior, precluding assessment of exposures at specific time intervals. As such, this study did not attempt to differentiate current and past history of exposures to predict PD incidence. Fourth, and as a consequence of the observational nature of this study, residual confounding due to unmeasured or inadequately measured confounders remains a concern. Fifth, the heterogeneous nature of sleep disorders might explain the observed overall lack of association in this study, highlighting the need for larger studies that can test such hypotheses. Sixth, temporality issues may result from the long latency period between diagnosis of sleep and/or affective disorders (i.e. the main exposures of interest) and PD onset (i.e. the main outcome of interest). Given limitations of Medicare data, it may not be possible to establish temporality between the two exposure variables of interest, namely, sleep disorders and affective disorders both of which were evaluated at the WHI baseline. Finally, the WHI is not population-based but involves volunteers at clinical centers, specifically targeting postmenopausal women. Therefore, its generalizability to men as well as younger and less educated women is limited. The exclusion of WHI participants with mental health diagnoses besides sleep and affective disorders may have also restricted the generalizability of findings.

In conclusion, among women ≥ 65 years of age at baseline, joint sleep and affective disorders as well as affective disorders alone were associated with nearly twice the risk of PD over an average of 14 years of follow-up, after taking into account socio-demographic, lifestyle and health characteristics. Screening for affective disorders at an early stage may aid healthcare practitioners in the early detection of high-risk populations for PD. Further studies are needed to confirm these findings in more demographically and socioeconomically diverse populations of older men and women. If substantiated by additional studies with further validation of ICD-9-CM/ICD-10 diagnostic codes, these findings which pertain to NMS of PD could be used to construct a risk prediction model that is essential for accelerating the diagnosis of late-onset PD (Yuan et al., 2021).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
CaD	Calcium and vitamin D supplementation
CCS	Clinical Classification Software
CI	Confidence interval
CT	Clinical trial
HR	Hazard ratio
HT	Hormone Therapy
ICD-9-CM	International Classification of Diseases (9th Revision, Clinical Modification)
ICD-10	International Classification of Diseases (10th Revision)
MEDPAR	Medicare Provider Analysis and Review
NMS	Non-motor symptoms
OR	Odds ratio
OS	Observational study
PD	Parkinson's disease
RBD	Rapid Eye Movement Behavior Disorder
WHI	Women's Health Initiative

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Highlights:

- Eight percent of the sample had both sleep and affective disorders
- PD incidence was 0.23% per year over an average of 14.3 years of follow-up
- The risk of PD was twice among women who had affective disorders alone
- Sleep disorders alone or with affective disorders were not associated with PD risk

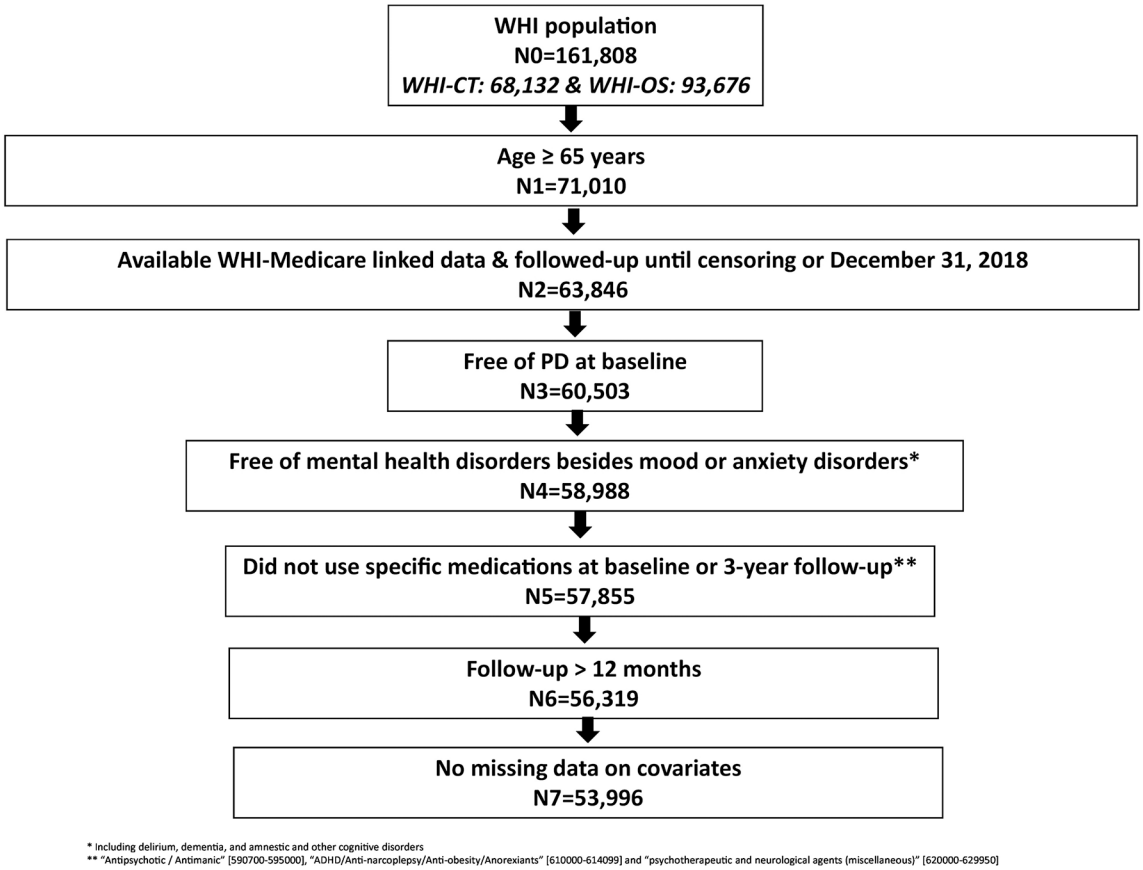

Figure 1.
Study flowchart

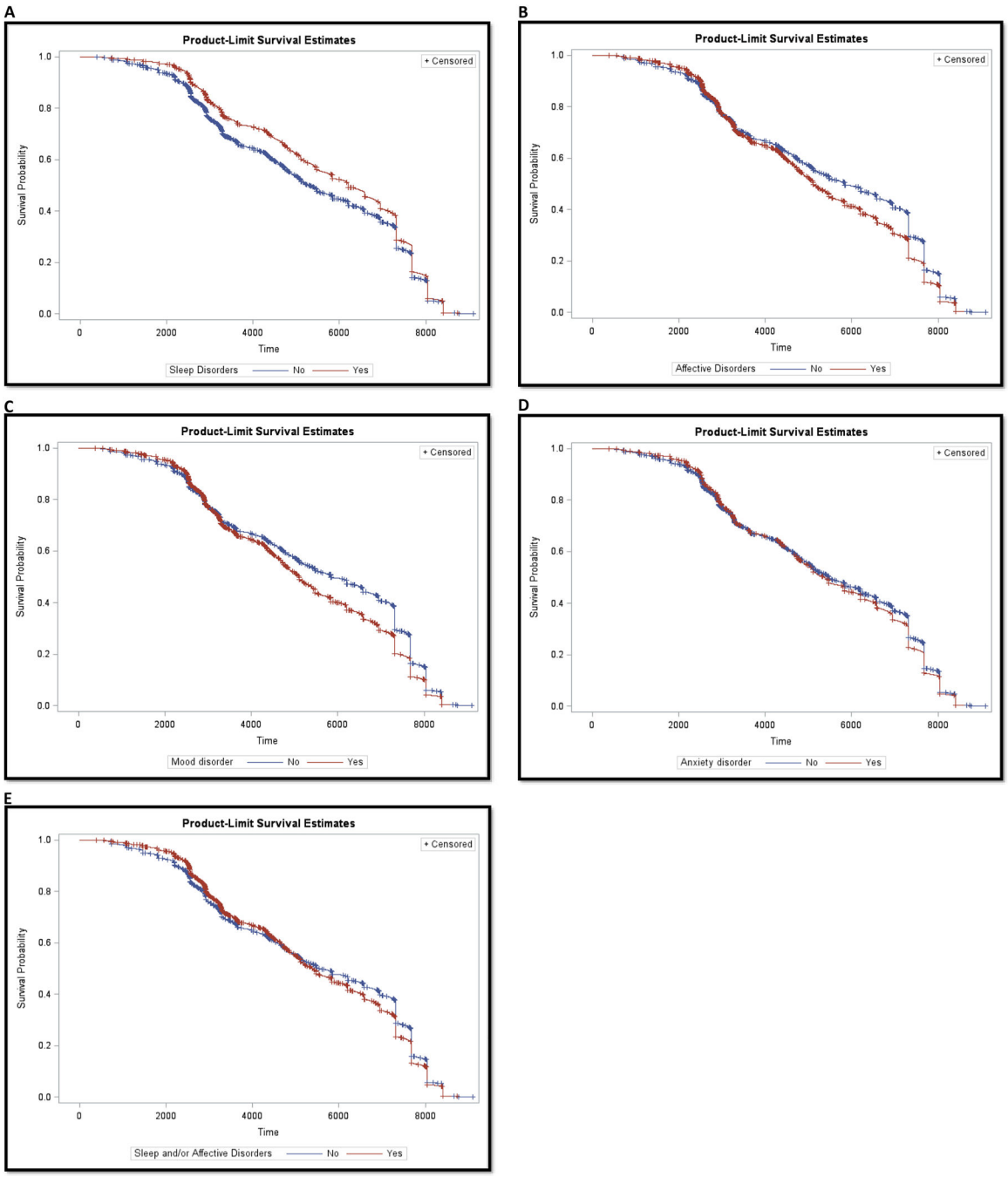

Figure 2.

Kaplan-Meier curves and log-rank test for cumulative PD survival by sleep and/or affective disorders

Panel A=Sleep disorders; Panel B=Affective disorders; Panel C=Mood disorders; Panel D= anxiety disorders; Panel E=Sleep and/or affective disorders.

Table 1.

Sleep and/or affective disorders by socio-demographic, lifestyle and health characteristics of study sample – Women's Health Initiative (n=53996) [a]

	Overall	Sleep and/or Affective Disorders			
		None	Sleep Only	Affective Only	Both
	N (%)	%	%	%	%
Overall	53996 (100)	26365 (48.83)	5400 (10.00)	17716 (32.81)	4515 (8.36)
WHI component:				P < 0.0001	
CT	20576 (38.11)	51.36	9.90	30.85	7.90
OS	33420 (61.89)	47.27	10.06	34.02	8.65
Age (years):				P < 0.0001	
65–69	27021 (50.04)	50.20	10.67	31.14	7.99
70–74	18950 (35.10)	47.28	9.72	34.31	8.70
> 74	8025 (14.86)	47.86	8.44	34.90	8.80
Race/Ethnicity:				P < 0.0001	
White	41558 (76.96)	47.48	10.70	32.91	8.91
Black	2431 (4.50)	54.59	10.12	27.68	7.61
Asian	8707 (16.13)	50.87	6.79	35.91	6.43
Other	1300 (2.41)	67.54	8.92	18.38	5.15
Marital status:				P<0.0001	
Married/Partnered	30330 (56.17)	48.43	10.33	32.32	8.91
Single	2122 (3.93)	51.74	10.74	30.82	6.69
Divorced	6526 (12.09)	48.51	9.13	34.62	7.74
Widowed	15018 (27.81)	49.35	9.60	33.29	7.76
Education:				P < 0.0001	
Less than high school	3172 (5.87)	48.83	7.85	34.93	8.39
High school graduate	10395 (19.25)	48.73	9.76	33.89	7.61
Some college	20794 (38.51)	48.68	9.78	32.90	8.65
College graduate	19635 (36.36)	49.03	10.71	31.80	8.45
Household income:				P<0.0001	
< $20,000	10978 (20.33)	49.05	8.72	34.63	7.60
$20,000–$49,999	25784 (47.75)	49.38	9.96	32.37	8.28
$50,000–$99,999	10861 (20.11)	48.38	10.91	31.65	9.06
≥$100,000	2685 (4.97)	46.15	12.44	32.18	9.24
Unknown	3688 (6.83)	47.53	9.63	34.35	8.49
Smoking status:				P<0.0001	
Never	28686 (53.13)	49.67	10.27	31.77	8.30
Past	22622 (41.90)	47.73	9.99	33.73	8.56
Current	2688 (4.98)	49.14	7.25	36.20	7.40
Alcohol use:				P<0.0001	
Non-drinker	6671 (12.35)	50.20	10.19	31.99	7.62
Former drinker	10299 (19.07)	45.42	9.05	37.01	8.53

	Overall	Sleep and/or Affective Disorders			
		None	Sleep Only	Affective Only	Both
	N (%)	%	%	%	%
< 1 drink / week	16995 (31.47)	49.55	9.71	32.23	8.51
≥1 drink / week	20031 (37.10)	49.51	10.63	31.42	8.40
Physical activity (Met-hours/week):				P<0.0001	
Mean (SD)	12.63 (13.39)	12.92 (13.47)	13.05 (13.53)	12.02 (13.17)	12.77 (13.54)
Body Mass Index (kg/m2):				P<0.0001	
< 25	19607 (36.31)	49.76	10.01	31.59	8.64
25–29.9	19692 (36.47)	49.10	9.79	32.54	8.57
≥ 30	14697 (27.22)	47.22	10.27	34.80	7.71
Medical history:					
Cardiovascular disease:				P<0.0001	
Yes	14267 (26.42)	43.90	9.42	37.91	8.78
No	39729 (73.58)	50.60	10.21	30.98	8.21
Hypertension:				P<0.0001	
Yes	27774 (51.44)	47.44	9.80	34.30	8.46
No	26222 (48.56)	50.30	10.21	31.23	8.26
Diabetes:				P<0.0001	
Yes	6515 (12.07)	46.45	9.56	36.36	7.63
No	47481 (87.93)	49.15	10.06	32.32	8.46
Hyperlipidemia:				P<0.0001	
Yes	9672 (17.91)	46.20	9.85	35.40	8.55
No	44324 (82.09)	49.40	10.03	32.24	8.32
Self-rated health:				P<0.0001	
Excellent	7778 (14.40)	55.99	10.71	26.38	6.92
Very good	22249 (41.20)	51.52	10.58	29.93	7.98
Good	19073 (35.32)	45.47	9.54	35.93	9.06
Fair	4580 (8.48)	38.76	8.08	43.36	9.80
Poor	316 (0.59)	31.65	7.91	52.53	7.91

Abbreviations: CT=Clinical Trial; OS=Observational Study; WHI=Women's Health Initiative.

[a] P values were the outcome of Pearson's Chi-square or one-way Analysis of Variance, as appropriate.

Table 2.

Sleep disorders and/or affective disorder diagnosis as a risk factor for Parkinson's disease – Women's Health Initiative (n=53996) [a]

	Unadjusted	Model I [a]	Model II [b]	Model III [c]
		HR (95% CI)		
Overall:		*n=53996*		
Sleep:				
Yes	1.03 (0.92, 1.15)	1.05 (0.93, 1.19)	1.05 (0.92, 1.19)	1.03 (0.91, 1.17)
No	Ref.	Ref.	Ref.	Ref.
Affective:				
Yes	*2.19 (1.99, 2.41)*	*2.13 (1.93, 2.37)*	*2.12 (1.91, 2.35)*	*2.05 (1.84, 2.27)*
No	Ref.	Ref.	Ref.	Ref.
Mood:				
Yes	*2.29 (2.09, 2.53)*	*2.27 (2.05, 2.52)*	*2.26 (2.04, 2.50)*	*2.18 (1.97, 2.42)*
No	Ref.	Ref.	Ref.	Ref.
Anxiety:				
Yes	*2.05 (1.84, 2.29)*	*2.04 (1.81, 2.29)*	*2.03 (1.80, 2.28)*	*1.97 (1.75, 2.22)*
No	Ref.	Ref.	Ref.	Ref.
Sleep and/or Affective:				
None	Ref.	Ref.	Ref.	Ref.
Sleep only	0.83 (0.69, 1.01)	0.87 (0.71, 1.07)	0.87 (0.71, 1.06)	0.85 (0.69, 1.04)
Affective only	*2.08 (1.87, 2.31)*	*2.02 (1.80, 2.27)*	*2.01 (1.79, 2.25)*	*1.93 (1.72, 2.17)*
Sleep + Affective	*2.29 (1.98, 2.67)*	*2.28 (1.94, 2.68)*	*2.26 (1.92, 2.66)*	*2.18 (1.85, 2.56)*
Time-to-event < 5 yrs		*n=2683*		
Sleep:				
Yes	*1.20 (0.75, 1.93)*	0.75 (0.41, 1.39)	0.76 (0.41, 1.40)	0.69 (0.36, 1.34)
No	Ref.	Ref.	Ref.	Ref.
Affective:				
Yes	*2.32 (1.72, 3.12)*	1.01 (0.67, 1.51)	1.02 (0.67, 1.54)	1.02 (0.65, 1.60)
No	Ref.	Ref.	Ref.	Ref.
Mood:				
Yes	*2.21 (1.64, 2.97)*	*0.91 (0.60, 1.37)*	*0.91 (0.59, 1.39)*	*0.90 (0.58, 1.42)*
No	Ref.	Ref.	Ref.	Ref.
Anxiety:				
Yes	*2.84 (2.04, 3.97)*	*1.56 (1.01, 2.42)*	*1.52 (0.97, 2.39)*	*1.65 (1.02, 2.68)*
No	Ref.	Ref.	Ref.	Ref.
Sleep and/or Affective:				
None	Ref.	Ref.	Ref.	Ref.
Sleep only	1.30 (0.60, 2.84)	0.75 (0.28, 1.99)	0.76 (0.28, 2.07)	0.73 (0.26, 2.03)
Affective only	*2.39 (1.75, 3.28)*	1.03 (0.67, 1.58)	1.04 (0.67, 1.61)	1.04 (0.65, 1.67)
Sleep + Affective	*2.18 (1.19, 4.03)*	0.77 (0.35, 1.69)	0.78 (0.35, 1.71)	0.70 (0.29, 1.68)
Time-to-event ≥ 5 yrs		*n=51313*		

	Unadjusted	Model I [a]	Model II [b]	Model III [c]
		HR (95% CI)		
Sleep:				
Yes	1.09 (0.96, 1.22)	1.09 (0.96, 1.23)	1.08 (0.95, 1.23)	1.07 (0.94, 1.21)
No	Ref.	Ref.	Ref.	Ref.
Affective:				
Yes	*2.25 (2.04, 2.49)*	*2.19 (1.97, 2.43)*	*2.18 (1.95, 2.42)*	*2.11 (1.89, 2.35)*
No	Ref.	Ref.	Ref.	Ref.
Mood:				
Yes	*2.38 (2.15, 2.63)*	*2.34 (2.11, 2.61)*	*2.33 (2.09, 2.59)*	*2.26 (2.03, 2.52)*
No	Ref.	Ref.	Ref.	Ref.
Anxiety:				
Yes	*2.03 (1.81, 2.28)*	*1.98 (1.75, 2.24)*	*1.97 (1.74, 2.23)*	*1.92 (1.69, 2.18)*
No	Ref.	Ref.	Ref.	Ref.
Sleep and/or Affective:				
None	Ref.	Ref.	Ref.	Ref.
Sleep only	0.88 (0.72, 1.07)	0.90 (0.73, 1.12)	0.90 (0.73, 1.11)	0.84 (0.72, 1.09)
Affective only	*2.13 (1.89, 2.38)*	*2.07 (1.84, 2.34)*	*2.06 (1.83, 2.33)*	*1.99 (1.76, 2.25)*
Sleep + Affective	*2.48 (2.12, 2.89)*	*2.41 (2.04, 2.84)*	*2.39 (2.02, 2.82)*	*2.31 (1.96, 2.73)*
Age < 70 yrs		*n=27021*		
Sleep:				
Yes	1.02 (0.87, 1.19)	1.01 (0.85, 1.19)	1.01 (0.85, 1.19)	0.98 (0.83, 1.16)
No	Ref.	Ref.	Ref.	Ref.
Affective:				
Yes	*2.45 (2.16, 2.79)*	*2.32 (2.03, 2.67)*	*2.32 (2.02, 2.66)*	*2.23 (1.93, 2.55)*
No	Ref.	Ref.	Ref.	Ref.
Mood:				
Yes	*2.59 (2.28, 2.94)*	*2.48 (2.16, 2.84)*	*2.47 (2.16, 2.84)*	*2.37 (2.06, 2.72)*
No	Ref.	Ref.	Ref.	Ref.
Anxiety:				
Yes	*2.27 (1.97, 2.63)*	*2.22 (1.89, 2.59)*	*2.21 (1.89, 2.58)*	*2.13 (1.82, 2.49)*
No	Ref.	Ref.	Ref.	Ref.
Sleep and/or Affective:				
None	Ref.	Ref.	Ref.	Ref.
Sleep only	0.87 (0.67, 1.13)	0.88 (0.67, 1.16)	0.88 (0.67, 1.15)	0.86 (0.65, 1.12)
Affective only	*2.36 (2.05, 2.73)*	*2.25 (1.93, 2.62)*	*2.24 (1.92, 2.61)*	*2.13 (1.83, 2.49)*
Sleep + Affective	*2.50 (2.04, 3.08)*	*2.36 (1.89, 2.95)*	*2.35 (1.88, 2.93)*	*2.23 (1.79, 2.78)*
Age ≥ 70 yrs		*n=26975*		
Sleep:				
Yes	1.04 (0.88, 1.24)	1.10 (0.92, 1.33)	1.10 (0.92, 1.33)	1.09 (0.91, 1.32)
No	Ref.	Ref.	Ref.	Ref.
Affective:				
Yes	*1.91 (1.66, 2.19)*	*1.90 (1.63, 2.22)*	*1.88 (1.61, 2.20)*	*1.84 (1.57, 2.15)*

	Unadjusted	Model I [a]	Model II [b]	Model III [c]
		HR (95% CI)		
No	Ref.	Ref.	Ref.	Ref.
Mood:				
Yes	*1.98 (1.72, 2.28)*	*2.02 (1.73, 2.36)*	*2.00 (1.72, 2.34)*	*1.95 (1.67, 2.28)*
No	Ref.	Ref.	Ref.	Ref.
Anxiety:				
Yes	*1.81 (1.54, 2.14)*	*1.84 (1.53, 2.20)*	*1.82 (1.52, 2.18)*	*1.79 (1.49, 2.15)*
No	Ref.	Ref.	Ref.	Ref.
Sleep and/or Affective:				
None	Ref.	Ref.	Ref.	Ref.
Sleep only	0.79 (0.59, 1.06)	0.85 (0.62, 1.17)	0.85 (0.62, 1.17)	0.84 (0.62, 1.15)
Affective only	*1.77 (1.51, 2.07)*	*1.76 (1.48, 2.09)*	*1.74 (1.46, 2.07)*	*1.69 (1.42, 2.02)*
Sleep + Affective	*2.06 (1.65, 2.56)*	*2.16 (1.71, 2.74)*	*2.15 (1.69, 2.78)*	*2.09 (1.65, 2.65)*
WHI-CT		*n=20576*		
Sleep:				
Yes	0.91 (0.74, 1.12)	0.93 (0.75, 1.16)	0.93 (0.75, 1.15)	0.91 (0.73, 1.12)
No	Ref.	Ref.	Ref.	Ref.
Affective:				
Yes	*2.17 (1.85, 2.54)*	*2.18 (1.84, 2.57)*	*2.15 (1.82, 2.54)*	*2.07 (1.75, 2.45)*
No	Ref.	Ref.	Ref.	Ref.
Mood:				
Yes	*2.30 (1.96, 2.69)*	*2.31 (1.95, 2.73)*	*2.28 (1.93, 2.69)*	*2.19 (1.85, 2.59)*
No	Ref.	Ref.	Ref.	Ref.
Anxiety:				
Yes	*2.05 (1.69, 2.49)*	*2.09 (1.72, 2.56)*	*2.28 (1.93, 2.69)*	*2.02 (1.66, 2.47)*
No	Ref.	Ref.	Ref.	Ref.
Sleep and/or Affective:				
None	Ref.	Ref.	Ref.	Ref.
Sleep only	0.79 (0.56, 1.10)	0.84 (0.59, 1.18)	0.83 (0.59, 1.17)	0.81 (0.57, 1.14)
Affective only	*2.12 (1.78, 2.53)*	*2.15 (1.79, 2.59)*	*2.12 (1.76, 2.55)*	*2.03 (1.68, 2.44)*
Sleep + Affective	*1.95 (1.49, 2.54)*	*1.98 (1.49, 2.62)*	*1.95 (1.47, 2.58)*	*1.87 (1.41, 2.47)*
WHI-OS		*n=33420*		
Sleep:				
Yes	1.08 (0.94, 1.24)	1.12 (0.96, 1.30)	1.11 (0.95, 1.29)	1.09 (0.94, 1.28)
No	Ref.	Ref.	Ref.	Ref.
Affective:				
Yes	*2.18 (1.94, 2.46)*	*2.11 (1.85, 2.40)*	*2.10 (1.85, 2.39)*	*2.04 (1.79, 2.33)*
No	Ref.	Ref.	Ref.	Ref.
Mood:				
Yes	*2.28 (2.02, 2.56)*	*2.25 (1.98, 2.56)*	*2.25 (1.98, 2.56)*	*2.18 (1.92, 2.49)*
No	Ref.	Ref.	Ref.	Ref.
Anxiety:				

	Unadjusted	Model I [a]	Model II [b]	Model III [c]
		HR (95% CI)		
Yes	*2.02 (1.77, 2.30)*	*2.00 (1.73, 2.33)*	*1.99 (1.72, 2.31)*	*1.94 (1.67, 2.24)*
No	Ref.	Ref.	Ref.	Ref.
Sleep and/or Affective:				
None	Ref.	Ref.	Ref.	Ref.
Sleep only	0.85 (0.67, 1.08)	0.88 (0.68, 1.14)	0.88 (0.68, 1.13)	0.87 (0.67, 1.12)
Affective only	*2.03 (1.78, 2.32)*	*1.95 (1.68, 2.23)*	*1.94 (1.68, 2.25)*	*1.88 (1.62, 2.18)*
Sleep + Affective	*2.45 (2.04, 2.93)*	*2.44 (2.00, 2.98)*	*2.43 (1.99, 2.97)*	*2.35 (1.92, 2.87)*

Abbreviations: CI=Confidence interval; CT=Clinical Trial; HR=Hazard ratio; OS=Observational Study; WHI=Women's Health Initiative.

[a]Model I controls for WHI component and socio-demographic factors only (age, race/ethnicity, marital status, education, household income) only, Model II controls for WHI component, socio-demographic and lifestyle (smoking status, alcohol use, physical activity) factors, Model III controls for WHI component, socio-demographic, lifestyle and health (body mass index, history of cardiovascular disease, history of hypertension, history of diabetes, history of hyperlipidemia, self-rated health) factors.