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Obstructive sleep apnea treatment and dementia risk in older adults

Galit L. Dunietz[1,*,], Ronald D. Chervin[1], James F. Burke[2], Alan S. Conceicao[2] and Tiffany J. Braley[1,3]

[1]Division of Sleep Medicine, Department of Neurology, University of Michigan, Michigan Medicine, Ann Arbor, MI, USA, [2]Department of Neurology, University of Michigan, Michigan Medicine, Ann Arbor, MI, USA and [3]Division of Neuroimmunology, Department of Neurology, University of Michigan, Michigan Medicine, Ann Arbor, MI, USA

The work was performed at the University of Michigan.

*Corresponding author. Galit L. Dunietz, Division of Sleep Medicine, Department of Neurology, University of Michigan, Ann Arbor, MI 48109, USA. Email: gldt@med.umich.edu.

Abstract

Study Objectives: To examine associations between positive airway pressure (PAP) therapy, adherence and incident diagnoses of Alzheimer's disease (AD), mild cognitive impairment (MCI), and dementia not otherwise specified (DNOS) in older adults.

Methods: This retrospective study utilized Medicare 5% fee-for-service claims data of 53,321 beneficiaries, aged 65 and older, with an obstructive sleep apnea (OSA) diagnosis prior to 2011. Study participants were evaluated using ICD-9 codes for neurocognitive syndromes (AD [$n = 1,057$], DNOS [$n = 378$], and MCI [$n = 443$]) that were newly identified between 2011 and 2013. PAP treatment was defined as the presence of at least one durable medical equipment (Healthcare Common Procedure Coding System [HCPCS]) code for PAP supplies. PAP adherence was defined as at least two HCPCS codes for PAP equipment, separated by at least 1 month. Logistic regression models, adjusted for demographic and health characteristics, were used to estimate associations between PAP treatment or adherence and new AD, DNOS, and MCI diagnoses.

Results: In this sample of Medicare beneficiaries with OSA, 59% were men, 90% were non-Hispanic whites and 62% were younger than 75 years. The majority (78%) of beneficiaries with OSA were prescribed PAP (treated), and 74% showed evidence of adherent PAP use. In adjusted models, PAP treatment was associated with lower odds of incident diagnoses of AD and DNOS (odds ratio [OR] = 0.78, 95% confidence interval [95% CI]: 0.69 to 0.89; and OR = 0.69, 95% CI: 0.55 to 0.85). Lower odds of MCI, approaching statistical significance, were also observed among PAP users (OR = 0.82, 95% CI: 0.66 to 1.02). PAP adherence was associated with lower odds of incident diagnoses of AD (OR = 0.65, 95% CI: 0.56 to 0.76).

Conclusions: PAP treatment and adherence are independently associated with lower odds of incident AD diagnoses in older adults. Results suggest that treatment of OSA may reduce the risk of subsequent dementia.

Statement of Significance

Emerging evidence has linked obstructive sleep apnea (OSA) to cognitive impairment and dementia incidence. However, research focused on the impact of OSA treatment on dementia is scarce. This analysis of Medicare Claims Data investigates associations between positive airway pressure (PAP) therapy and incident dementia diagnosis, at the population level. We demonstrate that treatment with PAP therapy was associated during a subsequent period of 3 years with lower odds of incident diagnoses of Alzheimer's dementia (AD) and dementia not otherwise specified. Adherence to PAP therapy was also associated with lower odds of incident AD diagnosis. These findings suggest a protective role of PAP therapy with respect to dementia among older adults with OSA.

Key words: obstructive sleep apnea; CPAP; Medicare; Alzheimer's disease; mild cognitive impairment

Introduction

Obstructive sleep apnea (OSA) is a common disorder characterized by repeated episodes of upper airway obstruction, sleep fragmentation, and hypoxia during sleep. This disorder is associated with many serious health and socioeconomic consequences, including cognitive impairment [1].

The risk of OSA increases with age [2–4]. Up to 56% of older Americans may suffer from OSA, even though the majority remain undiagnosed [5, 6]. Older individuals are also more likely to experience many of the health consequences that are associated with OSA, including adverse neurocognitive outcomes [7]. Prior work has revealed compelling relationships between OSA and objective measures of cognitive performance (e.g. executive function, attention, and memory) [8–12], both incident dementia [13] and Alzheimer's disease (AD) [14], as well as mild cognitive impairment (MCI) [15]. Still, data regarding the potential benefits of OSA *treatment* on cognitive performance are inconclusive [16–20], and any associations between OSA treatment and risk of incident neurodegenerative conditions, in particular, are lacking.

Although some evidence suggests a possible therapeutic benefit of positive airway pressure (PAP) therapy on cognitive performance in older individuals [21], advancement of knowledge on this topic has been limited by the use of small, single-center, or regional samples, heterogeneity in outcome measures, and limited enrollment of older individuals. Furthermore, the role of OSA treatment in the development of specific neurodegenerative conditions such as AD—the most frequent cause of dementia in older adults—has not been sufficiently studied. Specifically, whether the use of PAP therapy in older adults with OSA mitigates the risk of development of MCI or dementia syndromes remains unknown, as longitudinal, population-level data are lacking.

The purpose of this study was to determine, within a cohort of older Americans with OSA, longitudinal associations between OSA treatment and odds of new dementia diagnosis. We hypothesized that older adults who received and adhered to treatment for OSA (PAP therapy) would have a lower risk of incident diagnoses of MCI, AD, or other dementia subtypes compared to untreated or nonadherent individuals.

Methods

This was a retrospective cohort study of Medicare fee-for-service claims files (outpatient, durable medical equipment [DME], and carrier files). Data were extracted from a representative sample of older adults with OSA, aged 65 or older, derived from a 5% random sample (*n* = 2,758,197) from the Medicare Beneficiary Summary File in 2011, 2012, and 2013.

This study used only de-identified claims data. All study procedures were approved by the University of Michigan Institutional Review Board (IRBMED).

Study population

Medicare beneficiaries aged 65 and older who carried an OSA ICD-9 diagnosis code *prior* to 2011 were selected for analyses. To examine the temporal associations between preexisting OSA, OSA treatment patterns, and new dementia diagnoses, we excluded Medicare beneficiaries who were given an incident diagnosis of OSA (as reflected by the presence of polysomnography or home sleep apnea testing claims) during the 2011–2013 study period.

Beneficiaries with OSA who were offered and issued treatment with PAP were labeled as "treated" based on the presence of one or more PAP Healthcare Common Procedure Coding System (HCPCS) claims codes, indicating the presence of at least one prescription fill for PAP equipment, in the DME file for the 2011–2013 period under study. The HCPCS is a standardized code system used by medical providers to submit healthcare claims to Medicare and other health insurances. Beneficiaries were considered "adherent" to PAP treatment, if two more HCPCS claims for PAP supplies (e.g. filters, cushions, masks, or tubing), separated by at least 1 month from each other, were present during the study period (Supplementary Table 1). At least two equipment claims over the 3-year follow-up interval were chosen to be consistent with the work by Patel et al. [22], which validated a threshold value of 0.7 PAP equipment refills (claims) per year to best discriminate between PAP-adherent and nonadherent patients (using the Medicare definition of adherence of at least 4 h/night, at least 70% of nights).

New neurocognitive diagnoses of interest—AD, dementia not otherwise specified (DNOS—a category that included vascular dementia, dementia with Parkinsonism/Lewy bodies, and frontotemporal dementia), and MCI—were also identified with ICD-9 codes (Supplementary Table 2). These neurocognitive diagnoses were mutually exclusive. Beneficiaries with a prevalent neurocognitive diagnosis who were identified in the 2011 files were excluded from the analysis. In a recent sensitivity analysis of Medicare claims, this methodology correctly classifies dementia diagnoses in 85% of patients with dementia who were diagnosed clinically [23].

Additional comorbidity data extracted from Medicare files included diagnoses of hypertension, stroke, diabetes mellitus, and depression. Cardiovascular disease included a diagnosis of arrhythmia, congestive heart failure, or acute myocardial infarction (Table 1). Demographic information, i.e. age, sex, race/ethnicity, and state of residence, was also obtained from Medicare files. Age was classified into five categories: 65–69, 70–74, 75–79, 80–84, and 85 years or older. Self-reported race and ethnicity, as recorded by Medicare beneficiaries at the time of social security enrollment, included three categories: non-Hispanic white, non-Hispanic black, and Hispanic/Asian/other.

Statistical analyses

Descriptive statistics were used to estimate the frequencies and proportions of demographic and health characteristics of Medicare beneficiaries with OSA within three neurocognitive subgroups of interest: AD, DNOS, or MCI, as well as within subgroups defined by PAP treatment or adherence.

Bivariate analyses were used to estimate the frequencies of beneficiaries who were prescribed PAP treatment or were PAP-adherent within each of the neurocognitive groups.

Logistic regression was applied to estimate associations between PAP treatment and adherence to treatment in Medicare beneficiaries with an OSA diagnosis that preceded the diagnosis of AD, DNOS, or MCI. To account for the clustering of Medicare beneficiaries by state and county, we estimated the odds ratio (OR) and 95% confidence intervals (95% CIs) with regression

Table 1. Demographic characteristics and comorbidities among Medicare beneficiaries with obstructive sleep apnea

Demographic and health characteristics	All participants	Alzheimer's disease	DNOS	MCI
	N (column %)	N (row %)	N (row %)	N (row %)
Sample size	53,321 (100)	1,057 (2.0)	378 (0.7)	443 (0.8)
Sex				
Men	31,627 (59)	567 (1.8)	241 (0.8)	267 (0.8)
Women	21,694 (41)	490 (2.3)	137 (0.6)	176 (0.8)
Age (years)				
65–69	18,099 (34)	82 (0.5)	46 (0.3)	85 (0.5)
70–74	15,100 (28)	162 (1.1)	86 (0.6)	100 (0.7)
75–79	10,266 (19)	241 (2.4)	85 (0.8)	119 (1.2)
80–84	6,232 (12)	288 (4.6)	87 (1.4)	78 (1.3)
85+	3,624 (7)	284 (7.8)	74 (2.0)	61 (1.7)
Race/ethnicity				
Non-Hispanic white	48,097 (90)	936 (2.0)	340 (0.7)	404 (0.8)
Non-Hispanic black	3,353 (6)	67 (2.0)	24 (0.7)	27 (0.8)
Hispanic/Asian/Other*	1,871 (4)	54 (2.9)	14 (0.8)	12 (0.6)
Stroke	3,530 (7)	208 (5.9)	110 (3.1)	73 (2)
Hypertension	44,370 (83)	951 (2.0)	343 (0.8)	385 (0.9)
Diabetes mellitus	24,670 (46)	497 (2.0)	185 (0.8)	214 (0.9)
Cardiovascular diseases	23,147 (43)	653 (2.8)	237 (1.0)	233 (1)
Depression	9,353 (18)	442 (4.7)	164 (1.8)	176 (1.9)

*Other ethnicity = Pacific Islander and Native American.

procedures (generalized estimating equation) for correlated data. Adjustment for state and county was informed by data from our group that suggested variation in OSA treatment and treatment adherence among Medicare beneficiaries in different states and within states [24]. In adjusted analyses, we controlled for potential confounders, including age, sex, race, stroke, hypertension, cardiovascular disease, and depression. SAS 9.4 (Cary, NC) was used for descriptive and regression analyses.

Results

Of the entire 5% sample of Medicare beneficiaries (n = 2,758,197), approximately 4% (n = 102,618) had an OSA diagnosis. Among those beneficiaries with OSA, 53,321 received an OSA diagnosis prior to 2011 and therefore were included in this analysis (Figure 1). In this sample, 59% were men, 90% were non-Hispanic whites, and 62% were younger than 75 years. From 2011 to 2013 (inclusive), incident neurocognitive diagnoses were rare, with AD, DNOS, and MCI identified in 1,057 (2%), 378 (<1%), and 443 (<1%) of the Medicare beneficiaries with OSA diagnoses, respectively. AD was more frequent in women than men and in Hispanics and Asians than other races/ethnicities. AD frequency increased with age. Distributions of race/ethnicity and sex were similar among beneficiaries with DNOS or MCI. As with AD, the proportions of Medicare beneficiaries with DNOS and MCI increased with age (Table 1).

Among OSA-diagnosed beneficiaries, 78% were prescribed PAP treatment and 74% of those adhered to their treatment. The percentages of beneficiaries who received PAP treatment and were adherent—by gender, age, race, and comorbidities—are given in Table 2.

Bivariate estimates of PAP treatment and adherence suggest that among the 1,909 Medicare beneficiaries with dementia and OSA diagnoses, 1,309 (69%) were PAP-treated and of those, 895 (68%) were PAP-adherent (Figure 2). In analyses adjusted for demographic characteristics and comorbidities, beneficiaries
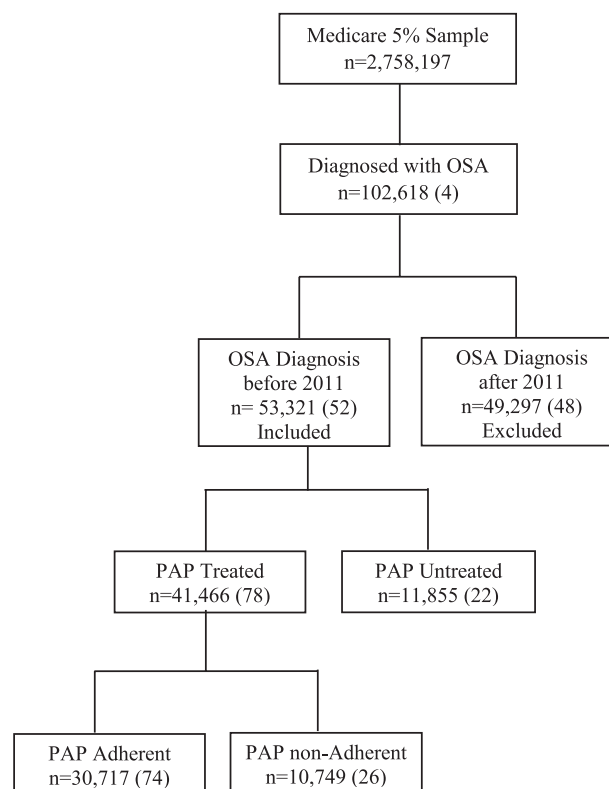
Figure 1. Distribution of PAP treatment and treatment adherence among Medicare beneficiaries with OSA; frequencies and proportions (in parenthesis).

who were prescribed PAP (in comparison to beneficiaries who were not prescribed PAP) had a significantly lower odds of developing AD and DNOS (OR = 0.78, 95% CI: 0.69 to 0.89; and OR = 0.69, 95% CI: 0.55 to 0.85), respectively. Lower odds of MCI, approaching statistical significance, were also observed among beneficiaries who were prescribed PAP, median OR = 0.82 (95%

Table 2. Demographic characteristics and comorbidities among Medicare beneficiaries with a diagnosis of obstructive sleep apnea by treatment and treatment adherence (*n* = 53,321)

| Demographic and health characteristics	Treated among diagnosed	Adhered among treated
Sample size N (%)	41,466 (78)	30,717 (74)
Gender		
Men	25,462 (81)	19,101 (75)
Women	16,004 (74)	11,616 (73)
Age (years)		
65–69	14,134 (78)	10,191 (72)
70–74	12,137 (80)	9,271 (76)
75–79	8,065 (79)	6,103 (76)
80–84	4,690 (75)	3,451 (74)
85+	2,440 (67)	1,701 (69)
Race/ethnicity		
Non-Hispanic white	37,676 (78)	28,268 (75)
Non-Hispanic black	2,504 (75)	1,602 (64)
Hispanic	314 (64)	170 (54)
Asian	204 (56)	131 (64)
Other	768 (76)	546 (71)
Stroke	2,546 (72)	1,815 (71)
Hypertension	34,622 (78)	26,167 (76)
Diabetes mellitus	19,547 (79)	14,653 (75)
Cardiovascular diseases	17,573 (76)	13,259 (75)
Depression	6,831 (73)	5,010 (73)

Other ethnicity = Pacific Islander and Native American.

CI: 0.66 to 1.02). Attenuation of this association in the adjusted model was attributable mainly to the inclusion of age, stroke, and depression as covariates. Adherence with PAP treatment was associated with lower odds of developing AD, OR = 0.65 (95% CI: 0.56 to 0.76), though not DNOS or MCI (Table 3). Exclusion of stroke-diagnosed or depression-diagnosed beneficiaries did not change the relationships between PAP therapy and dementia (data not shown).

Discussion

In a large, retrospective cohort of Medicare beneficiaries with OSA, 2%, 0.7%, and 0.8% received a new diagnosis of AD, DNOS, or MCI, respectively. Medicare beneficiaries with OSA who were given OSA treatment, in comparison to others who were not, had significantly lower odds of developing AD, DNOS, and MCI. Adherence to treatment was significantly associated with lower odds of AD, but not DNOS or MCI. These population-based data suggest temporal associations between PAP use and dementia, highlighting a potentially protective role for PAP therapy and continuous treatment with PAP on dementia risk in older adults with OSA.

The growing prevalence and impact of dementia syndromes such as AD, coupled with a lack of effective treatments to prevent, cure, or slow dementia progression, have galvanized the need to identify modifiable risk factors for these conditions. To this end, mounting evidence has implicated OSA as a potential risk factor for poor cognitive outcomes or incident dementia. In the Study of Osteoporotic Fractures, Yaffe et al. [25] found that women with evidence of sleep-disordered breathing (defined in this study as an apnea–hypopnea index [AHI] of 15 or more) were 85% more likely to develop MCI or dementia, as compared to women with
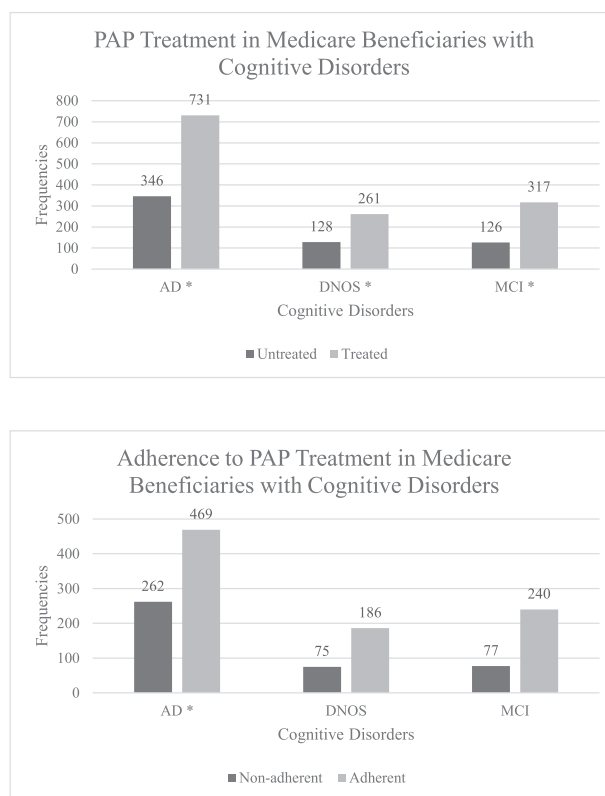
Figure 2. Frequencies of OSA-diagnosed Medicare beneficiaries treated with and adherent to PAP, by dementia diagnoses.

an AHI less than 15. In a separate study by Osorio et al. [26], the presence of self-reported sleep-disordered breathing in late life was also associated with a younger age of onset for MCI and AD. Numerous studies have also identified associations between impaired performance on cognitive testing and OSA, as well as relationships between OSA and AD biomarkers [27, 28].

The aforementioned work allows speculation that OSA may serve as a potential therapeutic target to slow or prevent the development of AD and related dementias or other poor neurocognitive outcomes. To date, however, studies that have examined this possibility have yielded conflicting results. In a multicenter, landmark randomized controlled trial that studied the effects of active or sham continuous positive airway pressure (CPAP) on cognitive performance in adults, treatment with active CPAP for 6 months had no significant effect on primary neurocognitive outcomes of interest [29]. This study, however, did not focus on the incidence of specific neurodegenerative conditions, and the study sample was not restricted to older individuals (mean age of active and sham CPAP groups was 52.2 and 50.8 years, respectively). In another study that examined the effects of PAP on several cognitive function tests in older adults (as secondary outcomes), PAP (vs a supportive care comparator) was not shown to have an effect on cognitive performance [30]. Conversely, other studies suggest that PAP use may improve performance in specific cognitive domains or delay cognitive decline [16, 31] in adults with OSA. A pilot study that evaluated the effects of PAP versus conservative care on cognitive function in older adults with severe OSA showed an improvement in multiple cognitive domains in those randomized to PAP [32]. Furthermore, in an exploratory analysis, the aforementioned

Table 3. Associations of OSA treatment and treatment adherence with dementia among 53,321 Medicare beneficiaries with OSA diagnosis

	Alzheimer's disease		DNOS		Mild cognitive disorder	
	Unadjusted, odds ratio (95% CI)	Adjusted*, odds ratio (95% CI)	Unadjusted, odds ratio (95% CI)	Adjusted*, odds ratio (95% CI)	Unadjusted, odds ratio (95% CI)	Adjusted*, odds ratio (95% CI)
OSA treatment	0.60 (0.52 to 0.69)	0.78 (0.69 to 0.89)	0.58 (0.47 to 0.71)	0.69 (0.55 to 0.85)	0.72 (0.58 to 0.90)	0.82 (0.66 to 1.02)
OSA adherence	0.62 (0.53 to 0.72)	0.65 (0.56 to 0.76)	0.87 (0.66 to 1.14)	0.92 (0.70 to 1.21)	1.09 (0.84 to 1.40)	1.13 (0.87 to 1.45)

*Adjusted for sex, age, race/ethnicity, stroke, hypertension, cardiovascular disease, and depression.

study by Osorio et al. also identified an association between older age of onset for MCI (though not AD) in adults with OSA who endorsed the use of CPAP as compared with those who did not endorse treatment [11]. Although these prior observations were limited by self-reported data and small sample size, they were among the first to report a potential benefit of CPAP to delay cognitive decline. Our study supports and advances this line of inquiry by providing new, population-based evidence through the use of objective ICD-9 diagnoses and HCPCS codes to demonstrate an association between OSA treatment and dementia, in adults older than age 65 who have OSA.

Strengths of our study included the use of a large, representative sample of older Americans, longitudinal design that allowed for new dementia diagnosis claims in an OSA cohort, adjustment for other comorbid conditions know to affect dementia risk, and use of fee-for-service data that maximized the likelihood of capturing all relevant claims.

Some limitations should also be acknowledged. This study has a relatively short follow-up interval (3 years) and—necessarily in the absence of a large prospective study over many years—could not take into account duration of OSA, length of treatment, or degree of adherence to therapy. However, as the typical onset of OSA is in middle age, whereas dementia typically appears later in life, the present findings may well reflect an influence of OSA on dementia decades after its onset [33, 34]. Demographic data, health characteristics, and behavior, i.e. education, diet, socioeconomic status, body mass index, and smoking, which may be independent risk factors for dementia, are not available in claims datasets. These risk factors may also reflect motivation and a health-conscious lifestyle in a manner that could influence both PAP therapy initiation and dementia risk. That said, several sociodemographic factors—race, sex, and age—are included in Medicare files and adjusted for in the present analysis. The role of education and socioeconomic status as potential confounders in the association between PAP treatment and cognitive outcomes has been examined previously with mixed results. A prospective study reported no relationship between PAP adherence and socioeconomic status, education, or type of personality in adults with a median age of 53 years [35]. Furthermore, a recent population-level analysis that examined associations between household income and PAP adherence indicated above 4-h average PAP use for those in both lowest and highest quartile of median household income, with respective adherence rates of 40% and 47%, with a 24-min difference of average nightly use [36]. In contrast, other studies suggested that lower socioeconomic status and smoking influence nonadherence of PAP treatment among older men with OSA [37–39]. Taken together, these data suggest that socioeconomic factors could play a role in PAP treatment and treatment adherence.

Data regarding the number of PAP equipment refills—beyond at least two fills separated by at least 1 month—were not available from the dataset, precluding assessment of dose–response associations between equipment refills and dementia.

The coexistence of several dementia diagnoses is plausible, although its prevalence in older adults may be lower than expected based on a recent study [40]. A possibility also exists that those who seek and are adherent to medical care for their OSA are also more likely to be evaluated and diagnosed with a neurocognitive disorder than those who do not seek treatment and therefore likely to receive better care and have better outcomes. In this case, however, we believe that our current findings may in fact represent an *underestimation* of the risk of neurocognitive disorders in untreated or nonadherent patients.

Information on symptoms of sleepiness and OSA severity, which may have differential roles in cognitive function [41–43], and could affect beneficiaries' eligibility for PAP coverage by Medicare, are not available from claims data. However, while sleep laboratories consider an AHI of 5 or more to qualify a patient for PAP treatment, *Medicare* rules require a minimum AHI of 15 for CPAP coverage, unless a secondary diagnosis is also present (including excessive daytime sleepiness, mood disorders, and hypertension).

We cannot rule out the possibility that beneficiaries whom we labeled as "untreated" or "nonadherent" could have obtained PAP equipment through other payers, or elected not to refill equipment prescribed from 2011 through 2013, in which case PAP treatment would not be captured in Medicare claims files. However, we believe that chances of such misclassification were reduced by restricting our analysis to fee-for-service beneficiaries.

Misclassification of neurocognitive diagnoses is also possible with claims data. Although a recent report estimated the sensitivity and specificity of Medicare claims data to detect AD diagnoses to be relatively high (85% and 77%, respectively), the sensitivity and specificity of Medicare claims algorithms to correctly classify MCI diagnoses are less robust [23]. Similarly, given the lack of confirmation of amyloid pathology from these Medicare claims data (e.g. lack of cerebrospinal fluid assays or amyloid neuroimaging), AD cannot be fully distinguished from other dementia subtypes with Medicare claims data.

Although we adjusted for several comorbidities (i.e. hypertension, CVD, stroke, and depression diagnoses), we should acknowledge that *treatment* for these comorbidities could potentially influence associations between PAP therapy and cognitive outcomes. That said, although information regarding the treatment of these comorbidities was not available in these claims, post-hoc findings showed that the association between PAP therapy and dementia remained essentially unchanged following exclusion of stroke-diagnosed beneficiaries, and those with a diagnosis of depression, suggesting that confounding by stroke or depression treatment would be comparatively low (data not shown). Adjustment for hypertensive therapy through the exclusion of

beneficiaries with hypertension diagnosis was not feasible in these post-hoc analyses, as more than 84% of beneficiaries carried a diagnosis of hypertension. Nonetheless, prior reports suggest that the proportion of beneficiaries with hypertension who are prescribed hypertensive therapy exceeds 90% [44]. In this case, it is plausible that hypertension diagnosis could serve as a proxy for hypertensive therapy in adjusted models.

As referrals for evaluation and treatment are intrinsic components of any medical claims data, their absence may introduce systematic bias in these datasets. Indeed, OSA is often underdiagnosed in older adults [5] and those with OSA may not obtain PAP treatment. To alleviate concerns of OSA underdiagnosis, we designed this study to only include Medicare beneficiaries with ICD-9-diagnosed OSA.

Finally, as with any observational study, causality and its direction cannot be established beyond doubt. While OSA diagnosis preceded the diagnosis of dementia, reverse causality cannot be fully ruled out. As noted above, the typical age of OSA onset greatly precedes the typical age of dementia onset, but future studies over longer time intervals may be needed to confirm that the association in the present data between OSA treatment or adherence and lower incidence of dementia does not arise because dementia impedes subsequent OSA treatment and adherence.

Conclusions

This population-based data highlight a potentially protective role for PAP therapy on short-term dementia risk in older adults with OSA. Additional research is necessary to explore mechanisms that may underlie this association; however, if a causal pathway exists, treatment of OSA may offer new opportunities to improve cognitive outcomes in older adults with OSA.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Disclosure Statement

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