RESEARCH ARTICLE

Positive Airway Pressure and Cognitive Disorders in Adults With Obstructive Sleep Apnea

A Systematic Review of the Literature

Monica Moon Shieu, PhD, MS, Afsara Binte Zaheed, MS, Carol Shannon, MPH, MA, Ronald David Chervin, MS, MD, Alan Conceicao, Henry Lauris Paulson, PhD, MD, Tiffany Joy Braley, MS, MD, and Galit Levi Dunietz, PhD, MPH

Correspondence
Dr. Shieu
mshie@med.umich.edu

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Abstract

Background and Objectives

Alzheimer disease (AD) and other forms of dementia represent a rising global public health crisis. Because effective treatments to prevent, cure, or slow progression of dementia are unavailable, identification of treatable risk factors that increase dementia risk such as obstructive sleep apnea (OSA) could offer promising means to modify dementia occurrence or severity. Here, we systematically reviewed the impact of positive airway pressure (PAP) therapy on the incidence of cognitive disorders and cognitive decline among middle-aged and older adults with OSA.

Methods

We performed a systematic search of MEDLINE, EMBASE, Scopus, and CINAHL before May 2021 to identify articles that focused on associations between PAP therapy use and cognitive disorders. We included studies that examined the effects of PAP treatment on (1) the incidence of cognitive disorders among individuals ≥40 years of age diagnosed with OSA and (2) the progression of cognitive decline among people with preexisting cognitive disorders and OSA.

Results

We identified 11 studies (3 clinical trials and 8 observational studies). In these studies, 96% participants had OSA (n = 60,840) and 9% had baseline cognitive impairment (mild cognitive impairment [MCI] or AD) (n=5,826). Of all study participants, 43,970 obtained PAP therapy, and 16,400 were untreated or in a placebo group. Nine out of 11 studies reported a protective effect of PAP therapy on MCI and AD incidence, e.g., delayed age at MCI onset, reduced MCI or AD incidence, slower cognitive decline, or progression to AD.

Discussion

These findings suggest a role for OSA as a modifiable risk factor for cognitive decline. Identification of modifiable risk factors is imperative for alleviating the impact of cognitive disorders on aging adults and their family members. Future research should build on this review and focus on PAP interventions as a potential means to alleviate the incidence of cognitive disorders and cognitive decline, particularly among ethnoracial groups who have been underrepresented and underinvestigated in the extant literature.

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From the Department of Neurology (M.M.S., R.D.C., A.C., T.J.B., G.L.D.), Division of Sleep Medicine, Department of Psychology (A.Z.), Taubman Health Sciences Library (C.S.), Department of Neurology (H.L.P.), Division of Cognitive Disorders, and Department of Neurology (T.J.B.), Division of Neuroimmunology & Division of Sleep Medicine, University of Michigan, Ann Arbor.

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Glossary

AD = Alzheimer disease; **AHI** = apnea-hypopnea index; **DNOS** = dementia not otherwise specified; **ICD** = *International Classification of Diseases*; **MCI** = mild cognitive impairment; **OR** = odds ratio; **OSA** = obstructive sleep apnea; **PAP** = positive airway pressure; **RCT** = randomized controlled trial; **WMH** = white matter hyperintensities.

Approximately 6.2 million older adults in the United States are currently living with dementia,[1] a term that describes a group of progressive, incurable neurologic syndromes associated with irreversible decline in cognitive functions and behavioral changes. Alzheimer disease (AD) is the most common type of dementia and is characterized by progressive neurodegeneration, while vascular dementia, the second most common type, results from reduced blood supply to the brain due to acute or chronic cerebrovascular diseases.[2] Age is the single greatest risk factor for AD, and the number of older Americans is projected to increase by 30 million in 2050.[3] This demographic shift will double the annual incidence of dementia cases by 2050, a threat to public health that disproportionally burdens women and ethnoracial groups underrepresented in medicine.[4]

Mild cognitive impairment (MCI) is a heterogeneous condition of cognitive impairment that does not meet the threshold for dementia.[5] Nearly 15% to 20% of adults >60 years of age present with MCI in various cognitive domains.[6] Furthermore, pathways to MCI are complex, and the annual conversion rate to dementia is estimated to be between 8% and 15%. However, not all individuals with MCI develop dementia; some revert to normal cognitive status,[7] suggesting that MCI may be modifiable.

Although lifestyle factors and medications, including cholinesterase inhibitors and a new anti–β-amyloid monoclonal antibody, may offer modest protective effects or symptomatic benefit,[8] the lack of effective treatments to prevent or substantially slow cognitive decline has motivated investigations to identify modifiable risk factors for cognitive disorders. A potential risk factor, obstructive sleep apnea (OSA), is a condition marked by hypoxia, sleep deprivation, and sleep fragmentation. Common in middle-aged and older adults, OSA frequently remains undiagnosed.[9] Although recent work has identified OSA as a potentially modifiable risk factor for cognitive decline and dementia,[10] relationships between positive airway pressure (PAP) therapy—the gold standard OSA therapy[11]—and neurocognitive disorders are poorly understood. Only a few studies have examined the influence of PAP therapy on cognitive function,[12] MCI, and dementia risk.[13,14] While these emerging data show promise for a protective role of PAP on dementia risk in older adults with OSA, a systematic review would provide an integration of existing studies and identify gaps in knowledge.[9] We therefore conducted a systematic search of the literature to examine the associations between PAP therapy, MCI, and dementia (with an emphasis on AD) in adults with OSA. In this review, we evaluate whether PAP therapy is associated with the incidence of MCI and dementia, as well as its influence on the progression of cognitive decline among those with MCI or dementia at baseline.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This review was deemed nonregulated by the Medical School Institutional Review Board at the University of Michigan because only publicly available and aggregate data were used.

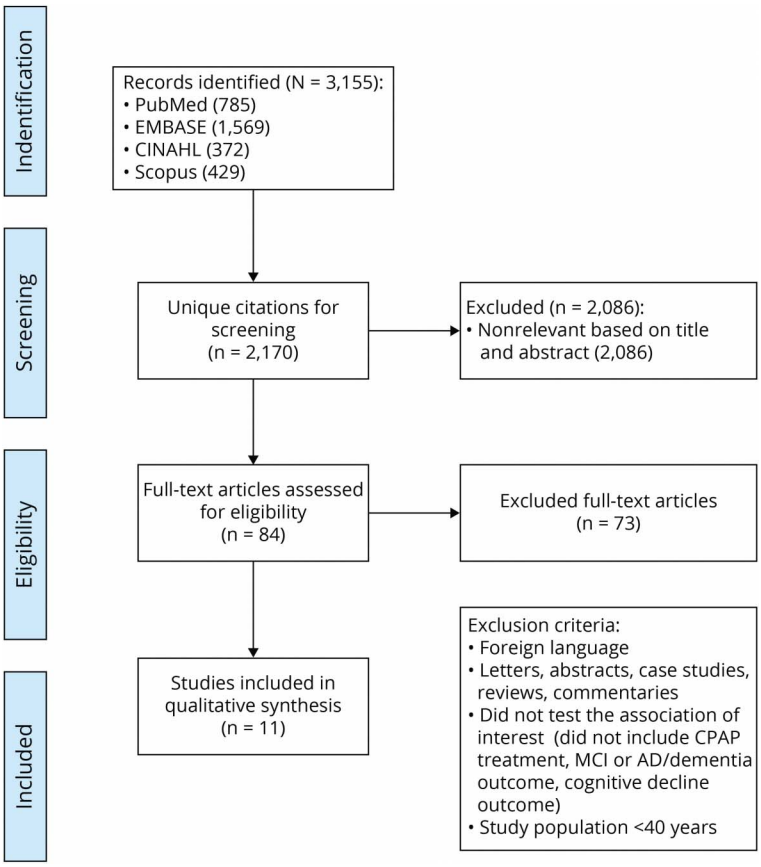
An experienced health science librarian (C.S.) conducted a systematic search of MEDLINE (PubMed), EMBASE, Scopus, and CINAHL Complete (EBSCOhost) to identify articles related to how interventions to treat OSA affect cognitive health. Five sentinel articles were used to harvest search terms, including Medical Subject Headings, Emtree, and key words (tagged as title/abstract) terms. Search terms included obstructive sleep apnea, central sleep apnea, sleep disordered breathing, continuous positive airway pressure, Alzheimer's disease, cognition disorders, and dementia (a comprehensive term that included vascular dementia; eMethods, links.lww.com/WNL/C17, provides the complete search strategy). The searches were completed by May 10, 2021, and included all articles published by this date.

The original PubMed search strategy was translated and adapted to other databases with the SR Accelerator[15] and at the searcher's discretion. To reduce bias, no filters (including publication date or language) were used, and both published peer-reviewed articles and unpublished abstracts were considered through searches in EMBASE and Scopus. Findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16] elaboration, and explanation[17] and Statement for Reporting Literature Searches for Systematic Reviews.[18]

This review included empirical studies that examined, among adults with OSA, the potential influence of PAP therapy on MCI or dementia incidence or progression of cognitive decline in middle-aged adults (≥40 years of age) who were diagnosed with MCI or dementia. We excluded letters, abstracts, case studies, reviews, or commentaries and publications in non-English languages.

Three reviewers (M.M.S., A.B.Z., and G.L.D.) screened abstracts and titles and read the full articles that met inclusion criteria. Any disagreement between reviewers over inclusion

Figure PRISMA Flow Diagram: Number of Articles Included and Excluded



AD = Alzheimer disease; CPAP = continuous positive airway pressure; MCI = mild cognitive impairment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

of studies was resolved with discussion and consensus. Bias assessment was performed by 1 reviewer (M.M.S.). For clinical trials, the reviewer used the Cochrane Risk of Bias for Randomized Trials[19] (with risk of bias rated as low, some concerns, or high on the basis of 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result). For observational studies, the reviewer used the Cochrane Risk of Bias in Non-Randomized Studies of Interventions tool[20] (with risk of bias rated as low, moderate, serious, or critical on the basis of 7 domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of the outcome, and selection of the reported result). Citations were imported into EndNote (Thomson Reuters, New York, NY) for deduplication and exported to Excel (Microsoft, Bellingham, WA) for analysis.

The heterogeneity of study designs, exposure, and outcomes assessments of the included studies precluded meta-analyses of PAP therapy utility for cognitive disroders incidence and progression.

Data Availability

The search strategy and data extraction sheets are available on request to the first author.

Results

Search Strategy

The initial search identified 3,155 articles. After the exclusion of 985 duplicates, 2,170 titles and abstracts were screened, and 84 articles received a full-text review. Seventy-three articles were removed after full-text review for the following reasons: written in a non-English language; were letters, abstracts, case studies, reviews, or commentaries; or included no examination of the association of interest (PAP treatment, MCI, dementia or cognitive decline outcomes). While age <40 years was an exclusion criterion, none of the studies were excluded on the basis of age <40 years alone (Figure).

Study Characteristics

We identified 11 studies that examined PAP therapy in relation to cognitive disorders: 1 randomized controlled trial (RCT), 2 quasi-experimental clinical trials, 2 prospective observational studies, 5 retrospective observational studies, and 1 cross-sectional study. The majority of studies (n = 8) were conducted in the United States[13,14,21-26]; 2 were conducted in Europe[27,28]; and 1 was conducted in Asia.[29] These studies used diverse cohorts, including nationwide databases (National Health Insurance Research Database of Taiwan,[29] a 5% sample of US Medicare beneficiaries),[14,22] a cohort from

Table 1 Characteristics of the Studies Included in the Systematic Review

Source	Exposure	Study period	Outcome	Study population	Age, mean and/or range, y[a]	Women, %	White, %
Ancoli-Israel et al.,[21] 2008, United States	Treatment: 6 wk of PAP	6 wk	Cognitive decline	52 with OSA diagnosis (AHI ≥10) and mild-moderate AD	78	25	98
	Control: 3 wk placebo + 3 wk PAP						
Cooke et al.,[26] 2009, United States	Treatment: continuous use PAP therapy after RCT	6–21 mo	Cognitive decline	10 with OSA diagnosis (AHI ≥10) and moderate AD	76 (65–84)	30	90
	Control: discontinued use of PAP therapy after RCT						
Dunietz et al.,[22] 2020, United States	Treatment: PAP therapy based on ≥1 PAP prescription	2 y	Prevalence of MCI and AD	102,618 with OSA diagnosis	65–90+	43	89
	Control: untreated						
Dunietz et al.,[14]2021, United States	Treatment: PAP therapy based on ≥1 PAP prescription	2 y	Incidence of MCI, DNOS,[b] and AD	53,321 with OSA diagnosis	65–90	41	90
	Control: untreated						
Liguori et al.,[27] 2021, Italy	Treatment: PAP therapy adherent, mean use ≥4 h/night for >5 nights/wk	3.8 y	Cognitive decline	24 with OSA diagnosis and MCI or AD	75 (65–84)	33	Italian population
	Control: PAP therapy –adherent group, mean use <4 h/per night for ≤5 nights/wk						
Osorio et al.,[23] 2015, United States	Treatment: PAP therapy	2–3 y	Age at MCI or AD onset	2,285 with normal cognition, early or late MCI, early AD dementia with OSA status (self-report)	55–90	46	91[49]
	Control: untreated OSA						
Richards et al.,[24] 2019, United States	Treatment: PAP therapy–adherent group, mean use ≥4 h/night for 1 y	1 y	Cognitive decline	54 with OSA diagnosis (AHI ≥10) and MCI	70 (55–89)	44	65
	Control: PAP therapy–nonadherent group, mean use <4 h/night for 1 y						
Skiba et al.,[13] 2020, United States	Treatment: PAP therapy mean use ≥4 h/night for 30 d	2.8 y	Cognitive decline in MCI and progression from MCI to dementia	96 with OSA diagnosis (mild AHI 5–14.9, moderate AHI 15–29.9, and severe AHI ≥30) and MCI	70 (40–92)	34	66
	Control: untreated OSA						
Troussière et al.,[28] 2014, France	Treatment: PAP therapy mean use >4 h/night for >5 nights/wk for at least 3 mo	4 y	Cognitive decline	23 with severe sleep apnea diagnosis (AHI ≥30) and probable mild-moderate AD	75 (68–80)	39	French population
	Control: PAP therapy mean use <4 h/night for <5 nights/wk for at least 3 mo						

Continued

Table 1 Characteristics of the Studies Included in the Systematic Review *(continued)*

Source	Exposure	Study period	Outcome	Study population	Age, mean and/or range, y[a]	Women, %	White, %
Tsai et al.,[29] 2020, Taiwan	Treatment: PAP therapy based on titration code	17 y	Incidence of AD	3,978 with OSA diagnosis	40–90+	34	Taiwanese population
	Control: untreated						
Wang et al.,[25] 2020, United States	Treatment: PAP therapy–adherent group, mean use ≥4 h/night for 1 y	1 y	Cognitive decline	17 with mild OSA diagnosis (AHI 10–14) and MCI	72 (55–89)	53	59
	Control: PAP therapy–nonadherent group, mean use <4 h/night for 1 y						

Abbreviations: AD = Alzheimer disease; AHI = apnea-hypopnea index; DNOS = dementia not otherwise specified; MCI = mild cognitive impairment; OSA = obstructive sleep apnea; PAP = positive airway pressure; RCT = randomized controlled trial.
[a] Age was reported as mean or range according to the information provided by each study.
[b] A category that included vascular dementia, dementia with parkinsonism/Lewy bodies, and frontotemporal dementia.

the Alzheimer's Disease Neuroimaging Initiative,[23] a cohort from the Alzheimer's Disease Research Center, and clinical samples of adults who obtained care at neurology, sleep, and memory clinics.[13,21,24-28] In US-based studies, participants were predominantly White (range 59%–98%), and across all studies, the proportion of women ranged between 25% and 53%. Six studies included both middle-aged and older participants,[13,23-25,27,29] while 5 focused on older adults (≥65 years of age).[14,21,22,26,28]

Most study participants carried a diagnosis of OSA (96%, n = 60,840), and most (70%, n = 43,970) received PAP therapy. Of the 11 identified studies, 6 considered apnea-hypopnea index (AHI) a measure for OSA severity (AHI ≥10, mild to severe[21,24,26]; AHI 10–14, mild[25]; and AHI ≥30, severe[28]) and all levels of OSA severity.[13] Baseline cognitive impairment (MCI or AD) was present among 9% (n = 5,826) of study participants. Data extraction summaries are reported in Tables 1 and 2.

Bias Assessment

Table 3 presents a summary of study designs and bias assessment of all studies included in this review. High risk of bias was found in all 3 clinical trials: 2 studies used a quasi-experimental design without randomization and limited controlling of confounders,[24,25] and 1 study modified the analytical strategy due to unachieved targeted recruitment.[21] Three observational studies[26-28] were considered to have a serious risk of bias due to limited controlling of confounders. The remaining 5 observational studies were categorized as having moderate risk of bias,[13,14,22,23,29] and while not comparable to a well-performed randomized trial, they provided sound evidence.

Exposure or Intervention Assessment

Assessment of PAP therapy varied by study. In 1 clinical trial, standard PAP therapy was randomly assigned to a treatment group for 6 weeks, while the control group wore placebo masks with a large air leak and pressure reducer for 3 weeks, followed by 3 additional weeks of standard PAP therapy. The standard PAP therapy provided new masks determined by a formal PAP titration polysomnography to establish the therapeutic pressure.[21] No significant difference in adherence to PAP therapy was found in treatment vs control groups, 5.8 h/night for 73% of nights vs 6.4 h/night for 67% of the nights in the first 3 weeks and 4.9 h/night for 62% of the nights in the standard PAP therapy period.

In 2 quasi-experimental studies, participants in the treatment group used standard PAP therapy for ≥4 h/night for 1 year, while controls used PAP therapy <4 h/night for 1 year.[24,25]

In all observational studies, PAP therapy was defined either by Healthcare Common Procedure Coding System code on ≥1 PAP prescription and titration Current Procedural Terminology codes from claims data[14,22,29] or by mean PAP use duration (ranging from 1 week–1 year).[13,23,26-28]

Table 2 Characteristics and Main Findings of the Studies Included in the Systematic Review

Source	Outcome assessment	Adjusted variables	Participants in treatment group, n	Participants in control group, n	Main findings	Primary objectives met
Ancoli-Israel et al.,[21] 2008, United States	Baseline, 3-wk, and 6-wk assessment of cognitive function by various tests[a]	NA	27	25	Significant improvement in cognition after 3 wk of PAP treatment in both groups (after vs before treatment) with a mean change of composite neuropsychological score 0.077 points (p = 0.01).	Partially
						Due to unexpected difficulties with recruiting in this patient population, the targeted recruitment was not achieved; hence, the study was underpowered to test the primary hypothesis according to the randomized design.
Cooke et al.,[26] 2009, United States	Assessment of cognitive function by various tests[a]	NA	5	5	Compared to control group, treatment group showed less cognitive decline on global cognition (effect size 0.4) and improvement in executive functioning (Wisconsin Card Sorting Test effect size 0.7; Stroop Color-Word score effect size −0.8; Trail B effect size −0.3; F-A-S Total Letter Score effect size −0.7) and psychomotor speed (WAIS effect size −1.9; Trails A effect size −0.5).	Yes
Dunietz et al.,[22] 2020, United States	ICD-9 diagnoses of MCI and AD	Age, sex, race/ethnicity, hypertension, type 2 diabetes, CVD, depression, stroke	2,164	1,101	PAP treatment was associated with lower risk of MCI and AD in both men (OR 0.95, 95% CI 0.92–0.98) and women (OR 0.80, 95% CI 0.70–0.90). PAP treatment adherence was associated with lower risk of MCI and AD in both men (OR 0.88, 95% CI 0.78–1.01) and women (OR 0.72, 95% CI 0.63–0.84). PAP treatment was associated with lower risk of AD and MCI for all ethnoracial groups (OR range 0.57–0.99). Sex and race/ethnicity each modified the associations between cognitive disorders (AD and MCI) and PAP treatment or adherence (p for interaction < 0.0001).	Yes
Dunietz et al.,[14] 2021, United States	ICD-9 diagnoses of MCI, DNOS, and AD	Age, sex, race/ethnicity, hypertension, CVD, depression, stroke	41,466	11,855	PAP treatment was associated with lower odds of incident diagnoses of AD (OR 0.78, 95% CI 0.69–0.89), DNOS (OR 0.69, 95% CI 0.55–0.85), and MCI (OR 0.82, 95% CI 0.66–1.02). PAP adherence was associated with lower odds of incident of AD (OR 0.65, 95% CI 0.56–0.76).	Yes
Liguori et al.,[27] 2021, Italy	Baseline and each follow-up visit of cognitive impairment on MMSE and CDR	NA	12	12	PAP adherence was not related to change in baseline-follow-up MMSE scores (p = 0.19), but PAP-nonadherent patients showed a higher mean change of CDR score (mean 1.43) than PAP-adherent patients (mean 0.44).	Yes
Osorio et al.,[23] 2015 US	Age at MCI and dementia	*APOE* ε4, sex, education, BMI, depression, CVD, hypertension, diabetes, age	47	148	PAP therapy delays age at MCI onset to a comparable age of those without SDB (age 72.63 vs 72.11 y). PAP therapy was not associated with later AD onset.	Yes

Continued

Table 2 Characteristics and Main Findings of the Studies Included in the Systematic Review *(continued)*

Source	Outcome assessment	Adjusted variables	Participants in treatment group, n	Participants in control group, n	Main findings	Primary objectives met
Richards et al.,[24] 2019, United States	Baseline, 6-mo, and 1-y assessments of cognitive function by various tests[b]	Age, race, marital status	29	25	PAP adherence was associated with improved psychomotor/cognitive processing speed (parameter estimate 1.68, 95% CI 0.73–2.62).	Yes
Skiba et al.,[13] 2020, United States	Progression to dementia based on a CDR score = 1 and assessments of cognitive function by various tests	Demographic variables	72	24	Patients with amnestic MCI had better PAP use (p = 0.016) and shorter progression time to dementia (median 52.1 vs > 84 mo, p = 0.042). However, the association was not significant in adjusted models (p = 0.32).	Yes
Troussière et al.,[28] 2014, France	Assessment of change in MMSE score every 6 mo	NA	14	9	Treatment group demonstrated lower median annual MMSE cognitive decline than control group (−0.7, 95% CI −1.7 to 0.8 vs −2.2, 95% CI −3.3 to −1.9, p = 0.013).	Yes
Tsai et al.,[29] 2020, Taiwan	ICD-9 diagnoses of AD incidence	Demographics, head injury, diabetes, hypertension, stroke, hyperlipidemia, CVDs, anxiety, and depression	127	3,186	PAP or surgical treatment was associated with reduced AD incidence (incidence rate ratio 0.23, 95% CI 0.06–0.98).	Yes
Wang et al.,[25] 2020, United States	Baseline and 1-y assessment of cognitive function by various tests[d]	NA	7	10	Compared to control group, treatment group showed significant improvement in processing speed only (parameter estimate 1.94, 95% CI 0.44–3.44).	Yes

Abbreviations: AD = Alzheimer disease; BMI = body mass index; CDR = Clinical Dementia Rating scale; CVD = cardiovascular disease; DNOS = dementia not otherwise specified; ICD-9 = *International Classification of Diseases, 9th revision*; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NA = not applicable; OR = odds ratio; OSA = obstructive sleep apnea; PAP = positive airway pressure; SDB = sleep disordered breathing; WAIS = Wechsler Adult Intelligence Scale.

[a] Basic attention and vigilance by the Digit Span of WAIS–Revised and the digit cancellation task, psychomotor speed by the Trail Making Test Part A and the WAIS, Third Edition Digit Symbol and Symbol Search subtests, verbal episodic memory by the Hopkins Verbal Learning Test–Revised, sensitive to various aspects of executive functioning by the Trail Making Test Part B, and the 64-card version of the Wisconsin Card Sorting Test, Interference trial of the Stroop Color and Word Test, and total correct words generated on the letter fluency (F-A-S) test and on the category (Animals) fluency test.

[b] Memory by the Hopkins Verbal Learning Test–Revised total recall; psychomotor/cognitive processing speed by the Digit Symbol Subset by WAIS–Revised; global cognition by MMSE; attention by Stroop Color and Word Test and psychomotor vigilance task transformed number of lapses.

[c] Speed of cognitive decline by modified Annual Consortium to Establish a Registry for Alzheimer's Disease score (orientation, clock drawing, verbal fluency, phonemic fluency, Boston Naming, word list learning, recall and recognition, constructional praxis learning and recall), simple and complex visuospatial praxis (Rey-Osterrieth Complex Figure test), simple calculations, and Trail Making Test parts A and B.

[d] Primary outcomes: cognition (memory via Hopkins Verbal Learning Test–Revised and processing speed via WAIS–Revised Digit Symbol coding subtest). Secondary outcomes: global cognition by the Montreal Cognitive Assessment, global progression by the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change Scale, progression of cognitive decline by CDR, functional status by Everyday Cognition scale.

Table 3 Summary of Study Design and Bias Assessment

Source	Study population, n	Treatment	Study design	Bias assessment tool	Bias score
Ancoli-Israel et al.,[21] 2008	52 with OSA and AD	n = 27 CPAP+, n = 25 CPAP−	RCT	RoB 2	High risk
Cooke et al.,[26] 2009	10 with OSA and AD	n = 5 CPAP+, n = 5 CPAP−	POS	ROBINS-I	Serious
Dunietz et al.,[22] 2020	3,265 with OSA with MCI or AD	n = 2,164 CPAP+, n = 1,101 CPAP−	CS	ROBINS-I	Moderate
Dunietz et al.,[14] 2021	53,321 with OSA	n = 41,466 CPAP+, n = 11,855 CPAP−	ROS	ROBINS-I	Moderate
Liguori et al.,[27] 2021	24 with OSA with MCI or AD	n = 12 CPAP+, n = 12 CPAP−	ROS	ROBINS-I	Serious
Osorio et al.,[23] 2015	767 with MCI, 1,518 with AD	Subset: CPAP+ (MCI n = 12, AD n = 35), CPAP− (MCI n = 50, AD n = 98)	ROS	ROBINS-I	Moderate
Richards et al.,[24] 2019	54 with OSA and MCI	n = 29 CPAP+, n = 25 CPAP−	QCT	ROBINS-I	High risk
Skiba et al.,[13] 2020	96 with OSA and MCI	n = 72 CPAP+, n = 24 CPAP−	ROS	ROBINS-I	Moderate
Troussière et al.,[28] 2014	23 with sleep apnea and AD	n = 14 CPAP+, n = 9 CPAP−	POS	ROBINS-I	Serious
Tsai et al.,[29] 2020	3,978 with OSA	n = 127 CPAP+, n = 3,186 CPAP−	ROS	ROBINS-I	Moderate
Wang et al.,[25] 2019	17 with OSA and MCI	n = 7 CPAP+, n = 10 CPAP−	QCT	ROBINS-I	High risk

Abbreviations: AD = Alzheimer disease; CPAP = continuous positive airway pressure; CS = cross-sectional study; MCI = mild cognitive impairment; OSA = obstructive sleep apnea; POS = prospective observational study; QCT = quasi-experimental clinical trial; RCT = randomized controlled trial; RoB 2 = Cochrane Risk of Bias tool version 2; ROBINS-I = Cochrane Risk of Bias in Nonrandomized Studies of Interventions tool; ROS = retrospective observational study.

Outcome Assessment

Of the 11 studies included, 4 examined the incidence, prevalence, or age at diagnosis of MCI or AD, and 7 examined progression of cognitive decline in adults with existing MCI or AD. Most studies assessed the progression of cognitive decline, MCI, or dementia by using comprehensive neuropsychological batteries, brief cognitive screening tools, or clinical diagnosis.

Incidence of MCI or Dementia

Several studies used clinical diagnosis codes from administrative claims data to assess cognitive disorders. In US Medicare beneficiaries claims data, 2 studies used Healthcare Common Procedure Coding System, Current Procedural Terminology, and ICD codes to examine associations between PAP therapy, PAP adherence, and prevalence and incidence of MCI, AD, and dementia not otherwise specified (DNOS).[14,22] Similarly, a large retrospective study in Taiwan compared AD incidence, captured by ICD-9 codes in a health insurance database, among adults diagnosed with OSA and sociodemographically matched controls over 16 years.[29] Last, a multisite US study of cognitively intact adults with OSA examined the age at incident MCI or AD among those who reported PAP therapy vs those who did not.[23] All participants completed a comprehensive neuropsychological evaluation, including functional measures, and those who met National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's Criteria were assigned an AD diagnosis by study clinicians.

Progression of Cognitive Decline

One RCT conducted in a US-based clinical research center examined improvement in cognitive functioning among adults with AD after PAP therapy over 3 to 6 weeks.[21] Cognitive change was assessed with a comprehensive neuropsychological battery, including a brief screening measure of global cognitive functioning; measures of learning and memory, executive functions, and attention and vigilance; and measures of processing speed. A follow-up study 6 to 21 months later assessed a subset of participants from the initial RCT with the same neuropsychological battery to evaluate differences in cognitive decline between those who continued PAP therapy and those who discontinued.[26]

Subjective measures of cognitive status were used in another pilot clinical trial conducted in a US-based sleep and geriatrics clinic[24] and its follow-up study.[25] Both studies used brief cognitive screening tools and a battery of neuropsychological tests to assess verbal memory, attention and vigilance, and processing speed. Change in cognition—improvement or decline—was compared between adults with MCI who were PAP adherent and those who were nonadherent over a 1-year period.

A brief cognitive screener and a single cognitive test to assess attention and executive functioning abilities were used in a retrospective chart review conducted in a large urban health center in the United States.[13] This study followed up adults with MCI and OSA with a 2.8-year follow-up on average and evaluated cognitive change among those who were PAP

adherent, those who were nonadherent, and those who did not use PAP therapy. Brief cognitive screening tools were also used in 2 independent studies: a retrospective multicenter study of Italian adults with MCI and AD and a prospective clinic-based study of French adults with AD. These studies examined change in cognition over ≈3 years.[27,28]

Analytic Strategy

Various statistical approaches were used to examine the associations between PAP therapy, incident MCI or AD, and cognitive decline among adults with MCI or AD. All studies conducted descriptive statistics procedures to estimate effect sizes of PAP therapy on progression of cognitive decline in MCI or AD. Due to limited sample size, only 6 studies pursued association analyses with regression methods. Logistic regression procedures were applied to quantify the impact of PAP therapy on the prevalence of MCI or AD.[22] When time-to-event data were available, Cox proportional hazard regression was used. Two studies adjusted for demographic variables in their analysis,[13,24] while others further adjusted for additional potential confounders, including comorbid conditions (hypertension, diabetes, cardiovascular disease, anxiety, depression) and *APOE* ε4 allele status.[14,22,23,29] However, some comorbid conditions, i.e., hypertension, diabetes, and cardiovascular disease, may be alleviated by PAP therapy and thus are potential mediators on the pathway between PAP therapy and cognitive disorders. Indeed, a primary risk factor for vascular dementia, cerebral small vessel disease, has been associated with moderate to severe OSA in cohorts of older adults and patients seeking sleep evaluation.[30,31] These studies highlight the mediating role of vascular morbid conditions in the pathophysiology of dementia. Similarly, impaired glucose and insulin function has been linked to dementia.[32] To avoid overadjustment bias that would reduce the effect estimates,[33] adjustment for mediators is discouraged. Two studies examined the role of effect modification in the association between PAP therapy and cognitive impairment. In one study, sex and race/ethnicity were examined as potential modifiers of the relationships between PAP therapy and MCI or AD,[22] while another study evaluated whether MCI type (nonamnestic/amnestic) and OSA severity modified the association between PAP therapy and rate cognitive decline.[13]

Impact of PAP Therapy on Cognition: Summary of Findings

Occurrence of MCI or Dementia

Most studies included in this review reported beneficial effects of PAP therapy on the occurrence MCI or AD, i.e., delayed age at MCI onset,[23] reduced MCI or AD prevalence,[22] and reduced incidence.[14,29]

Age at Onset of MCI or AD

PAP therapy was associated with delayed age at MCI onset among older adults with OSA compared to those who were untreated (age at onset 80.10 years vs 72.63 years).[23] However, PAP therapy was not associated with later AD onset.[23]

Prevalence of MCI or AD

Overall, PAP therapy and adherence were associated with lower odds of MCI and AD prevalence. However, sex and racial/ethnic disparities were noted in the associations between PAP therapy, PAP adherence, and MCI or AD (p for interaction < 0.0001).[22] Specifically, older women and racial/ethnic minorities with OSA were less likely to obtain and adhere to PAP therapy.

Incidence of MCI or AD

Lower odds of incident AD and DNOS were observed among Medicare beneficiaries who were prescribed PAP therapy for their OSA vs those who were untreated (odds ratio [OR] 0.78, 95% CI 0.69–0.89; and OR 0.69, 95% CI 0.55–0.85 for AD and DNOS, respectively). Associations between PAP therapy, PAP adherence, and incident MCI approached statistical significance (OR 0.82, 95% CI 0.66–1.02).[14] Last, a large study from Taiwan demonstrated reduced AD incidence among adults with OSA who received PAP therapy or underwent a surgery for their OSA compared to those without treatment (incidence rate ratio 0.23, 95% CI 0.06–0.98).[29]

Time to Dementia

A study of 96 adults with MCI and OSA diagnosis found no difference in time to dementia between adherent PAP therapy users, nonadherent users, or untreated individuals (p = 0.94).[13]

Progression of Cognitive Decline

In most studies, slower rate of cognitive decline was observed among PAP therapy users. Only 2 studies found no protective effect of PAP therapy in slowing cognitive decline,[13,27] while others reported improvement in some cognitive domains among PAP users.[21,24-26,28] Specifically, among adults with both MCI and OSA, there was no significant difference in cognitive decline (i.e., Trail Making Tests parts A and B) in the untreated, PAP-nonadherent, and PAP-adherent groups.[13] In addition, PAP adherence was not associated with change in baseline to follow-up Mini-Mental State Examination scores (p = 0.19).[27] Nonetheless, the study showed a greater mean change of Clinical Dementia Rating scale score (mean 1.43) in PAP-nonadherent adults with OSA compared with PAP-adherent adults (mean 0.44).[27]

A 6-week RCT of 52 adults with OSA reported a significant improvement in cognition after 3 weeks of PAP therapy in mean change of composite neuropsychological score (p = 0.01).[21] Moreover, PAP adherence was associated with improved psychomotor/cognitive processing speed (Digit Symbol subtest from the Wechsler Adult Intelligence age-adjusted total scaled score) (β = 1.68, 95% CI 0.73–2.62).[24] Similarly, a study of 17 adults with mild OSA found significant improvement in processing speed among treated vs untreated controls (β = 1.94, 95% CI 0.44–3.44).[25] Slower rate of decline in global cognition and improved executive functioning and psychomotor speed were also apparent among adults with OSA treated with PAP compared to

untreated controls.[26] Slower rate of cognitive decline (median annual Mini-Mental State Examination score) was also associated with PAP therapy in adults with AD and OSA (median [treated] −0.7, 95% CI −1.7 to 0.8 vs untreated −2.2, 95% CI −3.3 to −1.9, $p = 0.013$).[28]

Summary of Findings in Light of Study Design and Quality

Of the 5 studies with moderate risk of bias, 4 examined associations between PAP therapy and incidence of MCI or AD. These 4 studies reported significant associations between PAP therapy and incidence of MCI or AD. Six studies with serious or high risk of bias have examined mainly the role of PAP therapy in cognitive decline. Five of these 6 studies linked PAP therapy to slower rate of cognitive decline.

Discussion

Despite the high prevalence and consequences of OSA in older adults, the potential benefit of PAP therapy on cognitive function in older adults has rarely been examined. This systematic review identified 11 studies that investigated associations between PAP therapy and incidence or progression of cognitive decline in adults with OSA, providing information to suggest a protective effect of PAP therapy on incidence of MCI or AD. However, data on the rate of cognitive decline in relation to PAP therapy are mixed. Nonetheless, emerging evidence suggests that intervention with PAP therapy may alleviate the burden of cognitive impairment in older adults with OSA. These findings align with reports on the physiologic benefits of PAP.

OSA could contribute to cognitive impairment among middle-aged and older adults through cerebrovascular and neurodegenerative pathways.[34,35] Indicators of small vessel cerebrovascular disease such as white matter hyperintensities (WMH), asymptomatic lacunar infarctions, cerebral microbleeds, and enlarged perivascular spaces are nearly 4 times more prevalent among individuals with moderate to severe OSA than those without OSA.[30,31] Given the existing literature on WMH as a predictor of dementia,[36] the robust association between moderate to severe OSA and elevated WMH in the literature[37] may reflect a modifiable pathway underlying the association between OSA and cognitive impairment or dementia. Moreover, chronic intermittent hypoxia associated with uncontrolled OSA has been linked to neuronal damage and loss in the hippocampus, as well as CNS regions involved in executive functions, language, and perception such as the frontal, temporal, and parietal cortices.[38] Hypoxia and sleep fragmentation associated with OSA may also increase the risk for AD by increasing amyloid burden through either increased amyloid production or decreased clearance. Associations between hypoxia and CSF biomarkers of AD may vary according to genotypic predispositions such as *APOE* allele status, although inconsistent findings have been reported.[39,40] In a recent study of adults with mild to moderate AD, *APOE* status was not associated with the presence or severity of OSA.[41] In addition, elevated levels of tau and biomarkers of inflammation such as interleukin-6 observed in the blood plasma of younger adults with moderate to severe OSA may increase risk for the development of neurodegenerative diseases such as AD in later life.[42]

Emerging research suggests that PAP treatment may have restorative effects on white matter structural integrity and concomitant improvement in neurocognitive function.[37] Growing evidence also suggests that PAP may alleviate the neurodegenerative and cognitive effects of OSA by reducing inflammation and increasing cerebral blood flow.[43] PAP therapy may also enhance slow wave activity, which is critical for memory consolidation. In a case-matched study of adults with newly diagnosed OSA, those who completed 3 months of PAP treatment demonstrated improved slow wave sleep and performance on a declarative memory task consistent with healthy controls; however, those in the non-PAP treatment group did not show this level of improvement.[44] Moreover, prior studies have shown improved cognitive functioning and partial reversal of OSA-associated brain damage, including increased brain volume and neuroplasticity in affected regions after both short-term[45] and long-term PAP treatment.[46-48]

Although this review suggests a protective role of PAP therapy against cognitive impairment, current findings must be interpreted with caution given the high degree of bias in most of the reviewed studies, including RCTs. Furthermore, given the variability in populations (heterogeneity in cognitive status at baseline, pathophysiology, duration of follow-up, assessment of PAP exposure, and assessment of cognitive outcomes), clinical recommendations regarding who is most likely to benefit cognitively from PAP treatment, the duration of PAP therapy for observed benefit, and expected benefits cannot be ascertained from available data. That said, this systematic review, which summarizes the state of the evidence on the role of PAP therapy in cognitive impairment, highlights these key gaps in knowledge to inform high-quality, prospective studies on the effects of PAP for specific populations.

This systematic review included studies with diverse designs, populations, cognitive measures, and statistical approaches, features that influence their quality and the generalizability of their findings. For example, cross-sectional examinations may lack temporal associations between PAP therapy and cognitive impairment, and their findings could lead to information bias.[22] However, except for 1 study, most studies in this review used a prospective or retrospective design.

Heterogeneous sample sizes across studies influenced their statistical power. Seven studies that examined progression to MCI or AD relied on a relatively smaller sample sizes, ranging from 10 to 96 participants, and limited assessment of cognitive function. Of the 7 studies, 5 identified a protective role of PAP therapy against cognitive decline, while 2 reported no cognitive benefit of PAP therapy. In addition to limited statistical power to detect differences between study groups, the use of brief measures of cognition may have contributed to the

mixed results.[13,27] Conversely, consistent associations between PAP therapy and delayed incidence of MCI or AD were observed in studies with larger cohorts. Specifically, a protective effect of PAP therapy was suggested for reduced prevalence MCI or AD,[22] delayed age at MCI onset,[23] and reduced MCI or AD incidence.[14,29]

Beyond sample size, duration of follow-up studies could also lead to mixed results. For example, in 1 clinical trial, the duration of follow-up period was 6 weeks,[21] perhaps insufficient to capture the long-term beneficial effect of PAP therapy. Last, heterogeneity among study groups in demographic and health profiles and differences in severity of OSA or cognitive disorders may confound or dilute the impact of PAP therapy on cognitive function.

This review also evaluated the statistical methods used in relation to their respective research questions. Of the 11 studies included in this review, some studies considered a wide range of potential confounders, including sociodemographic variables (age, sex, race/ethnicity, socioeconomic status), access to health care, and baseline anthropometric measurements (body mass index). Furthermore, adjustment for potential mediators, for example, depression, chronic kidney disease, cardiovascular morbidity, hypertension, and diabetes, could lead to biased and attenuated effects estimates. Misclassification of continuous PAP therapy and incidence of cognitive disorders could arise from heavy reliance on self-report and claims data. Last, the majority of persons with OSA remain undiagnosed and untreated.[e1] Therefore, the participants included in these studies may not be fully representative of the population at large.

Disparities in diagnosis of AD have been shown in women and ethnoracial underrepresented in medicine groups. The disproportional burden of AD among women—nearly 1.6 times as high relative to men—has been reported in several European and US cohorts and becomes apparent as early as 75 years of age.[e2] While these sex differences have been attributed primarily to the longer life span of women,[e3] sex-specific etiologies involving biological and environmental determinants and lower thresholds of disease pathology for women are also plausible.[e2]

A disproportional burden of AD has also been shown among ethnoracial groups underrepresented in medicine, with 2-fold and 1.5-fold higher prevalence among non-Hispanic Black and Hispanic individuals, respectively, compared to White individuals.[e4] These ethnoracial differences in AD burden have biological, social, and cultural roots. Genetic factors and a higher prevalence of cardiovascular morbidity among ethnoracial groups underrepresented in medicine have been suggested as determinants of AD disparities.[e5] However, beyond disparities in these risk factors, greater symptom severity at first AD onset has been reported in Hispanic patients, but they have longer survival with the disease.[e5] A meta-synthesis of studies that evaluated barriers and facilitators to dementia care among ethnoracial groups underrepresented in medicine has indicated gaps in education on brain health and symptoms of cognitive decline, in addition to disparities in health care access, that jointly affect the timing of diagnosis and treatment of cognitive disorders.[e6,e7] Last, the use of universal assessments for neurocognitive disorders rather than cultural-specific tools adds further assessment challenges because daily living experiences and meanings associated with dementia vary across ethnoracial groups underrepresented in medicine.[e8]

As a potential risk factor for AD, OSA identification and treatment could alleviate cognitive decline and AD incidence. However, gaps in OSA evaluation, treatment, and treatment adherence in women, ethnoracial groups underrepresented in medicine, and older adults have been reported.[9,22] Addressing sex and ethnoracial inequities in both OSA and dementia has the potential to alleviate the development and progression of dementia and to decrease gaps in care and quality of life among older adults with dementia.

The current review has several limitations. First, the heterogeneity of study designs, exposure, and outcomes assessments of included reports precludes meta-analyses of PAP therapy utility for cognitive disorders incidence and progression. Second, across all studies, participants were predominately White, which limits the generalizability of the findings to other ethnoracial groups. This limitation calls for further investigations to address the impact of PAP therapy on the rate of neurodegeneration among ethnoracial groups underrepresented in medicine and potential disparities emerging from differential access to health care. Third, MCI may be associated with differential loss of cognitive abilities or influenced by sleep and mood.[e9] Challenges in MCI assessment, inherent in claims-based analyses, could result in misclassification of cognitive outcomes and generate biased effect estimates.

This systematic review provides a comprehensive summary of the current literature on the role of PAP therapy in cognition and highlights the need for rigorous, longitudinal studies with diverse cohorts. Overall, we found a protective effect of PAP therapy on incidence of MCI or AD. Findings regarding the impact of PAP therapy on cognitive decline were promising. Longer follow-up periods and in-depth cognitive testing are warranted. PAP therapy may serve as an effective intervention for cognitive health particularly among White older adults. Although preliminary evidence also holds promise for ethnoracial minorities, potential benefits of PAP therapy among non-Whites require further investigation.

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Appendix Authors

Name	Location	Contribution
Monica Moon Shieu, PhD, MS	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Afsara Binte Zaheed, MS	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Carol Shannon, MPH, MA	University of Michigan, Ann Arbor	Major role in the acquisition of data
Ronald David Chervin, MS, MD	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content
Alan Conceicao, BA	University of Michigan, Ann Arbor	Major role in the acquisition of data
Henry Lauris Paulson, PhD, MD	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content
Tiffany Joy Braley, MS, MD	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Galit Levi Dunietz, PhD, MPH	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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