

AMERICAN THORACIC SOCIETY DOCUMENTS

The Link between Obstructive Sleep Apnea and Neurocognitive Impairment

An Official American Thoracic Society Workshop Report

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Abstract

There is emerging evidence that obstructive sleep apnea (OSA) is a risk factor for preclinical Alzheimer's disease (AD). An American Thoracic Society workshop was convened that included clinicians, basic scientists, and epidemiologists with expertise in OSA, cognition, and dementia, with the overall objectives of summarizing the state of knowledge in the field, identifying important research gaps, and identifying potential directions for future research. Although currently available cognitive screening tests may allow for identification of cognitive impairment in patients with OSA, they should be interpreted with caution. Neuroimaging in OSA can provide surrogate measures of disease chronicity, but it has methodological limitations. Most data on the impact of OSA treatment on cognition are for continuous positive airway pressure (CPAP), with limited data for other treatments. The cognitive domains improving with CPAP show considerable heterogeneity across studies. OSA can negatively influence risk, manifestations, and

possibly progression of AD and other forms of dementia. Sleep-dependent memory tasks need greater incorporation into OSA testing, with better delineation of sleep fragmentation versus intermittent hypoxia effects. Plasma biomarkers may prove to be sensitive, feasible, and scalable biomarkers for use in clinical trials. There is strong biological plausibility, but insufficient data, to prove bidirectional causality of the associations between OSA and aging pathology. Engaging, recruiting, and retaining diverse populations in health care and research may help to decrease racial and ethnic disparities in OSA and AD. Key recommendations from the workshop include research aimed at underlying mechanisms; longer-term longitudinal studies with objective assessment of OSA, sensitive cognitive markers, and sleep-dependent cognitive tasks; and pragmatic study designs for interventional studies that control for other factors that may impact cognitive outcomes and use novel biomarkers.

Keywords: obstructive sleep apnea; neurocognitive dysfunction; Alzheimer's disease

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Overview

Obstructive sleep apnea (OSA) is a very common problem and is increasing in incidence worldwide. Mild cognitive impairment (MCI) is often considered a prodromal stage of Alzheimer's disease (AD) and can progress to dementia at the rate of 10–15% per year. OSA is highly prevalent in patients with AD, and there is emerging evidence that OSA is a risk factor for preclinical AD. OSA has been associated with MCI, with some studies reporting a 25% prevalence of cognitive dysfunction in OSA. There has never before been an American Thoracic Society (ATS) workshop on this important topic of OSA and cognitive impairment. This workshop was convened with a strong multidisciplinary group of experts to summarize and review the state of knowledge in the field, identify important research gaps, and provide potential directions for future research.

The key conclusions from the workshop were:

1. There is a growing body of evidence showing an association between OSA and cognitive impairment and decline.
2. Currently available cognitive screening tests may allow for identification of MCI in patients with OSA, but caution is needed in using and interpreting these tests.
3. Neuroimaging in OSA can provide surrogate measures of disease chronicity; however, several methodological challenges and limitations remain.
4. Most data on the impact of OSA treatment on cognition are for continuous positive airway pressure (CPAP); very limited data exist for other treatments.
5. There is considerable heterogeneity as to which cognitive domains improve with CPAP; this heterogeneity may relate to study design, cognitive reserve, the aspect of each cognitive domain that is studied, and other factors.
6. OSA is recognized as a factor that negatively influences risk (through modulation of preclinical AD biomarkers), manifestations, and possibly progression of AD and other forms of dementia.
7. Sleep-dependent memory tasks need greater incorporation into OSA testing, with better delineation of sleep fragmentation versus intermittent hypoxia effects.
8. Plasma biomarkers may prove to be sensitive, feasible, and scalable biomarkers for use in clinical trials. Whether AD biomarkers can be used in young and middle-age populations with OSA where there is minimal AD pathology, or healthy elderly with normal cognition, remains a subject of debate.
9. At the present time there is strong biological plausibility, but insufficient data, to prove the bidirectional causality of the associations between OSA and aging pathology, and a greater emphasis needs to be placed on understanding how AD biomarkers respond to treatment.
10. Engaging, recruiting, and retaining diverse populations in healthcare and research may help to decrease the racial and ethnic disparities in OSA and AD.
11. Key considerations for intervention studies include selection of the population to be recruited, use of pragmatic or alternative study designs, longer duration of intervention, new approaches to improve PAP adherence, and studying changes using more easily accessible biomarkers.

Introduction

There has never been a previous ATS Workshop on the important topic of OSA and cognitive impairment. Given the gaps in knowledge identified in this field through attendee surveys and by other means, and the advances in the field, assessment of this topic via an ATS workshop was warranted.

The overall objective and goal of this ATS Workshop was to assemble a strong multidisciplinary group of experts with varied expertise and perspectives to summarize and review the state of knowledge in the field, identify important research gaps, and provide potential directions for future research. The major areas of focus of the workshop group were: 1) epidemiological evidence linking OSA to cognitive decline; 2) the biomarkers of cognitive impairment (CI) in OSA, such as structural and functional brain imaging and genetic and proteomic biomarkers; 3) the

effect of treatment of OSA and improved sleep on cognition; and 4) future directions for research in this field, particularly optimizing clinical trial design.

OSA is a very common disorder. Based on the American Academy of Sleep Medicine 2012 diagnostic criteria and apnea–hypopnea index (AHI) threshold values of $\geq 5/h$ and $\geq 15/h$, a recent study found that 936 million adults aged 30–69 years have mild to severe OSA, and 425 million adults aged 30–69 years have moderate to severe OSA globally (1).

AD accounts for 60–70% of all dementias (2). AD is one of the major causes of disability/dependency among older people. OSA is highly prevalent in patients with MCI and AD (3). Studies have reported a 25% prevalence of cognitive dysfunction in OSA (4). The relationship between OSA and AD is a complex bidirectional one (5, 6).

Methods

The workshop proposal was peer reviewed and funded through the ATS Assembly project funding mechanism, with the primary project assembly being the Assembly on Sleep and Respiratory Neurobiology. An 8-hour workshop was held virtually on 2 separate days, for 4 hours each, in June 2021. The workshop included 15 participants who were identified based on their expertise and experience in OSA, cognition, and dementia and included both clinicians, and basic scientists. The panel was multidisciplinary, involving pulmonologists, neurologists, a psychiatrist, a clinical neuropsychologist, as well as clinical and basic science researchers. All workshop participants disclosed potential conflicts of interest, and these were managed in accordance with standard ATS policies.

The workshop involved presentations of the most updated information in the major areas of focus as outlined above, followed by an interactive discussion, with the goal of producing a cohesive document summarizing the findings of the panel, as well as delineating specific areas in which further research is needed. After the workshop, the presenters wrote their specific sections to create a workshop report to be submitted for publication. All workshop participants had the opportunity to contribute substantively to the report and to review and revise the manuscript in its final form.

This workshop report summarizes the findings of the workshop.

Section 1: Epidemiology of Cognitive Impairment in OSA

Growing evidence from population-based longitudinal studies have explored the association between OSA and cognitive decline. The first report was from the Study of Osteoporotic Fractures in 298 older women. Those with OSA (AHI ≥ 15 , $n = 105$) were at greater risk of developing MCI or dementia over 5 years (adjusted odds ratio [95% confidence interval], 1.85 [1.11–3.08]) than those without OSA ($n = 193$) (7). Some subsequent studies have also shown OSA to be associated with an increased risk of dementia (8, 9) or cognitive decline (10, 11); however, even within studies results can be inconsistent across cognitive domains, whereas others have shown no association (12). Inconsistent results are most likely due to OSA definitions used and varying study designs, population characteristics, and cognitive outcomes, as well as duration of follow-up in longitudinal studies. Meta-analyses, however, have consistently reported an association between OSA and future cognitive decline. In a pooled analysis of 212,943 individuals from six longitudinal studies, those with sleep-disordered breathing were 26% (risk ratio [95% confidence interval], 1.26 [1.05–1.50]) more likely to develop CI or dementia (4). Other meta-analyses have also shown consistent associations (13, 14), and studies in individuals with MCI specifically have shown higher rates of hypoxemia in such samples (15).

Section 2: Screening Tests for Cognitive Impairment in OSA

Screening tests for cognitive impairment take 3–20 minutes to administer and provide a broad overview of an individual's gross cognitive functions. The presence of MCI is typically determined by comparing a patient's total score to a validated threshold score. Although many screening tests have been developed, their validity to detect MCI may not translate to patient populations outside those used to develop them (16–20), and they may lack sensitivity to detect cognitive impairment in early stages of disease or in those with high levels of

education or intellect. In these cases, neuropsychological assessment provides more sensitivity.

With respect to OSA, this limitation was highlighted by Gagnon and colleagues (16), who found the Mini-Mental State Examination (MMSE) had only fair to poor discriminatory ability to detect patients with OSA with MCI (determined via comprehensive neuropsychological examination). Moreover, the MMSE's validated total score of <26 to indicate MCI (21) correctly identified only 60–62% of patients with OSA with MCI, with optimal threshold scores to detect MCI in mild and moderate-to-severe OSA found to be <30 and <29 , respectively. However, these optimal threshold scores correctly identified only 61–64% of patients with OSA with MCI. By contrast, Gagnon and colleagues (16) found the Montreal Cognitive Assessment had good discriminatory ability to detect MCI in patients with OSA, although its validated total score of <26 to indicate MCI (22) correctly identified only 69–75% of patients with OSA with MCI. Threshold scores of <28 and <27 to indicate MCI were found to be optimal for patients with mild and moderate-to-severe OSA, although they still only correctly identified 72–81% of patients with OSA with MCI. Overall, the results of this study emphasize the difficulties of applying cognitive screening tests derived from one clinical population to another clinical setting, such as patients with OSA, and their potential lack of sensitivity in detecting more subtle cognitive deficits.

In summary, currently available cognitive screening tests may allow for early identification of MCI in patients with OSA. However, caution is needed in interpreting these tests, as they may lack sensitivity, and typical thresholds indicative of MCI may not translate directly to patients with OSA.

Section 3: Brain Changes in OSA and CI

Sleep loss or fragmentation is believed to lead to atrophy within the frontal and parietal regions (23), with hypoxemia being associated with an increase in sympathetic vasoconstriction and simultaneous decrease in vascular protective mechanisms (24–26). That said, at least one study demonstrated associations of OSA with increased gray matter volume, which may reflect inflammatory or

edematous changes (27). These neuroanatomical changes could reflect the cognitive deficits associated with OSA (28).

Using magnetic resonance imaging (MRI), voxel-based morphometry studies report gray matter density reduction in frontal, parietal, temporal, and hippocampal regions in OSA (29–35), whereas white matter density reduction is reported in the bilateral hippocampus and frontotemporal regions (36). In older subjects, decreased thickness of the bilateral temporal pole has been observed, which was associated with hypoxemia and poorer verbal learning, as well as changes in functional connectivity of the default mode network (37, 38). Decreased thickness has also been reported in the pre- and postcentral gyri and the superior temporal gyrus (39). Fractional anisotropy values using diffusion imaging show loss of white matter integrity and structural connectivity (40, 41). Decreased concentrations of *N*-acetylaspartate, a marker of neuronal injury, and increased glutamate concentrations were observed in the hippocampal, thalamic, putamen, and midbrain regions in OSA (29). Together, this evidence suggests that the hippocampus is consistently impacted in OSA (36).

One month of CPAP treatment with lifestyle modifications and sleep hygiene education was shown to induce hypertrophy in the bilateral thalamus (42), whereas 3-month CPAP treatment was associated with increases in gray matter volume within the hippocampal and frontal structures (26). Conversely, O'Donoghue and colleagues reported no changes in gray matter density or volume after 6 months of CPAP treatment (35). Adherence to CPAP might underlie the discrepancy among these studies.

Although neuroimaging studies can reliably assess and quantify the abnormal brain changes and suggest that neuroanatomical changes are evident in OSA, it is worth noting the several methodological challenges and limitations that can constrain interpretation: association does not imply causation. The majority of the reported changes in patients with OSA draw parallels with those seen in healthy aging (43). Neuroimaging patients with OSA who do not show any symptoms or have fewer symptoms than similar-aged clinical populations is disputed. Furthermore, it should be noted that a majority of the cohorts in whom neuroimaging was undertaken were relatively younger than the

elderly cohorts in whom reports of cognitive impairment are more common (38). Furthermore, because of a lack of long-term follow-up, progression of neurodegeneration in the brain regions observed to be impacted by OSA is not known. Studies that use T1-weighted structural MRI modality alone (particularly for gray matter density) should be supplemented by other modalities to separate the effects of myelin or iron content from neuronal loss (44).

In summary, neuroimaging studies in OSA feasibly provide surrogate markers of the chronicity of the disease. However, more intensive longitudinal studies that track neuroanatomical changes over longer periods of time are needed. Ideally, these studies would chart the ramifications of OSA and its treatment while delineating the expected changes with aging. In addition, research combining neuroimaging with high-density electroencephalogram or AD biomarker imaging with positron emission tomography (PET) (discussed in later sections) could better link these structural and functional brain changes in OSA with cognitive impairments and AD neurodegeneration.

Section 4: Impact of OSA Treatment on Cognitive Function

A meta-analysis of 13 randomized controlled trials (RCTs) (45) ($n = 554$ patients with OSA) only found a small significant effect on attention in favor of CPAP, with modest improvement in sleepiness. A systematic review and meta-analysis of RCTs in elderly patients with OSA (four RCTs, 680 participants) (46) compared CPAP to a control group. CPAP was found to be associated with a 2.62-point improvement in the Epworth Sleepiness Scale but only slight improvements in cognitive (digital span, digital symbol) tests.

In the PROOF (Prognostic Indicator of Cardiovascular and Cerebrovascular Events) cohort (126 subjects ≥ 65 years of age) (47), cognitive testing was done in all subjects with OSA at baseline (2002–2003) and again 10 years later (between 2009 and 2012). CPAP treatment sustained maintenance of memory (delayed free recall), attention, and executive functioning.

A retrospective study used Medicare 5% fee-for-service claims data in 53,321

beneficiaries, aged ≥ 65 years with an OSA diagnosis before 2011 (48). PAP adherence was associated with lower odds of a new diagnosis of AD between 2011 and 2013 (odds ratio, 0.65).

Three months of CPAP treatment showed a significant improvement in MMSE scores (49), episodic and short-term memory, as well as executive function (50) in patients with OSA. One month of CPAP treatment resulted in improved verbal episodic memory in patients with OSA (51) and in patients with MCI; improvements in verbal memory were seen after 12 weeks (52). However, with a shorter duration (2 wk) of treatment, cognitive benefits have not been found (53). Some cognitive domains appear to be more sensitive to the effect of OSA treatment than others (54). Difficulties with visuo-constructive abilities and executive function in OSA appear to be more chronic, despite treatment, and may reflect an underlying neuropathology (55). Data on the impact of non-PAP treatment, such as oral appliances (56), and upper airway surgery (57) on cognition in OSA are sparse, but one RCT showed improvements in processing speed with mandibular advancement splint (58).

The panel noted that cognitive reserve is difficult to measure and can change over a lifetime. Impact of circadian rhythm on cognitive task performance should be accounted for in clinical trials. It was noted that overnight motor learning has not been well studied in OSA.

In conclusion, most data on the impact of OSA treatment on cognition are for CPAP; very limited data exist for other treatments. Duration of CPAP treatment is important. Cognitive domains that have been shown to improve with CPAP vary across studies: this heterogeneity may relate to study design, cognitive reserve, and the particular cognitive domain that is studied, among other factors. Clinical trial designs should identify which cognitive domains are most impacted by OSA and most likely to show improvement. Endpoints such as treatment response, improvement in cognitive performance, progression to MCI, etc. need to be better defined. Minimum treatment duration required to produce optimal improvement in cognitive functioning needs to be identified.

Section 5: OSA and AD

Worldwide, at least 50 million people are believed to be living with AD or other dementias (59). The number of Americans with AD aged ≥ 65 is 6.1 million, and the prevalence is expected to reach 13.8 million by 2060 (60). Almost two-thirds of Americans with AD are women (61), and for those ≥ 65 years, 6.9% of whites, 9.4% of African Americans, and 11.5% of Hispanics have AD or other dementias (62).

The major AD risk factors are age, family history, and genetics. Of these factors, age is the greatest; family history represents 15–20% of late-onset AD, and the apolipoprotein E, epsilon 4 (APOE $\epsilon 4$) genotype is a genetic risk factor for AD (60).

The core clinical diagnostic criteria for probable AD are criteria for dementia (including functional decline), insidious onset, clear history of worsening cognition, cognitive deficits, and/or no evidence of neurologic conditions including other dementias (63). Brain changes can begin decades before the onset of overt cognitive symptoms. The National Institute on Aging and Alzheimer's Association have proposed a framework that views AD through a biologic (rather than solely symptomatic) lens, allowing for characterization of the continuum of brain changes even in cognitively normal older individuals (64). This AT(N) model groups fluid and imaging biomarkers into those impacting brain amyloid (A β) deposition (A), pathologic tau (T), and neurodegeneration (N). Progression to AD is characterized by decreases in cerebrospinal fluid (CSF) and plasma concentrations of A β_{42} and A β_{40} (A), increases in phosphorylated tau (T), and increases in total tau and plasma neurofilament light (N). Brain deposits of A β and tau, as measured with PET imaging, increase with AD progression and neurodegeneration, which can be appreciated with standard structural brain MRI.

The continuum of Alzheimer's disease, including the clinical symptoms, associated fluid and imaging biomarkers, and pathological features at each stage, is shown in Figure 1. The pathological course often follows this pattern (in years) before AD symptom onset: brain A β and tau deposition (65) (31.7), glucose metabolism decline (65) (14.1), and structural brain atrophy (4.5) (66). The clinical course is

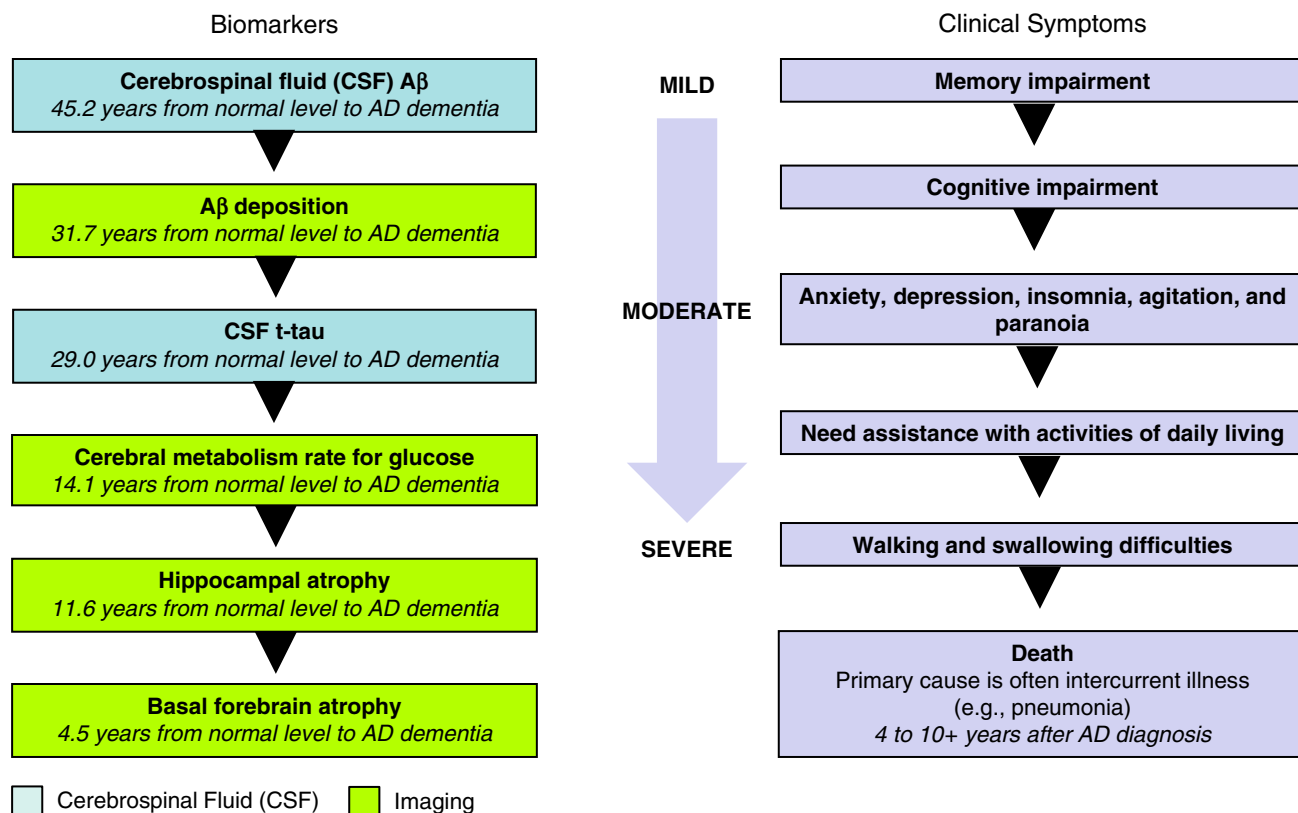


Figure 1. The continuum of Alzheimer's disease (AD), including the clinical symptoms, associated fluid and imaging biomarkers, and pathological features at each stage (65, 66).

heterogeneous but typically follows the pattern of memory decline, as well as impairment in language, visuospatial, and executive functioning. Neuropsychiatric features may occur early in the disease course but become more pronounced with disease progression and include anxiety, depression, insomnia, agitation, and paranoia. A decline in activities of daily living occurs, and, in later stages, waking and swallowing difficulties and incontinence occur. Death, with the primary cause often an intercurrent illness (e.g., pneumonia), may occur 4 to ≥ 10 years after diagnosis.

MCI is an at-risk state for AD, with progression rates of around 10–15% per year (67–69). It is characterized by objective CI beyond age and education expectations that occurs in the context of only minimal impairment in activities of daily living.

OSA is recognized as a factor that negatively influences risk (through modulation of preclinical AD biomarkers), manifestations, and possibly progression of AD (70).

Impact of OSA on Memory and Conversion to MCI

There is evidence that OSA impacts memory across declarative, episodic, spatial, emotional, and motor domains (71). In addition to memory domain, the extent to which OSA impacts memory depends on population demographics and memory testing paradigm. "Sleep-dependent" paradigms are those in which encoding and recall of memories are separated by a period of offline processing containing sleep. OSA has been shown to negatively impact a sleep-dependent form of spatial navigational memory that uses medial temporal lobe structures that include regions affected earliest by AD pathology, in particular tau tangle deposition (72). OSA negatively impacted the pattern of morning performance in a sleep-dependent spatial navigation task in a case/control study of cognitively normal older individuals (73). Using a sleep-dependent declarative verbal word-pairs task, OSA was linked to poorer overnight memory consolidation for cognitively intact control subjects but not for those

with MCI (74), where hippocampal atrophy, daytime episodic memory, and sleep spindles were more pertinent predictors. OSA also negatively impacted overnight change in performance in a rapid eye movement-specific, within-subject, PAP withdrawal model in individuals with severe OSA (75). In a small clinical trial (RCT) of diet/exercise lifestyle modifications with or without PAP, those who received 3 months of PAP showed improvements in overnight consolidation of word pairs, with memory restored to levels observed in individuals without OSA (76). Improvements were also correlated with the increase in slow-wave sleep after starting PAP.

Subjects in the AD Neuroimaging Initiative were followed longitudinally for several years with clinical assessment of cognition and measurement of both neuroimaging and fluid biomarker assessments of AD risk. Among subjects converting to MCI, the average age of onset was significantly earlier (72.6 yr) in subjects with self-reported, untreated OSA compared with subjects without self-reported OSA

(83.6 yr) (77). In those who used PAP, the average age of conversion to MCI was 82.1 years, similar to subjects without self-reported OSA.

In conclusion, the panel agreed that sleep-dependent memory tasks need greater incorporation into OSA testing, with better delineation of sleep fragmentation versus intermittent hypoxia effects. OSA treatment effects on memory remain understudied and can potentially be divided into effects on the prospective formation of new memories versus slowing the deterioration of established memories. OSA can have negative effects on additional aspects of cognition, such as attention or executive function, which can have indirect effects on memory.

Biomarkers of CI and Screening for CI in OSA

The use of AD biomarkers in patients with OSA is based on the assumption that OSA increases AD risk, but whether these biomarkers can be used in young and middle-age populations where there is minimal AD pathology, or healthy elderly with normal cognition, remains a subject of debate (78). In middle-aged and older adults, small sample size cross-sectional data suggest that there is an association between OSA and both established (amyloid PET [79–81], CSF A β [82, 83]) and novel (serum A β and tau [84, 85], CSF neuronal derived proteins [82], plasma cytokines [85]) biomarkers of AD pathology; the results seem more conclusive in those studies that included sleep clinic populations than those that were performed in community or memory clinic settings, and at least two negative studies have been published (86, 87).

In two studies performed in elder adults, OSA severity was associated with higher A β burden (measured as longitudinal decreases in CSF A β 42 and increases in amyloid PET uptake) over a 2-year follow-up in cognitively normal elderly (88), whereas self-reported clinical diagnosis of OSA was associated with greater longitudinal increases in A β and tau burden by both CSF and PET imaging measured over a 2.5-year period in normal cognition and MCI groups (89). In middle-aged adults with newly diagnosed OSA beginning PAP treatment, there were significant associations between change in AHI4% (hypopneas as a decrease in airflow with $\geq 4\%$ desaturation) and change in CSF A β 42, A β 40, and T-tau, such that greater

improvement in AHI4% was associated with a greater decline in each CSF AD biomarker from baseline (90). However, another study was not able to demonstrate associations between OSA diagnosed in middle age and adverse morphological brain changes 15 years later (91).

In patients with mild to moderate AD, recruited prospectively from a cognitive impairment unit, OSA was not associated with sleepiness or worse cognitive function, and APOE ϵ 4 was not related to the presence or severity of OSA (3). However, there is strong biological plausibility for a bidirectional causal association between these conditions (92): arousals associated with OSA can regionally increase neural activity, which is believed to increase production of amyloid and tau (93). OSA may also reduce glymphatic flow, resulting in poorer clearance of amyloid and tau (94). Finally, OSA may cause direct neural injury through hypoxemia, free-radical generation from ischemia/reperfusion injury, or vascular/parenchymal inflammation (95). Conversely, the neurological deterioration that underlies aging and AD could affect breathing and the mechanisms causing OSA.

The panel discussed that at the present time there is strong biological plausibility, but insufficient data, to prove the bidirectional causality of the associations between OSA and aging pathology, and a greater emphasis needs to be placed on understanding how AD biomarkers respond to treatment. To do so would require a successful intervention for either condition (OSA or AD) as well as a medium- to long-term follow-up to observe clinical changes. However, blood-based AD biomarkers are becoming more reliably indicative of intracerebral amyloid and tau load, which may accelerate their utility as treatment outcomes in future OSA clinical trials; disease-modifying medications for AD are slowly unfolding, and the first was recently approved, albeit with some controversy, to treat AD.

Section 6: Racial and Ethnic Disparities in AD and OSA

Estimates show that the proportion of minoritized populations aged >65 years will increase from 22% to 45% by 2060 (96), although they currently remain underrepresented in biomedical (97–99)

research. This projected exponential growth, alongside the extant research consistently demonstrating racial/ethnic disparities in OSA and AD, underscores the importance of determining and reducing disparities in these relationships.

Black/African American adults are 88% more likely to have OSA and 2.1 times more likely to have severe OSA, with the older adult populations maintaining the higher severity rates but demonstrating similar prevalence rates with their non-Hispanic White counterparts (100–102). A community-based study demonstrated that 18% of Hispanic/Latinx women and 33% of men had OSA (103). In addition, although they make up only 8–9% of older adults in the United States, Black/African American and Hispanic/Latinx individuals represent 12–18% of those diagnosed with AD (60, 61), with studies indicating a 1.5–2 times higher prevalence of AD (60, 61, 96, 104).

Emerging associations of OSA with increased A β (105), and AD neuropathology in the brainstem of individuals with OSA, provide the impetus for researching the bidirectional role of OSA in AD (106). These findings demonstrate the importance of OSA, a disorder disproportionately more prevalent in Black/African American and Hispanic/Latinx populations, as a possible mechanism in their demonstrated higher rates of AD.

In summary, evidence proposes increased risk related to the social/cultural construct of race/ethnicity may stem from disparities in health conditions, socioeconomic, and life experiences, secondary to systemic racism (60, 105). Therefore, the path toward reducing health disparities, especially in interrelated disorders disproportionately affecting minoritized populations like OSA and AD, should include increasing diversity and cultural competence; engaging, recruiting, and retaining diverse populations in health care and in research studies; and considering inclusion of measures of systemic racism as directly or indirectly impacting cognition, OSA, and AD.

Section 7: Future Directions

Approaches and Challenges in Planning a Clinical Trial

Research shows that up to 40% of dementia risk is due to modifiable risk factors (107), with OSA emerging as a key risk factor.

Coupled with evidence that dementia pathology begins to accumulate in the brain up to 20 years before clinical symptoms emerge (108), robust trials targeting OSA for dementia prevention are warranted.

Study population and setting. Although ideal, prevention trials targeting OSA in cognitively normal individuals would need to be large-scale and therefore costly (109). A lengthy follow-up would be required to detect clinically significant benefits, which is often not feasible or well suited to the typical timeframes of funding bodies (i.e., 5–10 yr) (110, 111). Selective prevention trials may be more realistic.

Targeting individuals with OSA in sleep clinics would eliminate the need for large-scale community OSA screening and may yield participants with greater cognitive decline (112). Such approaches could be aligned with real-world translation goals, such as the implementation of cognitive screening in sleep clinics.

An alternative approach is to target individuals attending a memory clinic, such as those with MCI (113). In these settings, OSA is evident in up to 71% of patients with MCI (114). However, it is not yet clear if the critical window for intervention has passed and if targeting OSA in preclinical AD before the onset of CI may confer greater benefits.

Strategies that enrich for dementia risk are worth consideration, such as those with concomitant cardiovascular risk (115), positive for the APOE $\epsilon 4$ genotype (116), with more severe OSA or hypoxemia (37, 117), or with evidence of preclinical AD (118). For the latter, measurement of AD biomarkers using PET scanning or CSF could be used, but these are burdensome and costly (119–121). Blood-based biomarkers for AD could be a viable, scalable, and cost-effective screening alternative (122).

Selection of study outcomes. Because there are low base rates of A β in those in midlife (116), trials aiming to detect changes in AD biomarkers in midlife would need to incorporate very long treatment and follow-up periods or focus on those aged >60 years, where A β deposition is more evident (123). The choice of cognitive test is critical. Global cognitive scores (e.g., MMSE or Montreal Cognitive Assessment) and other composite scores lack sensitivity to detect short-term and domain-specific changes (124–126). Indeed, effects on memory may predominate (112, 127) in OSA, but executive functioning and processing speed

outcomes also warrant consideration in midlife samples. The benefits of interventions on overnight memory consolidation should be considered (74), given emerging work showing the benefits of sleep for this critical process (74, 128), and cross-validation of digital cognitive tests or videoconference-based neuropsychological tests could be considered for large-scale trials and/or those in nonmetropolitan communities. Neuroimaging, although costly and less scalable, does represent another surrogate marker of brain health, especially if incorporating MRI markers of cerebrovascular disease (e.g., white matter lesions), hippocampal integrity, functional connectivity, or PET markers of neuroinflammation, glucose metabolism, or AD. As noted, CSF to measure AD pathology may be used but is invasive and not widely used worldwide. Plasma biomarkers such as neurofilament light (NFL), glial fibrillary acidic protein, and phosphorylated-tau assays (e.g., p-tau 181, 217, 231), may prove to be sensitive, feasible, and scalable biomarkers for use in clinical trials (129).

Future studies should also account for mediating factors, such as cerebrovascular disease, blood–brain barrier integrity, neuroinflammation, depression, substance use, and other factors that may impact cognition, brain health, or CPAP adherence and examine secondary impacts of treatments on overall functioning, as well as consider incorporating implementation science and health economics into trials to inform larger health system implementation.

In summary, treatment of OSA may slow the onset of dementia and AD, yet optimal design of randomized trials presents several challenges in terms of feasibility and cost. In addition, selection of study population and setting may require identifying individuals who are presymptomatic but at elevated risk of future dementia. Studies of sufficient size and duration to detect clinical outcomes are largely not feasible; therefore, careful consideration of surrogate outcomes, including more sensitive cognitive tests and biomarkers of AD and dementia, is essential.

Alternative Approaches to Clinical Trials

The impact of CPAP in improving cognitive function and preventing dementia is unclear. Observational studies suggest that CPAP

may delay MCI by up to 10 years, but this finding was based on only 35 patients using CPAP (77). Large RCTs would be an ideal way to assess CPAP effectiveness.

However, conducting RCTs to address long-term health effects is challenging. Patients with substantial OSA symptoms and/or severe hypoxemia cannot ethically be randomized to control, given the efficacy of CPAP in improving symptoms and health outcomes (130–133). Furthermore, even patients with moderate symptoms may choose not to participate if they may be randomized to a control group for a prolonged time period. Excluding these patients from trials removes the subset of patients who might be most likely to experience robust CPAP benefit. Clinical trials tend to recruit minimally symptomatic patients, likely leading to lower adherence, as they do not generally feel better with CPAP (134). In the largest RCT of CPAP for cardiovascular disease prevention ($N = 2,717$) (135), CPAP adherence was low (3.3 h/night), likely accounting for the null results (133).

A complementary design to large RCTs would be long-term observational cohort studies that can recruit symptomatic and severe patients and enable rigorous propensity score (PS) matching (132).

PS matching (133, 136) estimates treatment effects by accounting for covariates that are associated with outcomes and that may differ between groups. A PS could be the probability of being CPAP adherent as a function of baseline covariates. A rich set of covariates known or suspected to be associated with both adherence and outcomes is required to develop a robust PS design. Selection into a PS subclass is the observational equivalent of being randomized (137–139). Several analysis methods using PS exist to reduce confounding in nonrandomized observational cohort studies (140).

PS models do not result in a balance of unmeasured confounders and are not a true substitute for RCTs. Nevertheless, they may be a useful alternative to RCTs, as they can be implemented in large database research cohorts and might be especially useful if randomization is not possible.

In summary, RCTs to study the impact of CPAP (and other OSA interventions) on long-term health effects is challenging because of issues with clinical equipoise

(e.g., randomizing symptomatic patients for prolonged time periods) and adherence. Alternative designs such as rigorous observational studies may complement RCT and address some of these limitations.

Conclusions

The key conclusions from the workshop were:

1. There is a growing body of evidence showing an association between OSA and cognitive impairment and decline
2. Currently available cognitive screening tests may allow for early identification of MCI in patients with OSA, but caution is needed in interpreting these tests.
3. Neuroimaging in OSA can provide surrogate measures of disease chronicity; however, several methodological challenges and limitations remain
4. Most data on the impact of OSA treatment on cognition are for CPAP; very limited data exist for other treatments.
5. There is considerable heterogeneity as to which cognitive domains have been shown to improve with CPAP; this heterogeneity may relate to study design, cognitive reserve, the aspect of each cognitive domain that is studied, and other factors.
6. OSA is recognized as a factor that negatively influences risk (through modulation of preclinical AD biomarkers), manifestations, and possibly progression of AD.
7. Sleep-dependent memory tasks need greater incorporation into OSA testing, with better delineation of sleep fragmentation versus intermittent hypoxia effects.
8. Plasma biomarkers may prove to be sensitive, feasible, and scalable biomarkers for use in clinical trials. Whether AD biomarkers can be used in

young and middle-age populations with OSA where there is minimal AD pathology, or healthy elderly with normal cognition, remains a subject of debate.

9. At the present time there is strong biological plausibility, but insufficient data, to prove the bidirectional causality of the associations between OSA and aging pathology, and a greater emphasis needs to be placed on understanding how AD biomarkers respond to treatment.
10. Engaging, recruiting, and retaining diverse populations in health care and research may help to decrease the racial and ethnic disparities in OSA and AD.
11. Key considerations for intervention studies include selection of the population to be recruited, use of pragmatic or alternative study designs, longer duration of intervention, new approaches to improve PAP adherence, and studying changes in more easily accessible biomarkers. ■

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