Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-179936
IOS Press

Review

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: AD risk, Alzheimer's disease, amyloid, obstructive sleep apnea, OSA phenotypes

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 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 two 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

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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 criterion 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-β (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 toward 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 (>60 years) 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 (Fig. 1).

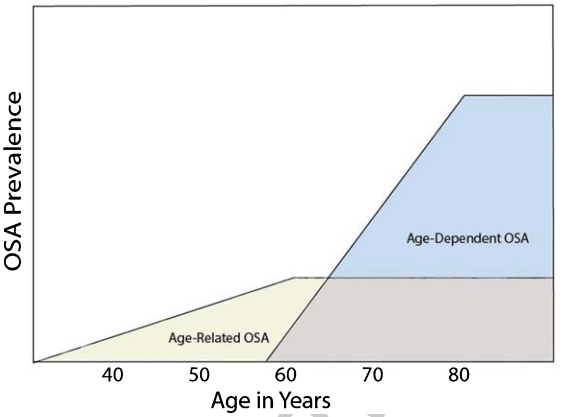

Fig. 1. Proposed prevalence of OSA age-phenotypes. Age-Related OSA would be more common in younger subjects, with its prevalence stabilizing in older age. Age-Dependent OSA prevalence would start to increase in older ages, contributing to the higher prevalence of OSA in this age group.

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 Fig. 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

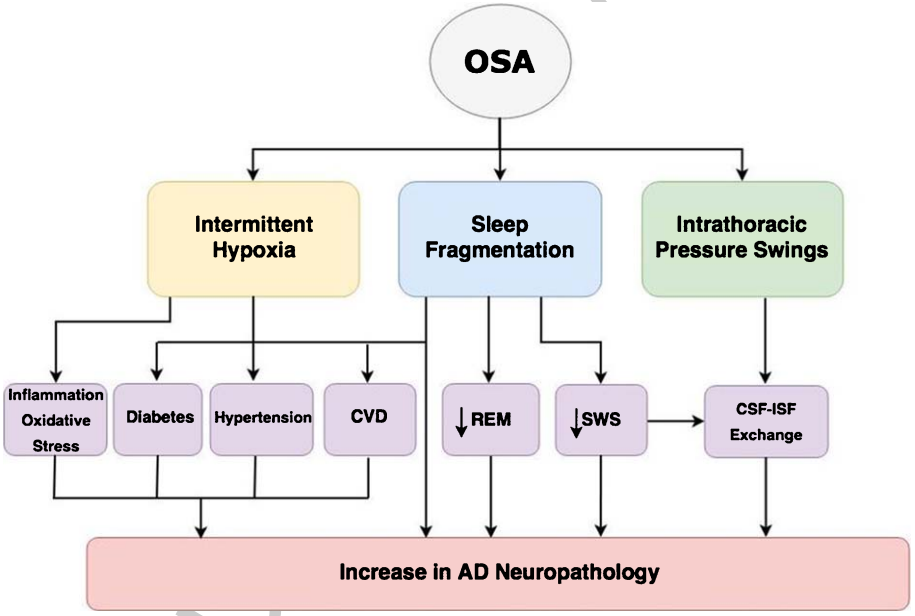

Fig. 2. Possible intermediate mechanisms in the relationship between OSA and AD. The effect of OSA in increasing the risk for AD can be mediated by several of its associated mechanisms. Chronic exposure to intermittent hypoxia may lead to increased inflammation and oxidative stress, diabetes, hypertension 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.

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 these 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, 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 [154, 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, NFTs, 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 (Fig. 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 toward 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.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/17-9936).

REFERENCES

[1] Remmers JE, deGroot WJ, Sauerland EK, Anch AM (1978) Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* **44**, 931-938.

[2] Sanchez-de-la-Torre M, Campos-Rodriguez F, Barbe F (2013) Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med* **1**, 61-72.

[3] Morgenthaler TI, Kagramanov V, Hanak V, Decker PA (2006) Complex sleep apnea syndrome: Is it a unique clinical syndrome? *Sleep* **29**, 1203-1209.

[4] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Ward SLD, Tangredi MM; American Academy of Sleep Medicine (2012) Rules for scoring respiratory events in sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* **8**, 597-619.

[5] Guilleminault C, Partinen M, Quera-Salva M, Hayes B, Dement WC, Nino-Murcia G (1988) Determinants of daytime sleepiness in obstructive sleep apnea. *Chest* **94**, 32-37.

[6] Beebe DW, Groesz L, Wells C, Nichols A, McGee K (2003) The neuropsychological effects of obstructive sleep apnea: A meta-analysis of norm-referenced and case-controlled data. *Sleep* **26**, 298-307.

[7] Engleman HM, Douglas NJ (2004) Sleep 4: Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. *Thorax* **59**, 618-622.

[8] Basoglu OK, Tasbakan MS (2014) Elevated risk of sleepiness-related motor vehicle accidents in patients with obstructive sleep apnea syndrome: A case-control study. *Traffic Inj Prev* **15**, 470-476.

[9] Garbarino S, Guglielmi O, Sanna A, Mancardi GL, Magnavita N (2016) Risk of occupational accidents in workers with obstructive sleep apnea: Systematic review and meta-analysis. *Sleep* **39**, 1211-1218.

[10] Punjabi NM, Beamer BA (2009) Alterations in glucose disposal in sleep-disordered breathing. *Am J Respir Crit Care Med* **179**, 235-240.

[11] Phillips CL, Yee BJ, Marshall NS, Liu PY, Sullivan DR, Grunstein RR (2011) Continuous positive airway pressure reduces postprandial lipidemia in obstructive sleep apnea: A randomized, placebo-controlled crossover trial. *Am J Respir Crit Care Med* **184**, 355-361.

[12] Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T (2008) Sleep apnea and cardiovascular disease: An American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* **118**, 1080-1111.

[13] Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD, Lorenzi-Filho G (2011) Obstructive sleep apnea: The most common secondary cause of hypertension associated with resistant hypertension. *Hypertension* **58**, 811-817.

[14] Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL (2008) Obesity and obstructive sleep apnea: Pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc* **5**, 185-192.

[15] Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S (2006) Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. *Am J Respir Crit Care Med* **173**, 910-916.

[16] Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E (2010) Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The sleep heart health study. *Circulation* **122**, 352-360.

[17] Arzt M, Young T, Finn L, Skatrud JB, Bradley TD (2005) Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med* **172**, 1447-1451.

[18] Valham F, Mooe T, Rabben T, Steinlund H, Wiklund U, Franklin KA (2008) Increased risk of stroke in patients with coronary artery disease and sleep apnea: A 10-year follow-up. *Circulation* **118**, 955-960.

[19] Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA (2003) Alzheimer disease in the US population: Prevalence estimates using the 2000 census. *Arch Neurol* **60**, 1119-1122.

[20] Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW (1991) The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cereb Cortex* **1**, 103-116.

[21] Braak H, Thal DR, Ghebremedhin E, Del Tredici K (2011) Stages of the pathologic process in Alzheimer disease: Age categories from 1 to 100 years. *J Neuropathol Exp Neurol* **70**, 960-969.

[22] Reitz C, Mayeux R (2014) Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochem Pharmacol* **88**, 640-651.

[23] Daulatzai MA (2015) Evidence of neurodegeneration in obstructive sleep apnea: Relationship between obstructive sleep apnea and cognitive dysfunction in the elderly. *J Neurosci Res* **93**, 1778-1794.

[24] Nair D, Dayyat EA, Zhang SX, Wang Y, Gozal D (2011) Intermittent hypoxia-induced cognitive deficits are mediated by NADPH oxidase activity in a murine model of sleep apnea. *PloS One* **6**, e19847.

[25] Osorio RS, Gumb T, Pirraglia E, Varga AW, Lu SE, Lim J, Wohlleber ME, Ducca EL, Koushyk V, Glodzik L, Mosconi L, Ayappa I, Rapoport DM, de Leon MJ (2015) Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology* **84**, 1964-1971.

[26] Emamian F, Khazaie H, Tahmasian M, Leschziner GD, Morrell MJ, Hsiung GY, Rosenzweig I, Sepehry AA (2016) The association between obstructive sleep apnea and Alzheimer's disease: A meta-analysis perspective. *Front Aging Neurosci* **8**, 78.

[27] Shiota S, Takekawa H, Matsumoto SE, Takeda K, Nurwidya F, Yoshioka Y, Takahashi F, Hattori N, Tabira T,

Mochizuki H, Takahashi K (2013) Chronic intermittent hypoxia/reoxygenation facilitate amyloid-beta generation in mice. *J Alzheimers Dis* **37**, 325-333.

[28] Gao L, Tian S, Gao H, Xu Y (2013) Hypoxia increases Abeta-induced tau phosphorylation by calpain and promotes behavioral consequences in AD transgenic mice. *J Mol Neurosci* **51**, 138-147.

[29] Ancoli-Israel S, Klauber MR, Butters N, Parker L, Kripke DF (1991) Dementia in institutionalized elderly: Relation to sleep apnea. *J Am Geriatr Soc* **39**, 258-263.

[30] Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, Stone KL (2011) Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* **306**, 613-619.

[31] Bubu OM, Brannick M, Morimer J, Umasabor-Bubu O, Sebastiao YV, Wen Y, Schwartz S, Borenstein AR, Wu Y, Morgan D, Anderson WM (2017) Sleep, cognitive impairment, and Alzheimer's disease: A systematic review and meta-analysis. *Sleep* **40**, zsw032.

[32] Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, Wohlleber M, Miller MD, Andrade A, Lewis C, Tweardy S, Buj M, Yau PL, Sadda R, Mosconi L, Li Y, Butler T, Glodzik L, Fieremans E, Babb JS, Blennow K, Zetterberg H, Lu SE, Badia SG, Romero S, Rosenzweig I, Gosselin N, Jean-Louis G, Rapoport DM, de Leon MJ, Ayappa I, Osorio RS (2018) Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly: A longitudinal study. *Am J Respir Crit Care Med* **197**, 933-943.

[33] Liguori C, Mercuri NB, Izzi F, Romigi A, Cordella A, Sancesario G, Placidi F (2017) Obstructive sleep apnea is associated with early but possibly modifiable Alzheimer's disease biomarkers changes. *Sleep* **40**, zsx011.

[34] Kushida CA, Nichols DA, Holmes TH, Quan SF, Walsh JK, Gottlieb DJ, Simon RDJ, Guilleminault C, White DP, Goodwin JL, Schweitzer PK, Leary EB, Hyde PR, Hirshkowitz M, Green S, McEvoy LK, Chan C, Gevins A, Kay GG, Bloch DA, Crabtree T, Dement WC (2012) Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* **35**, 1593-1602.

[35] Ancoli-Israel S, Plamer BW, Cooke JR, Corey-Bloom J, Fiorentino L, Natarajan L, Liu L, Ayalon L, He F, Loredo JS (2008) Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: A randomized controlled study. *J Am Geriatr Soc* **56**, 2076-2081.

[36] Cooke JR, Ayalon L, Plamer BW, Loredo JS, Corey-Bloom J, Natarajan L, Liu L, Ancoli-Israel S (2009) Sustained use of CPAP slows deterioration of cognition, sleep, and mood in patients with Alzheimer's disease and obstructive sleep apnea: A preliminary study. *J Clin Sleep Med* **5**, 305-309.

[37] Troussiere AC, Charley CM, Salleron J, Richard F, Delbeuck X, Derambure P, Pasquier F, Bombois S (2014) Treatment of sleep apnoea syndrome decreases cognitive decline in patients with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **85**, 1405-1408.

[38] Bliwise DL (1993) Sleep in normal aging and dementia. *Sleep* **16**, 40-81.

[39] Young T (1996) Sleep-disordered breathing in older adults: Is it a condition distinct from that in middle-aged adults? *Sleep* **19**, 529-530.

[40] Duran J, Esnaola S, Rubio R, Iztueta A (2001) Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* **163**, 685-689.

[41] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* **328**, 1230-1235.

[42] Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM (2002) Predictors of sleep-disordered breathing in community-dwelling adults: The Sleep Heart Health Study. *Arch Intern Med* **162**, 893-900.

[43] Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A (2001) Prevalence of sleep-disordered breathing in women: Effects of gender. *Am J Respir Crit Care Med* **163**, 608-613.

[44] Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, Vollenweider P, Tafti M, Haba-Rubio J (2015) Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study. *Lancet Respir Med* **3**, 310-318.

[45] Launois SH, Pepin JL, Levy P (2007) Sleep apnea in the elderly: A specific entity? *Sleep Med Rev* **11**, 87-97.

[46] White DP, Lombard RM, Cadieux RJ, Zwillich CW (1985) Pharyngeal resistance in normal humans: Influence of gender, age, and obesity. *J Appl Physiol (1985)* **58**, 365-371.

[47] Martin SE, Mathur R, Marshall I, Douglas NJ (1997) The effect of age, sex, obesity and posture on upper airway size. *Eur Respir J* **10**, 2087-2090.

[48] Malhotra A, Huang Y, Foghel R, Lazic S, Pilar G, Jakab M, Kikinis R, White DP (2006) Aging influences on pharyngeal anatomy and physiology: The predisposition to pharyngeal collapse. *Am J Med* **119**, 72.e9-72.14.

[49] Worsnop C, Kay A, Kim Y, Trinder J, Pierce R (2000) Effect of age on sleep onset-related changes in respiratory pump and upper airway muscle function. *J Appl Physiol (1985)* **88**, 1831-1839.

[50] Hudgel DW, Devadatta P, Hamilton H (1993) Pattern of breathing and upper airway mechanics during wakefulness and sleep in healthy elderly humans. *J Appl Physiol (1985)* **74**, 2198-2204.

[51] Burger CD, Stanson AW, Sheedy PF, Daniels BK, Shepard JWJ (1992) Fast-computed tomography evaluation of age-related changes in upper airway structure and function in normal men. *Am Rev Respir Dis* **145**, 846-852.

[52] Mayer P, Pepin JL, Bettega G, Veale D, Ferretti G, Deschaux C, Levy P (1996) Relationship between body mass index, age and upper airway measurements in snorers and sleep apnoea patients. *Eur Respir J* **9**, 1801-1809.

[53] Fogel RB, White DP, Pierce RJ, Malhotra A, Edwards JK, Dunai J, Kleverlaan D, Trinder J (2003) Control of upper airway muscle activity in younger versus older men during sleep onset. *J Physiol* **553**, 533-544.

[54] Varga AW, Ducca EL, Kishi A, Fischer E, Parekh A, Koushyk V, Yau PL, Gumb T, Leibert DP, Wholleber ME, Burschtin OE, Convit A, Rapoport DM, Osorio RS, Ayappa I (2016) Effects of aging on slow wave sleep dynamics and human spatial navigational memory consolidation. *Neurobiol Aging* **42**, 142-149.

[55] Enright PL, Newman AB, Whal PW, Manolio TA, Haponik EF, Boyle PJR (1996) Prevalence and correlates of snoring and observed apneas in 5,201 older adults. *Sleep* **19**, 531-538.

[56] Bliwise DL, Bliwise NG, Partinen M, Pursley AM, Dement WC (1988) Sleep apnea and mortality in an aged cohort. *Am J Public Health* **78**, 544-547.

[57] Ancoli-Israel S, Klauber MR, Kripke DF, Parker L, Cobarrubias M (1989) Sleep apnea in female patients in a nursing home. Increased risk of mortality. *Chest* **96**, 1054-1058.

[58] Lavie P, Lavie L, Herer P (2005) All-cause mortality in males with sleep apnoea syndrome: Declining mortality rates with age. *Eur Respir J* **25**, 514-520.

[59] Gooneratne NS, Richards KC, Joffe M, Lam RW, Pack F, Staley B, Dinges DF, Pack AI (2010) Sleep disordered breathing with excessive daytime sleepiness is a risk factor for mortality in older adults. *Sleep* **34**, 435-442.

[60] Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM (2009) Sleep-disordered breathing and mortality: A prospective cohort study. *PLoS Med* **6**, e1000132.

[61] Ancoli-Israel S, Kripke DF, Klauber MR, Fell R, Stepnowsky C, Estline E, Khazeni N, Chinn A (1996) Morbidity, mortality and sleep-disordered breathing in community dwelling elderly. *Sleep* **19**, 277-282.

[62] Mant A, King M, Saunders NA, Pond CD, Goode E, Hewitt H (1995) Four-year follow-up of mortality and sleep-related respiratory disturbance in non-demented seniors. *Sleep* **18**, 433-438.

[63] Phillips BA, Berry DTR, Lipke-Molby TC (1994) Sleep-disordered breathing in healthy, aged persons. *Chest* **110**, 654-658.

[64] Lavie L, Lavie P (2006) Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. *Med Hypotheses* **66**, 1069-1073.

[65] Haas DC, Foster GL, Nieto FJ, Redline S, Resnick HE, Robbins JA, Young T, Pickering TG (2005) Age-dependent associations between sleep-disordered breathing and hypertension: Importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. *Circulation* **111**, 614-621.

[66] Janssen I (2007) Morbidity and mortality risk associated with an overweight BMI in older men and women. *Obesity* **15**, 1827-1840.

[67] Bliwise DL (2015) Never too old: Beneficial neurobehavioural effects of continuous positive airway pressure in the elderly. *Eur Respir J* **46**, 13-5.

[68] Ancoli-Israel S (2007) Sleep apnea in older adults - is it real and should age be the determining factor in the treatment decision matrix? *Sleep Med Rev* **11**, 83-85.

[69] Bonnet MH (2005) Acute sleep deprivation A2. In *Principles and Practice of Sleep Medicine (Fourth Edition)*, Kryger MH, Roth T, Dement WC, eds. W.B. Saunders, pp. 51-66.

[70] Ellenbogen JM, Payne JD, Stickgold R (2006) The role of sleep in declarative memory consolidation: Passive, permissive, active or none? *Curr Opin Neurobiol* **16,** 716-722

[71] Roman V, Van der Borght K, Leemburg SA, Van der Zee EA, Meerlo P (2005) Sleep restriction by forced activity reduces hippocampal cell proliferation. *Brain Res* **1065**, 53-59.

[72] Arrigoni E, Lu J, Vetrivelan R, Saper CB (2009) Long-term synaptic plasticity is impaired in rats with lesions of the ventrolateral preoptic nucleus. *Eur J Neurosci* **30**, 2112-2120.

[73] Tartar JL, Ward CP, McKenna JT, Thakkar M, Arrigoni E, McCarley RW, Brown RE, Strecker RE (2006) Hippocampal synaptic plasticity and spatial learning are impaired in a rat model of sleep fragmentation. *Eur J Neurosci* **23**, 2739-2748.

[74] Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, Huang T, Brown KM, Li XY, Descalzi G, Kim SS, Chen T, Shang YZ, Zhou M, Houslay MD, Abel T (2009) Sleep deprivation impairs cAMP signalling in the hippocampus. *Nature* **461**, 1122-1125.

[75] Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Ensrud KE, Stefanick ML, Laffan A, Stone KL (2011) Association of sleep characteristics and cognition in older community-dwelling men: The MrOS Sleep Study. *Sleep* **34**, 1347-1356.

[76] Blackwell T, Yaffe K, Ancoli-Israel S, Schneider JL, Cauley JA, Hiller TA, Fink HA, Stone KL (2006) Poor sleep is associated with impaired cognitive function in older women: The study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci* **61**, 405-410.

[77] Ju YE, McLeland JS, Toedebusch CD, Xiong C, Fagan AM, Duntley SP, Morris JC, Holtzman DM (2013) Sleep quality and preclinical Alzheimer disease. *JAMA Neurol* **70**, 587-593.

[78] Sprecher KE, Koscik RL, Carlsson CM, Zetterberg H, Blennow K, Okonkwo OC, Sager MA, Asthana S, Johnson SC, Benca RM, Bendlin BB (2017) Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. *Neurology* **89**, 445-453.

[79] Lim ASP, Kowgier M, Yu L, Buchman AS, Bennett DA (2013) Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep* **36**, 1027-1032.

[80] Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard (2013) Sleep drives metabolite clearance from the adult brain. *Science* **342**. 10.1126/science.1241224

[81] Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, Fujiki N, Nishino S, Holtzman DM (2009) Amyloid-β dynamics are regulated by orexin and the sleep-wake cycle. *Science* **326**, 1005-1007.

[82] Lucey BP, Hicks TJ, McLeland JS, Toedebusch CD, Boyd J, Elbert DL, Patterson BW, Baty J, Morris JC, Ovod V, Mawuenyega KG, Bateman RJ (2017) Effect of sleep on overnight CSF amyloid-β kinetics. *Ann Neurol* **83**, 197-204.

[83] Diekelmann S, Born J (2010) The memory function of sleep. *Nat Rev Neurosci* **11**, 114-126.

[84] Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C (2002) Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. *J Neurosci* **22**, 10914-10923.

[85] Llewellyn S, Hobson JA (2015) Not only... but also: REM sleep creates and NREM Stage 2 instantiates landmark junctions in cortical memory networks. *Neurobiol Learn Mem* **122**, 69-87.

[86] Boyce R, Glasgow SD, Williams S, Adamantidis A (2016) Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science* **352**, 812-816.

[87] McSharry DG, Saboisky JP, DeYoung P, Jordan AS, Trinder J, Smales E, Hess L, Chamberlin NL,

Malhotra A (2013) Physiological mechanisms of upper airway hypotonia during REM sleep. *Sleep* **37**, 561-569.

[88] Findley LJ, Wilhoit SC, Suratt PM (1985) Apnea duration and hypoxemia during REM sleep in patients with obstructive sleep apnea. *Chest* **87**, 432-436.

[89] Mokhlesi B, Varga AW (2017) Obstructive sleep apnea and cardiovascular disease: REM sleep matters! *Am J Respir Crit Care Med* **197**, 554-556.

[90] Haba-Rubio J, Marti-Soler H, Tobback N, Andries D, Marques-Vidal P, Waeber G, Vollenweider P, von Gunten A, Preisig M, Castelao E, Tafti M, Heinzer R, Popp J (2017) Sleep characteristics and cognitive impairment in the general population: The HypnoLaus study. *Neurology* **88**, 463-469.

[91] Song Y, Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Stone KL (2015) Relationships between sleep stages and changes in cognitive function in older men: The MrOS Sleep Study. *Sleep* **38**, 411-421.

[92] Varga AW, Kishi A, Mantua J, Lim J, Koushyk V, Leibert DP, Osorio RS, Rapoport DM, Ayappa I (2014) Apnea-induced rapid eye movement sleep disruption impairs human spatial navigational memory. *J Neurosci* **34**, 14571-14577.

[93] Montplaisir J, Petit D, Lorrain D, Gauthier S, Nielsen T (1995) Sleep in Alzheimer's disease: Further considerations on the role of brainstem and forebrain cholinergic populations in sleep-wake mechanisms. *Sleep* **18**, 145-148.

[94] Reynolds CF, Kupfer DJ, Houck PR, Hoch CC, Stack JA, Berman SR, Zimmer B (1988) Reliable discrimination of elderly depressed and demented patients by electroencephalographic sleep data. *Arch Gen Psychiatry* **45**, 258-264.

[95] Rauchs G, Schabus M, Parapatics S, Bertran F, Clochon P, Hot P, Denise P, Desgranges B, Eustache F, Gruber G, Anderer P (2008) Is there a link between sleep changes and memory in Alzheimer's disease? *Neuroreport* **19**, 1159-1162.

[96] Pase MP, Himali JJ, Grima NA, Beiser AS, Satizabal CL, Aparicio HJ, Thomas RJ, Gottlieb DJ, Auerbach SH, Seshadri S (2017) Sleep architecture and the risk of incident dementia in the community. *Neurology* **89**, 1244-1250.

[97] Yaffe K, Falvey CM, Hoang T (2014) Connections between sleep and cognition in older adults. *Lancet Neurol* **13**, 1017-1028.

[98] Brayet P, Petit D, Frauscher B, Gagnon JF, Gosselin N, Gagnon K, Rouleau I, Montplaisir J (2016) Quantitative EEG of rapid-eye-movement sleep: A marker of amnestic mild cognitive impairment. *Clin EEG Neurosci* **47**, 134-141.

[99] Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, Catcheside PG (2009) Marked reduction in obstructive sleep apnea severity in slow wave sleep. *J Clin Sleep Med* **5**, 519-524.

[100] Berry RB, Asyali MA, McNellis MI, Khoo MC (1998) Within-night variation in respiratory effort preceding apnea termination and EEG delta power in sleep apnea. *J Appl Physiol (1985)* **85**, 1434-1441.

[101] Berry RB, Bonnet MH, Light RW (1992) Effect of ethanol on the arousal response to airway occlusion during sleep in normal subjects. *Am Rev Respir Dis* **145**, 445-452.

[102] Ratnavadivel R, Stadler D, Windler S, Bradley J, Paul D, McEvoy RD, Catcheside PG (2010) Upper airway function and arousability to ventilatory challenge in slow wave versus stage 2 sleep in obstructive sleep apnoea. *Thorax* **65**, 107.

[103] Kam K, Castillo B, Chua N, Sanders H, Rapoport DM, Ayappa I, Osorio RS, Varga AW (2017) Role of intermittent hypoxia and sleep fragmentation from OSA during slow wave sleep on spatial memory. *Sleep* **40**, A98-A98.

[104] Guilleminault C, Do Kim Y, Chowdhuri S, Horita M, Ohayon M, Kushida C (2001) Sleep and daytime sleepiness in upper airway resistance syndrome compared to obstructive sleep apnoea syndrome. *Eur Respir J* **17**, 838-847.

[105] Ondze B, Espa F, Dauvilliers Y, Billiard M, Besset A (2003) Sleep architecture, slow wave activity and sleep spindles in mild sleep disordered breathing. *Clin Neurophysiol* **114**, 867-874.

[106] Brillante R, Cossa G, Liu PY, Laks L (2012) Rapid eye movement and slow-wave sleep rebound after one night of continuous positive airway pressure for obstructive sleep apnoea. *Respirol Carlton Vic* **17**, 547-553.

[107] Marshall L, Helgadottir H, Molle M, Born J (2006) Boosting slow oscillations during sleep potentiates memory. *Nature* **444**, 610-613.

[108] Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. *Nature* **430**, 78-81.

[109] Landsness EC, Crupi D, Hulse BK, Peterson MJ, Huber R, Ansari H, Coen M, Cirelli C, Benca RM, Ghilardi MF, Tononi G (2009) Sleep-dependent improvement in visuomotor learning: A causal role for slow waves. *Sleep* **32**, 1273-1284.

[110] Maquet P, Dive D, Salmon E, Sadzot B, Franco G, Poirrier R, von Frenckell R, Franck G (1990) Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose method. *Brain Res* **513**, 136-143.

[111] Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, Schoepp DD, Paul SM, Mennerick S, Holtzman DM (2005) Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. *Neuron* **48**, 913-922.

[112] Cheng X, Wu J, Geng M, Xiong J (2014) Role of synaptic activity in the regulation of amyloid beta levels in Alzheimer's disease. *Neurobiol Aging* **35**, 1217-1232.

[113] Yamada K, Holth JK, Liao F, Stewart FR, Mahan TE, Jiang H, Cirrito JR, Patel TK, Hochgrafe K, Mandelkow EM, Holtzman DM (2014) Neuronal activity regulates extracellular tau in vivo. *J Exp Med* **211**, 387-393.

[114] Varga AW, Wohlleber ME, Gimenez S, Romero S, Alonso JF, Ducca EL, Kam K, Lewis C, Tanzi EB, Tweardy S, Kishi A, Parek A, Fisher E, Gumb T, Alcolea D, Fortea J, Lléo A, Blennow K, Zetterberg H, Mosconi L, Glodzik L, Pirraglia E, Burschitin OE, de Leon MJ, Rapoport DM, Lu SE, Ayappa I, Osorio RS (2016) Reduced slow-wave sleep is associated with high cerebrospinal fluid Abeta42 levels in cognitively normal elderly. *Sleep* **39**, 2041-2048.

[115] Ju YS, Ooms SJ, Sutphen C, Macauley SL, Zangrilli MA, Jerome G, Fagan AM, Mignot E, Zempel JM, Claassen JAHR, Holtzman DM (2017) Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain* **140**, 2104-2111.

[116] Foster GD, Sanders MH, Millman R, Zammit G, Borradaile KE, Newman AB, Wadden TA, Kelley D, Wing RR, Sunyer FX, Darcey V, Kuna ST (2009) Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care* **32**, 1017-1019.

[117] Resnick HE, Redline S, Shahar E, Glipin A, Newman A, Walter R, Ewy GA, Howard BV, Punjabi NM (2003) Diabetes and sleep disturbances: Findings from the Sleep Heart Health Study. *Diabetes Care* **26**, 702-709.

[118] Moon K, Punjabi NM, Aurora RN (2015) Obstructive sleep apnea and type 2 diabetes in older adults. *Clin Geriatr Med* **31**, 139-147, ix.

[119] Chou YT, Chuang LP, Li HY, Lin SW, Yang CT, Chen NH (2010) Hyperlipidaemia in patients with sleep-related breathing disorders: Prevalence & risk factors. *Indian J Med Res* **131**, 121-125.

[120] Hla KM, Young T, Finn L, Peppard PE, Szklo-Coxe M, Stubbs M (2008) Longitudinal association of sleep-disordered breathing and nondipping of nocturnal blood pressure in the Wisconsin Sleep Cohort Study. *Sleep* **31**, 795-800.

[121] Fung MM, Peters K, Redline S, Ziegler MG, Ancoli-Israel S, Barrett-Connor E, Stone KL (2011) Decreased slow wave sleep increases risk of developing hypertension in elderly men. *Hypertension* **58**, 596-603.

[122] O'Connor GT, Caffo B, Newman AB, Quan SF, Rapoport DM, Redline S, Resnick HE, Samet J, Shahar E (2009) Prospective study of sleep-disordered breathing and hypertension: The Sleep Heart Health Study. *Am J Respir Crit Care Med* **179**, 1159-1164.

[123] Peppard PE, Young T, Palta M, Skatrud J (2000) Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* **342**, 1378-1384.

[124] Bazzano LA, Khan Z, Reynolds K, He J (2007) Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension* **50**, 417-423.

[125] Haentjens P, Van Meerhaeghe A, Moscariello A, De Weerdt S, Poppe K, Dupont A, Velkeniers B (2007) The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: Evidence from a meta-analysis of placebo-controlled randomized trials. *Arch Intern Med* **167**, 757-764.

[126] Montesi SB, Edwards BA, Malhotra A, Bakker JP (2012) The effect of continuous positive airway pressure treatment on blood pressure: A systematic review and meta-analysis of randomized controlled trials. *J Clin Sleep Med* **8**, 587-596.

[127] Noda A, Okada T, Yasuma F, Nakashima N, Yokota M (1995) Cardiac hypertrophy in obstructive sleep apnea syndrome. *Chest* **107**, 1538-1544.

[128] Yumino D, Tsurumi Y, Takagi A, Suzuki K, Kasanuki H (2007) Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. *Am J Cardiol* **99**, 26-30.

[129] Arias MA, Garcia-Rio F, Alonso-Fernandez A, Mediano O, Martinez I, Villamor J (2005) Obstructive sleep apnea syndrome affects left ventricular diastolic function: Effects of nasal continuous positive airway pressure in men. *Circulation* **112**, 375-383.

[130] Arias MA, Baranchuk A (2013) Atrial fibrillation and obstructive sleep apnea: Something more than a coincidence. *Rev Esp Cardiol Engl Ed* **66**, 529-531.

[131] Hersi AS (2010) Obstructive sleep apnea and cardiac arrhythmias. *Ann Thorac Med* **5**, 10-17.

[132] Marin JM, Carrizo SJ, Vicente E, Agusti AGN (2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. *Lancet* **365**, 1046-1053.

[133] Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK (2010) Interactions between obesity and obstructive sleep apnea: Implications for treatment. *Chest* **137**, 711-719.

[134] Johnson KG, Johnson DC (2010) Frequency of sleep apnea in stroke and TIA patients: A meta-analysis. *J Clin Sleep Med* **6**, 131-137.

[135] Somers VK, Dyken ME, Clary MP, Abboud FM (1995) Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* **96**, 1897-1904.

[136] Somers VK, Mark AL, Zavala DC, Abboud FM (1989) Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. *J Appl Physiol (1985)* **67**, 2101-2106.

[137] Lavie L (2003) Obstructive sleep apnoea syndrome–an oxidative stress disorder. *Sleep Med Rev* **7**, 35-51.

[138] Dyugovskaya L, Lavie P, Lavie L (2002) Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med* **165**, 934-939.

[139] Rubinstein I (1995) Nasal inflammation in patients with obstructive sleep apnea. *Laryngoscope* **105**, 175-177.

[140] Yamauchi M, Tamaki S, Tomoda K, Yoshikawa M, Fukuoka A, Makinodan K, Koyama N, Suzuki T, Kimura H (2006) Evidence for activation of nuclear factor kappaB in obstructive sleep apnea. *Sleep Breath* **10**, 189-193.

[141] Rangemark C, Hedner JA, Carlson JT, Gleerup G, Winther K (1995) Platelet function and fibrinolytic activity in hypertensive and normotensive sleep apnea patients. *Sleep* **18**, 188-194.

[142] von Kanel R, Dimsdale JE (2003) Hemostatic alterations in patients with obstructive sleep apnea and the implications for cardiovascular disease. *Chest* **124**, 1956-1967.

[143] Pallayova M, Donic V, Gresova S, Peregrim I, Tomori Z (2010) Do differences in sleep architecture exist between persons with type 2 diabetes and nondiabetic controls? *J Diabetes Sci Technol* **4**, 344-352.

[144] Tasali E, Leproult R, Ehrmann DA, Van Cauter E (2008) Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci U S A* **105**, 1044-1049.

[145] Rao MN, Blackwell T, Redline S, Stefanick ML, Ancoli-Israel S, Stone KL (2009) Association between sleep architecture and measures of body composition. *Sleep* **32**, 483-490.

[146] Barba R, Martinez-Espinosa S, Rodriguez-Garcia E, Pondal M, Vivancos J, Del Ser T (2000) Poststroke dementia: Clinical features and risk factors. *Stroke* **31**, 1494-1501.

[147] DeCarli C (2003) The role of cerebrovascular disease in dementia. *Neurologist* **9**, 123-136.

[148] de Bruijn RF, Ikram MA (2014) Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med* **12**, 130.

[149] de la Torre JC (2012) Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovasc Psychiatry Neurol* **2012**, 367516.

[150] Goldberg I, Auriel E, Russell D, Korczyn AD (2012) Microembolism, silent brain infarcts and dementia. *J Neurol Sci* **322**, 250-253.

[151] Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR (1997) Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA* **277**, 813-817.

[152] Jellinger KA (2002) Alzheimer disease and cerebrovascular pathology: An update. *J Neural Transm* **109**, 813-836.

[153] Dolan H, Crain B, Troncoso J, Resnick SM, Zonderman AB, Obrien RJ (2010) Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of Aging cohort. *Ann Neurol* **68**, 231-240.

[154] Garcia-Alloza M, Gregory J, Kuchibhotla KV, Fine S, Wei Y, Ayata C, Frosch MP, Greenberg SM, Bacskai BJ (2011) Cerebrovascular lesions induce transient beta-amyloid deposition. *Brain* **134**, 3697-3707.

[155] Iadecola C (2013) The pathobiology of vascular dementia. *Neuron* **80**, 844-866.

[156] Launer LJ, Petrovitch H, Ross GW, Markesbery W, White LR (2008) AD brain pathology: Vascular origins? Results from the HAAS autopsy study. *Neurobiol Aging* **29**, 1587-1590.

[157] den Heijer T, Launer LJ, Prins ND, van Dijk EJ, Vermeer SE, Hofman A, Koudstaal PJ, Breteler MM (2005) Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* **64**, 263-267.

[158] Petrovitch H, White LR, Izmirillian G, Rose GW, Havlik RJ, Markesbery W, Nelson J, Davis DG, Hardman J, Foley DJ, Launer LJ (2000) Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: The HAAS. Honolulu-Asia aging Study. *Neurobiol Aging* **21**, 57-62.

[159] Xu W, Qiu C, Winblad B, Fratiglioni L (2007) The effect of borderline diabetes on the risk of dementia and Alzheimer's disease. *Diabetes* **56**, 211-216.

[160] Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P (2006) Risk of dementia in diabetes mellitus: A systematic review. *Lancet Neurol* **5**, 64-74.

[161] Helzner EP, Luchsinger JA, Scarmeas N, Consentino S, Brickman AM, Glymour MM, Stem Y (2009) Contribution of vascular risk factors to disease progression in Alzheimer's Disease. *Arch Neurol* **66**, 343-348.

[162] Jellinger KA (2007) The enigma of vascular cognitive disorder and vascular dementia. *Acta Neuropathol (Berl)* **113**, 349-388.

[163] Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L (2011) Midlife overweight and obesity increase late-life dementia risk: A population-based twin study. *Neurology* **76**, 1568-1574.

[164] Shan X, Chi L, Ke Y, Luo C, Qian S, Gozal D, Liu R (2007) Manganese superoxide dismutase protects mouse cortical neurons from chronic intermittent hypoxia-mediated oxidative damage. *Neurobiol Dis* **28**, 206-215.

[165] Simiakakis M, Kapsimalis F, Chaligiannis E, Loukides S, Sitaras N, Alchanatis W (2012) Lack of effect of sleep apnea on oxidative stress in obstructive sleep apnea syndrome (OSAS) patients. *PloS One* **7**, e39172.

[166] Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ (2002) Increased 8-isoprostane and interleukin-6 in breath condensate of obstructive sleep apnea patients. *Chest* **122**, 1162-1167.

[167] Li RC, Row BW, Kheirandish L, Brittian KR, Gozal E, Guo SZ, Sachleben LR, Gozal D (2004) Nitric oxide synthase and intermittent hypoxia-induced spatial learning deficits in the rat. *Neurobiol Dis* **17**, 44-53.

[168] Row BW, Liu R, Xu W, Kheirandish L, Gozal D (2003) Intermittent hypoxia is associated with oxidative stress and spatial learning deficits in the rat. *Am J Respir Crit Care Med* **167**, 1548-1553.

[169] Xu W, Chi L, Row BW, Xu R, Ke Y, Xu B, Luo C, Kheirandish L, Gozal D, Liu R (2004) Increased oxidative stress is associated with chronic intermittent hypoxia-mediated brain cortical neuronal cell apoptosis in a mouse model of sleep apnea. *Neuroscience* **126**, 313-323.

[170] Baril AA, Gagnon K, Brayet P, Montplaisir J, De Beaumont L, Carrier J, Lafond C, L'Heureux F, Gagnon JF, Gosselin N (2017) Gray matter hypertrophy and thickening with obstructive sleep apnea in middle-aged and older adults. *Am J Respir Crit Care Med* **195**, 1509-1518.

[171] Kallenberg K, Bailey DM, Christ S, Mohr A, Roukens R, Menold E, Steiner T, Bartsch P, Knauth M (2007) Magnetic resonance imaging evidence of cytotoxic cerebral edema in acute mountain sickness. *J Cereb Blood Flow Metab* **27**, 1064-1071.

[172] Aviles-Reyes RX, Angelo MF, Villarreal A, Rios H, Lazarowski A, Ramos AJ (2010) Intermittent hypoxia during sleep induces reactive gliosis and limited neuronal death in rats: Implications for sleep apnea. *J Neurochem* **112**, 854-869.

[173] Ng KM, Lau CF, Fung ML (2010) Melatonin reduces hippocampal beta-amyloid generation in rats exposed to chronic intermittent hypoxia. *Brain Res* **1354**, 163-171.

[174] Randall J, Mortberg E, Provuncher GK, Fournier DR, Duffy DC, Rubertsson S, Blennow K, Zetterberg H, Wilson DH (2013) Tau proteins in serum predict neurological outcome after hypoxic brain injury from cardiac arrest: Results of a pilot study. *Resuscitation* **84**, 351-356.

[175] Glodzik L, Rusinek H, Pirraglia E, McHugh P, Tsui W, Williams S, Cummings M, Li Y, Rich K, Randall C, Mosconi L, Osorio R, Murray J, Zetterberg H, Blennow K, de Leon M (2014) Blood pressure decrease correlates with tau pathology and memory decline in hypertensive elderly. *Neurobiol Aging* **35**, 64-71.

[176] Konecny T, Khanna AD, Novak J, Jama AA, Zawadowski GM, Orban M, Pressman G, Bukartuk J, Kara T, Cetta F, Borlaug BA, Somers VK, Reeder GS (2014) Interatrial pressure gradients during simulated obstructive sleep apnea: A catheter-based study. *Catheter Cardiovasc Interv* **84**, 1138-1145.

[177] Wszedybyl-Winklewska M, Wolf J, Swierblewska E, Kunicka K, Mazur K, Gruszecki M, Winklewski PJ, Frydrychowski AF, Bieniaszewski L, Narkiewicz K (2017) Increased inspiratory resistance affects the dynamic relationship between blood pressure changes and subarachnoid space width oscillations. *PLoS One* **12**, e0179503.

[178] Ju YE, Finn MB, Sutphen CL, Herries EM, Jerome GM, Ladenson JH, Crimminis DL, Fagan AM, Holtzman (2016) DM Obstructive sleep apnea decreases central nervous system-derived proteins in the cerebrospinal fluid. *Ann Neurol* **80**, 154-159.

[179] Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K (2015) A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med* **212**, 991.

[180] O'Donoghue FJ, Briellmann RS, Rochford PD, Abbott DF, Pell GS, Chan CH, Tarquinio N, Jackson GD, Pierce RJ (2005) Cerebral structural changes in severe obstructive sleep apnea. *Am J Respir Crit Care Med* **171,** 1185-1190.

[181] Isono S, Remmers JE, Tanaka A, Sho Y, Sato J, Nishino T (1997) Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. *J Appl Physiol (1985)* **82**, 1319-1326.

[182] Patil SP, Schneider H, Marx JJ, Gladmon E, Schwartz AR, Smith PL (2007) Neuromechanical control of upper airway patency during sleep. *J Appl Physiol (1985)* **102**, 547-556.

[183] Buchman AS, Bennett DA (2011) Loss of motor function in preclinical Alzheimer's disease. *Expert Rev Neurother* **11**, 665-676.

[184] Peppard PE, Hagen EW (2018) The last 25 years of obstructive sleep apnea epidemiology-and the next 25? *Am J Respir Crit Care Med* **197**, 310-312.