Published in final edited form as:

J Alzheimers Dis. 2018 ; 64(Suppl 1): S255–S270. doi:10.3233/JAD-179936.

The relationship between Obstructive Sleep Apnea and Alzheimer's Disease

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Abstract

Obstructive Sleep Apnea (OSA) and Alzheimer's disease (AD) are highly prevalent conditions with growing impact on our aging society. While the causes of OSA are now better characterized, the mechanisms underlying AD are still largely unknown, challenging the development of effective treatments. Cognitive impairment, especially affecting attention and executive functions, is a recognized clinical consequence of OSA. A deeper contribution of OSA to AD pathogenesis is now gaining support from several lines of research. OSA is intrinsically associated with disruptions of sleep architecture, intermittent hypoxia and oxidative stress, intrathoracic and hemodynamic changes as well as cardiovascular comorbidities. All of these could increase the risk for AD, rendering OSA as a potential modifiable target for AD prevention. Evidence supporting the relevance of each of these mechanisms for AD risk, as well as a possible effect of AD in OSA expression, will be explored in this review.

Keywords

Obstructive sleep apnea (OSA); Alzheimer's disease (AD); AD risk; OSA phenotypes; amyloid

INTRODUCTION

Obstructive Sleep Apnea (OSA) is a common medical condition with increasingly recognized impact on global health worldwide. Obstructive apneic events occur when there is transient partial or complete closure of the upper airway during sleep [1]. These apneic episodes are associated with cycles of hypoxia/hypercapnia/reoxygenation, transitory

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increases in intrathoracic pressure, hemodynamic disruptions, and recurrent brain arousals with sleep fragmentation [2]. OSA is the most common form of sleep-disordered breathing (SDB) accounting for about 85% of the cases, with central sleep apnea being less common [3]. OSA is frequently classified for both clinical and research purposes according to the Apnea-Hypopnea Index, AHI (number of apneas and hypopneas per hour of sleep). While apneas have been consistently defined as decreases in respiratory airflow greater than 90% for more than 10 seconds, one conundrum in the field is that there are at least 2 commonly used definitions of hypopneas. The most recent revision by the American Academy of Sleep Medicine (AASM) defines hypopneas as decreases in inspiratory airflow of more than 30% for >10 seconds, associated with a drop of at least 3% in oxygen saturation or arousal (AHI3a) [4]. The older definition of hypopnea, which was used in research for many years, required an oxygen desaturation of at least 4%, irrespective of whether an arousal occurred, and indices using this criteria are sometimes denoted AHI4%. OSA severity has traditionally been predicated on AHI4% values in which 5–14 events/hour constitutes mild OSA, 15–29 events/hour constitutes moderate OSA and ≥30 events/hour constitutes severe OSA. The fact that these same cut-offs are inappropriately applied to AHI3a may account for some of the disparate results in the sleep research literature. Some use the term OSA syndrome (OSAS) to refer to the presence of OSA plus daytime sleepiness.

Clinically, OSA can remain asymptomatic, accounting for its presumed high underdiagnosis rate, or present with a wide variety of symptoms. These can range from mild snoring and feelings of unrefreshing sleep, to several degrees of excessive daytime sleepiness (EDS) [5], cognitive impairment (especially affecting attention and executive functions) [6], depression, and functional impairment [7]. OSA not only impacts quality of life, but is also associated with increased risk of work and traffic accidents [8,9], adding to its importance as a major health concern that should be effectively recognized and treated.

OSA is also often accompanied by several comorbidities. All aspects of the metabolic syndrome, namely insulin resistance or diabetes [10], dyslipidemia [11], hypertension [12,13] and obesity [14], have been associated with OSA. It has been suggested that the metabolic syndrome or “syndrome X” should also comprise OSA and be then called syndrome “Z”. Cardiac arrhythmias, heart failure, and stroke are also documented more frequently among OSA patients [15–18]. Besides its recognized direct effect on cognitive performance, gathering evidence is now supporting a role of OSA in dementias’ pathophysiology.

Alzheimer’s disease (AD) is the most common form of dementia worldwide, accounting for more than 70% of all cases. Vascular dementia and other neurodegenerative types of dementia account for most of the remaining cases. More than 4.7 million people aged over 65 years in the United States are now affected by AD, and its prevalence is expected to increase up to 13.8 million people in 2050 if new preventive and treatment measures are not implemented [19]. Its main neuropathological hallmarks, extracellular amyloid beta (Aβ) plaques and intraneuronal neurofibrillary tangles (NFT), characteristically accumulate throughout the brain, culminating in the progressive and irreversible cognitive decline seen in AD patients [20,21]. A combination of genetic and environmental factors is now considered an accepted framework to explain individual predisposition for AD development,

however, its specific underlying pathophysiological mechanisms are still elusive. Age and genetic background, including the presence of the ApoE4 genotype, are important non-modifiable risk factors for AD. Cognitive reserve and physical activity are recognized protective factors and numerous medical diseases such as traumatic brain injury, depression, midlife obesity, diabetes and cardiovascular and cerebrovascular disease have all been associated with increased risk of AD [22].

OSA, besides being more prevalent in older populations (as is AD) [23], has also been associated with both cognitive decline [24] and dementia [25]. Several mechanisms that characterize OSA, such as disruption of sleep architecture, intermittent hypoxia, increased oxidative stress, intrathoracic pressure changes, and cardiovascular comorbidities, could contribute to an increased risk of AD. Exploring the evidence supporting these possible interactions will be the focus of this review. The possible effects of AD on OSA expression will also be briefly mentioned.

EVIDENCE OF A LINK BETWEEN OSA AND AD

Evidence from animal, epidemiological and human AD studies, suggests an interdependent relationship between OSA and AD. These are both highly prevalent diseases in older populations, and frequently coexist. A recent meta-analysis found that AD patients have a 5-fold increased risk of presenting with OSA compared to age-matched controls, and that about 50% of AD patients experience OSA after their initial diagnosis [26].

Conversely, OSA may promote the worsening of existing AD. For example, in triple transgenic AD mice, induced chronic intermittent hypoxia was associated with increased levels of brain $A\beta_{42}$ [27] and an increase of tau phosphorylation [28] compared to control mice. In humans, earlier studies from Ancoli-Israel et al. showed a strong correlation between severity of OSA and severity of AD symptoms [29], suggesting that AD clinical expression is aggravated by OSA in patients with full-blown dementia.

The interaction between these two diseases could even begin before overt clinical symptoms are present in AD, and several studies support this hypothesis. First, in a prospectively longitudinal study, 105 elderly women with OSA had a higher risk of developing mild cognitive impairment (MCI) or dementia compared to 193 women without OSA (adjusted OR, 1.85; 95% CI, 1.11–3.08) [30]. Second, our group documented a positive association between the presence of reported OSA and an earlier age of MCI onset, as well as a possible delay of this effect in continuous positive airway pressure (CPAP) treated subjects [25]. In addition, our recent meta-analysis determined a 1.55, 1.65 and 3.78 increased risk of AD, cognitive impairment, and preclinical AD, respectively, in patients with sleep problems compared to controls. Sub-group analyses also revealed that OSA participants had approximately twice the risk of non-OSA participants of cognitive decline and/or AD [31].

Studies evaluating AD specific cerebrospinal fluid (CSF) biomarkers further support this hypothesis. In a recent 2-year follow up study, baseline OSA severity was associated with higher rate of CSF $A\beta_{42}$ decline and with a trend towards increased cortical Pittsburgh compound B (PiB)-PET uptake [32] in cognitively normal elderly. In another study, among

subjects with subjective cognitive impairment, the ones with untreated OSA had higher T-tau/$A\beta_{42}$ ratio and lower levels of $A\beta_{42}$ compared to CPAP treated and non-OSA subjects [33].

Clinical trials exploring the effect of CPAP treatment on cognition and AD also strengthen the suspected link between OSA and AD. A large randomized controlled trial (RCT) demonstrated a mild but measurable improvement of executive function in OSA patients treated for 6 months with CPAP versus untreated subjects [34]. In mild to moderate AD subjects with OSA, a small RCT showed that CPAP treatment partially improved verbal learning, memory and executive functions [35]. A later reassessment of part of these subjects suggested that sustained use of CPAP improved sleep and mood, and slowed cognitive decline [36]. This initial finding was corroborated by a 3-year pilot study performed in France where AD patients that underwent CPAP treatment showed significantly slower cognitive decline when compared to the non-CPAP AD group [37].

In summary, growing evidence from animal and human studies supports an interdependent relationship between OSA and AD. The immediate deleterious effect of OSA in cognition, especially on executive function and attention, may contribute to a worsening of the AD clinical presentation, and in addition, OSA may influence relevant ADs pathophysiological mechanisms in preclinical AD stages before overt cognitive symptoms exist. Importantly, adequate diagnosis and treatment of OSA may hold a promising beneficial preventive effect in preclinical AD as well as in slowing cognitive decline in clinical AD.

OSA PHENOTYPES

OSA has been extensively studied in middle-aged adults, where its underlying anatomical causes and associated comorbidities are well characterized. Recent studies have focused on OSA in older populations, and the existence of two separate entities is now debated. The terms “age-dependent”, in which aging determines pathogenesis, and “age-related”, where pathogenesis occurs during a specific age range, have been proposed to define old and middle-age OSA, respectively [38,39]. Multiple lines of evidence support this categorization. First, epidemiological studies show a prevalence of OSAS in middle-aged populations different from the estimated in the elderly [39-43]. A recent large prospective study assessing AHI3a by polysomnography (PSG) determined a prevalence of mild to moderate OSA of 83.8% in men and 60.8% in women, while severe forms were noted in 49.7% and 23.4% of men and women respectively. Older age (>60yo) was associated with significantly higher prevalence of moderate to severe OSA and attenuation of the sex discrepancy compared to younger subjects [44]. Age-dependent structural and functional changes of the upper airways could account at least partially for these differences [45]. In fact, higher airway resistance [46], decreased pharyngeal diameter [47,48], increased pharyngeal fat deposits [50], and sleep-induced changes in the upper airway muscular activity [49], were all found more frequently in the elderly compared to younger subjects, although other studies showed contradictory results [50–53]. Alternatively, sleep-architecture modifications that occur with aging, as sleep fragmentation, reductions of slow wave sleep (SWS) duration [54], and increased percentage of non-rapid eye movement

(NREM) stages 1 and 2, could also determine an increased susceptibility to OSA [38]. Possibly, all of these changes could add to, or accentuate, preexisting middle-age OSA [41].

OSA also often presents differently in these two age groups. For example, contrasting with the higher prevalence of OSA, snoring has been found to be less frequent in older populations [55]. Furthermore, symptoms such as EDS, snoring, nocturia and mild cognitive complaints, that are viewed as pathological in middle-aged adults and should prompt OSA evaluation, may be neglected and considered part of “normal aging” in older adults. OSA in the elderly may also be masked by a more heterogeneous presentation mixed with other health problems, which may obscure the diagnosis [41].

Epidemiological studies on OSA mortality have shown conflicting results. While early reports pointed to higher mortality rates in older OSA patients [56,57], in other studies, OSA has been linked with increased mortality only if severe or in patients younger than 50 [58]. Recent results from longitudinal cohorts that included older subjects (>65), have shown an increased mortality in older OSA patients only when associated with EDS [59] and although in 40–70 year-olds OSA determined increased mortality, this association was not found in those 70 and older [60]. In other studies mortality rates in elderly OSA populations are found to resemble those of younger subjects without OSA [61–63]. This has been hypothesized either to relate to a preconditioning cardiovascular protective effect of chronic exposure to intermittent hypoxia in older adults with OSA [64], to a greater tendency for fatal cardiovascular outcomes in younger OSA patients [45], or to survivor bias. Some studies, but not all, suggest that elderly may be less susceptible to OSA related cardiovascular (but not brain) morbidity [55,63,65]. Furthermore, obesity, while frequent and relevant to mortality in middle-age OSA, may not be present and even be associated with better outcomes in older subjects [66]. A more consistent view prevails on the beneficial effect on quality of life and morbidity/mortality for both younger and older populations with CPAP treatment [45,67,68].

In conclusion, the existence of two separate OSA clinical phenotypes is still a matter of debate. While the clinical manifestations and associated morbidities may be somewhat different in these age groups, it seems reasonable to argue that part of the increased prevalence still derives from the aging of middle-age OSA patients. We believe in a contribution of both middle-age and old-age predisposing factors, acting with different weight in each phase of the continuum of chronological age (Figure 1).

THE POSSIBLE LINKS BETWEEN OSA AND AD

EFFECTS OF SLEEP DISTURBANCES

OSA CAUSES SLEEP FRAGMENTATION—The interplay between sleep and cognition has been vastly explored and its influence on attention, executive function, and memory consolidation is well recognized (for reviews on this topic see [69,70]). Experimental studies with rodents have documented that sleep is important for hippocampal neurogenesis [71] and synaptic plasticity [72], and that sleep fragmentation is associated with decreased hippocampal plasticity and spatial learning [73,74]. OSA fragments sleep architecture due to recurrent brain arousals resulting from reflex responses initiated by upper airway

mechanoreceptors and central and peripheral chemoreceptors. This may have not only a direct impact on cognitive performance by disrupting sleep-related memory and attention promoting processes, but also potentially by increasing the risk for dementia.

Two large cross-sectional studies have shown an association between poor sleep quality and worse cognitive outcomes in older populations [75,76]. In a study performed in cognitively normal individuals, reduced sleep efficiency correlated with lower CSF $A\beta_{42}$ levels, assumed to correspond to preclinical AD [77]. In another study, poor sleep quality reported by healthy adults at increased risk for AD, was associated with CSF biomarker patterns of AD [78]. Recently, a large prospective study established a robust association specifically between sleep fragmentation and both increased incidence of AD and rate of cognitive decline [79]. At a mean follow-up of 3-years, subjects with higher sleep fragmentation levels had a 1.5-fold increased risk to develop AD compared to subjects with low sleep fragmentation, evaluated by actigraphy.

In parallel, sleep has been suggested to be a fundamental piece in brain toxic metabolite clearance processes [80]. Recently, circadian fluctuations of Aβ CSF levels were described, with characteristic increases in wakefulness and decreases during sleep, suggesting that sleep decreases Aβ production and promotes Aβ clearance [81]. Adding to this, chronic sleep disruption was associated with increased Aβ plaque deposition in amyloid-β precursor protein (AβPP) transgenic mice [81]. Finally, Lucey et al. recently compared CSF Aβ kinetics in sleep deprived subjects compared to normal sleeping controls, finding a 25–30% increase in overnight soluble $A\beta_{38}$, $A\beta_{40}$ and $A\beta_{42}$ in the former group, suggesting that sleep deprivation contributes to AD risk by promoting Aβ production [82]. In conclusion, sleep appears to play a key role in the production-clearance dynamics of Aβ, which if disturbed could predispose to AD pathogenesis [77,81]. This could constitute an additional mechanism by which sleep fragmentation, characteristic of OSA, may promote cognitive decline and AD pathogenesis (see Figure 2).

OSA CAUSES REM SLEEP DISRUPTION—Although its complex functions are still incompletely understood, REM sleep has been implicated in sleep-related synaptic consolidation, neuroplasticity, and memory consolidation processes [83–86]. Muscular hypotonia is a characteristic of REM sleep, and a lower genioglossus muscle response in maintaining an adequate airway patency in this stage predisposes to apneic episodes. These episodes are in fact found to be more frequent, longer and associated with greater hypoxemia in REM compared to N2 sleep stages [87-89]. The higher propensity for apneas during REM sleep in OSA could lead to a preferential disruption of this stage and its associated memory promoting processes. In older populations, REM sleep was found to be decreased in subjects with cognitive impairment compared to controls, which correlated with OSA severity [90]. A prospective 3-year follow-up study in older men corroborated that reduced REM stages were associated with greater cognitive decline over time [91]. Finally, a recent study in humans demonstrated that active and specific induction of OSA through CPAP withdrawal exclusively during REM sleep in patients with severe OSA resulted in spatial navigation learning deficits [92].

Several studies have additionally suggested a link between REM sleep disturbances and AD. At cross-section, AD patients had decreased REM sleep when compared to controls [93] and to depressed patients [94], although these findings were not replicated in other studies [95]. A recent prospective study on 321 subjects from the Framingham Heart Study cohort, examined the influence of PSG assessed sleep architecture features on the risk of AD. Lower total percentages and greater latencies to REM sleep at baseline associated strongly with AD incidence over a mean follow-up of 12 years, while all other sleep stages were not significantly associated with dementia risk [96]. The authors argued for a possible decrement in cholinergic activity known to accompany AD since early stages as a possible cause for this finding [97], but a primary role of REM reduction in AD pathogenesis could also be hypothesized. In this study, each percentage unit of REM sleep reduction was associated with a 9% increase in the risk of dementia, a value that was reduced to 6% when people with frequent arousals due to hypopneas were excluded. This suggested that OSA contributed to this observed association [96]. Additionally, a study using EEG detected frontal brain activity slowing, especially during REM sleep, in amnestic MCI compared to non-amnestic MCI and controls. This supports a possible impairment of REM sleep starting in the early clinical AD stages [98], however still without determining the causal direction of this relationship. Taken together, these studies point to a link between REM sleep, OSA, and AD. Whether OSA associated disruption of REM sleep contributes to cognitive decline and AD, or REM sleep disruptions are just (early) epiphenomena of AD is still unclear and more studies are required.

OSA CAUSES SWS DISRUPTION—SWS is a stage of sleep that may be somewhat more resistant to OSA compared to lighter NREM stages [99]. This has been hypothesized to relate either to a greater upper airway stability being required for progression to deeper sleep stages [100,101] or to an increased tolerance to hypoventilation during SWS leading to fewer arousals during this stage [102]. Nonetheless, it is clear that with increasing severity, OSA has the capacity to disrupt SWS. By selectively withdrawing CPAP exclusively in SWS in subjects with severe OSA, we found that there was both a reduction in %SWS and an increase in SWS fragmentation [103]. Guilleminault et al. reported a decrease in total SWS in older patients with severe OSA, both on the first NREM sleep cycle and on total night-time [104]. Another study with younger subjects and mild OSA, did not replicate this finding, however, a different time course of slow wave activity (SWA) was still found [105]. Additionally, severe OSA patients show up to a 40% homeostatic rebound in SWS duration following OSA treatment with CPAP, which suggest that changes in SWS quality are likely present in severe OSA [106].

OSA-induced reductions of SWS can be presumed to lead to cognitive impairment and increased AD risk for several reasons. First, SWS has been implicated in overnight memory [107], learning [108] and perceptual and visuomotor performance, all of which could be impaired in the presence of disturbances of this stage [109]. Second, neuronal activity is typically reduced during SWS, with an estimated decrement of up to 43% of glucose metabolism levels in ^{18}F-fluorodeoxyglucose (FDG) PET studies when compared to wakefulness [110]. Recent studies suggest that Aβ [111,112] and tau release into the cerebral interstitial fluid (ISF) is increased during periods of higher synaptic activity, and

that their clearance from this pool is higher during SWS [113]. SWS could be a beneficial stage due to both lower production of and increased removal of toxic metabolic byproducts. Corroborating this, our group recently found an association between reduced SWS and higher CSF levels of $A\beta_{42}$ [114]. Recently Ju et al., through SWS disruption with auditory tones, also found a strong association between SWS disruption and higher Aβ, and between lower sleep quality and increased tau CSF levels [115]. A possible decrease in SWS in OSA patients could therefore, by altering this production-clearance dynamics, predispose to AD.

EFFECTS OF VASCULAR COMORBIDITIES

OSA IS ASSOCIATED WITH ADVERSE CARDIOVASCULAR OUTCOMES

OSA is commonly accompanied by cardiovascular comorbidities. These include insulin resistance and diabetes, dyslipidemia, hypertension and cardiac diseases including dysrhythmias and congestive heart failure.

Epidemiological studies show that about half of type 2 diabetic patients are diagnosed with moderate or severe OSA and that approximately half of OSA patients have diabetes. Although both are highly prevalent disorders and a causal link is not yet proved, a bi-directional association between these conditions is suggested by some authors [116–118]. Insulin resistance was also found to correlate positively with OSA severity after controlling for potential confounders [10].

Dyslipidemia has been observed more frequently in OSA patients. In a prospective study, Chou et al. reported a prevalence of hypercholesterolemia and hypertriglyceridemia in OSA patients, of 61.1% and 55.3%, respectively [119]. A later randomized controlled trial study using CPAP demonstrated a reduction of postprandial lipidemia in OSA [11].

Hypertension is one of the best studied conditions accompanying OSA. OSA is common among hypertensive patients, with a global prevalence of 30% that increases up to 80% if only treatment-resistant cases are considered [2,12.] On the other hand, as many as half of OSA patients have comorbid hypertension, and a systolic nondipping pattern of blood pressure during sleep is frequently observed in OSA [12,120]. The causal weight of OSA on hypertension is nonetheless still debated and not as strong as originally thought. Conflicting conclusions were drawn from two large longitudinal studies, possibly due to age differences and the confounding effect of obesity, and a milder correlation between them is now suggested [121–123]. Reports from OSA clinical trials evaluating the effect of CPAP on hypertension are more convincing, with reductions of up to 2 mmHg in blood pressure, especially in cases of higher baseline hypertension and better compliance [124–126].

In OSA, both repetitive episodes of hypoxia and multiple arousals are thought to impair ventricular relaxation and myocardial contraction, contributing to the higher prevalence of ventricular hypertrophy and congestive heart failure in OSA [127]. Additionally, OSA results in recurrent decreases in intrathoracic pressure, by increasing left ventricular afterload and reducing pre-left ventricular load, which could also lead to reduction of ventricular ejection fraction [15,128,129]. Coronary heart disease has been inconsistently linked to OSA and more studies are required [2]. Cardiac arrhythmias, including atrial

fibrillation (AF), are frequent in OSA patients [130,131], but whether they constitute a direct consequence of OSA or are mediated by heart failure is still debated [15]. CPAP treatment has been found to decrease the incidence of cardiovascular events [132].

Obesity is also frequently found in OSA patients and is suspected to be an important causal mechanism particularly in middle-aged adults, increasing also cardiovascular risk [133].

Finally, the incidence of stroke is higher in OSA patients [17,18], and stroke, possibly due to its motor/respiratory sequelae, increases the risk for OSA. Prevalence of OSA in stroke patients rounds 50–70% and increases with recurrent strokes [134]. Some authors also suggest a bidirectional causal relationship between stroke and OSA [2].

Several mechanisms have been proposed to mediate the increased cardiovascular risk in OSA patients. These include sympathetic system activation [135,136], oxidative stress [137,138], local and systemic inflammation [139,140], endothelial dysfunction, hypercoaguability [141,142] and metabolic dysregulation (for a review see [2]). Additionally, the effect of OSA on cardiovascular risk could be partially mediated by a decrease in SWS. Reduced SWS has been linked to metabolic, hormonal and autonomic disturbances [143,144]. Interestingly, a prospective study in older men implicated SWS reduction but not OSA indices on hypertension risk [120], and in the same cohort, an inverse correlation between SWS and obesity was found [145].

ADVERSE CARDIOVASCULAR OUTCOMES INCREASE RISK OF AD

Although all of these vascular and metabolic comorbidities could primarily contribute to vascular dementia [146], and not AD, a growing body of evidence is now attributing a pivotal role of cardiovascular disease in AD pathogenesis [147]. First, cardiac diseases such as atrial fibrillation, coronary heart disease, and heart failure, can directly lead to hypoperfusion and microemboli formation, which have been implicated in AD development [148–150]. Second, stroke can not only potentiate the clinical expression of AD [151], but several studies have shown that cerebral microinfarcts and intracranial atherosclerosis can increase the risk of AD [152,153]. It has been proposed that cerebrovascular disease could directly promote Aβ production and reduce its clearance [1543,155], however available data on this hypothesis is still inconsistent [155,156]. Besides its accepted implication in neuropathic cerebrovascular mechanisms, hypertension in midlife has been directly associated with a higher development of neuritic plaques, neurofibrillary tangles, and brain atrophy, suggesting another link to AD pathogenesis [157,158]. Both type 2 diabetes and pre-diabetes have been shown to increase the risk of dementia and AD, possibly due to microvascular damage and neurotoxicity of higher levels of glucose and insulin leading to oxidative stress [159,160]. A cross-sectional study in 156 patients with incident AD, documented an association between pre-diagnosis dyslipidemia (higher total and LDL cholesterol) and diabetes, and faster cognitive decline. This association seems to be conditioned by ApoE4 status, as a previous history of stroke or heart disease was associated with cognitive deterioration only in ApoE4 carriers [161]. In conclusion, although it is more commonly accepted that vascular and metabolic OSA associated comorbidities may lead to stroke and vascular dementia, an alternative role of cerebrovascular pathology in AD pathogenesis is now recognized, with both pathologies synergistically promoting cognitive

decline [162]. Finally, midlife obesity, possibly due to its association with many chronic vascular diseases, has been documented to increase the risk of dementia and AD [163]. Together, these data suggest that OSA associated vascular and metabolic comorbidities could, through chronic impairment of cerebrovascular integrity and/or neurometabolic systems, lead to an increased risk of AD.

AD PATHOLOGY IS ASSOCIATED WITH INTERMITTENT HYPOXIA AND OXIDATIVE STRESS

Oxidative stress is caused by an imbalance between the production and clearance of reactive oxygen species (ROS) [2]. These oxygen-rich molecules are highly reactive with proteins, lipids, and nucleic acids, and have been implicated in neuronal dysfunction and death in neurodegenerative diseases [2,164]. Mounting evidence suggests that repetitive cycles of intermittent hypoxia followed by reoxygenation, characteristic of OSA, promote ROS production [137,138] and reduce blood antioxidant capacity [165]. In humans, OSA is associated with higher systemic biomarkers of oxidative stress and inflammation, that parallel disease severity [166]. This intermittent hypoxia-induced oxidative stress effect has been hypothesized to underlie, at least partially, cognitive changes in OSA [24]. In fact, several studies in rodents, have shown that intermittent hypoxia during rest is associated with increased oxidative stress and inflammation biomarkers, increased neuronal loss and reduced spatial learning [167–169]. This deleterious effect was shown to be reduced by the use of pharmacological inhibitors of oxidative stress pathways [164]. Baril et al. recently demonstrated a thickening of gray matter paralleling OSA severity [170], which they hypothesized to stem from edema [171] and reactive gliosis [172] associated with hypoxemia.

Some studies further suggest a contribution of intermittent hypoxia to AD pathophysiology. Ng et al., showed that short-term chronic intermittent hypoxia increased Aβ peptide generation in rat hippocampi and that this effect was prevented by melatonin administration [173]. A study using neuronal culture from triple transgenic AD mice documented a significant increase in $A\beta_{42}$ in brain cortex associated with intermittent hypoxia, both supporting a role of OSA in AD progression [27]. Furthermore, there is evidence of tau-phosphorylation activation with chronic hypoxia in double transgenic (APP/PS1) mice [28], increases of CSF and serum T-tau after cardiac arrest [174], and increases in P-tau in hypertensive patients with blood pressure reductions in possible relation with hypoperfusion [175]. A large clinical longitudinal study confirmed an association between measures of OSA and incidence of MCI and dementia in older women, and this effect was attributed to hypoxemia effects rather than sleep fragmentation or duration [30]. In summary, growing evidence shows that intermittent hypoxia in OSA can be an important factor contributing to an increased risk of cognitive decline and AD progression in these patients.

OSA IS ASSOCIATED WITH DECREASED CSF-ISF CLEARANCE

The respiratory effort against collapsed airways during OSA apneic episodes (Mueller maneuver) is associated with elevated intrathoracic and intracranial pressures, and hemodynamic disturbances [176,177]. These have been hypothesized to acutely and

repetitively impede the circulation of brain metabolites from ISF into CSF [178], through the glymphatic system, leading to increased $A\beta_{42}$ accumulation in the ISF. This mechanism was proposed by a recent study where all assessed CSF neuronally derived proteins, but not total protein (mainly derived from blood albumin), were decreased in severe OSA subjects compared to controls [178], suggesting that clearance glymphatic processes were impaired in OSA. As an alternative, the authors proposed that an increased venous pressure seen in OSA due to intermittent hypoxia and right heart strain could limit the clearance of subarachnoid CSF into the dural lymphatic system, leading to the reduced concentrations of metabolites observed in the CSF [178,179]. Another possible pathway for CSF-ISF exchange impairment in OSA could be cerebral edema secondary to intermittent hypoxia as described previously. In this study, severity of OSA correlated with increased volume and thickness of the left lateral prefrontal cortex, as well as increased thickness of the right frontal pole, the right lateral parietal lobules, and the left posterior cingulate cortex [170]. In a previous interventional study, these findings were found to reverse after six months of treatment with CPAP, suggesting the existence of brain edema in OSA [180]. In conclusion, decreased clearance of amyloid is believed to be one of the mechanisms underlying AD pathogenesis and could be affected by mechanical and brain localized OSA changes, comprising an additional pathway through which OSA could contribute to increased AD risk (Figure 2).

AD CAN CONTRIBUTE TO OSA

The characteristic progressive brain accumulation of amyloid plaques and NFTs in AD, may determine changes in sleep patterns, sometimes even before overt dementia is recognized. A reduction in SWS is frequently observed in AD patients and since this stage is associated with fewer apneic events [102], this could lead to increased OSA severity in AD patients. Relatedly, lighter sleep stages as N1 and N2 NREM prevail in AD subjects. As these stages are associated with a higher propensity for apneas, this may also generate a trend towards worsening of OSA severity in AD [99]. Additionally, potential age-dependent anatomical [181] and functional neuromuscular [181] upper airway changes that affect nocturnal respiratory patency, may be aggravated in AD patients. Either through accumulating pathology or neuronal loss, both gray matter and white matters structures responsible for motor response can be affected in AD patients [183], potentially increasing their susceptibility for OSA. Taken together, all these mechanisms could render AD as a risk factor for OSA. Ultimately both diseases could have a bidirectional and cyclic potentiating effect on each other’s pathogenesis.

CONCLUSION

Although it is known that OSA is a highly prevalent disease with growing impact in our society, data from epidemiological studies is still lacking the consistency and strength to fully understand its relationship to frequently associated comorbidities and mortality, especially in milder forms of the disease. Its classification based only on AHI cutoffs seems to be now too simplistic, as OSA appears to be a more complex and heterogeneous disorder, continuously interacting with aging, other risk factors and its own comorbidities. The leading contributing causes for OSA in the young, as craniofacial predisposing morphology,

obesity, family history and male sex, may differ from the ones in the elderly, where the impact of possible anatomical, functional and sleep architecture changes determined by the aging process seems to prevail. Improvements in epidemiologic study design that may promote a better understanding of this pressing issue and necessary advancements in the field are currently being discussed and proposed [184].

Multiple lines of evidence suggest that OSA potentiates neuropathological and clinical progression of AD. Probably by a combination of mechanisms including disruption of sleep architecture, intermittent hypoxia and hemodynamic changes, and the deleterious effects of its vascular comorbidities, OSA may determine a cumulative predisposing context for AD development. While AD does not have an effective treatment, several pathologic mechanisms in OSA can be reverted by OSA treatment, including correct and sufficient CPAP use, and exploring this relationship may converge in possible manipulations of this risk factor to help prevent cognitive decline and dementia.

ACKNOWLEDGMENTS

The authors thank Ms. Jatnna Rivas for her contribution to figures construction and formatting. This work was supported by grants from: NIH/NIA/NHLBI R21AG055002, R01HL118624, R21AG049348, R01AG022374, R01AG056682, and P30AG008051; Foundation for Research in Sleep Disorders, the American Sleep Medicine Foundation Junior Faculty Award, the American Thoracic Society Foundation, and the Friedman Brain Institute.

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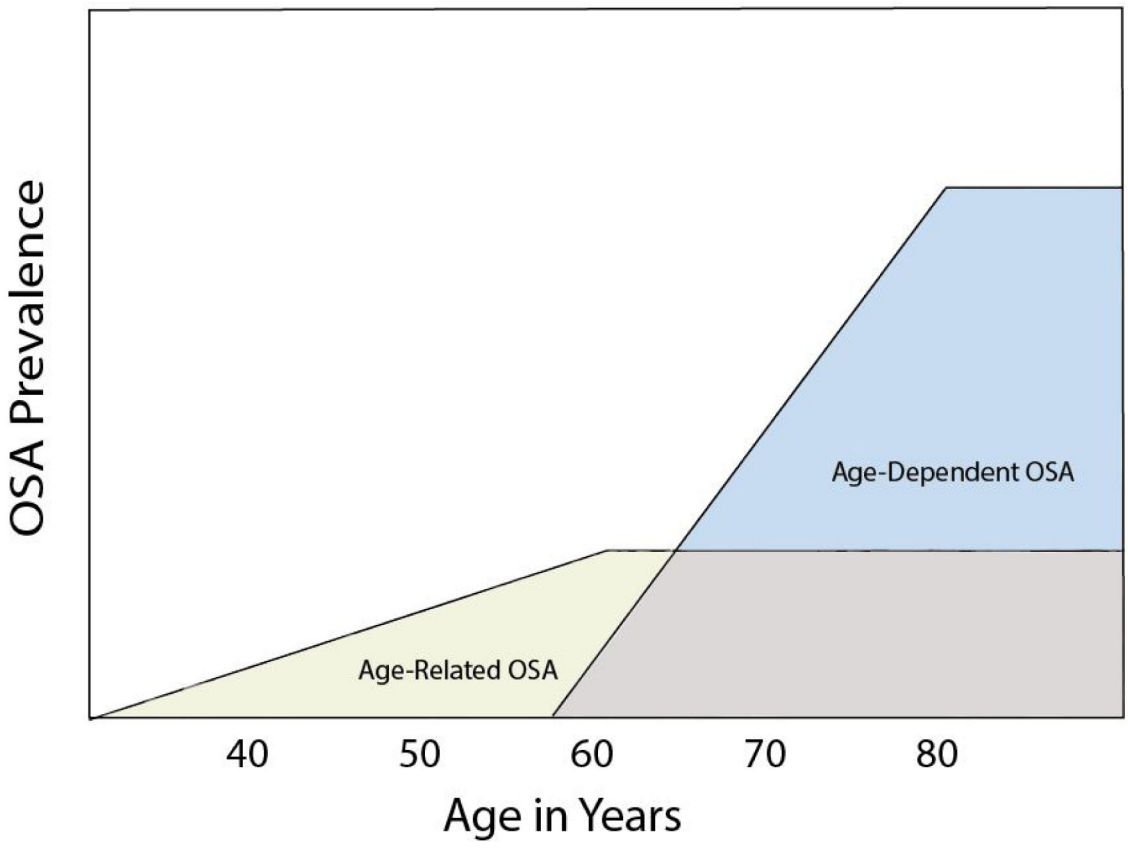

Figure 1:
Proposed prevalence of OSA age-phenotypes. Age-Related OSA would be more common in younger subjects, with its prevalence stabilizing in older age. Age-Dependent OSA prevalence would start to increase in older ages, contributing to the higher prevalence of OSA in this age group.

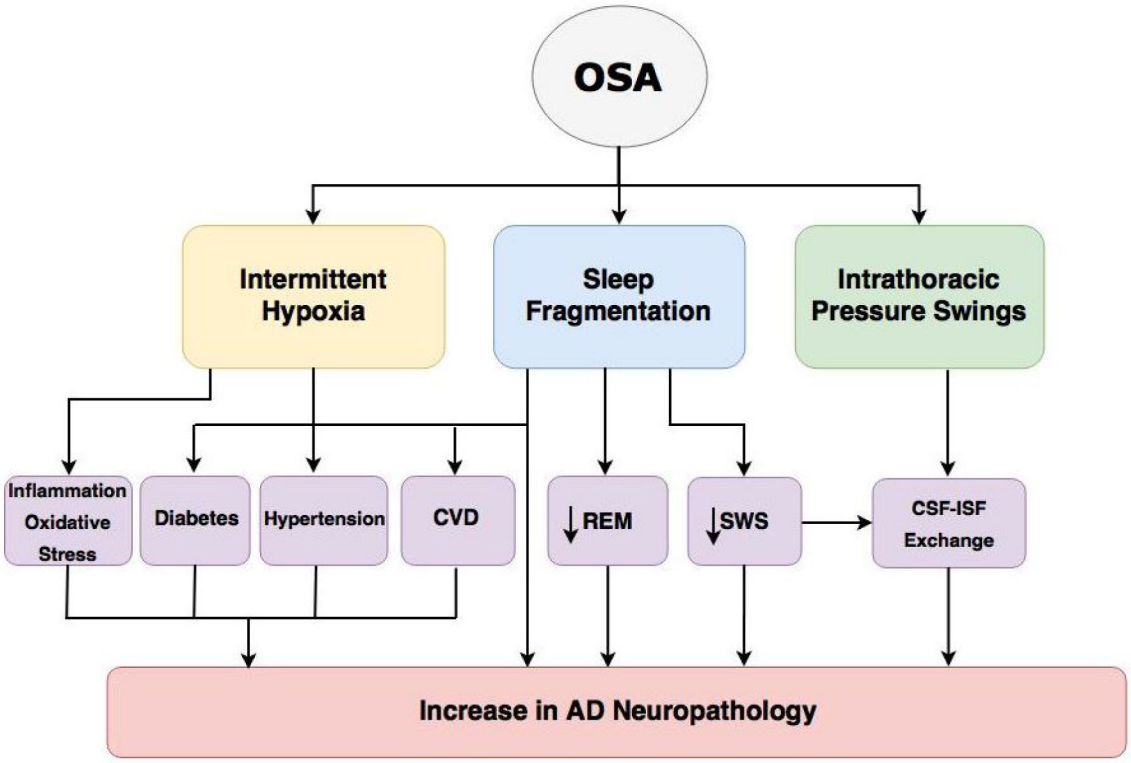

Figure 2:

Possible intermediate mechanisms in the relationship between OSA and AD. The effect of OSA in increasing the risk for AD can be mediated by several of its associated mechanisms. Chronic exposure to intermittent hypoxia may lead to increased inflammation and oxidative stress, diabetes, hypertension and CVD, all potentially contributing to AD pathology development. Sleep fragmentation, both by itself and by leading to decreased REM and SWS stages, can additionally promote AD pathogenesis. Finally, intrathoracic pressure swings associated with OSA may disrupt CSF-ISF exchange integrity and lead to AD neuropathology accumulation. OSA: Obstructive Sleep Apnea; CVD: Cardiovascular Disease; REM: Rapid Eye Movement; SWS: Slow Wave Sleep; CSF-ISF: Cerebrospinal Fluid-Interstitial Fluid; AD: Alzheimer's Disease.