

Obstructive Sleep Apnea, Positive Airway Pressure, and Implications of Early Treatment in Parkinson Disease

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 Supplemental content

IMPORTANCE Obstructive sleep apnea (OSA) is associated with many health conditions, including dementia and early mortality. Prior epidemiological studies linking OSA with Parkinson disease (PD) are conflicting, and no studies have examined the influence of continuous positive airway pressure (CPAP), the criterion standard treatment for OSA, on PD risk.

OBJECTIVE To examine the association between OSA with incident Parkinson disease among US veterans and risk modification by CPAP.

DESIGN, SETTING, AND PARTICIPANTS This electronic health record (EHR)-based cohort study was conducted among US veterans from January 1, 1999, to December 30, 2022, with mean (SD) follow-up of 4.9 (1.8) years. Veterans with PD at the time of exposure or incomplete records were excluded. Data analysis was completed from September 2024 to September 2025.

EXPOSURE OSA was defined by its appropriate administrative code; CPAP usage was extracted from a semistructured medical interview field in the EHR.

MAIN OUTCOMES AND MEASURES The primary outcome, cumulative incidence of PD, was calculated adjusting for competing risk of death after balancing for age, race, sex, and smoking status.

RESULTS A total of 13 737 081 US veterans were screened, and 11 310 411 veterans (1 109 543 female veterans [9.8%]) with mean (SD) age of 60.5 (14.7) years were included in analyses. Of included veterans, 1 552 505 (13.7%) had OSA. Veterans with OSA demonstrated 1.61 additional cases of PD (point estimate; 95% CI, 1.13-2.09) at 6 years from diagnosis per 1000 people compared to those without OSA. Results were confirmed when adjusting for body mass index, vascular comorbidities, psychiatric conditions, and relevant medications and were of greater magnitude in female veterans. Case numbers were significantly reduced when treated with CPAP early in the disease course.

CONCLUSIONS AND RELEVANCE In this EHR-based cohort study, OSA appeared to be an independent risk factor for the later development of PD and could be modified by early treatment with CPAP. Effective screening measures and protocols for consistent adherence to CPAP may have large impacts on brain health.

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Parkinson disease (PD) is the fastest-growing neurological disorder worldwide, likely due to a combination of aging, increased awareness, and other lifestyle factors.¹ While some expert recommendations have been proposed for lifestyle modifications to delay neurodegenerative disease,² evidence-based guidelines are lacking in PD care. One condition gaining attention is obstructive sleep apnea (OSA), both because of its increasing prevalence³ and its known association with cognitive dysfunction.⁴

OSA is characterized by apneas (momentary cessations in breathing rhythm) and/or hypopneas (reductions in breath amplitude) due to a compromised upper airway.⁵ This obstruction can be sufficient to cause significant intermittent arterial hypoxemia and hypercapnia, which triggers a cascade of hemodynamic, metabolic, and inflammatory events.⁶ In the brain, this chronic intermittent hypoxia results in mitochondrial dysfunction,⁷ a process thought to underlie PD pathogenesis.⁸ Further evidence of biological plausibility is that in people with OSA, both total and phosphorylated α -synuclein are elevated in plasma,⁹ and striatal dopamine transporter availability is reduced.¹⁰ Nevertheless, the epidemiological association between OSA and PD is unclear. One meta-analysis¹¹ suggested that OSA is not a consequence of PD-related neurodegeneration, and a larger prospective case-control study¹² showed no difference in OSA rates, as measured by a screening questionnaire alone, predating a self-reported diagnosis of PD after 3 years of follow-up. In contrast, 2 nationwide electronic health record (EHR)-based studies^{13,14} did indicate an association between OSA and PD. However, these EHR studies had the following important limitations: the outcome of PD relied on a low-specificity approach; key demographic variables were missing, limiting the ability to assess confounders; and competing risk of death was unaccounted for, particularly relevant given the high mortality associated with OSA.¹⁵ Moreover, to our knowledge, no existing studies have yet investigated whether continuous positive airway pressure (CPAP), the criterion standard treatment for symptomatic OSA, modifies the risk of PD incidence.

Key Points

Question Is obstructive sleep apnea (OSA) associated with an increased risk of incident Parkinson disease (PD) diagnosis among US veterans?

Findings In this electronic health record-based cohort study of more than 11 million veterans with mean (SD) of 4.9 (1.8) years of follow-up, OSA was associated with incident PD, even after adjusting for competing risk of death, age, body mass index, and comorbidity burden. This risk was attenuated by OSA treatment with positive airway pressure.

Meaning OSA may be a modifiable midlife risk factor for PD.

Thus, this cohort study aims to rigorously test the association between OSA and PD using the US Department of Veterans Affairs (VA) Corporate Data Warehouse (CDW) nationwide EHR database. We further hypothesize this association is attenuated with CPAP usage.

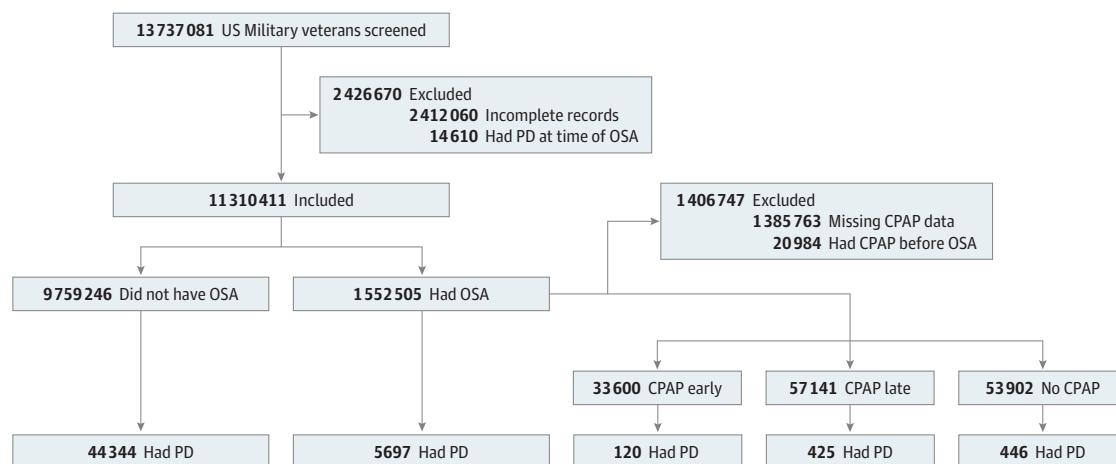
Methods

Study Design

An EHR-based cohort study design measured the association of OSA with incident PD. Data were obtained from the CDW under the Portland VA Health Care System institutional review board (04744) using a waiver of participant consent. All time periods available within the CDW were included. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.¹⁶

All veterans who received VA care were initially reviewed. Veterans younger than 40 years were excluded. All dated *International Classification of Diseases, Ninth Revision (ICD-9)* and *Tenth Revision (ICD-10)* codes were extracted from the CDW to capture primary and secondary outcomes. The first instance of OSA or start of medical records in controls marked the beginning of follow-up time.

Figure 1. Study Design Flowchart



CPAP indicates continuous positive airway pressure; OSA, obstructive sleep apnea; PD, Parkinson disease.

Table 1. Cohort Characteristics

Characteristic	No. (%)				
	OSA, primary analysis		OSA with CPAP data		
	OSA–	OSA+	OSA+CPAP early	OSA+CPAP late	OSA+CPAP–
No.	9 759 021	1 551 390	33 600	57 141	53 902
Birth year, mean (SD)	1945 (16)	1957 (12)	1958 (12)	1954 (11)	1950 (11)
Sex					
Female	999 319 (10.2)	110 224 (7.1)	2486 (7.4)	2960 (5.2)	3559 (6.6)
Male	8 759 702 (89.8)	1 441 166 (92.9)	31 114 (92.6)	54 181 (94.8)	50 343 (93.4)
Smoking					
Never smoker	3 261 441 (33.4)	591 155 (38.1)	11 864 (35.3)	19 594 (34.3)	15 863 (29.4)
Former smoker	3 196 744 (32.8)	436 843 (28.2)	7125 (21.2)	17 632 (30.9)	16 868 (31.3)
Current smoker	3 300 836 (33.8)	523 392 (33.7)	14 611 (43.5)	19 915 (34.9)	21 171 (39.3)
Race ^a					
African American, Black	1 489 747 (15.3)	335 450 (21.6)	7813 (23.3)	12 119 (21.2)	11 687 (21.7)
Asian	101 957 (1.0)	23 388 (1.5)	477 (1.4)	531 (0.9)	382 (0.7)
Native American, Alaskan Native	68 711 (0.7)	13 182 (0.8)	241 (0.7)	430 (0.8)	381 (0.7)
Native Hawaiian or Other Pacific Islander	95 184 (1.0)	20 001 (1.3)	475 (1.4)	702 (1.2)	690 (1.3)
White	8 003 422 (82.0)	1 159 369 (74.7)	24 594 (73.2)	43 359 (75.9)	40 762 (75.6)
Ethnicity ^a					
Hispanic	478 483 (4.9)	119 402 (7.7)	2339 (7.0)	4484 (7.8)	3522 (6.5)
Not Hispanic	9 280 538 (95.1)	1 431 988 (92.3)	31 261 (93.0)	52 657 (92.2)	50 380 (93.5)
BMI, mean (SD) ^b	28.4 (5.1)	33.2 (5.8)	33.5 (5.8)	35.1 (6.0)	33.1 (6.4)

Abbreviations: BMI, body mass index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

^a Race and ethnicity were collected from standard patient demographic fields in the VA data warehouse.

^b Calculated as weight in kilograms divided by height in meters squared.

OSA was defined by the presence of *ICD-10* code G47.33, with noncases being defined as the absence of this code. A random sample ($n = 500$) from our cohort were manually reviewed and yielded a positive predictive value (PPV) of 94.0%, consistent with other published validations using VA data.¹⁷ During the manual validation, documentation of apnea-hypopnea index (AHI) greater than 5 or respiratory disturbance index (RDI) greater than 5 was considered accurate ascertainment consistent with the American Academy of Sleep Medicine recommendations.^{18,19} In the absence of polysomnography data, documentation by a licensed clinician that OSA was an active problem being managed was also considered accurate. For example, placing OSA in the problem list was insufficient, but placing OSA among the impressions with a severity label or a recommendation, such as refer to CPAP clinic for new supplies was also considered accurate. A secondary strategy using a custom-built rules-based system for extracting text was carried out looking for the term “OSA” or variants thereof and removing negations and ambiguities. This was then filtered for patient files with both “AHI” and modifiers of severity (eg, “mild”). A random sample ($n = 500$) from this cohort was manually reviewed and all records (100%) correctly ascertained OSA per the aforementioned criteria. Records were further reviewed for appropriate classification of mild vs severe based on whether any of the following criteria were met: AHI or RDI of 5 to 15 for mild; greater than 30 for severe; or severity designation given in the impression of a note by a licensed physician. In cases where the clinician documented mild to moderate, it was categorized as mild, and if

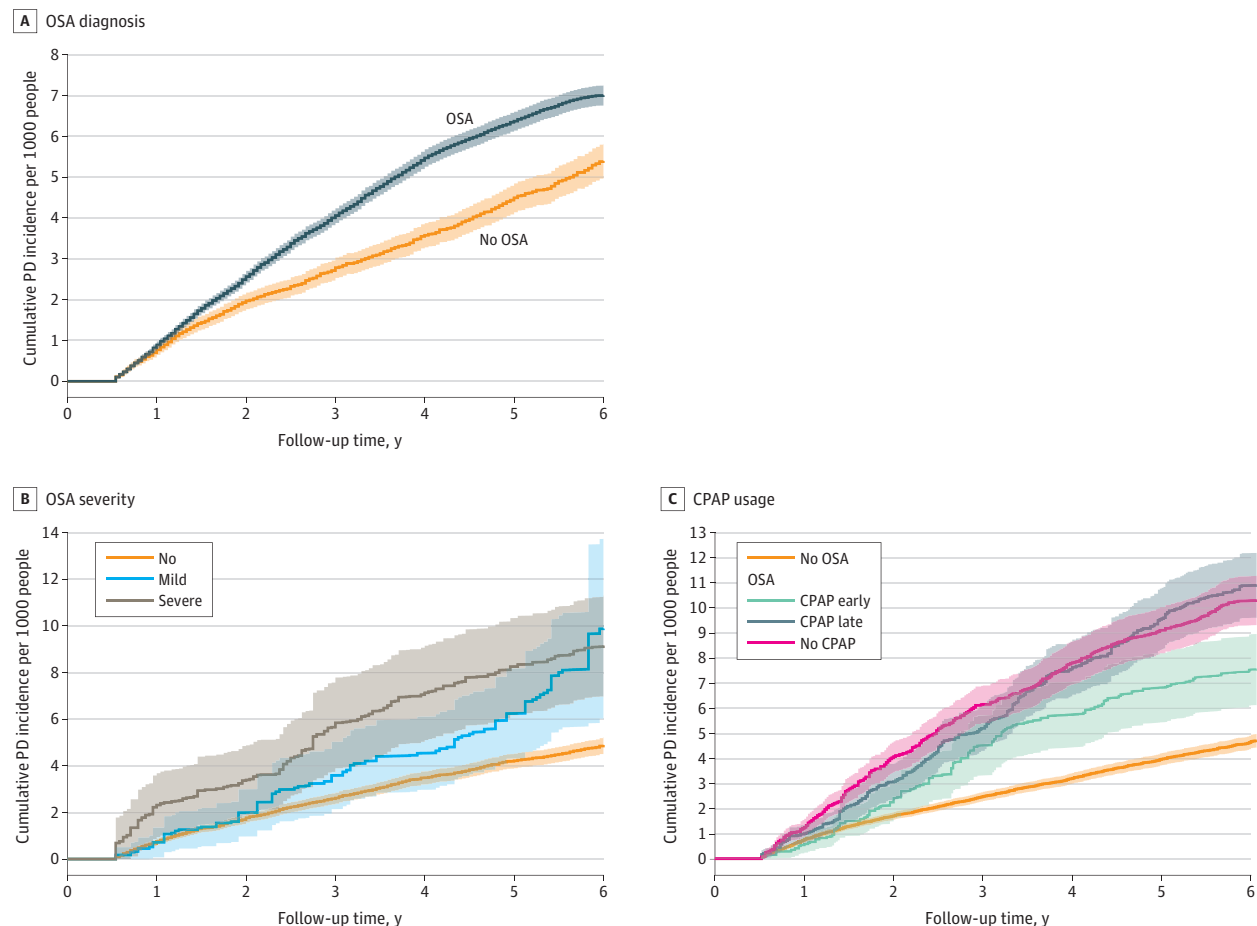
documented moderate to severe, it was categorized as severe. If the AHI fell within the moderate range (AHI/RDI = 15–30) without clinician interpretation, it was considered misclassification. All but a few outliers ($n = 28$ [or 5.6% of patient records]) contained 2 of the 3 criteria. Overall, this yielded a PPV of 99.0% for correct classification of severity.

Extraction of race, ethnicity, sex, birth year, and body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) came from their own distinct fields in the CDW, with smoking information categorized using a cross-walk method validated previously at the VA.²⁰ Additional covariates and negative control conditions were defined by diagnostic codes as previously validated.^{21,22} Additional outcomes data (psychosis, fractures, falls, and mortality) were determined using the relevant and high-accuracy *ICD-10* codes as reported in Goldman and colleagues.²³ Missing data for baseline characteristics were imputed using multiple imputation by chained equations.²⁴

The primary outcome was incident PD. PD was defined by criteria described previously,²¹ showing a PPV of 78.6%. In brief, PD was defined as (1) age greater than 40 years; (2) minimum of 1 PD-related *ICD-9* (332.0) or *ICD-10* (G20) code; (3) minimum 5 years of medical records before the first PD *ICD* code; and (4) having 2 PD medication prescriptions filled. PD medication was defined by the VA nationwide common data model for operations and research.²⁵ Cases were excluded if PD was identified within 6 months of OSA diagnosis to mitigate reverse causation bias.

CPAP usage was abstracted from the HealthFactor field, a semistructured field containing data from medical inter-

Figure 2. Cumulative Incidence of Parkinson Disease (PD) Based on Antecedent Diagnosis of Obstructive Sleep Apnea (OSA)



Cumulative incidence is shown with 95% confidence intervals after adjustment for competing risk of death. A, Incidence rates of PD are greater in the OSA+ group compared to the OSA- group. B, When stratified by severity, incidence rates of PD are greater in both the mild and severe groups compared to those

without OSA. C, When stratified by continuous positive airway pressure (CPAP) usage, those who were documented to be using CPAP within 2 years of the index OSA code (CPAP-Early) showed an attenuated risk of incident PD.

views. Only 9.3% of veterans affirmed CPAP usage (CPAP+); therefore, individuals missing CPAP-related HealthFactor data were excluded from the secondary CPAP analysis. CPAP + Early was defined as mentions of CPAP within 2 years of OSA diagnosis. A random sample of charts ($n = 200$) representing both CPAP+ and CPAP- were manually reviewed for accuracy, each showing 98% PPV.

Statistical Analysis

Inverse probability of treatment weighting was performed, followed by calculation of cumulative incidence for PD adjusted for competing risk of death (implemented via WeightIt and adjustedCurves R packages²⁶). Baseline characteristics of age, sex, race, ethnicity, and smoking history (current, former, or never) were balanced between all exposed and unexposed groups. Sensitivity analysis included trimming weights above the 99.5 percentile and excluding the OSA- group to remove extreme weights and improve covariate balance or adjustment. Differences between exposure groups were calculated with respect to cumulative incidence functions adjusted for competing risk of death,

pseudorandomization by covariates, and BMI, tabulated at years 1 through 6 from the initial OSA diagnosis. Relative effects were calculated using the Fine-Gray proportional subdistribution hazards model. Group comparisons of the proportion of PD symptoms and sequelae were evaluated using a χ^2 test of independence, followed by post hoc test of proportions between OSA+CPAP+ and OSA+CPAP-. Statistical analyses were conducted using RStudio version 4.4.1 (R Foundation).

Results

Following appropriate exclusions, a total of 11 310 411 participants were included in analyses (1 109 543 female veterans [9.8%]; mean [SD] age, 60.5 [14.7] years) (Figure 1). Of those, 1552 505 (13.7%) had OSA, with 144 643 veteran records (9.3%) containing affirmative data on CPAP. Veterans were mostly male (8 759 702 [90.1%]); 1 825 197 veterans (16.1%) were Black or African American, 125 345 were Asian (1.1%), 81 893 were Native American or Alaska Native (0.7%), 115 185 were Native Ha-

Table 2. Hazard Ratios (HRs) for Continuous Positive Airway Pressure (CPAP) Effect on Parkinson Disease (PD) Incidence in Those With Obstructive Sleep Apnea (OSA)

Variable	OSA-no CPAP	OSA-CPAP	HR (95% CI) of incident PD, CPAP vs no CPAP ^a
Main analysis, No.	53 902	33 600	0.69 (0.56-0.85)
Additional covariates tested, No. (%)			
Body mass index, mean (SD) ^b	33.1 (6.4)	33.5 (5.8)	0.70 (0.57-0.86)
Diabetes	30 118 (55.9)	12 439 (37.0)	0.70 (0.57-0.87)
Hypertension	47 093 (87.4)	23 906 (71.1)	0.70 (0.57-0.86)
Coronary artery disease	20 854 (38.7)	7457 (22.2)	0.69 (0.56-0.85)
Heart failure	13 586 (25.2)	4050 (12.1)	0.67 (0.55-0.83)
Atrial fibrillation	10 300 (19.1)	3858 (11.5)	0.68 (0.56-0.84)
Depression	31 796 (59.0)	15 443 (46.0)	0.77 (0.63-0.95)
Anxiety disorder	17 697 (32.8)	9721 (28.9)	0.72 (0.58-0.88)
Traumatic brain injury	15 416 (28.6)	6302 (18.8)	0.71 (0.57-0.87)
REM sleep behavior disorder	2417 (4.5)	1529 (4.6)	0.69 (0.56-0.85)
Hypersomnia	11 329 (21.0)	5656 (16.8)	0.70 (0.57-0.86)
Anti-PD medication	3608 (6.7)	1586 (4.7)	0.69 (0.56-0.85)
Antipsychotic medication	13 319 (24.7)	5162 (15.4)	0.75 (0.61-0.92)

Abbreviation: REM, rapid eye movement.

^a HRs with 95% confidence intervals are calculated using the Fine-Gray model. The main analysis is performed adjusting for age, sex, race, ethnicity, and competing risk of death. HR calculations for additional adjustments of covariates are also reported.

^b Calculated as weight in kilograms divided by height in meters squared.

waiian or Other Pacific Islander (1.0%), and 9 162 791 were White (81.0%). Race and ethnicity were collected from standard patient demographic fields in the VA data warehouse. Age, sex, race, ethnicity, and smoking status varied between groups (Table 1) and were adjusted between exposed and unexposed groups during analysis. Those with OSA had a greater mean (SD) BMI (33.2 [5.8] vs 28.4 [5.1]; $P < .001$).

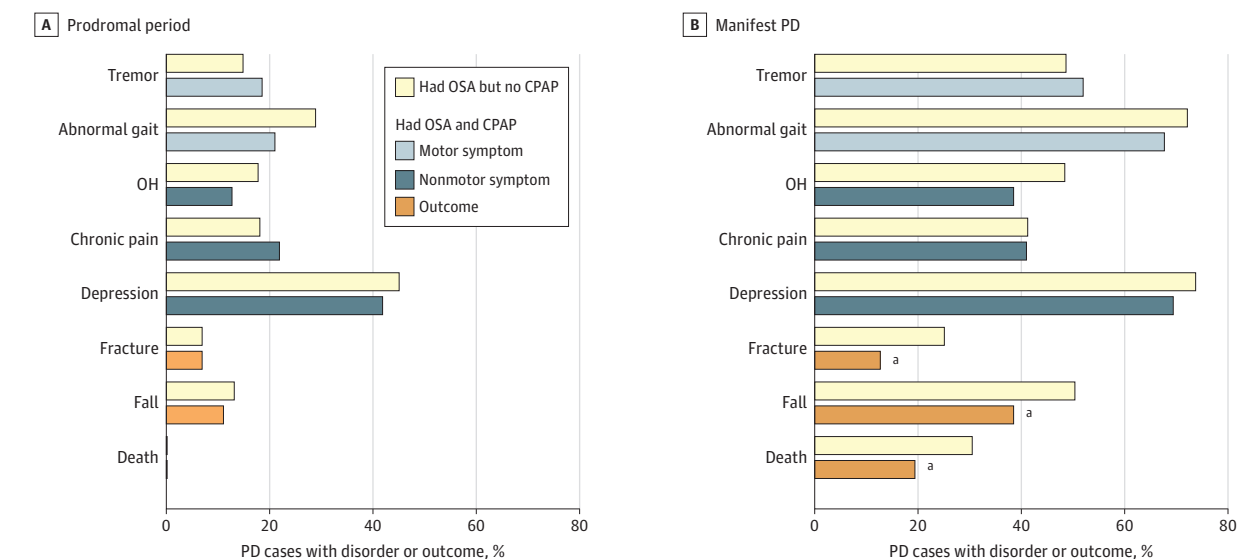
The cohort was followed up for a mean (SD) of 4.9 (1.8) years. Veterans with OSA had a greater cumulative incidence of PD compared with the OSA– group beginning at 2 years from the start of follow-up. The number of additional cases of PD per 1000 people due to OSA ranged from 0.51 (95% CI, 0.26-0.76) at the 2-year follow-up to 1.61 (95% CI, 1.13-2.09) at the 6-year follow-up (Figure 2A; eTable 3 in Supplement 1). Expressed as relative effects, OSA was associated with an increased risk of PD, with a hazard ratio (HR) of 1.92 (95% CI, 1.55-2.38; $P < .001$) compared with no OSA. When trimming the most extreme weights and keeping all covariates balanced (standardized max differences <0.1 and variance ratios <2.0), the results were confirmed (HR, 2.85; 95% CI, 2.28-3.57). Sensitivity analyses adjusted for BMI confirmed the primary results (HR, 1.41; 95% CI, 1.32-1.52). While the primary analysis was performed using 6 months of lag time, a secondary analysis was also performed extending the lag period to a 1-year delay in outcome ascertainment (eTable 2 in Supplement 1). Overall, the OSA effect persisted (HR, 2.76; 95% CI, 2.20-3.47). Analysis by sex (eFigure in Supplement 1) showed greater relative impact of OSA on PD risk in female veterans (HR, 4.24; 95% CI, 2.69-6.68) vs male veterans (HR, 2.21; 95% CI, 1.78-2.74).

An alternative approach—exploiting natural language processing for affirmative mentions of OSA and AHI—was used to ascertain OSA in veterans and further stratify them by OSA severity (Figure 2B). This approach reduced the sample size to 20 905 and 34 607 individuals with mild and severe OSA, respectively. When dichotomized into mild and severe strata, both groups were significantly associated with a higher risk of

developing incident PD (mild: HR, 3.17; 95% CI, 2.45-4.11; severe: HR, 3.42; 95% CI, 2.87-4.09; $P < .001$). Those with mild OSA had a greater cumulative incidence of PD beginning at year 5, and veterans with severe OSA had a greater cumulative incidence beginning at year 1 after the start of follow-up (eTable 3 in Supplement 1). Severe OSA had a higher cumulative incidence of PD compared to mild OSA at all time points except at year 6 (eTable 3 in Supplement 1).

Because OSA is amenable to intervention, we explored the hypothesis that CPAP usage within 2 years of initial OSA diagnosis would attenuate the risk of later development of PD. There was a significant reduction in incident PD as early as 2 years after OSA diagnosis in those who received CPAP compared to those who did not (Figure 2C), with a reduction of 2.28 cases of PD (OSA-no CPAP: 9.10; 95% CI, 8.18-10.01 vs OSA-CPAP: 6.81; 95% CI, 5.43-8.19; $P < .001$) 5 years after OSA. This absolute risk reduction translates to an estimate of 439 people needing to be treated promptly with CPAP to protect 1 person from developing PD 5 years later. Expressed as relative effects, CPAP was associated with a decreased risk of PD, with an HR of 0.69 (95% CI, 0.56-0.85) compared with no CPAP. Sensitivity analyses with trimming the most extreme weights and balancing baseline covariates through eliminating the no OSA group (eTable 1 in Supplement 1), adjusting for BMI, relevant vascular comorbidities (diabetes, hypertension, coronary artery disease, heart failure, and atrial fibrillation), common sleep-related comorbidities (depression, anxiety, rapid eye movement [REM] sleep behavior disorder, and hypersomnia), traumatic brain injury, and medication effects (both dopaminergic medications and neuroleptics) did not change the primary result (Table 2). Like before, a secondary analysis lengthening from 6 months to a 1-year delay in outcome ascertainment was also performed (eTable 2 in Supplement 1). Overall, the CPAP effect persisted (HR, 0.70; 95% CI, 0.57-0.88). Analysis by sex (eFigure in Supplement 1) showed a significant impact of CPAP on PD risk in male veterans (HR, 0.68; 95% CI, 0.55-0.84), whereas this was not significant—and con-

Figure 3. Parkinson Disease (PD) Symptoms and Relevant Outcomes Preceding and ≤10 Years Following Incipient Obstructive Sleep Apnea (OSA) Diagnosis



Data are from cases of PD after diagnosis of OSA with ($n = 120$) or without ($n = 446$) early continuous positive airway pressure (CPAP) treatment, with the colors (light blue, dark blue, and orange) corresponding to motor symptoms, nonmotor symptoms, and outcomes, respectively. PD-relevant disorders were captured in 2 epochs: prodromal or preclinical time points after OSA $\pm$ CPAP (A)

and before PD diagnosis or from the date of PD diagnosis ≤ 10 years later (B). The y-axis shows proportion of the cohort with documented diagnosis. OH indicates orthostatic hypotension.

^a $p < .05$.

fidence intervals were wide—for female veterans (HR, 0.98; 95% CI, 0.26–3.67).

To assess the possibility of health care utilization bias, we next examined the association between OSA, stratified by CPAP use, compared to multiple negative control outcomes (tinnitus and biliary cancer), with results suggesting those without OSA could have fewer health care encounters. Next, the total number of outpatient visits before the index date was collected. Those with OSA had mean (SD) of 34.9 (49.0) visits prior to the index compared to 2.6 (5.1) visits for those without OSA. When adjusting for this difference, the risk of incident PD persisted (HR, 2.26; 95% CI, 1.80–2.82). Further, after adjusting for health care utilization in CPAP users, the reduced risk of PD seen in the primary analysis persisted (HR, 0.68; 95% CI, 0.55–0.84). Next, to follow up the primary analysis showing that CPAP attenuated risk of incident PD, we performed a sensitivity analysis using a stricter definition that required (1) a minimum of 2 CPAP codes; (2) containing affirmative language indicating CPAP usage; and (3) the CPAP codes spanned longer than 12 months. We recapitulated the primary results showing that those with greater CPAP adherence had no change in risk of developing PD, although due to smaller sizes, the confidence intervals were slightly wider (HR, 0.65; 95% CI, 0.49–0.87). Finally, to determine if other health factors not previously assessed may have biased the effect of CPAP on PD risk, we examined the proportions of various motor and nonmotor symptoms and functional outcomes in those with OSA with and without CPAP who ultimately developed PD (Figure 3). In the prodromal period, there were no statistically significant differences. Interestingly, following the diagnosis of PD, there

were still no differences in motor and nonmotor symptoms. However, there was a statistically significant reduction in the rates of falls, fractures, and mortality in those with early CPAP use (Figure 3).

Discussion

Our major finding in this EHR-based cohort study of US veterans was that OSA was associated with greater incidence of PD. This risk difference was seen as early as 2 years after diagnosis and widened in the subsequent years of follow-up. A major strength of this study was to deploy a series of sensitivity analyses to affirm the primary result using multiple high-specificity definitions of OSA, balancing of key covariates, adjustments for several potential confounders, and accounting for the possibility of increased health care utilization. Therefore, this study represents a substantial advance over 2 prior studies purporting an association between OSA and PD.^{14,27} In addition to each being as much as 90-fold smaller with respect to participants with OSA, both prior studies relied on a single ICD code to determine PD status, which has been shown to have positive predictive values of less than 50% and equivalently poor sensitivities.²⁸ Moreover, our study adjusted for several appropriate confounders—including sleepiness and other prodromal symptoms, which may herald PD and inappropriately bias our result—accounted for competing risks, and used long follow-up times to mitigate reverse causation. The latter is particularly important for the following reasons: prolonged supine positioning, or upper airway dysfunction, may

reflect subclinical rigidity while also contributing to worse sleep-disordered breathing,²⁹ and intrinsic sleep fragmentation and/or abnormal ventilatory responses from early brainstem pathologic involvement can predispose to a vicious cycle of respiratory disturbances and arousals.⁶ Furthermore, the parallel approaches to OSA diagnosis used in this study do not support that ascertainment bias would account for the effect of OSA on PD incidence. An additional novelty not previously reported is OSA severity. Herein, we were able to categorically classify those with mild vs severe OSA using natural language processing and showed that the beneficial effect of CPAP on PD incidence held for both groups. While this cohort study examined exclusively veterans, potentially limiting generalizability, it is particularly important to this population, and the substantially greater prevalence of OSA diagnoses among veterans than the general population suggests, at least in part, improved sensitivity.³⁰ In fact, for this reason, VA datasets have been suggested as the ideal setting for examining OSA.¹⁷ Nevertheless, the results of our study should be interpreted in light of the issues of underdiagnosis and bias in diagnosis, which likely persist.

Significantly, we demonstrate that CPAP usage within 2 years of diagnosis attenuated the risk of incident PD. While no studies have examined this previously, others have suggested that uvulopalatopharyngoplasty, a surgical corrective procedure for those resistant to CPAP, may reduce incident PD.³¹ Analogous evidence from dementia research also supports our findings. A large Medicare claims-based analysis showed that those with OSA and adherent to CPAP demonstrated lower odds of incident dementia of all etiologies.³² Secondly, this beneficial effect is consistent with other reports that CPAP adherence may contribute to a symptomatic benefit in those with manifest PD.³³ Kaminska and colleagues³³ showed that in an unblinded study of 41 participants with PD

and OSA offered CPAP, those who did use CPAP had improved sleep and nonmotor symptom composite scores over the course of 6 months. While our study could not ascertain specific scores due to variance in practice patterns and recording practices representing disease progression, we were able to show that there were benefits in multiple long-term milestones, including falls, fractures, and mortality. Further studies are warranted to confirm and extend those findings.

Limitations

While our data provide strong evidence that CPAP reduces PD risk on a population level, the present methods did not allow us to assess CPAP adherence beyond the use of administrative codes or to understand the physical, cognitive, or other social factors influencing the decision to wear—or tolerate—CPAP, which may be moderators of the expected benefit. Therefore, the possibility remains that the individuals who are offered and adhere to CPAP are already the most likely to benefit, and it is unknown whether this benefit would extend to any potential user if CPAP adherence were enforced more broadly. Further prospective studies evaluating these factors and examining residual data on CPAP machines are warranted, as are studies that aim to establish causality and elucidate the mechanistic link.

Conclusions

In conclusion, in this cohort study, our findings suggest that US veterans with OSA had a significantly higher risk of developing PD, and this risk was reduced with early CPAP intervention. These data establish additional clinical rationale for early screening and intervention of sleep-disordered breathing as a key strategy in supporting brain health.

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Author Contributions: Dr Scott had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data:

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Drafting of the manuscript: Neilson, Montano, Sicard, Elliott, Scott.

Critical review of the manuscript for important intellectual content: All authors.

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Obtained funding: Lim, Scott.

Administrative, technical, or material support: May, Elliott, Scott.

Supervision: Lim, Scott.

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