# UC San Diego

## UC San Diego Previously Published Works


### Title

Association of sleep disturbance with Parkinson disease: evidence from the Womens Health Initiative.


### Permalink

https://escholarship.org/uc/item/5vh7s2m7



### Journal

Menopause, 29(3)



### Authors

Beydoun, Hind

Naughton, Michelle

Beydoun, May

et al.



### Publication Date

2022-01-10

### DOI

10.1097/GME.0000000000001918

Peer reviewed



eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

*Menopause*. Author manuscript; available in PMC 2024 April 08.

Published in final edited form as:

*Menopause*. ; 29(3): 255–263. doi:10.1097/GME.0000000000001918.

# Association of sleep disturbance with Parkinson's Disease: Evidence from the Women's Health Initiative

**Hind A. Beydoun, PhD**[a,*], **Michelle J. Naughton, PhD**[b], **May A. Beydoun, PhD**[c], **Aladdin H. Shadyab, PhD**[d], **Robert L. Brunner, PhD**[e], **Jiu-Chiuan Chen, MD, ScD**[f], **Mark Espeland, PhD**[g], **Sally A. Shumaker, PhD**[h], **Alan B. Zonderman, PhD**[c]

[a]Department of Research Programs, Fort Belvoir Community Hospital, Fort Belvoir, VA, USA 22060

[b]Department of Internal Medicine, College of Medicine, Ohio State University, Columbus, OH 43201

[c]Laboratory of Epidemiology and Population Sciences, National Institute on Aging, NIA/NIH/IRP, Baltimore, MD, USA 21225

[d]Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA 92093

[e]Department of Family and Community Medicine (Emeritus), School of Medicine, University of Nevada (Reno), Auburn CA 95602

[f]Departments of Preventive Medicine and Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089

[g]Department of Gerontology & Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27101

[h]Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Winston-Salem, NC 27101

## Abstract

**Objective:** To examine the association of sleep disturbance with Parkinson's Disease (PD) during 10+ years of follow-up among post-menopausal women, 50–79 years of age at baseline.

**Methods:** Longitudinal data on 130,502 study-eligible women (mean ± standard deviation baseline age=63.16±7.20 years) from the Women's Health Initiative Clinical Trials (WHI-CT) and Observational Study (WHI-OS) were analyzed. The cohort was followed for 15.88 ± 6.50 years, yielding 2,829 (2.17%) PD cases. Sleep disturbance (habitual sleep duration, insomnia symptoms, obstructive sleep apnea (OSA) risk factors, sleep aids among those with WHI Insomnia Rating Scale scores (WHIIRS)>9) was measured at baseline and one follow-up time by September 12,

[*]**Corresponding author:** Hind A. Beydoun, PhD, MPH, Department of Research Programs, Fort Belvoir Community Hospital, 9300 DeWitt Loop, Fort Belvoir, VA 22060, Fax: 571-231-6667, hind.a.Baydoun.civ@mail.mil.

**Conflict of interest/financial disclosure:** none declared.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2005. Cox proportional hazards models evaluated relationships controlling for socio-demographic, lifestyle and health characteristics.

**Results:** PD was significantly associated with long sleep duration (≥9 hours) versus a benchmark of 7–8 hours (hazard ratio (HR)=1.296, 95% confidence interval (CI):1.153–1.456), WHIIRS (>9vs.≤9) (HR=1.114, 95% CI:1.023–1.214), and use of sleep aids (yesvs.no) (HR=1.332, 95% CI:1.153–1.539) among those with WHIIRS >9. Compared to 7–8 hours, short (<7 hours) sleep duration was unrelated to PD. Finally, the presence of OSA risk factors was not associated with PD.

**Conclusions:** Among post-menopausal women, sleep disturbance was associated with approximately 10–30% increased PD risk after ~16 years follow-up. Prospective cohort studies with objective exposures and adjudicated outcomes that include men and women of diverse backgrounds are required to confirm and extend these findings.

### Keywords

Cohort; Insomnia; Menopause; Parkinson's Disease; Sleep; Women

## INTRODUCTION:

Empirical evidence has established sleep as a restorative process that can have an impact on multiple organ systems.[1] Aging is frequently accompanied by worsening of sleep quality with a prevalence rate of poor sleep quality up to 36–69% among older adults.[2,3] Previous work has shown that both short and long sleepers experience increased morbidity and mortality risks.[4] Insomnia symptoms such as difficulties falling asleep, waking during the night, staying asleep, waking early, getting back to sleep and non-restorative sleep are implicated in earlier onset of chronic conditions, including type 2 diabetes, cardiovascular disease, cancer and cognitive decline.[2,5] Obstructive sleep apnea (OSA), a sleep disorder that has been shown to increase with age, especially among postmenopausal women, is characterized by repetitive upper airway closure, resulting in disrupted sleep and nocturnal hypoxemia and has been linked to oxidative stress, systemic inflammation and increased risks of hypertension, type 2 diabetes, metabolic syndrome, coronary heart disease, stroke, depression, cognitive impairment, motor vehicle accidents and death.[6–9] There has been more limited work linking sleep to onset, progression and exacerbation of neurodegenerative disorders such as Alzheimer's disease (AD), Huntington's disease, Amyotrophic lateral sclerosis and Parkinson's disease (PD).[10] Neuropathological pathways that may be involved in the putative sleep-neurodegenerative disorder link include the neuroendocrine stress axis, hippocampal neuroinflammation and oxidative stress, interrupted hippocampal neurogenesis, aging-related protein misfolding, and consequently brain aging.[11]

Caused by the loss of dopaminergic cells in the substantia nigra pars compacta, PD is the second most frequently diagnosed neurodegenerative disorder after AD, affecting 2% of older adults.[12–14] Cardinal motor symptoms[15] of PD are tremor, rigidity and bradykinesia, but non-motor symptoms (NMS) including impairments of memory, affect, autonomic function, and sleep are often present and may adversely impact quality of life.[10] Sleep disorders commonly diagnosed among individuals with PD including insomnia[10,16], Rapid

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

eye movement behavior disorder (RBD)[3,10,16–18], OSA[3,10,17,18], periodic limb movement disorder[3,10,16,17], restless leg syndrome[3,10,16,17,19], and nocturia[10], may precede onset of PD motor symptoms or can manifest as sleep disturbances associated with underlying neurodegeneration.[10,15] As such, sleep disturbance identified at an early stage could be a biomarker of undiagnosed PD or be associated with the future diagnosis of PD.

Although research has established PD as more prevalent among men versus women, women are more likely than men to experience sleep problems especially after menopause, with 35%−60% of postmenopausal women reporting significant sleep disturbance.[20] Among PD-diagnosed individuals, sleep disturbances were more frequent among women than men, with evidence for sex differences in terms of difficulty maintaining sleep, excessive dreaming, but not difficulty initiating sleep.[3] Whereas the bulk of evidence linking sleep disturbance to PD has originated from small clinical studies that often measured sleep disturbance and PD simultaneously while emphasizing the role played by RBD[3,15–19,21–24], epidemiologic studies linking other sleep disturbances to PD are scarce. To date, few of these studies have capitalized on large, prospective cohort studies to examine multiple indicators of sleep disturbance as predictors of future PD diagnosis among postmenopausal women. The purpose of this prospective cohort study is to examine habitual sleep duration, insomnia symptoms, OSA risk factors and use of sleep aids (in the context of insomnia symptoms) in relation to PD diagnosis over a follow-up period that exceeds 10 years among postmenopausal women who were 50–79 years at baseline and participated in the Women's Health Initiative Clinical Trials (WHI-CT) or the Women's Health Initiative Observational Study (WHI-OS). Establishing an association between the presence of sleep disturbances and future PD diagnosis is a first step towards informing the need for more advanced study designs that can evaluate screening for sleep disturbance as a strategy for early detection and treatment of PD and other neurodegenerative disorders.

## METHODS:

### Data Source:

The Women's Health Initiative (WHI) is a long-term study focused on strategies for preventing heart disease, breast and colorectal cancers and osteoporosis in postmenopausal women. The WHI study design, eligibility criteria, recruitment methods and measurement protocols are described elsewhere.[25,26] Briefly, WHI-CTs (n=68,132) and WHI-OS (n=93,676) are two components of the WHI (n=161,808). WHI collected data on a multiethnic sample of postmenopausal women who were recruited and enrolled between 1993 and 1998 at 40 geographically diverse U.S. clinical centers. The WHI study received institutional review board approval with informed consent from all participating clinical centers. Whereas the 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. The main WHI studies occurred between 1993 and 2005, and of 150,076 participants who were actively followed-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).[1,2,4–6,27]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

### Study Participants:

We performed secondary data analyses on WHI participants, 50–79 years of age at baseline, who were followed-up for >10 years (using Extension Studies 1–2) to determine incident PD. For current analyses, we excluded women who self-reported PD ("yes" for "Parkinson's Disease" when asked "Has a doctor told you that you have any of the following conditions or have you had any of the following procedures?") or had missing data on PD or sleep variables at baseline. All WHI participants completed the same baseline self-administered questionnaire covering demographics, general health, clinical and anthropometric characteristics, functional status, healthcare behaviors, reproductive, medical and family history, personal habits, thoughts and feelings, therapeutic class of medication, hormones, supplements and dietary intake, and several of these characteristics were assessed at later follow-up times.

### Study variables:

**Exposure variables:** The baseline questionnaire includes 10 items focused on sleep, and several of these items can be used to define exposure variables, namely, habitual sleep duration, insomnia symptoms, OSA risk factors and use of sleep aids.[8,27,28] Five of these 10 items constitute the WHI Insomnia Rating Scale (WHIIRS), a valid and reliable instrument developed by WHI researchers. The WHIIRS was administered at multiple time points (forms 37 and 38) between baseline and follow-up visits by September 12, 2005, with follow-up visits depending on the participants' enrollment in WHI-CT or WHI-OS. Among WHI-CT participants, WHIIRS was administered at baseline, year 1 and study closeout (~ year 9) and a sub-sample completed sleep measures at years 3, 6 and 9. Among WHI-OS participants, the WHIIRS was administered at baseline and year 3. We defined baseline and time-varying sleep-related exposure variables using available measurements taken at baseline and the time point closest to an event, taking follow-up exposure times into consideration. Although measured at distinct follow-up times for each WHI participant, repeated sleep measurements were highly consistent between baseline and follow-up time points. The mean differences between baseline and follow-up time points in habitual sleep duration and WHIIRS score were close to zero and the correlation in these measurements between time points was approximately 0.64.

**Subjective measure of habitual sleep duration:** Participants were asked "about how many hours of sleep did you get on a typical night during the last 4 weeks?" Taking current evidence, sample size and recommendations by the American Academy of Sleep Medicine and the Sleep Research Society into consideration, we identified self-reported short sleepers as 6 or less hours, standard sleepers as 7–8 hours and long sleepers as ≥9 hours.[2,4,9,28–34]

**Insomnia symptoms:** Insomnia symptoms were evaluated using the WHIIRS[35–37] which consists of five items covering sleep quality, trouble falling asleep, waking up several times at night, waking up earlier than planned, and having trouble getting back to sleep after early awakening during the past 4 weeks. By adding these five item scores, we calculated a global score of insomnia symptoms that ranges between 0 and 20, with higher scores suggesting more symptoms of insomnia. Based on previous studies, WHIIRS scores>9 were consistent with diagnostic criteria for insomnia.[1,2,11,20,28,30,31,33,34,36–39]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Obstructive sleep apnea risk factors:** Data on OSA risk factors not covered by WHIIRS were collected at baseline, including obesity, snoring, diagnosis of hypertension and presence of daytime sleepiness.[6,30,33,37] Directly measured body mass index (BMI) was categorized as "<25", "25–29.9" and "≥30" kg/m$^2$ and obesity was defined as BMI≥30 kg/m$^2$. Sleep variables included snoring ("Did you snore?") and daytime sleepiness ("Did you fall asleep during quiet activities like reading, watching TV, or riding in a car?"). Hypertension was defined as being told by a physician that they had high blood pressure, systolic blood pressure>140 mm Hg and/or diastolic blood pressure>90 mm Hg, and/or use of antihypertensive medication. The presence of OSA risk factors was defined as having BMI≥30 kg/m$^2$, snoring≥3 times per week, daytime sleepiness≥3 times per week and/or diagnosis of hypertension. We excluded restless or poor sleep quality and nighttime awakenings≥3 times per week from the overall index of OSA risk factors since these indicators were already covered by the WHIIRS.[6,30,33,37]

**Sleep aids:** WHI participants were asked "Did you take any kind of medication or alcohol at bedtime to help you sleep?", with possible responses being "No, not in past 4 weeks", "Yes, less than once a week", "Yes 1 or 2 times a week", "Yes, 3 or 4 times a week", "Yes, 5 or more times a week" and "Missing". Self-reported use of sleep aids was defined as a "Yes" or "No" variable.

**Parkinson's Disease:** Incident PD was defined at each available year of follow-up, and included self-reported PD diagnosis ("yes" when asked "Has a doctor ever told you that you have Parkinson's disease"), deaths attributed to PD and/or use of medications consistent with PD diagnosis (Medication forms 44 and 153, Therapeutic Classes of 730000–734030), as previously reported by another WHI-based study.[40] Time-to-event, whether incident PD, death or loss to follow-up, was calculated from the baseline questionnaire until March 1, 2019.

**Covariates:** Socio-demographic (WHI component, age, race/ethnicity, marital status, education, household income), lifestyle (smoking status, alcohol use, physical activity) and health (BMI, history of cardiovascular disease, history of hypertension, history of diabetes, history of hyperlipidemia, depressive symptoms, self-rated health) characteristics were examined only at baseline, irrespective of their availability at later time points. 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 (myocardial infarction, coronary angioplasty and/or coronary artery bypass graft), 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. A depressive symptoms screening algorithm previously developed by Burnam and colleagues with scores ranging between 0 and 1 and higher scores consistent with greater burden of depressive symptoms was generated using 6 items from the 20-item Center for Epidemiological Studies

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Depression scale (CES-D) and 2 items from the National Institute of Mental Health's Diagnostic Interview Schedule (DIS).[9,30,41,42]. Self-rated health was assessed using one questionnaire item: "In general would you say your health is excellent, very good, good, fair or poor?"[2,9,11,20,30,34,41,42]

### Statistical analysis:

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Bivariate associations were examined using Chi-square or independent samples t-tests or corresponding non-parametric tests, as appropriate. Cumulative incidence as well as incidence density of PD were calculated after stratifying by levels of sleep disturbance variables at baseline. Kaplan-Meier curves were constructed and log-rank tests evaluated differences in incident PD for each selected sleep indicator defined at baseline or as time-varying exposures. Moreover, we fit Cox proportional hazards models to examine relationships between measures of sleep disturbance and PD diagnosis, before and after controlling for confounders. Specifically, we examined each sleep disturbance indicator (at baseline and as a time-varying exposure) as a predictor of incident PD, while sequentially controlling for socio-demographic, lifestyle and health characteristics (Models I-III). Of note, when examining OSA risk factors, BMI and history of hypertension were not included in Model III. Proportional hazards assumptions were verified using exposure-by-time interactions within fully-adjusted models. Multiple testing was accounted for using familywise Bonferroni correction. After examining patterns of missingness, complete participant analyses using available data on key exposure and outcome variables were performed with and without multiple imputation of covariate data. Under assumption of missing at random, we used SAS MI to generate five distinct datasets; however, given the relatively small percentage of missing data (<10%) and similarity of results between non-imputed and imputed analyses, only non-imputed results were reported. Finally, we performed sensitivity analyses to explore independent effects of sleep exposures, temporal relationships, design differences between WHI components and distinct data sources for PD diagnosis, by examining fully-adjusted models with (1) main sleep indicators added together, (2) exclusion of PD cases that developed within 3 years of sleep exposure assessment, (3) stratified analyses by age at baseline (<70 vs. ≥ 70) or WHI component (CT vs. OS) and (4) analyses involving distinct definitions of PD using self-report, death certificates and medications as data sources. Two-tailed statistical tests were assessed at an alpha level of 0.05.

## RESULTS:

Among 161,808 women who completed the baseline questionnaire and participated in WHI-CT (n=68,132) or WHI-OS (n=93,676), 287 (0.2%) reported prior diagnosis of PD and 9,375 (5.8%) had unknown PD at baseline. Of the remaining 152,146 participants, 3,522 had missing data on 1+ sleep variable at baseline, leaving 148,624 participants with useful data after covariate imputation. After exclusion of 18,122 with missing data on 1+ covariate, non-imputed analyses were restricted to 130,502 participants (Figure 1).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1 displays baseline characteristics of the study sample. Nearly 60% were WHI-OS participants and mean age was 63.17 ± 7.20 years. Whereas 84% reported being White, 62% were married/partnered, 40% were college graduates, and ~90% reported household income<$100,000. While 38% reported 1+ alcoholic drink/week, 50% never smoked and 35% had BMI<25 kg/m$^2$. Prevalence of cardiovascular risk factors ranged between 12% (diabetes) and 42% (hypertension) and >90% reported excellent/very good/good health. Finally, the mean scores for depressive symptoms and metabolic equivalents were 0.04 and 12.44, respectively.

Eligible women were followed over a mean of 15.88 years; 2,829 (2.17%) women self-reported PD (n=2,344), died from PD (n=280) or received medication consistent with PD (n=255) by end of follow-up. The mean durations of time between repeated sleep measurements were 2.18, 1.03 and 2.99 years among WHI, WHI-CT and WHI-OS participants, respectively. At baseline, 59% reported 7–8 hours of sleep, 36% were short-sleepers (<7 hours), 5% were long-sleepers (>8 hours), with 25.8% reporting WHIIRS score>9. Furthermore, 30% had BMI≥30 kg/m$^2$, 16.0% snored≥3 times/week, 15.2% reported daytime sleepiness≥3 times/week and 42.4% had hypertension. Nearly 39% of women having WHIIRS score>9 reported using sleep aids. Similar results were obtained with time-varying sleep exposures.

Bivariate associations between the exposure variables and PD onset were displayed in Table 2 and Supplemental Digital Content 1 Figures S1–S4. The overall incidence density for PD was 3.73 per 1,000,000 person-days, with attributable risks for indicators of sleep disturbance of < 1.2 per 1,000,000 person-days. Kaplan-Meier curves with log-rank tests suggested significantly greater PD risk (P<0.001) among women who slept <7 vs. 7–8 hours, women who slept ≥9 hours vs. 7–8 hours, women with high insomnia symptoms score (WHIIRS>9) vs. low insomnia symptoms score (WHIIRS≤9) and those who used sleep aids vs. those who did not use sleep aids in the context of WHIIRS>9.

Table 3 presents Cox proportional hazards models for each sleep-related exposure at baseline in relation to PD, before and after adjustment for socio-demographic, lifestyle and health characteristics. Consistent with log-rank tests, unadjusted, partially adjusted (Model I and II) and fully-adjusted (Model III) models implied positive but weak relationships between sleep indicators and PD with estimated hazard ratios (HR) that did not exceed 1.40.

In fully-adjusted models, the following time-varying exposures were significantly associated with PD: long (≥9 hours) vs. standard (7–8 hours) sleep (hazard ratio (HR)=1.296, 95% confidence interval (CI): 1.153–1.456), WHIIRS score>9 (HR=1.114, 95% CI: 1.023–1.214), and use of sleep aids (HR=1.332, 95% CI: 1.153–1.539) among those with WHIIRS score>9. Compared to standard (7–8 hours) sleep, short (<7 hours) sleep was unrelated to PD. Similarly, OSA risk factors were not associated with PD (Table 4). Pre-specified sensitivity analyses yielded similar results providing evidence for independent effects of each sleep exposure on PD risk, consistency across WHI components and similar results after exclusion of PD events happening within 3 years of follow-up. Heterogeneity of findings according to PD definition (self-report, death certificates, medications) are likely attributed to sample size limitations (Supplemental Digital Content 2 Tables S1–S5).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

## DISCUSSION:

In this cohort study, we performed secondary analyses of data on 130,502 WHI participants to evaluate sleep disturbance in relation to PD diagnosis among postmenopausal women over a follow-up period of ~16 years. Study results showed a nearly 10–30% increased risk of PD diagnosis among postmenopausal women with several indicators of sleep disturbance. Women who slept ≥9 hours but not <7 hours were at slightly higher risk for PD diagnosis than those who slept 7–8 hours/day, reflecting a J-shaped rather than a U-shaped relationship between hours of sleep and PD. Similarly, having insomnia symptoms and use of sleep aids was associated with slightly more PD diagnoses. Baseline sleep measures alone or inclusion of repeated sleep measures had similarly positive, but weak, associations with PD. By contrast, a composite index of OSA risk factors at baseline was not associated with PD, after controlling for socio-demographic, lifestyle and health characteristics.

Our study findings are consistent with past research examining habitual hours of sleep and insomnia symptoms in relation to a wide range of health outcomes. A U-shaped or J-shaped relationship between hours of sleep and adverse outcomes were previously reported in population-based studies including the National Health and Nutrition Examination Survey, the Monitoring Trends and Determinants on Cardiovascular Diseases and the Nurses' Health Study. Furthermore, the health effects of insomnia symptoms are thought to be mediated through increased vulnerability to physical or mental decline, frailty and inflammation in the context of aging.[4,43] Health outcomes associated with use of sleep aids have been previously reported although not specifically in the context of PD.[44,45]

Aging itself is a risk factor for PD and postmenopausal women may be at particularly high-risk for both poor sleep and PD because of hormonal changes not present in other age and sex groups. The association of menopause-related factors with sleep and PD should be carefully examined in future studies. So far, epidemiologic evidence for a putative relationship between sleep and PD has mostly originated from small case-control studies, with only one similarly designed cohort study.[46] For instance, Kim et al[10] conducted a case-control study of 31 participants with idiopathic PD compared to 23 participants with clinically probable AD and 36 healthy controls on indicators of RBD; the idiopathic PD group had higher scores on validated RBD questionnaire than in any other group.[10] Liu et al[19] compared 98 participants with PD, 210 siblings of participants with PD and 250 healthy controls on selected NMS, namely, depression, anxiety, cognitive function, sleep status, constipation, daytime sleepiness, RBD and RLS. The participants with PD had the highest anxiety, depression, and RBD scores followed by siblings of participants with PD and then healthy controls.[19] Abbott and colleagues evaluated excessive daytime sleepiness (EDS) in relation to incident PD among 3,078 men 71–93 years of age at baseline who were enrolled in the Honolulu-Asia Aging Study (1991–1993) and had repeat neurological assessments between 1994 and 2001, yielding a total of 43 PD (19.9/10,000 person-years) cases.[46] Their results suggested nearly 3-fold increased odds of PD among men with EDS vs. men without EDS in age-adjusted (OR=3.3, 95% CI: 1.4, 7.0) and fully-adjusted (OR=2.8, 95% CI: 1.1, 6.4) models.[46] PD risk did not vary according to insomnia, daytime napping, early morning grogginess or frequent nocturnal awakening at baseline.[46]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

This study has many strengths. First, the WHI database comprises large samples with longer follow-up and comprehensive rigorously collected data useful for evaluating hypothesized relationships while controlling for confounders. Second, WHI findings are potentially generalizable to postmenopausal women of different racial and ethnic groups and from distinct geographical areas across the United States. Third, this study examined repeated measurements of multiple indicators of sleep disturbance frequently used in epidemiologic studies, including self-reported WHIIRS, a validated screening tool. Nevertheless, results need to be interpreted with caution in light of several important limitations. First, missing data could have resulted in selection bias, although multiple imputations of covariates resulted in similar estimated associations. Second, several measurements were self-reported potentially leading to non-differential misclassification and biased estimates toward the null value. In particular, we relied on indicators of sleep disturbance that were subjective in nature since few WHI participants had available objective sleep measures taken using actigraphy or polysomnography. The focus of our analyses was on sleep disturbance rather than sleep disorders. Specifically, RBD, which is currently recognized as an early-stage α-synucleinopathy, was not assessed among WHI participants and OSA risk factors rather than OSA, per se, were evaluated in this study. Moreover, PD cases were defined using multiple data sources including follow-up questionnaires and the National Death Index, but PD was not among the adjudicated health outcomes in WHI. Third, sleep-related exposures were measured repeatedly at baseline and at distinct follow-up times for each participant. Despite their stability over time, further research is needed to elucidate whether these exposures are relevant to PD onset if they occurred > 10 years prior to the end of the study period. Fourth, residual confounding due to unmeasured or inadequately measured confounders such as socioeconomic status and healthcare access remains a concern in observational studies. Fifth, establishing a temporal relationship between exposures and outcomes may be an issue because sleep problems are also considered PD symptoms. In particular, WHI participants may have had undiagnosed PD for many years and early stage biomarkers of PD are needed to truly establish a temporal relationship between sleep disturbance and PD. Overall evidence from published studies suggests that sleep disturbance is a symptom of PD rather than a risk factor for PD, rendering it a potentially useful biomarker for future PD diagnosis. Finally, WHI targeted postmenopausal women and is not population-based but rather involves volunteers at clinical centers limiting generalizability to men as well as younger and less educated women.

## CONCLUSIONS:

In conclusion, among postmenopausal women, sleep disturbance indicators were associated with approximately 10–30% increased risk of PD after an average follow-up of ~16 years. Sleep disturbance may be a marker of future PD diagnosis, although it may also be marker of undiagnosed PD. Establishing a temporal relationship between sleep disturbance and PD will necessitate the availability of markers of PD susceptibility, onset and progression in addition to PD diagnosis. Prospective cohort studies with objective exposure and adjudicated outcome measurements that involve men and women of diverse backgrounds are required to confirm and extend these findings.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements:

The manuscript was supported in part by the Intramural Research Program of the National Institute on Aging in Baltimore, Maryland. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A listing of WHI investigators can be found at: http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf.

**Disclaimer:**

The views expressed in this article are those of the authors and do not reflect the official policy of Fort Belvoir Community Hospital, the Defense Health Agency, Department of Defense, or the U.S. Government. Any discussion or mention of commercial products or brand names does not imply or support any endorsement by the Federal Government.

## References

1. Grieshober L, Wactawski-Wende J, Hageman Blair R, et al. A Cross-Sectional Analysis of Telomere Length and Sleep in the Women's Health Initiative. American journal of epidemiology. Sep 1 2019;188(9):1616–1626. doi:10.1093/aje/kwz134 [PubMed: 31145433]
2. Cauley JA, Hovey KM, Stone KL, et al. Characteristics of Self-Reported Sleep and the Risk of Falls and Fractures: The Women's Health Initiative (WHI). Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. Mar 2019;34(3):464–474. doi:10.1002/jbmr.3619 [PubMed: 30461066]
3. Salawu F, Olokoba A. Excessive daytime sleepiness and unintended sleep episodes associated with Parkinson's disease. Oman medical journal. Jan 2015;30(1):3–10. doi:10.5001/omj.2015.02 [PubMed: 25829994]
4. Carroll JE, Irwin MR, Levine M, et al. Epigenetic Aging and Immune Senescence in Women With Insomnia Symptoms: Findings From the Women's Health Initiative Study. Biological psychiatry. Jan 15 2017;81(2):136–144. doi:10.1016/j.biopsych.2016.07.008 [PubMed: 27702440]
5. Hartz A, Ross JJ, Noyes R, Williams P. Somatic symptoms and psychological characteristics associated with insomnia in postmenopausal women. Sleep medicine. Jan 2013;14(1):71–8. doi:10.1016/j.sleep.2012.08.003 [PubMed: 23041035]
6. Koo P, McCool FD, Hale L, Stone K, Eaton CB. Association of obstructive sleep apnea risk factors with nocturnal enuresis in postmenopausal women. Menopause. Feb 2016;23(2):175–82. doi:10.1097/GME.0000000000000517 [PubMed: 26325085]
7. Mirer AG, Peppard PE, Palta M, Benca RM, Rasmuson A, Young T. Menopausal hormone therapy and sleep-disordered breathing: evidence for a healthy user bias. Annals of epidemiology. Oct 2015;25(10):779–84 e1. doi:10.1016/j.annepidem.2015.07.004 [PubMed: 26358364]
8. Phipps AI, Bhatti P, Neuhouser ML, et al. Pre-diagnostic Sleep Duration and Sleep Quality in Relation to Subsequent Cancer Survival. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. Apr 15 2016;12(4):495–503. doi:10.5664/jcsm.5674 [PubMed: 26612513]
9. Sands M, Loucks EB, Lu B, et al. Self-reported snoring and risk of cardiovascular disease among postmenopausal women (from the Women's Health Initiative). The American journal of cardiology. Feb 15 2013;111(4):540–6. doi:10.1016/j.amjcard.2012.10.039 [PubMed: 23219175]
10. Albers JA, Chand P, Anch AM. Multifactorial sleep disturbance in Parkinson's disease. Sleep medicine. Jul 2017;35:41–48. doi:10.1016/j.sleep.2017.03.026 [PubMed: 28619181]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript


11. Chen JC, Espeland MA, Brunner RL, et al. Sleep duration, cognitive decline, and dementia risk in older women. Alzheimer's & dementia : the journal of the Alzheimer's Association. Jan 2016;12(1):21–33. doi:10.1016/j.jalz.2015.03.004
12. McClelland S 3rd, Baker JF, Smith JS, et al. Impact of Parkinson's disease on perioperative complications and hospital cost in multilevel spine fusion: A population-based analysis. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. Jan 2017;35:88–91. doi:10.1016/j.jocn.2016.10.008 [PubMed: 27765561]
13. Newman JM, Sodhi N, Wilhelm AB, et al. Parkinson's disease increases the risk of perioperative complications after total knee arthroplasty: a nationwide database study. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. Jul 2019;27(7):2189–2195. doi:10.1007/s00167-018-4970-y [PubMed: 29785449]
14. Willis AW, Thibault DP, Schmidt PN, Dorsey ER, Weintraub D. Hospital care for mental health and substance abuse conditions in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. Dec 2016;31(12):1810–1819. doi:10.1002/mds.26832 [PubMed: 27943472]
15. Wu L, Mu N, Yang F, Zang J, Zheng JP. A study of the non-motor symptoms in early Parkinson's disease with olfactory deficits. European review for medical and pharmacological sciences. Sep 2016;20(18):3857–3862. [PubMed: 27735030]
16. Mao CJ, Yang YP, Chen JP, et al. Poor nighttime sleep is positively associated with dyskinesia in Parkinson's disease patients. Parkinsonism & related disorders. Mar 2018;48:68–73. doi:10.1016/j.parkreldis.2017.12.022 [PubMed: 29305084]
17. Neikrug AB, Maglione JE, Liu L, et al. Effects of sleep disorders on the non-motor symptoms of Parkinson disease. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. Nov 15 2013;9(11):1119–29. doi:10.5664/jcsm.3148 [PubMed: 24235892]
18. Pushpanathan ME, Loftus AM, Thomas MG, Gasson N, Bucks RS. The relationship between sleep and cognition in Parkinson's disease: A meta-analysis. Sleep medicine reviews. Apr 2016;26:21–32. doi:10.1016/j.smrv.2015.04.003 [PubMed: 26365136]
19. Liu JB, Leng JL, Zhang XJ, et al. Investigation of non-motor symptoms in first-degree relatives of patients with Parkinson's disease. Parkinsonism & related disorders. Jul 2018;52:62–68. doi:10.1016/j.parkreldis.2018.03.021 [PubMed: 29606605]
20. Creasy SA, Crane TE, Garcia DO, et al. Higher amounts of sedentary time are associated with short sleep duration and poor sleep quality in postmenopausal women. Sleep. Jul 8 2019;42(7)doi:10.1093/sleep/zsz093
21. Kim HJ, Im HK, Kim J, et al. Brain Atrophy of Secondary REM-Sleep Behavior Disorder in Neurodegenerative Disease. Journal of Alzheimer's disease : JAD. Apr 5 2016;52(3):1101–9. doi:10.3233/JAD-151197 [PubMed: 27060938]
22. Mao ZJ, Liu CC, Ji SQ, et al. Clinical characteristics of sleep disorders in patients with Parkinson's disease. Journal of Huazhong University of Science and Technology Medical sciences = Hua zhong ke ji da xue xue bao Yi xue Ying De wen ban = Huazhong keji daxue xuebao Yixue Yingdewen ban. Feb 2017;37(1):100–104. doi:10.1007/s11596-017-1701-4 [PubMed: 28224427]
23. Prashanth R, Roy SD, Mandal PK, Ghosh S. Parkinson's disease detection using olfactory loss and REM sleep disorder features. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference. 2014;2014:5764–7. doi:10.1109/EMBC.2014.6944937
24. Wang Y, Yang YC, Lan DM, Wu H, Zhao ZX. An observational clinical and video-polysomnographic study of the effects of rotigotine in sleep disorder in Parkinson's disease. Sleep & breathing = Schlaf & Atmung. May 2017;21(2):319–325. doi:10.1007/s11325-016-1414-0 [PubMed: 27726069]
25. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. Annals of epidemiology. Oct 2003;13(9 Suppl):S5–17. doi:10.1016/s1047-2797(03)00043-7 [PubMed: 14575938]
26. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. Annals of epidemiology. Oct 2003;13(9 Suppl):S18–77. doi:10.1016/s1047-2797(03)00042-5 [PubMed: 14575939]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript


27. Jiao L, Duan Z, Sangi-Haghpeykar H, Hale L, White DL, El-Serag HB. Sleep duration and incidence of colorectal cancer in postmenopausal women. British journal of cancer. Jan 15 2013;108(1):213–21. doi:10.1038/bjc.2012.561 [PubMed: 23287986]
28. Royse KE, El-Serag HB, Chen L, et al. Sleep Duration and Risk of Liver Cancer in Postmenopausal Women: The Women's Health Initiative Study. Journal of women's health. Dec 2017;26(12):1270–1277. doi:10.1089/jwh.2017.6412
29. Hale L, Parente V, Dowd JB, et al. Fibrinogen may mediate the association between long sleep duration and coronary heart disease. Journal of sleep research. Jun 2013;22(3):305–14. doi:10.1111/jsr.12020 [PubMed: 23217092]
30. Kling JM, Manson JE, Naughton MJ, et al. Association of sleep disturbance and sexual function in postmenopausal women. Menopause. Jun 2017;24(6):604–612. doi:10.1097/GME.0000000000000824 [PubMed: 28141665]
31. Ochs-Balcom HM, Hovey KM, Andrews C, et al. Short Sleep Is Associated With Low Bone Mineral Density and Osteoporosis in the Women's Health Initiative. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. Nov 6 2019;doi:10.1002/jbmr.3879
32. Vogtmann E, Levitan EB, Hale L, et al. Association between sleep and breast cancer incidence among postmenopausal women in the Women's Health Initiative. Sleep. Oct 1 2013;36(10):1437–44. doi:10.5665/sleep.3032 [PubMed: 24082303]
33. Rissling MB, Gray KE, Ulmer CS, et al. Sleep Disturbance, Diabetes, and Cardiovascular Disease in Postmenopausal Veteran Women. The Gerontologist. Feb 2016;56 Suppl 1:S54–66. doi:10.1093/geront/gnv668 [PubMed: 26768391]
34. Soucise A, Vaughn C, Thompson CL, et al. Sleep quality, duration, and breast cancer aggressiveness. Breast cancer research and treatment. Jul 2017;164(1):169–178. doi:10.1007/s10549-017-4245-1 [PubMed: 28417334]
35. Levine DW, Dailey ME, Rockhill B, Tipping D, Naughton MJ, Shumaker SA. Validation of the Women's Health Initiative Insomnia Rating Scale in a multicenter controlled clinical trial. Psychosomatic medicine. Jan-Feb 2005;67(1):98–104. doi:10.1097/01.psy.0000151743.58067.f0 [PubMed: 15673630]
36. Levine DW, Kaplan RM, Kripke DF, Bowen DJ, Naughton MJ, Shumaker SA. Factor structure and measurement invariance of the Women's Health Initiative Insomnia Rating Scale. Psychological assessment. Jun 2003;15(2):123–36. doi:10.1037/1040-3590.15.2.123 [PubMed: 12847773]
37. Beverly Hery CM, Hale L, Naughton MJ. Contributions of the Women's Health Initiative to understanding associations between sleep duration, insomnia symptoms, and sleep-disordered breathing across a range of health outcomes in postmenopausal women. Sleep health. Nov 4 2019;doi:10.1016/j.sleh.2019.09.005
38. Generaal E, Vogelzangs N, Penninx BW, Dekker J. Insomnia, Sleep Duration, Depressive Symptoms, and the Onset of Chronic Multisite Musculoskeletal Pain. Sleep. Jan 1 2017;40(1)doi:10.1093/sleep/zsw030
39. Levine DW, Kripke DF, Kaplan RM, et al. Reliability and validity of the Women's Health Initiative Insomnia Rating Scale. Psychological assessment. Jun 2003;15(2):137–48. doi:10.1037/1040-3590.15.2.137 [PubMed: 12847774]
40. Burstyn I, LaCroix AZ, Litvan I, Wallace RB, Checkoway H. Occupation and Parkinson disease in the Women's Health Initiative Observational Study. American journal of industrial medicine. Sep 2019;62(9):766–776. doi:10.1002/ajim.23022 [PubMed: 31328814]
41. Patel KV, Cochrane BB, Turk DC, et al. Association of Pain With Physical Function, Depressive Symptoms, Fatigue, and Sleep Quality Among Veteran and non-Veteran Postmenopausal Women. The Gerontologist. Feb 2016;56 Suppl 1:S91–101. doi:10.1093/geront/gnv670 [PubMed: 26768395]
42. Zaslavsky O, LaCroix AZ, Hale L, Tindle H, Shochat T. Longitudinal changes in insomnia status and incidence of physical, emotional, or mixed impairment in postmenopausal women participating in the Women's Health Initiative (WHI) study. Sleep medicine. Mar 2015;16(3):364–71. doi:10.1016/j.sleep.2014.11.008 [PubMed: 25620200]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

43. Chen JC, Brunner RL, Ren H, et al. Sleep duration and risk of ischemic stroke in postmenopausal women. Stroke. Dec 2008;39(12):3185–92. doi:10.1161/STROKEAHA.108.521773 [PubMed: 18635832]

44. Kripke DF. Mortality Risk of Hypnotics: Strengths and Limits of Evidence. Drug safety. Feb 2016;39(2):93–107. doi:10.1007/s40264-015-0362-0 [PubMed: 26563222]

45. Sivertsen B, Madsen IE, Salo P, Tell GS, Overland S. Use of Sleep Medications and Mortality: The Hordaland Health Study. Drugs - real world outcomes. Jun 2015;2(2):123–128. doi:10.1007/s40801-015-0023-8 [PubMed: 27747767]

46. Abbott RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology. Nov 8 2005;65(9):1442–6. doi:10.1212/01.wnl.0000183056.89590.0d [PubMed: 16275833]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

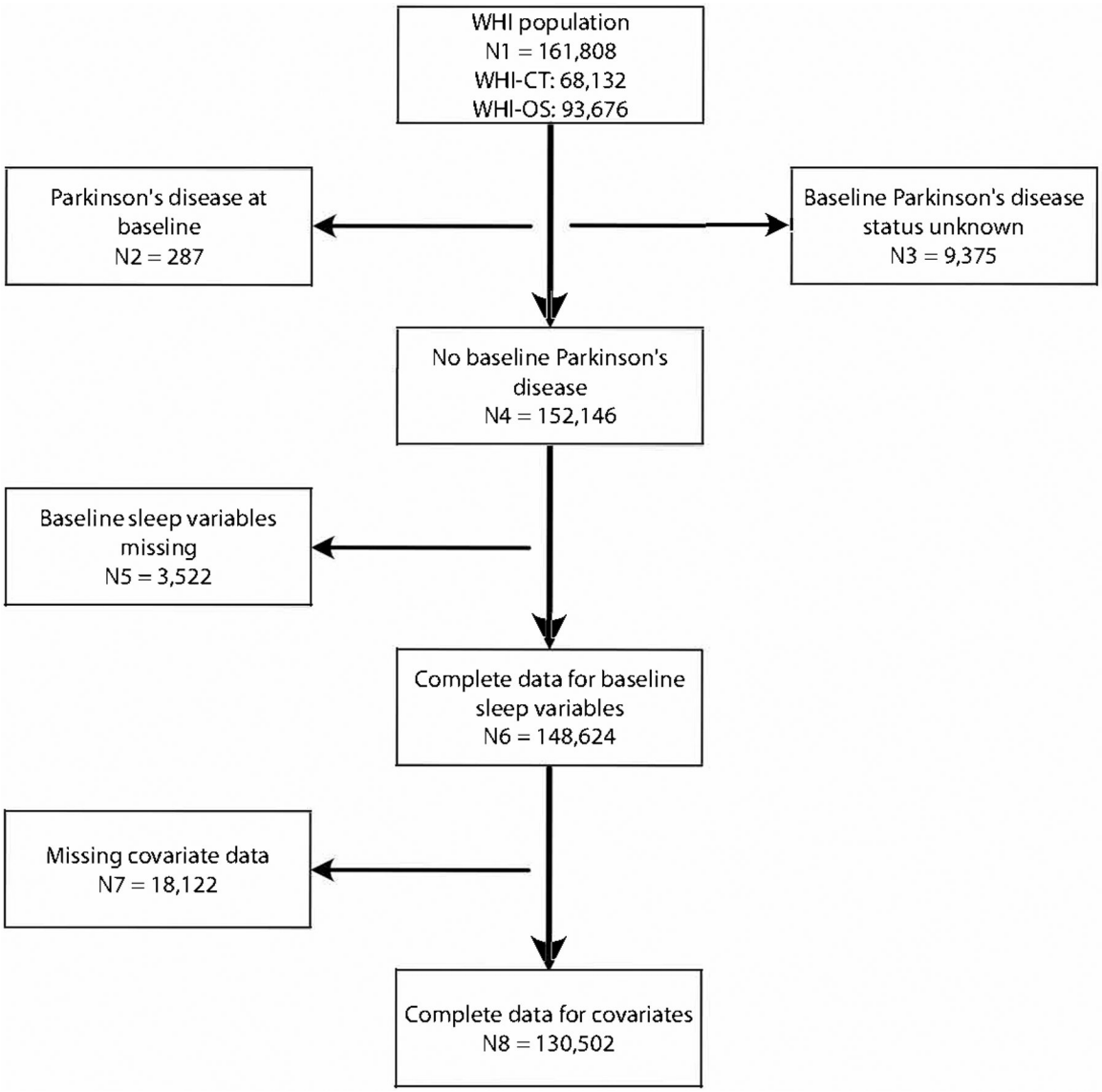


**Figure 1.**
Study Flowchart

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 1.**

Baseline socio-demographic, lifestyle and health characteristics of study sample – Women's Health Initiative (n=130,502)

| | N | % | Mean ± SD |
|---|---|---|---|
| ***WHI component:*** | | | |
| CT | 52784 | 40.45 | |
| OS | 77718 | 59.55 | |
| ***Age (years):*** | | | |
| <55 | 17368 | 13.31 | |
| 55–59 | 26061 | 19.97 | |
| 60–64 | 30330 | 23.24 | |
| 65–69 | 28513 | 21.85 | |
| 70–74 | 19877 | 15.23 | |
| > 74 | 8353 | 6.40 | |
| ***Race/Ethnicity:*** | | | |
| Black | 11121 | 8.52 | |
| White | 109766 | 84.11 | |
| Latina | 4540 | 3.48 | |
| Asian | 3630 | 2.78 | |
| Other[a] | 1445 | 1.11 | |
| ***Marital status:*** | | | |
| Married/Partnered | 81176 | 62.20 | |
| Single | 5696 | 4.36 | |
| Divorced | 21273 | 16.30 | |
| Widowed | 22357 | 17.13 | |
| ***Education:*** | | | |
| Less than high school | 5886 | 4.51 | |
| High school graduate | 22181 | 17.00 | |
| Some college | 49659 | 38.05 | |
| College graduate | 52776 | 40.44 | |
| ***Household income:*** | | | |
| < $20,000 | 20830 | 15.96 | |
| $20,000-$49,999 | 58533 | 44.85 | |
| $50,000-$99,999 | 38296 | 29.35 | |
| ≥$100,000 | 12843 | 9.84 | |
| ***Smoking status:*** | | | |
| Never | 66042 | 50.61 | |
| Past | 55396 | 42.45 | |
| Current | 9064 | 6.95 | |
| ***Alcohol use:*** | | | |
| Non-drinker | 13707 | 10.50 | |
| Former drinker | 24126 | 18.49 | |

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

| | N | % | Mean ± SD |
|---|---|---|---|
| < 1 drink / week | 43249 | 33.14 | |
| ≥1 drink / week | 49420 | 37.87 | |
| ***Physical activity (Met-hours/week):*** | | | |
| Continuous | | | 12.44 ± 13.63 |
| ***Body Mass Index (kg/m $^2$ ):*** | | | |
| < 25 | 46269 | 35.45 | |
| 25–29.9 | 45279 | 34.70 | |
| ≥ 30 | 38954 | 29.85 | |
| ***Medical history:*** | | | |
| *Cardiovascular disease:* | | | |
| Yes | 26858 | 20.58 | |
| No | 103644 | 79.42 | |
| *Hypertension:* | | | |
| Yes | 55348 | 42.41 | |
| No | 75154 | 57.59 | |
| *Diabetes:* | | | |
| Yes | 15444 | 11.83 | |
| No | 115058 | 88.17 | |
| *Hyperlipidemia:* | | | |
| Yes | 18168 | 13.92 | |
| No | 112334 | 86.08 | |
| ***Depressive symptoms score:*** | | | |
| Continuous | | | 0.040± 0.13 |
| ***Self-rated health:*** | | | |
| Excellent | 22664 | 17.37 | |
| Very good | 54009 | 41.39 | |
| Good | 42671 | 32.70 | |
| Fair | 10260 | 7.86 | |
| Poor | 898 | 0.69 | |

[a]Includes participants who self-identify as American Indian or Alaskan Native, multiracial and other race besides those specified. *Abbreviations:* CT=Clinical Trial; OS=Observational Study; WHI=Women's Health Initiative.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 2.**

Number of PD events, number of participants, person-days of follow-up, cumulative incidence and incidence density of PD by levels of sleep indicators at baseline – Women's Health Initiative (n=130,502)

| | PD events | Number of participants | Cumulative incidence (%) | Person-days of follow-up | Incidence density Per 1000,000 person-days |
|---|---|---|---|---|---|
| **Overall:** | 2829 | 130502 | 2.17 | 756,689,535 | 3.73 |
| ***Habitual sleep duration (hours):*** | | | | | |
| ≤ 6 | 965 | 46549 | 2.07 | 260,322,090 | 3.70 |
| 7–8 | 1714 | 78323 | 2.19 | 465,193,085 | 3.68 |
| ≥ 9 | 150 | 5630 | 2.66 | 31,174,360 | 4.81 |
| ***Insomnia symptoms score***[a]: | | | | | |
| ≤ 9 | 2027 | 96851 | 2.09 | 567,770,363 | 3.57 |
| > 9 | 802 | 33651 | 2.38 | 188,919,172 | 4.24 |
| ***OSA risk factors (any)***[b]: | | | | | |
| 0 | 964 | 45240 | 2.13 | 280,181,205 | 3.44 |
| 1+ | 1865 | 85262 | 2.19 | 476,508,330 | 3.91 |
| ***Sleep aids***[c]: | | | | | |
| Yes | 355 | 13026 | 2.72 | 71,227,128 | 4.98 |
| No | 447 | 20625 | 2.16 | 117,692,044 | 3.79 |

[a]Based on the 5-item Women's Health Initiative Insomnia Rating Scale covering sleep quality, trouble falling asleep, waking up several times at night, waking up earlier than planned, and having trouble getting back to sleep after early awakening during the past 4 weeks.

[b]Presence of OSA risk factors was defined as having BMI≥30 kg/m$^2$, snoring≥3 times per week, daytime sleepiness≥3 times per week and/or diagnosis of hypertension;

[c]Among women with a insomnia symptoms score greater than 9; *Abbreviations:* OSA=Obstructive Sleep Apnea; PD=Parkinson's Disease.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 3.**

Sleep indicators at baseline in relation to PD onset – Women's Health Initiative (n=130,502)

| | Unadjusted | Model I[a] | Model II[b] | Model III[c] |
|---|---|---|---|---|
| | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| ***Habitual sleep duration (hours):*** | | | | |
| ≤ 6 | 1.026 (0.948–1.110) | 1.055 (0.974–1.143) | 1.046 (0.966–1.133) | 1.009 (0.931–1.094) |
| 7–8 | Ref. | Ref. | Ref. | Ref. |
| ≥ 9 | 1.389 (1.184–1.629) | 1.347 (1.149–1.580) | 1.338 (1.140–1.569) | 1.301 (1.109–1.526) |
| ***Insomnia symptoms score:*** | | | | |
| ≤ 9 | Ref. | Ref. | Ref. | Ref. |
| > 9 | 1.224 (1.127–1.328) | 1.210 (1.114–1.313) | 1.206 (1.111–1.309) | 1.130 (1.039–1.229) |
| ***OSA risk factors (any):*** | | | | |
| 0 | Ref. | Ref. | Ref. | Ref. |
| 1+ | 1.217 (1.125–1.315) | 1.174 (1.084–1.270) | 1.128 (1.041–1.222) | 1.067 (0.982–1.158) |
| ***OSA risk factor 1 (BMI ≥ 30 kg/m$^2$):*** | | | | |
| Yes | 1.107 (1.021–1.200) | 1.136 (1.045–1.234) | 1.095 (1.006–1.192) | 1.011 (0.926–1.013) |
| No | Ref. | Ref. | Ref. | Ref. |
| ***OSA risk factor 2 (Snoring ≥ 3 times per week):*** | | | | |
| Yes | 1.046 (0.948–1.154) | 1.096 (0.993–1.210) | 1.086 (0.984–1.200) | 1.077 (0.977–1.187) |
| No | Ref. | Ref. | Ref. | Ref. |
| ***OSA risk factor 3 (daytime sleepiness ≥ 3 times per week):*** | | | | |
| Yes | 1.219 (1.102–1.349) | 1.108 (1.001–1.228) | 1.091 (0.985–1.208) | 1.056 (0.947–1.178) |
| No | Ref. | Ref. | Ref. | Ref. |
| ***OSA risk factor 4 (diagnosis of hypertension):*** | | | | |
| Yes | 1.225 (1.137–1.320) | 1.136 (1.052–1.227) | 1.119 (1.036–1.209) | 1.041 (0.961–1.127) |
| No | Ref. | Ref. | Ref. | Ref. |
| ***Sleep aids:***[d] | | | | |
| Yes | 1.345 (1.170–1.546) | 1.336 (1.162–1.536) | 1.364 (1.185–1.569) | 1.316 (1.142–1.515) |
| No | Ref. | Ref. | Ref. | Ref. |

[a]Adjusted for socio-demographic characteristics (WHI component, age, race/ethnicity, marital status, education, household income);

[b]Adjusted for socio-demographic (WHI component, age, race/ethnicity, marital status, education, household income) and lifestyle (smoking status, alcohol use, physical activity) characteristics;

[c]Adjusted for socio-demographic (WHI component, age, race/ethnicity, marital status, education, household income), lifestyle (smoking status, alcohol use, physical activity) and health (BMI, history of cardiovascular disease, history of hypertension, history of diabetes, history of hyperlipidemia, depressive symptoms, self-rated health) characteristics; when examining OSA risk factors, BMI and history of hypertension were not included in this model;

[d]Among women with insomnia symptoms score greater than 9. *Abbreviations:* BMI=Body Mass Index; CI=Confidence Interval; HR=Hazard ratio; OSA=Obstructive Sleep Apnea; PD=Parkinson's Disease.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 4.**

Sleep indicators (time-varying exposure variables) in relation to PD onset – Women's Health Initiative (n=130,502)

| | Unadjusted | Model I[a] | Model II[b] | Model III[c] |
|---|---|---|---|---|
| | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| ***Habitual sleep duration (hours):*** | | | | |
| ≤ 6 | 1.029 (0.973–1.089) | 1.065 (1.006–1.127) | 1.056 (0.997–1.118) | 1.018 (0.961–1.078) |
| 7–8 | Ref. | Ref. | Ref. | Ref. |
| ≥ 9 | 1.382 (1.230–1.553) | 1.338 (1.191–1.504) | 1.330 (1.184–1.495) | 1.296 (1.153–1.456) |
| ***Insomnia symptoms score:*** | | | | |
| ≤ 9 | Ref. | Ref. | Ref. | Ref. |
| > 9 | 1.219 (1.121–1.325) | 1.196 (1.100–1.301) | 1.193 (1.097–1.297) | 1.114 (1.023–1.214) |
| ***OSA risk factors (any):*** | | | | |
| 0 | Ref. | Ref. | Ref. | Ref. |
| 1+ | 1.212 (1.147–1.281) | 1.130 (1.065–1.199) | 1.136 (1.073–1.203) | 1.057 (0.997–1.121) |
| ***OSA risk factor 1 (BMI ≥ 30 kg/m$^2$):*** | | | | |
| Yes | 1.086 (1.026–1.151) | 1.128 (1.064–1.197) | 1.088 (1.024–1.156) | 1.006 (0.945–1.071) |
| No | Ref. | Ref. | Ref. | Ref. |
| ***OSA risk factor 2 (Snoring ≥ 3 times per week):*** | | | | |
| Yes | 1.063 (0.991–1.139) | 1.108 (1.033–1.188) | 1.098 (1.024–1.178) | 1.056 (0.984–1.133) |
| No | Ref. | Ref. | Ref. | Ref. |
| ***OSA risk factor 3 (daytime sleepiness ≥ 3 times per week):*** | | | | |
| Yes | 1.253 (1.164–1.349) | 1.140 (1.058–1.229) | 1.121 (1.040–1.208) | 1.073 (0.995–1.156) |
| No | Ref. | Ref. | Ref. | Ref. |
| ***OSA risk factor 4 (diagnosis of hypertension):*** | | | | |
| Yes | 1.210 (1.147–1.276) | 1.131 (1.071–1.195) | 1.114 (1.054–1.177) | 1.037 (0.980–1.097) |
| No | Ref. | Ref. | Ref. | Ref. |
| ***Sleep aids:***[d] | | | | |
| Yes | 1.359 (1.178–1.567) | 1.347 (1.168–1.554) | 1.381 (1.197–1.594) | 1.332 (1.153–1.539) |
| No | Ref. | Ref. | Ref. | Ref. |

[a]Adjusted for socio-demographic characteristics (WHI component, age, race/ethnicity, marital status, education, household income);

[b]Adjusted for socio-demographic (WHI component, age, race/ethnicity, marital status, education, household income) and lifestyle (smoking status, alcohol use, physical activity) characteristics;

[c]Adjusted for socio-demographic (WHI component, age, race/ethnicity, marital status, education, household income), lifestyle (smoking status, alcohol use, physical activity) and health (BMI, history of cardiovascular disease, history of hypertension, history of diabetes, history of hyperlipidemia, depressive symptoms, self-rated health) characteristics; when examining OSA risk factors, BMI and history of hypertension were not included in this model;

[d]Among women with a insomnia symptoms score greater than 9. *Abbreviations:* BMI=Body Mass Index; CI=Confidence Interval; HR=Hazard ratio; OSA=Obstructive Sleep Apnea; PD=Parkinson's Disease.