Sleep Medicine Reviews 55 (2021) 101375

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

THEORETICAL REVIEW

Sleep-disordered breathing and the risk of Alzheimer's disease

Claudio Liguori [a, b, *], Michelangelo Maestri [c], Matteo Spanetta [a], Fabio Placidi [a, b], Enrica Bonanni [c], Nicola B. Mercuri [b, d], Biancamaria Guarnieri [e, f]

[a] Sleep Medicine Centre, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[b] Neurology Unit, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[c] Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy
[d] Santa Lucia Foundation, Rome, Italy
[e] Center of Sleep Medicine, Department of Neurology, Villa Serena Hospital, Città S. Angelo, Pescara, Italy
[f] Villa Serena Foundation for the Research, Città S. Angelo, Pescara, Italy

ARTICLE INFO

Article history:
Received 2 January 2020
Received in revised form
28 May 2020
Accepted 28 May 2020
Available online 6 September 2020

Keywords:
Sleep
Alzheimer's disease
CPAP
OSA
Sleep-disordered breathing
Cognitive impairment
Neuropsychological function
Brain MRI
Nuclear medicine imaging
Biofluid

SUMMARY

Sleep-disordered breathing is highly prevalent in the elderly population. Obstructive sleep apnea (OSA) represents the most common sleep disorder among the adult and elderly population. Recently, OSA diagnosis has been associated with an increased risk of developing cognitive decline and dementia, including vascular dementia and Alzheimer's disease (AD). Subsequently, there have been studies on AD biomarkers investigating cerebrospinal fluid, blood, neuroimaging, and nuclear medicine biomarkers in patients with OSA. Furthermore, studies have attempted to assess the possible effects of continuous positive airway pressure (CPAP) treatment on the cognitive trajectory and AD biomarkers in patients with OSA. This review summarizes the findings of studies on each AD biomarker (cognitive, biofluid, neuroimaging, and nuclear medicine imaging) in patients with OSA, also accounting for the related effects of CPAP treatment. In addition, the hypothetical model connecting OSA to AD in a bi-directional interplay is analyzed. Finally, the sex-based differences in prevalence and clinical symptoms of OSA between men and women have been investigated in relation to AD risk. Further studies investigating AD biomarkers changes in patients with OSA and the effect of CPAP treatment should be auspicated in future for identifying strategies to prevent the development of AD.

Background

Sleep-disordered breathing (SDB) groups disorders characterized by abnormalities of breathing during sleep (and in some cases also during wakefulness). Obstructive sleep apnea (OSA), the most frequent SDB, is a highly prevalent sleep disorder. It is characterized by obstruction of the upper airways during sleep, causing intermittent hypoxia (IH), sleep fragmentation, and daytime sleepiness. OSA can significantly affect physical and mental health via several mechanisms, such as endothelial dysfunction, oxidative stress, systemic inflammation, glucose dyshomeostasis, hypertension, and brain and white matter (WM) pathological changes [1,2]. The overall estimated prevalence of OSA has not yet been identified, but large studies (performed ≈20 years ago) suggest a prevalence of 2–4% in the general population, with an increased rate in older people [3–5]. Studies on the prevalence of OSA have been performed across continents and provide different prevalence ranges [6]. A very recent review tried to define the prevalence of OSA according to the results of several studies. It concluded that the prevalence of OSA in the general adult population can range from 9% to 38%; in men it varied from 13% to 33% and in women it varied from 6% to 19%. Notably, in advanced age groups, the prevalence can be as high as 84%, and as high as 90% in men [7]. However, the methodological heterogeneity of studies (different OSA definition and inclusion/exclusion criteria) and the difficulty to diagnose "asymptomatic" people hamper the possibility of achieving an undisputed prevalence of OSA. Owing to this gap in the scientific literature, a population-based study recently reported a prevalence of moderate-to-severe SDB (≥15 apnea-hypopnea events per hour) as 23.4% in women and 49.7% in men [8]. This study, named HypnoLaus, included a cohort of subjects recruited between 2003 and 2006 and composed by 6733 people aged 35–75 years, randomly

* Corresponding author. Sleep Medicine Centre, Department of Systems Medicine, University of Rome "Tor Vergata", Viale Oxford 81, 00133, Rome, Italy. Fax: +390620902116.
E-mail address: dott.claudioliguori@yahoo.it (C. Liguori).

https://doi.org/10.1016/j.smrv.2020.101375
1087-0792/

Abbreviation list

AASM	American Academy of Sleep Medicine
Aβ	β-amyloid
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
AHI	Apnea-Hypopnea Index
APP	amyloid precursor protein
ApoE4	apolipoprotein E (ApoE) epsilon 4
BQ	Berlin questionnaire
CN	cognitively normal
CPAP	continuous positive airway pressure
CSF	cerebrospinal fluid
EDS	excessive daytime sleepiness
ESS	epworth sleepiness scale
FA	functional anisotropy
GMV	gray matter volume
IH	intermittent hypoxia
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
ODI	oxygen desaturation index
OSA	Obstructive sleep apnea
PSG	polysomnography
REM	rapid eye movement
SCI	subjective cognitive impairment
SDB	Sleep-disordered breathing
SWS	slow-wave sleep
VBM	voxel-based morphometry
WM	white matter

selected from the population of Lausanne in Switzerland. All subjects performed a polysomnography (PSG) to investigate the presence of SDB, detected by using the more liberal 2012 American Academy of Sleep Medicine (AASM) criteria for defining apnea and hypopnea events [9].

In this review we focus on SDB, considering that OSA represent the most frequent SDB in the adult and elderly populations, since there is increasing attention on the diagnosis and management of OSA in these populations. In the HypnoLaus study, the recruited population was divided into two age categories; specifically, < 60 and ≥ 60 years old. There was a significant increase in the prevalence of moderate-to-severe OSA among older participants compared with the younger age group [8]. Moreover, a longitudinal study on cognitively normal (CN) participants that investigated cerebrospinal fluid (CSF) biomarkers reported that the prevalence of mild and moderate-severe OSA was 36.53% and 16.82%, respectively, in participants aged from 55 to 90 years [10]. This prevalence of OSA is higher than the one reported in the previous studies [3–6] and reflects the more recent epidemiological data [8].

The increasing attention to OSA diagnosis and treatment could also be attributed to the reported cardiovascular, neurocognitive, and metabolic negative effects of OSA, which subsequently have significant health consequences [11]. OSA has been reported to be independently associated with several disorders, including hypertension, diabetes, metabolic syndrome, osteoporosis, and cardiovascular diseases [12–16]. IH and hypercapnia, nocturnal arousals and sleep fragmentation, and increased inflammation and oxidative stress concomitantly contribute to the detrimental effects of OSA [11].

OSA has been recently recognized as a risk factor for cognitive impairment and Alzheimer's disease (AD) [17]. However, the mechanisms underlying OSA-induced AD neuropathological changes remain unclear. Sleep impairment has been identified as a potential risk factor for AD [18] and there has been an increase of studies about the effects of sleep on amyloidopathy biomarkers in the aging population. Since it has been very recently documented that sleep alteration may be also associated with tau pathology, and considering that the spreading of tau aggregation drives the transition from normal cognition to mild cognitive impairment (MCI) and early AD, sleep impairment has been identified as a putative marker for both β-amyloid (Aβ) and tau pathology along AD neurodegeneration [11,19,20]. Therefore, literature has proposed a progressive increase in studies on AD signs and symptoms (CSF biomarkers, neuroimaging, and cognitive status) in patients with OSA. However, the use of different patients groups, diagnostic tools, laboratory cut-offs, and imaging modalities limits the establishment of a definite status of AD biomarkers in patients with OSA. Since OSA can be treated by continuous positive airway pressure (CPAP), the effects of CPAP on OSA-induced changes have only been partially studied. Further, the identification of the beneficial effects of CPAP on these preclinical and early AD biomarker changes in patients with OSA is not yet completely understood. Notably, preclinical AD is characteristically defined by the occurrence of specific biological biomarkers without clinical symptoms, which emphasizes the importance of assessing and managing risk factors several decades prior to the initial clinical manifestations of AD [21]. Consequently, research on OSA as a possible cause and risk factor for preclinical AD is still ongoing and could allow the development of new strategies for screening OSA in the adult and elderly populations to potentially reduce the prevalence of AD. To this end, CSF and neuroimaging/nuclear medicine biomarkers have become a fundamental part of AD research on preventive strategies and early recognition of individuals at risk of developing AD [22].

Two clinical reviews recently identified the most promising fluid biomarkers of dementia in patients with OSA and the hypothetical trajectory of AD pathology triggered by OSA and possibly hampered by CPAP treatment [23,24]. The first focused on the clinical potential of measuring CSF and blood biomarkers in patients with OSA; the second explored the possible mechanisms precipitating AD neuropathological changes triggered by OSA, and also the hypothetical neurodegenerative factors promoting OSA in patients with AD. In contrast with these two recent reports, in this review we examine the possible occurrence of neuropsychological, brain magnetic resonance imaging (MRI), CSF, and brain nuclear medicine biomarkers in patients with OSA recognized as having AD pathology. Furthermore, we consider the CPAP-induced modifications of AD biomarkers to provide an overall summary of the current knowledge on OSA and the risk for AD pathology based on biomarker changes. Finally, we hypothesize a model explaining the interplay between OSA and AD pathology in the preclinical and early stages of the disease, and promote the clinical potential of investigating AD biomarkers in patients with OSA in order to identify AD clinical-pathological changes early, and thus possibly prevent the cascade of events leading to MCI and AD by treating OSA with CPAP.

OSA and AD: comorbidity and causality

AD is the most prevalent form of dementia and is currently identified as a multifactorial disorder. Prevention of the occurrence and progression of AD has proven to be very challenging in our

society [25]. Sleep disturbances, and in particular OSA, have been tested as a potentially modifiable risk factor for AD; therefore, studies investigating the prevalence and potential of developing AD are increasing in the adult and elderly populations with sleep disorders.

A multicenter cross-sectional Italian study reported a high prevalence of sleep disturbances in 431 patients with MCI or dementing disorders (such as AD, Lewy body dementia, vascular dementia, or fronto-temporal lobar degeneration), including insomnia, OSA, excessive daytime sleepiness (EDS), restless legs syndrome, and rapid eye movement (REM) behavior disorder. The Berlin questionnaire (BQ) was used to identify the subjects at higher risk of OSA, and its prevalence was identified as occurring in 53.9% of patients with AD and 58.7% of patients with MCI, with no significant differences between the two groups [26]. Consistently, the BQ represents a clinical screening test and epidemiological tool in the sleep clinic population [27]. A study with a larger population of patients with AD reported that the prevalence of probable OSA, which was determined using caregiver reports, showed a prevalence of 14.9% with a high possibility of underestimation due to the instrument used [28]. A study conducted more than 30 years ago reported that OSA, diagnosed by PSG, and defined as an Apnea-Hypopnea Index (AHI) $\geq$5 events per hour of sleep, affects 42.9% of patients with AD, 17.6% of patients with depression, and 4.3% of controls (healthy subjects) [29]. A meta-analysis on the association between OSA and AD published in 2016 selected only five cross-sectional or case–control studies conducted between 1983 and 1989 [30]. OSA was diagnosed in three of the five studies using PSG, while the remaining two studies used 24-channel polygraph or respiratory inductive plethysmography. The aggregate odds-ratio (OR) for the presence of OSA in AD vs. healthy controls was 5.05, suggesting that nearly 50% of patients with AD presented with OSA. Notably, considering the three studies using PSG for diagnosing OSA, the OR increased to 7.248. Even if this study cannot demonstrate a clear direction of the temporal link between OSA and AD, it emphasizes the clinical risk of an additive impact of OSA on AD [30]. However, the speculative point of view considering the possible causative role of OSA on AD pathology remains unanalyzed.

A retrospective study on a large cohort of individuals aged 55–90 years (mean age = 73.81 years) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study reported that SDB was present in 14.9% of patients with AD and MCI; however, since SDB was self-reported, underestimation of the comorbidity between SDB and OSA remains a major concern [31]. A more recent (2019) systematic review on OSA prevalence in patients with MCI reported that it ranged from 11% to 71% [32]. Stratification of the OSA prevalence according to the diagnostic procedures used was: 11%, self-reported; 27%, home sleep apnea testing; 59%, BQ; and 71%, PSG [32]. There is a single study in adult and elderly populations not reporting significant differences in OSA prevalence (AHI$\geq$15/h measured by home sleep apnea testing without reporting data about oxygen desaturations) between subjects with (27%) and without (26%) MCI [32]. Although authors concluded their review describing the similar prevalence of OSA between individuals with MCI and the general population based on a single report and not widely recognized evidence, further studies with better diagnostic methods for OSA and MCI are needed. Besides, the difference in the prevalence of OSA in patients with MCI according to the diagnostic procedure used significantly reflects the importance of using standardized methods for OSA diagnosis (PSG as a gold standard).

Taken together, these aforementioned studies indicate a high prevalence of OSA in patients affected by MCI and AD. Since the recent identification of a very early stage of AD, named subjective cognitive impairment (SCI), studies investigating the occurrence of OSA in this population of patients should be encouraged [33]. SCI is clinically characterized by the subjective perception of memory loss (compared to the previous 5–10 years) unconfirmed by objective neuropsychological testing [21]. Stage 3 of non-REM sleep and REM sleep appeared to be already affected in patients with SCI and possibly correlated to both the occurrence of cognitive impairment and the alteration of CSF AD biomarkers [34]. A complex principal component analysis (a variant of the factorial analysis), performed in a recent study including large groups of patients affected by SCI, MCI, and AD and compared to CN controls, showed the mutual interplay among the sleep architecture changes, already evident in the SCI stage and progressively deteriorating along the progression to AD dementia, the neurocognitive and memory functioning, and the CSF biomarkers of AD [34]. Although this study suggests that sleep dysregulation is not just a risk factor, but may also serve as an early marker of AD, longitudinal studies on patients affected by SCI and followed during the progression of the disease should be performed for monitoring the modification of sleep architecture in relation to cognitive performances and both amyloid and tau burden, in order to identify a possible causal role of OSA in AD.

OSA negatively impacts on sleep architecture (by producing sleep fragmentation and reducing deep sleep) and seems to be quite common among patients diagnosed with SCI. A single cross-sectional observational study on CSF biomarkers in patients with SCI found a high prevalence of moderate-severe OSA (AHI $\geq$15/h, and diagnosed by PSG) in 35 of 50 patients [33]. However, the prevalence of OSA in SCI needs to be further investigated: studies on this population should be very informative regarding the relationship among OSA, AD pathology, and cognitive performance.

Considering the increasing literature investigating the relationship between sleep disturbances and AD, a recent meta-analysis of longitudinal studies reported that individuals presenting sleep disturbances (insomnia, SDB, EDS, sleep-wake rhythm disorders) have a high risk of developing all-cause dementia, AD, and vascular dementia [17]. Moreover, a subgroup analysis showed that insomnia presentation increased the risk of AD but not vascular or all-cause dementia; further, SDB (snoring, sleep apnea) was associated with an increased risk of all-cause dementia, AD, and vascular dementia. This meta-analysis included seven studies that mainly used scales, questionnaires, and telephone interviews to detect OSA (but did not use validated questionnaires for screening OSA, as BQ) [17]. Only one study investigated the prevalence of OSA by using the PSG [35]. Briefly, this was a prospective study on 298 women with a mean age of 82 years, longitudinally followed for a mean of 4.7 years, demonstrating that the diagnosis of SDB (coded by using a cut-off of 15 for the AHI) and/or hypoxia (coded by using a cut-off of 15 for the oxygen desaturation index[1]) at baseline represented a risk factor for the development of MCI or dementia at follow-up [35]. This study strongly suggested the relationship between SDB and MCI/dementia, and tried to demonstrate that this interplay can be driven by the IH [35]. Following the meta-analysis by Shi and co-authors, a further study was published in 2018 and investigated the prevalence of OSA diagnosed by using an in-house PSG in 1667 individuals with a mean age of 62.7 years (52.6% women) recruited for the *Atherosclerosis Risk in Communities Study*. The authors identified four OSA severity groups according to the AHI[2]: <5.0/h (normal, 50.9% of participants), 5.0–14.9/h (mild, 30.2%), 15–29.9/h (moderate, 12.8), $\geq$30.0/h (severe, 6.1%). In the longitudinal analysis, the authors documented that the risk of dementia or MCI due to AD appeared higher in individuals with severe OSA vs. subjects with a normal sleep breathing pattern after adjustment for demographics;

[1] $\geq$3% oxygen desaturations.
[2] hypopnea was defined by using $\geq$4% oxygen desaturations.

however, this risk was attenuated by correction for cardiovascular risk factors [36]. The authors correctly underlined some limitations of their study underpowering the results, as the small number of participants with severe OSA developing cognitive decline, and the number and clinical characteristics (i.e., smoking, diabetes, and antihypertensive medications) of subjects not participating in the longitudinal analysis (n = 584) [36].

A study that needs to be taken into consideration investigated the role of SDB in advancing cognitive decline in the elderly population recruited in the ADNI cohort [31]. SDB was self-reported and corresponded to "sleep apnea" and "OSA" [31]. In this report, patients with a history of SDB presented with an MCI or AD diagnosis at follow-up at a younger age than subjects without a history of SDB. In the very small subgroup of patients who received treatment for SDB with CPAP, the onset of MCI or AD appeared to be delayed compared to those who were not treated for SDB with CPAP [31]. These findings highlight the importance of recognizing SDB, and treating it as soon as possible, in the elderly population for the prevention or delay of the onset of MCI and then AD.

Hence, OSA and AD seem to share a bi-directional relationship based on the evidence that OSA is frequently comorbid in patients already diagnosed with MCI or AD [26,28,31], but OSA may also represent a risk factor for developing MCI and/or AD in the adult and elderly populations promoting and advancing cognitive decline, possibly inducing or accelerating AD neurodegenerative processes throughout IH and sleep dysregulation [34,35]. OSA may contribute to AD neurodegeneration by sleep disruption and IH, which alter Aβ processing and clearance, promote aggregation of neurofibrillary tangles (NFTs) of tau pathology, aggravate age-related memory deficits, and promote white and grey brain matter changes, as this review tries to define [37,38].

OSA and AD biomarkers

There is ongoing research on sleep disorders as possible pathogenic factors that trigger neurodegenerative diseases, with their effects on AD pathology receiving greater attention. The recent discovery of the glymphatic system has encouraged the investigation of sleep and the risk of neurodegeneration [39]. OSA, as the main SDB, has been recently investigated as a possible risk factor for AD pathology. Related studies have reported that patients with OSA present with changes in several biomarkers consistent with AD pathology.

There have been previous studies on AD neurodegeneration biomarkers based on the following suppositions: 1) OSA and AD share numerous risk factors, including vascular disease [40]; 2) patients with AD present with an increased prevalence of OSA [26,41]; 3) OSA negatively affects memory function (nearly five times greater odds of impairment) in apolipoprotein E (ApoE) epsilon 4 (ApoE4) carriers, who presented a higher risk of developing AD [42,43]. This background has allowed studies to be conducted in patients affected by OSA on AD pathology biomarkers.

AD biomarkers are important for early diagnosis in routine clinical practice and research. There have been studies on neuropsychological functioning and behavior, as well as CSF and neuroimaging biomarkers, in patients with OSA. Moreover, there have been studies on the possible disease-modifying effect of CPAP against AD biomarkers' alterations in patients with OSA. We describe the studies identified by our research analysis and their results (Table 1).

OSA and neuropsychological functioning

The typical early cognitive profile of Alzheimer-type dementia includes prominent hippocampal-type memory deficits, while the atypical cognitive profile of AD could include additional cognitive dysfunction in the attention, visuo-spatial, executive, and behavioral domains [44,45]. There are similarities and differences between the neuropsychological decline typical of AD and cognitive consequences of OSA. OSA can affect several cognitive domains, although there is no evidence of a typical cognitive profile in patients with OSA. The initially researches and reviews investigating cognition in patients with OSA focused on vigilance, attention, and executive function [46,47]. More recent data suggest the main impairment of other cognitive functions, such as memory. It has been demonstrated that sleep-dependent memory and offline memory processing deteriorated in patients with OSA possibly due to both intermittent hypoxia and sleep fragmentation [48]. In keeping with this evidence, memory processing and consolidation may be affected by OSA, but few studies were primarily focused on this cognitive process [48].

From a clinical point of view, the pivotal paper by Ferini-Strambi et al. reported that patients with OSA present significant impairment in sustained attention, visuo-spatial learning, executive function, motor performance, and constructional abilities compared to controls [49]. In a subsequent study, patients with moderate-severe OSA presented deficits in short- and long-term memory [50]. Studies on the cognitive effects of OSA are heterogeneous, mainly in the OSA diagnosis (in some cases, using a clinical interview without PSG confirmation) and clinical analysis, which indicates the need for caution before making definitive conclusions. A recent review by Leng et al. published in 2017 analyzed seven cross-sectional studies and reported an association of OSA with worse executive function, but not with cognitive or memory impairment [51]. Moreover, brain injury in the hippocampus in people with OSA should not be overlooked. Apart from neuroimaging data, histopathological investigations on post-mortem brain tissues from subjects with OSA showed cortical thinning in the molecular layer of the dentate gyrus and entorhinal cortex, which are related to several memory pathways and may underpin the impairment observed in episodic, semantic, and spatial memory [52]. The link between hippocampal damage and cognitive symptoms in OSA requires further investigation.

To our knowledge, there is only one recent report evaluating the cognitive characteristics of patients with comorbid OSA and AD, evaluating a cohort of 128 AD subjects with an incidence of OSA in 90.6% patients. The study failed to reveal any significant differences between AD patients with and without severe OSA in any of the cognitive domains [53]. There are several reports (both studies and reviews) that have attempted to analyze the cognitive pattern of patients with OSA [46,47,54–58]. However, several critical issues make it difficult to derive a definite conclusion about cognitive impairment in patients with OSA [59]. First, inclusion and exclusion criteria frequently differ among studies. Second, the criteria for diagnosing OSA were not homogeneous (self-reported, questionnaires or PSG; definition of AHI and oxygen desaturation index - ODI). Third, neuropsychological tests were not standardized. Fourth, several confounding factors exist in evaluating cognitive functioning and are related to OSA severity, EDS, age, cognitive reserve, education, comorbidities, and genetics.

With regard to disease severity, most studies only included patients with moderate and severe OSA, and insufficient data are present for mild OSA. Moreover, correlations between the severity of OSA and cognitive deficits are reported inconsistently. Even if studies are not recent, EDS seems to influence attention and memory, but not motor and executive functions [23]. Moreover, age seems to determine the cognitive consequences of OSA [23]. Briefly, in young and middle-aged patients, OSA diagnosis is associated with cognitive impairment, while in older adults the association between OSA and cognitive performance is less evident [23,58].

Table 1
A-T-N(-C) biomarkers, positive and negative results, in patients with OSA.

	A	T	N	C
+	**CSF Data:** • $A\beta_{42}$ levels decrease, Ju et al. (2016) [66]; Liguori et al. (2017) [33]; Liguori et al. (2019) [67] • $A\beta_{40}$ levels decrease, Ju et al., 2016 [66]; Liguori et al., 2019 [67] • longitudinal reduction of $A\beta_{42}$ levels, Sharma et al. (2018) [10], Bubu et al. (2019) [77] **PET Data:** • increased Aβ uptake in posterior cingulate gyrus and temporal cortex, Yun et al. (2017) [109] • increased global load of Aβ, Elias et al. (2018) [110] • increased Aβ deposition in left precuneus, posterior cingulate, and cuneus regions, Andrè et al. (2020) [63]	**CSF Data:** • Longitudinal increase of tau protein levels, Bubu et al. (2019) [77] **Plasma Data:** • P-tau increase, Bu et al. (2015) [80] • T-tau increase, Motamedi et al. (2018) [81]	**Brain MRI Data:** • Decreased GMV in anterior cingulate cortex, Shi et al. (2017) [95], Huang et al. (2019) [98] • Decreased GMV in left and right middle temporal gyrus, Torelli et al. (2011) [49], Weng et al. (2014) [97], Shi et al. (2017) [95] • Decreased GMV in bilaterale hippocampus, Torelli et l. (2011) [49] • Increased GMV, as compensatory mechanism, in bilateral precuneus and posterior cingulate cortex, Andrè et al. (2020) [63] **PET Data:** • Reduced FDG uptake in amygdala, hippocampus and medial parietal cortex, Dani et al. (1996) [105] • Reduced FDG uptake in precuneus, middle and posterior cingulate gyrus, parietal cortex, Yaouhi et al. (2009) [106] • Reduced FDG uptake in bilateral precentral gyri, right angular gyrus, left superior parietal lobule and left cingulate cortex, Ju et al. (2012) [107] • Increased glucose metabolism, as compensatory mechanism, in precuneus, posterior cingulate, and lingual areas, bilaterally, Andrè et al. (2020) [63]	• Memory impairment including immediate and delayed recall, Gagnon et al. (2014) [58] • Memory impairment including immediate and delayed recall, Digit span backward, Torelli et al. (2011) [49]
-	**PET Data:** No longitudinal increase of Aβ global load, Bubu et al. (2019) [77], Sharma et al. (2018) [10]	**CSF Data:** • No tau proteins alteration, Ju et al. (2016) [66]; Liguori et al. (2017) [33]; Liguori et al. (2019) [67] • No longitudinal modifications of tau protein levels, Sharma et al. (2018) [10] **PET Data:** • No pathological accumulation of NFT, Elias et al. (2018) [110]	**Brain Mri Data:** • No GMV changes, Huynh et al. (2014) [130]; Celle et al. (2018) [103]; Yeung et al. (2019) [99]	• No cognitive or memory impairment, Leng et al. (2017) [50] • No cognitive or memory impairment, Andrè et al. (2020) [63]

A, amyloid biomarker; T, tau biomarker; N, neurodegenerative biomarker − 18F-FDG PET and MRI; C, cognitive biomarker; +, positive results; -, negative results.

Education and cognitive reserve possibly have a protective effect against the neuropsychological complications of OSA [60] and seem to hamper its cognitive consequences [61]. Several comorbidities associated with OSA, such as depression, obesity, hypertension, diabetes, heart diseases, and cerebrovascular injuries, tend to increase cognitive impairment in patients with OSA [59]. With regard to genetics, patients with OSA carrying the ApoE4 (a well-known risk factor for AD) showed a more significant correlation between OSA parameters and cognitive deficits than non-ApoE4 carriers [42]. Initial findings have been subsequently confirmed by other larger population-based studies suggesting an interplay between ApoE4 and OSA in determining cognitive deficits [42,43,62,63].

Considering prospective and longitudinal evaluations, a pooled-analysis of six studies reported that patients with SDB or OSA were 26% more likely to develop cognitive impairment at follow-up (OR 1.26; 95% CI, 1.05−1.50) [51]. Several limitations are present in these studies and further investigations are needed; however, the recommendations to treat patients with OSA do not allow performing longitudinal studies to monitor the effects of OSA.

In conclusion, patients with OSA present a neuropsychological pattern characterized by worsening of executive function, but reports on memory impairment, which is a more typical pattern of AD, are inconsistent (see Table 1). Hence, cognitive impairment due to OSA could be schematically represented in: 1) alteration of

vigilance, attention, and executive function; 2) impairment of sleep-related memory process; 3) brain alterations and damage, mainly in the hippocampus.

Since OSA is currently considered a risk factor for AD-related neurodegeneration, cognitive testing could be a useful instrument to better detect patients at risk for AD, who should be followed with a more accurate diagnostic work-up and follow-up. However, as recently documented in large studies performed in CN adults, AD biomarker changes (neuroimaging, CSF, and nuclear medicine imaging) can appear earlier than cognitive impairment in patients with moderate-severe SDB [64].

OSA and CSF/plasma validated AD biomarkers

Although numerous studies identified the three main CSF biomarkers (t-tau, p-tau, and Ab42) as established biomarkers for consistent clinical AD diagnosis [22], different CSF biomarkers have been evaluated throughout the current literature for improving AD diagnosis and predicting the clinical course of the disease. These biomarkers can be grouped in:

- biomarkers of neurodegeneration: t-tau, NFL, NSE, VLP-1, and HFABP
- biomarkers of amyloid precursor protein (APP) metabolism: $A\beta_{42}$, $A\beta_{40}$, $A\beta_{38}$, sAPPα, and sAPPβ
- biomarkers of tangle pathology: p-tau
- biomarkers of glial activation: YKL-40, MCP-1, and GFAP

With the exclusion of t-tau, p-tau, and $A\beta_{42}$, which are largely considered as the core CSF biomarkers for AD diagnosis, NFL has been found to have a large effect size for discriminating controls from patients with AD to support the three core CSF biomarkers [65]. Further, NSE, VLP-1, HFABP, and YKL-40 have demonstrated a moderate corresponding effect size and are considered as emerging biomarkers that require further investigation [66].

Considering blood biomarkers only plasma t-tau levels have been strongly associated with AD, while plasma $A\beta_{42}$ and $A\beta_{40}$ levels are not associated with AD diagnosis [66]. Therefore, in this review, we exclusively considered the core CSF biomarkers for AD diagnosis (t-tau, p-tau, and $A\beta_{42}$) and plasma t-tau levels. Except for one study that reported reduced CSF VLP-1 levels in a small group of patients with OSA [67], there has been no study investigating other CSF biomarkers in patients with OSA. Since $A\beta_{40}$ is the second most studied amyloid marker after $A\beta_{42}$, we also included it in this review. Additionally, we included orexin and lactate, investigated in both patients with AD and OSA [33,68,69]. Orexin gained scientific interest in 2009 after the Holtzman group reported that the orexinergic system and sleep-wake cycle had an effect on brain Aβ dynamics and AD pathology [70,71]. Lactate is a candidate biomarker for assessing energy metabolism malfunction; specifically, mitochondrial dysfunction [72]. CSF lactate levels could consistently reflect the state of neuronal energy metabolism and sleep-wake cycle changes [72,73].

CSF t-tau and p-tau levels in patients with OSA

Microtubule-associated tau proteins are a family of closely related phosphoproteins that are enriched in axons during brain development [74]. The axonal tau proteins copolymerize with microtubules and modulate the dynamic instability of tubulin assembly in cell-free reactions [75]. NFTs of tau proteins result from abnormal microtubule-associated tau protein phosphorylation and are a key pathological hallmark in patients with AD. NFT agglomeration begins in the hippocampus at the very early disease stages with subsequent diffusion to the other brain areas. However, a recent study suggested that brainstem nuclei are among the areas initially affected by tau protein abnormalities in the course of sporadic AD to cause behavioral and cognitive symptoms, as well as sleep disturbances [76].

CSF t-tau and p-tau levels have been investigated in patients with OSA. The first study to evaluate CSF AD biomarkers in patients with OSA reported that CSF tau protein levels do no correlate with the AHI in subjects with the ApoE4 genotype [77]. Subjects carrying the ApoE3+ genotype exclusively showed a correlation between AHI4%, but not AHI all (considering different cut-offs for hypopnea detection), and the CSF levels of p-tau and t-tau [77].

Related cross-sectional studies reported that there were no differences in the CSF t-tau and p-tau levels between patients with OSA and controls [33,67,68]. Moreover, longitudinal studies did not report changes in CSF tau protein levels in patients with OSA in a two-year prospective observation [10]. However, another longitudinal study investigating CSF AD biomarker alterations in CN individuals and patients with MCI or AD reported that OSA could induce a faster longitudinal increase in CSF t-tau and p-tau levels [78].

Plasma t-tau and p-tau levels in patients with OSA

Plasma is an ideal biofluid candidate for biomarker analysis since it allows easy sample collection, and facilitates longitudinal prospective studies [79]. Although AD biomarkers are exclusively found in the CSF, plasma tau protein levels have been reported as a biochemical marker of brain neuronal injury. However, this promising target is currently facing criticism given the weak correlations between plasma and CSF levels [80]. Moreover, there is currently no widely available standardized method for measuring plasma tau protein levels. Therefore, including the assessment of plasma tau protein levels might improve the accuracy of AD diagnosis; however, it is currently not fully available [66].

Two controlled studies investigated plasma tau protein levels in patients with OSA. Compared with controls, the first study reported that patients with OSA presented increased plasma levels of p-tau but not t-tau [81]. Compared with controls, the second study reported increased t-tau protein levels in patients with severe OSA (AHI >30/h) but not in patients with mild OSA (AHI between 5 and 15) [82]. Currently, no longitudinal study has been performed. Given the promising nature of plasma tau levels in AD diagnosis, there is a need for prospective longitudinal studies of patients with OSA.

CSF Aβ levels in patients with OSA

A decrease in CSF $A\beta_{42}$ levels precedes AD dementia by at least 10 years [83]. This finding has encouraged research on means of predicting and treating AD prior to the onset of cognitive impairment. Indeed, in the amyloidogenic cascade the increase in CSF $A\beta_{42}$ levels has been suggested as a very early manifestation of cerebral Aβ dysregulation, and it is immediately followed by the reduction of CSF $A\beta_{42}$ levels corresponding to the deposition of Aβ plaques in the brain in a consecutive temporal ordering [84]. These pathological changes in CSF Aβ levels reflect an imbalance between Aβ production and clearance (with the increased production and the reduced clearance), or alternatively, a modification in the physiochemical cerebral microenvironment promoting Aβ aggregation, deposition and CSF levels reduction [85].

In 2014, a group led by Osorio reported an association between a higher AHI and lower CSF $A\beta_{42}$ levels in CN individuals carrying the ApoE2 or ApoE4 genotype [77]. Based on this finding, subsequent studies have reported decreased CSF $A\beta_{42}$ levels in patients with OSA compared to controls [33,67,68]. Determination of the CSF $A\beta_{42}$ levels associated with pathology (below the evidence-based cut-off value) has further increased the scientific value of this finding; in particular, one study reported a pathological CSF $A\beta_{42}$ level

reduction (<500 pg/mL measured by ELISA) in 64% (16/25) of patients with severe OSA (AHI >30/h) [33]. Subsequent positron emission tomography (PET) studies have assessed brain Aβ deposition using tracers for Aβ (see the next paragraph). Moreover, patients with OSA have been reported to show reduced CSF $A\beta_{40}$ levels [67,68]. Therefore, patients with OSA are featured by dysregulation of Aβ metabolism in the brain; however, the mechanisms underlying these findings can only be speculated. Following the evidence of literature drawn from animal model studies, on the one hand IH has been hypothesized to alter brain Aβ metabolism and, on the other hand, it is conceivable that sleep fragmentation may induce glymphatic dysfunction. These concurrent mechanisms may be responsible for changes in CSF Aβ levels and brain Aβ deposition [18,39,86,87]. Moreover, *in vitro* and *in vivo* hypoxia and ischemia have been reported to upregulate APP, leading to Aβ accumulation through β-secretase activation [88,89]. Based on these findings and taking the aforementioned Aβ cascade into account, the process leading to CSF Aβ levels reduction and plaques formation and deposition can be exclusively hypothesized in patients with OSA. The role of IH in directly modifying the activity of the β-secretases and the alteration of the glymphatic system not cleaning Aβ from the brain may represent the main candidate in inducing cerebral Aβ pathological changes in OSA.

Subsequent longitudinal studies have further confirmed the association between OSA and AD risk. Consistently, after adjustment for age, sex, body mass index (BMI), and ApoE4 status, the annual change rate of CSF $A\beta_{42}$ levels has been reported to be associated with OSA severity in CN elderly individuals [10]. In this previous study, individuals aged between 55 and 90 years with a minimum of 12 years of education underwent OSA assessment using a home sleep apnea test during a two-night period; further, they underwent CSF analysis for AD biomarkers [10]. This study used a novel methodology involving longitudinal observation where 179 individuals underwent lumbar puncture (LP) at baseline and 104 individuals underwent a second LP after a follow-up period of 2.42 ± 0.88 years [10].

Considering the high OSA prevalence in the elderly population, there is an increasing requirement for longitudinal studies. Consistently, a study conducted by Sharma et al. reported that OSA severity was associated with two-year longitudinal decreases in CSF $A\beta_{42}$ levels [10]. Moreover, the effect of OSA severity on the longitudinal decrease in CSF $A\beta_{42}$ levels was more significant than that of the ApoE4 allele, which is the most important risk factor for sporadic AD [42]. Another study by the same group further highlighted the significance of the association between OSA and AD, which is mediated by AD neuropathological changes induced by OSA-related sleep fragmentation and IH [78]. In the aforementioned study, there was a faster increase in the Aβ load (indicated by a longitudinal decrease of CSF $A\beta_{42}$ levels) in CN individuals and patients with MCI. In contrast, there was no progressive decrease in CSF $A\beta_{42}$ levels in patients with AD, which could be attributed to Aβ load plateauing in the advanced disease stage [78].

We did not include studies that measured the plasma or serum Aβ isoform levels in patients with OSA. This is because of the lack of significant differences in the plasma or serum Aβ marker levels in patients with AD and controls, which supports the hypothesis that plasma Aβ levels are indicative of peripheral Aβ generation rather than AD brain pathology [90]. Moreover, no studies have presented evidence on the potential use of plasma or serum Aβ levels in AD diagnosis [91]. However, very recent evidence suggests the possibility to determine plasma Aβ biomarkers by immunoprecipitation coupled with mass spectrometry [92]. Although this study opens a new frontier in the measurement of Aβ biomarkers in AD pathology, it has not been replicated, and thus the time for the detection of plasma Aβ levels has not yet come.

CSF orexin and lactate levels in patients with OSA

Several studies have assessed serum and plasma orexin-A/hypocretin-1 levels in patients with SBD. However, it is widely recognized that only CSF orexin-A/hypocretin-1 levels reflect the integrity of the orexinergic/hypocretinergic hypothalamic brain system [93]. Only two studies have investigated the CSF orexin levels in patients with OSA [68,94]. Orexin is a wake-promoting neurotransmitter that supports wakefulness maintenance; moreover, there is increased orexinergic system activity during REM sleep suppression [95,96]. Further, orexin neurons have the highest sensitivity to CO_2/H+ and are activated by CO_2 *in vivo* [97,98]. Therefore, the higher CSF orexin levels detected in patients with moderate-severe OSA might be related to the following: 1) sleep dysregulation (reduced REM sleep); 2) presence of EDS with an increase in orexin levels as a hypothetical compensatory mechanism to counteract daytime somnolence; 3) the hypercapnic condition due to apnea events and IH [68].

There are changes in lactate levels during the sleep and wake state; briefly, there are decreased and increased lactate levels at sleep onset and wakefulness, respectively [72]. Moreover, mitochondrial inefficiency induces increased lactate levels and promotes AD progression [69]. Patients with moderate-severe OSA have been reported to have increased CSF lactate levels, which reflects both sleep impairment with increased nighttime wakefulness and energy metabolism dysfunction [33].

There is a need for further studies on CSF lactate and orexin levels in patients with OSA to determine the correlation between alterations of these biomarkers and the underlying mechanisms of AD neurodegeneration.

Brain MRI studies in patients with OSA

In recent years, several research groups have used both morphometric and functional MRI techniques to study the neurobiological effects of OSA on brain structure and functionality. Given that we aimed to evaluate AD biomarkers in patients with OSA, we focused on morphometric studies, which analyze gray matter volume (GMV) by means of voxel-based morphometry (VBM) and brain WM microstructure by measuring water diffusion using diffusion tensor imaging (DTI).

Five recent meta-analyses pooled data from VBM studies in patients with OSA [99–102]. The results of these studies are inconsistent, due to differences in the methodology, inclusion criteria, and statistical analyses used. However, the meta-analysis reported gray matter reduction in the bilateral anterior cingulate [99,102], superior frontal gyrus [99,101], left cerebellum [99,102], as well as the left [101] and right middle temporal gyrus [99]. A majority of these brain areas are involved in integrative cognitive and emotional processes (the anterior cingulate and cerebellum have several connections with the amygdala). Consistently, a cognitive and neuroimaging study reported a significantly reduced cortical GMV in patients with OSA compared to controls [50]. This difference remained significant even after adjusting for age, sex, and sleepiness; however, it did not remain significant after adjustment for BMI. In addition, patients with OSA presented focal GMV reduction in the right and left hippocampus, as well as in some lateral temporal areas of both hemispheres [50]. Finally, the hippocampal volume reduction in patients with OSA was correlated with memory impairment and executive dysfunction [50].

In contrast, in 2019 Yeung [103] reported a larger GMV in the right insula in patients with OSA compared to healthy controls, which could be related to increased compensatory activity and maladaptive alterations for preventing further limbic system hypofunction. In keeping with these findings, a very recent

investigation documented greater GMV in the precuneus and posterior cingulate cortex, bilaterally, in CN older adults [64].

Several studies were performed in middle-aged adults with OSA using DTI analysis [104]. The DTI technique investigates regional brain WM microstructure *in vivo* by measuring water diffusion. Functional anisotropy (FA) is a marker of WM integrity and is typically reduced in MCI and AD. Decreased FA suggesting altered WM integrity is frequently found in middle-aged individuals with OSA.

These data were recently confirmed in a paper on adult-elderly subjects (55–85 years old) including 18 healthy controls, and 27 patients with mild and 20 patients with moderate-severe OSA [104]. Mild OSA presented a more extensive WM alteration than moderate-severe OSA, possibly due to compensatory mechanisms producing the bulging of WM due to underlying neurodegeneration at an early stage of the disease [104].

VBM studies of GMV are scarce in elderly subjects with OSA and suggest conflicting results. A study on 71 patients with OSA aged between 55 and 76 years reported a correlation of higher hypoxemia levels with increased volume and thickness of the left lateral prefrontal cortex and thickness of the right frontal pole, right lateral parietal lobules, and left posterior cingulate cortex [105]. In contrast, a study on 83 adults aged between 51 and 88 years reported reduced cortical thickness in the bilateral temporal lobes, increased thickness in the right postcentral gyrus pericalcarine and pars opercularis, and increased volume in the hippocampus and amygdala [106]. These results were inconsistent with those of the PROOF study in an elderly population (Evaluation of Ageing, Autonomic Nervous System Activity, and Cardiovascular Events). This study conducted by Celle et al., which was published in 2018 [107], reported no GMV differences in controls and patients with treated and untreated OSA.

Brain MRI studies in patients with OSA demonstrate changes in brain regions involved in the integration of cognitive, emotional, and decision-making processes, including the frontal areas, amygdala, hippocampus, and other functionally related regions. The huge variability in the methodology and results make it difficult to identify a pattern of grey and white matter changes in patients with OSA. DTI showed a constant reduction in FA in all studies, but the possible biphasic pattern (with larger alterations in mild compared to moderate-severe OSA) should be further studied and could be an important limitation. Moreover, studies in elderly populations are quite scarce, although very recent studies have been published with novel data. Finally, no MRI study has yet been performed in patients with MCI or AD and OSA, and one should be planned in the future to better define the effect of OSA on grey and white matter changes.

Brain nuclear medicine imaging studies in patients with OSA

Nuclear medicine imaging is being applied in neurology and neuroscience with the use of PET tracers to investigate brain function. Notably, functional brain imaging using glucose (fluorodeoxyglucose, FDG) has been used to investigate cerebral activity. Consequently, FDG-PET is currently considered a useful tool for detecting AD signs since reduced cerebral FDG uptake in the temporal and parietal regions of the brain is an *in vivo* AD biomarker [22]. Furthermore, the recent approval of tracers for identifying brain Aβ plaques and tau deposits increases the chances of performing AD diagnosis *in vivo*. PET imaging has allowed easier detection of Aβ plaque deposition and tau NFT proteins [22]. Although there have been studies using single-photon emission computed tomography (SPECT) to assess patients with OSA, we did not include them in this review. This is because SPECT is no longer considered an instrument for investigating AD biomarkers [22]. Rather, PET imaging has taken up a significant role in the AD diagnostic setting [91] and is considered to have greater accuracy in differentiating AD pathology from other dementing neurodegenerative processes [108].

FDG-PET studies

There have been only a few FDG-PET studies in patients with OSA, with most of them including very small group of patients. The first preliminary studies investigated brain cerebral glucose metabolism in five and eight patients, respectively, and reported that they had reduced FDG uptake in the amygdala, hippocampus, medial parietal cortex, and anterior cingulate gyrus [109], which are significantly associated with AD pathology and are altered in the earliest disease stages [108]. Subsequently, controlled studies have attempted to assess the correlation between brain glucose consumption and neuropsychological test results. Yaouhi et al. reported significant glucose hypometabolism in 16 patients with OSA (AHI >10/h) in several brain areas in the right hemisphere, including the precuneus, middle and posterior cingulate gyrus, and parietal cortex [110]. There was a correlation between FDG uptake in the cerebellum and neuropsychological data, which was not well explained by the researchers [110]. Another study on 13 patients with severe OSA reported cerebral glucose hypometabolism in several brain areas, which included AD-related regions such as the bilateral precentral gyri, left cuneus, right angular gyrus, left superior parietal lobule, and left cingulate cortex [111]. A very recent study in a large population of CN older adults documented increased FDG uptake in the bilateral precuneus, posterior cingulate, and lingual areas in patients with moderate-severe SDB compared to mild and non-SDB subjects [64]. Notably, patients with moderate and severe SDB did not differ in terms of glucose metabolism, thus demonstrating that an AHI $\geq$15/h can serve as a cut-off for identifying patients at risk of developing AD biomarker changes (likewise for Aβ load and GMV).

Amyloid PET studies

Identification of amyloid plaque deposition *in vivo* through PET tracers has great potential in the identification of AD pathology from the earliest and preclinical AD stages. An inverse correlation between the amyloid imaging load and CSF $A\beta_{42}$ levels has been reported, with both tools being considered as hallmarks for detecting the mandatory AD biomarker, i.e., Aβ pathology. Therefore, a reduction in CSF $A\beta_{42}$ levels appears from the earliest disease stages while Aβ deposition is strongly related to disease progression. This finding indicates that a reduction in CSF $A\beta_{42}$ levels appears earlier than Aβ plaque deposition with a yet-to-be-identified cascade of events with a different temporal sequence [112].

Based on the reported reduction in CSF $A\beta_{42}$ levels, subsequent studies have investigated the amyloid burden in patients with OSA. Consistent with previous studies on CSF $A\beta_{42}$ levels, these subsequent studies reported that patients with OSA had an increased brain amyloid load in the posterior cingulate gyrus and temporal cortex, which are both involved in the early AD stage [113]. A subsequent study on 119 patients reported a higher global Aβ load in patients with OSA compared to controls; however, the results among the OSA group were heterogeneous. Moreover, ApoE4 carriers showed a higher Aβ burden than those who were not carriers [114]. The most recent report documenting Aβ accumulation in the left precuneus, posterior cingulate, calcarine, and cuneus regions was achieved in a large population of CN older adults affected by moderate-severe OSA compared to mild and non-OSA [64]. Notably, this Aβ burden corresponded to the increased GMV detected in the same areas. This overlapping pattern suggests the likelihood of common underlying mechanisms, based on early neurodegenerative processes owing to AD pathology. Indeed, SDB-

associated neuroinflammatory processes and neuronal hyperactivity may be the basis for the increased Aβ production and accumulation. Therefore, greater GMV and neuronal metabolism colocalized with amyloid deposition may induce the development of neuronal injury, such as hypometabolism and atrophy [64].

Longitudinal studies were performed based on the conclusions of the aforementioned controlled studies. Compared with CN individuals, patients with OSA present an increasing trend in Aβ deposits, as shown by a two-year longitudinal follow-up study that reported statistical significance for CSF $A\beta_{42}$ levels but not for amyloid PET uptake. This could be attributed to the small number of patients included in this subset analysis [10,115]. Furthermore, patients with MCI with comorbid OSA have been reported to show increased Aβ deposition compared to those without OSA (mean follow-up of 2.52 years) [116].

EDS is a frequent symptom in patients with OSA [117]. Two longitudinal studies investigated brain amyloid deposition in CN adults or elderly individuals [117,118]. EDS was defined as either an Epworth Sleepiness Scale (ESS) score of at least 10 [117] or as positive answers to questions related to falling asleep or napping [118]. Although both methods have some limitations (despite being widely validated, ESS is not considered as the best instrument for EDS assessment in elderly or cognitively impaired subjects; direct questions might not reflect the actual situation), both studies reported an association between EDS and longitudinal amyloid load increase. However, EDS might be associated with OSA in the elderly; furthermore, it might be related to conditions other than OSA, including mood disorders, insufficient sleep, and circadian rhythm alterations [119–121].

Tau PET studies

Tau PET imaging has been proposed as a validated instrument for the identification of tau NFT pathology in AD, and thus it appears in the AD diagnostic criteria [91]. Only one study on tau NFT deposition was performed in patients with OSA and did not report differences between the patients and controls [114]. Since further investigations examining the evidence on the correlation between p-tau in CSF and tau PET imaging are needed in AD, tau PET imaging studies in patients with OSA should be delayed until validation of tau PET in AD.

The effects of CPAP therapy on AD biomarkers

CPAP is the gold standard treatment for OSA, especially for moderate-severe OSA and OSA with comorbid EDS. CPAP has been reported to reduce several health consequences of OSA. Furthermore, CPAP treatment has been shown to improve the cardiovascular and cerebrovascular responses, inflammation, and cognitive performance [122].

Consistent with the objectives of this review, we focus on the effects of CPAP treatment on AD biomarkers in patients with OSA. However, there has been no study on the effects of other OSA treatments, e.g., surgery or oral appliance, on AD biomarkers.

CPAP and neuropsychological functioning

There have been conflicting reports on the effect of CPAP on neuropsychological functioning in patients with OSA. Most studies documented an improvement of attention and vigilance; however, there are inconsistent reports on improvements in global cognitive functions, executive function, and memory [123]. The recent review by Bubu et al. [23] analyzed seven studies in young and middle-aged adults and four in elderly patients confirming the substantial heterogeneity in the outcomes, particularly in the latter group, which does not permit definition of the effects of CPAP on cognition. In addition to methodological issues (study design, population, inclusion and exclusion criteria, cognitive testing), the inconsistency could be attributed to two major variables namely CPAP treatment duration and adherence (measured as hours per night). The minimum CPAP treatment duration required to induce cognitive improvement was initially reported to be approximately three months; however, in more recent studies it can vary from 1–2 wks to 12 months [23]. The adherence effects appear to be more complex since memory deficit reversal has been reported with optimal CPAP treatment levels; furthermore, undergoing more than 6 h of therapy seems to be necessary for significant improvement [124].

Regarding the use of CPAP in patients with MCI and AD, a few case series and studies have investigated the effects of CPAP on neuropsychological functioning. Ancoli-Israel et al. compared 27 patients with AD randomized to three weeks of therapeutic CPAP vs. 25 treated with sham-CPAP and documented the improvement of episodic verbal learning, memory, and executive function in the therapeutic CPAP group, but there was no significance after the randomization [125].

In a smaller group, but with a longer follow up, Cooke et al. compared five patients with AD+OSA treated with CPAP to six patients with AD+OSA who discontinued CPAP [126]. After a mean follow-up period of 13.3 months, the CPAP+ group showed less cognitive decline and an improvement in sleepiness, sleep quality, and behavioral symptoms. Similarly, Troussiere et al. [127] assessed 14 patients with mild-to-moderate AD with comorbid severe OSA and reported that after a three-year follow-up period, CPAP treatment reduced the median annual decline in the Mini-Mental State Examination scores (used to globally quantify the cognitive status) compared to that in the non-CPAP group (nine individuals) [127].

A study on the PROOF cohort reported the CPAP effects on neuropsychological test scores in a population with high AD risk, including individuals aged ≥65 years. This study conducted a 10-year follow-up on 126 patients with OSA (26% undergoing CPAP treatment) and found a significant improvement in the mental agility and memory performance in the treated patients, which suggests an association between CPAP therapy and memory performance maintenance in elderly individuals [128].

In 2019, Richards et al. published a quasi-experimental pilot study to determine whether CPAP treatment had an effect on cognitive and daily functions after one year in older adults with MCI. In this study, 54 participants aged 55–89 years with an AHI ≥10 were allocated to the following groups: MCI+CPAP group (29 individuals) and MCI-CPAP group (25 individuals). There were significant improvements in the psychomotor/cognitive processing speed in the MCI+CPAP group compared with the MCI-CPAP group one year after adjustment; furthermore, they reported small to moderate effect sizes for memory, attention, daytime sleepiness, and everyday function [129].

These findings suggest that OSA treatment with optimal compliance could improve cognitive function after an adequate follow-up. However, the small number of studies, small sample sizes, and short follow-up duration should be taken into consideration; thus, further studies are required. In patients with MCI or mild-to-moderate AD, preliminary evidence suggests that CPAP treatment may slow the rate of global cognitive decline [130].

CPAP and CSF biomarkers

A preliminary cross-sectional observational study reported that patients with SCI with comorbid OSA undergoing CPAP treatment presented normal CSF levels of t-tau, p-tau, and $A\beta_{42}$, which suggested that CPAP treatment could restore, stop, or prevent AD biomarker changes in patients with OSA [33]. In this study, 10

patients with OSA presenting SCI and undergoing CPAP treatment had CSF AD biomarker levels comparable to those in controls; moreover, the patients showed higher $A\beta_{42}$ levels and lower t-tau and p-tau levels compared to those in patients with untreated OSA [33]. Furthermore, CPAP treatment was shown to be beneficial based on the other evaluated parameters, including cognitive performance, CSF lactate levels, and sleep architecture.

Only one study and one case report have reported the effects of CPAP treatment on CSF AD biomarkers in patients with OSA [131,132]. The study involved a small number of patients (n = 18) who underwent CPAP treatment and completed the study [132]. There was no significant change in CSF $A\beta_{42}$ and $A\beta_{40}$ levels after CPAP treatment; however, there was a correlation between a greater OSA (AHI) improvement and reduced CSF $A\beta_{42}$ and $A\beta_{40}$ levels. In contrast, there was a negative correlation between changes in CSF t-tau levels and AHI improvement [132]. Therefore, the authors suggested a model whereby OSA can affect both the production and clearance of Aβ and that CPAP can improve both affected mechanisms.

The single case report indicated that one-year CPAP treatment of patients with severe OSA improved the sleep architecture and cognitive symptoms. These effects were associated with increased CSF $A\beta_{42}$ and $A\beta_{40}$ levels (from pathological to normal levels); moreover, CPAP therapy reduced the CSF t-tau, p-tau, and orexin levels [131].

This preliminary evidence indicates that CPAP might restore pathological changes in CSF AD biomarkers in patients with OSA; furthermore, this effect seems to be mediated by nocturnal sleep improvement and is probably driven by amelioration of slow-wave sleep (SWS) [132].

CPAP and neuroimaging

VBM studies have shown insignificant GMV differences in patients with OSA after CPAP treatment. After correction for multiple comparisons, O' Donoghue et al. reported that there were no GMV changes after a six-month CPAP treatment [133]. Subsequent studies did not confirm these findings. A study on 17 treatment-naive patients with OSA and 15 age-matched healthy controls reported an association of neuropsychological impairments with focal GMV reductions in the left hippocampus (entorhinal cortex), left posterior parietal cortex, and right superior frontal gyrus. Further, three-month CPAP treatment was shown to induce neuropsychological improvements and a parallel GMV increase in the hippocampal and frontal structures [134]. Another study on 27 patients with moderate-to-severe OSA showed no significant differences in GMV properties between the CPAP and sham CPAP treatment groups [135]. Finally, a long-term study (mean CPAP therapy duration: 18.2 ± 12.4 months; range 8–44 months) reported widespread neocortical and cerebellar atrophy in patients with OSA compared with controls; further, it reported that the treatment-induced volume increase was correlated with longer treatment duration [136]. However, there was a post-treatment volume increase in the areas overlying the hippocampal dentate gyrus and cerebellar dentate nucleus with a dissimilar initial atrophy pattern. This finding might not only indicate recovery, but also a possible secondary compensatory neurogenesis process [137].

With regard to DTI, a single study documented the diffuse reduction of WM fiber integrity, reflected by diminished FA, in 17 untreated consecutive patients with moderate-severe OSA compared to 15 healthy controls. In the longitudinal analysis, WM fiber integrity did not recover at the three-month follow-up analysis, but completely reverted in patients compliant to CPAP treatment at the 12-month follow-up [132].

Hence, FA observed using the DTI technique could represent a biomarker reflecting the beneficial effect of CPAP on WM integrity. Conversely, data on VBM seem less promising. However, data are extremely scarce to draw more than a research agenda point.

CPAP and nuclear medicine imaging studies

There have been few brain nuclear medicine imaging studies on the effects of CPAP treatment. In this review, we report only one study on 13 patients with SDB who underwent FDG-PET at baseline and at the three-month follow-up under CPAP treatment [111]. Baseline data from this study has been mentioned previously in this review, specifically, there was a post-treatment increase in cerebral glucose metabolism in the bilateral precentral gyri and left anterior cingulate cortices. There were no post-treatment improvements in cerebral FDG uptake; however, this study had a short follow-up and subsequent studies with longer follow-up periods were not repeated. Furthermore, this study found no correlation between the mean change in some parameters, including AHI, sleep quality, and ESS, as well as glucose metabolism changes, indicating that the improvement in AHI, sleep patterns, and daytime sleepiness was not related to changes in brain FDG uptake. Notably, this study analysis could be affected by its short follow-up and small sample size.

With respect to studies on Aβ pathology in patients with OSA, there has been no evidence regarding the potential of CPAP treatment to reverse Aβ deposition. Elias et al. did not report changes in florbetaben uptake between patients using (n = 24) and not using (n = 14) CPAP. Similar findings were reported for PET tracers measuring tau NFT pathology [114]. However, the two groups were not well balanced; therefore, further studies are required to allow stronger conclusions.

Hypothetical model connecting OSA to the increased risk for AD

Based on the aforementioned findings, OSA can be suggested to promote AD. However, its consequences, rather than the sleep disorder itself, can be associated with the pathological biomarker changes.

Sleep impairment and deprivation, SWS disruption, glymphatic system dysfunction, IH, and increased intrathoracic and intracranial pressure due to apnea events could be triggering events for AD neuropathological changes.

Briefly, sleep deprivation (specifically studies assessing one night of sleep deprivation) has been associated not only with pathological changes in CSF Aβ levels but also with increased brain Aβ deposition [18,87,138]. The relationship between sleep quality and continuity reduction (featuring the OSA condition) with Aβ pathology could be mainly associated with glymphatic system dysfunction. This system, which has been widely described since its discovery, cleanses the brain from toxic substrates that accumulate during wakefulness [39]. This clearance is mediated by the capillary-venular system, which drains these pathological proteins and substances from the brain to the venous system [39]. In patients with OSA, increased intrathoracic and intracranial pressure resulting from apnea-hypopnea events has been reported to reduce the ability of the venous system to drain blood and toxic substrates from the brain, which alters glymphatic system activity [139]. IH occurs concomitantly with pathological modification of Aβ metabolism given that it promotes secretase activity to induce β-cleaving of APP and reduces γ-secretase activity (Fig. 1) [140,141].

Further, it can be speculated that sleep quality reduction associated with REM and SWS impairment coupled with cerebrovascular reactivity dysregulation might induce glymphatic system damage. Concomitantly, SWS impairment increases neuronal

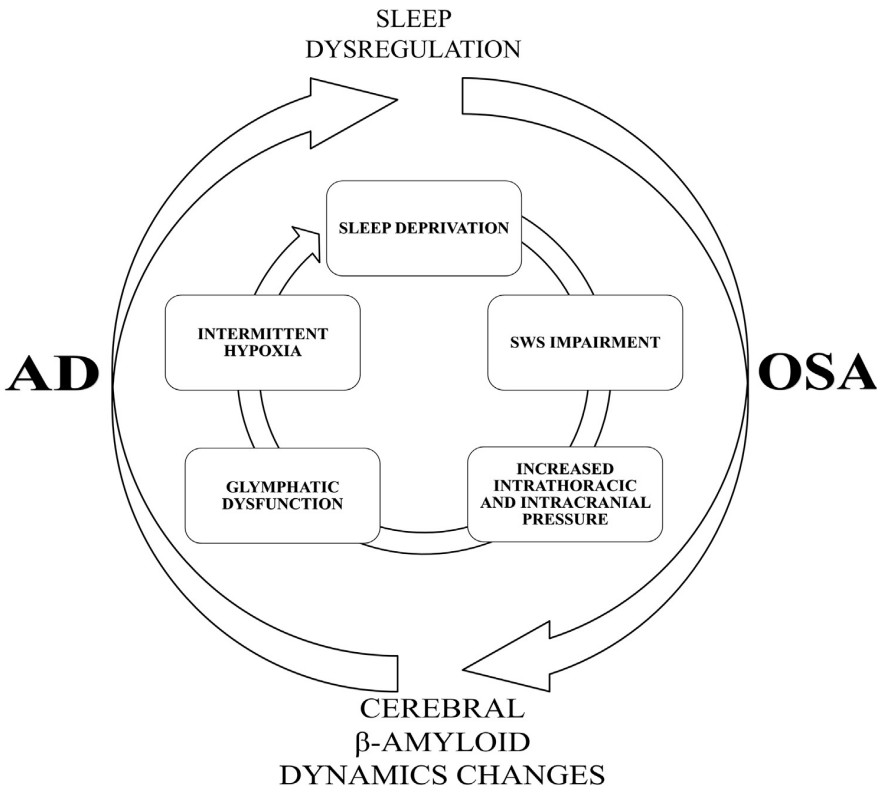

Fig. 1. Graphical model showing the interplay among the main factors inducing AD pathology in patients with OSA.

activity while reduced REM sleep promotes orexin system signaling [142]. Increased orexin activity is associated with Aβ accumulation in the interstitial fluid, which is probably induced by reduced sleep quality and increased wakefulness during the sleeping period, as demonstrated in animal model studies [70,71]. Increased brain Aβ deposition concurrently impairs sleep quality through cholinergic circuit alteration, which subsequently reduces sleep quality and continuity and impairs REM sleep (Fig. 2) [142,143].

The discussed findings indicate that several mechanisms might contribute to AD pathological changes in patients with OSA; however, they are currently merely hypotheses. There is a need for future animal model and/or human studies. Further, since CPAP is a treatment option for OSA, future studies could use the hypothesis that it improves the aforementioned pathological modifications.

OSA and AD risk: relevant future directions related to sex-based differences

In 2014, a report from the Society for Women's Health Research emphasized the importance of considering the role of sex differences in sleep habits and disturbances at any age [144]; however, we are still far off producing significant literature evidence about this topic.

Preparing this review, a question about the interconnection between OSA and AD diagnosis was raised and was related to the evidence that OSA is more frequent in the male population whereas AD is more frequently diagnosed in the female population.

Based on the evidence that OSA may represent a risk factor for AD, the present review focuses on AD biomarkers in patients with OSA [17]. However, there is a need to determine how to connect differences in the sex distribution of OSA (predominantly affecting men) and AD (more frequent in women). There is a significantly higher AD prevalence in women; specifically, almost two-thirds of patients with AD are women [145]. However, age-based stratification of the AD population yields conflicting results on the incidence rate, since the Cache County Study in the USA reported a higher AD incidence in men up to the age of 78 years and in women after this age [145]. Two studies in Europe and Asia have confirmed a higher AD incidence in women aged 80–85 years [145]. The rate of progression from MCI to AD is similar in both sexes from the age of 70–79 years but is higher in women aged >80 years. Conversely, it is well known that OSA is more prevalent in men than women [146]. In keeping with this evidence, the HypnoLaus study recently documented that moderate-severe SDB (AHI $\geq$15/h) is present in 49.7% of the male population and 23.4% of the female population [8]. Notably, post-menopausal women more frequently present SDB than younger women; moreover, compared to men, women in the post-menopausal category less frequently show EDS (measured by ESS) and are older [8]. Accordingly, it has already been documented that the prevalence of OSA in women increases significantly after menopause [147]. Similarly, the onset of menopause in women increases their risk of AD, possibly due to depletion of estrogens, hypertension, increased endothelial dysfunction, and systemic inflammation, among others [148]. These factors are also triggered by OSA, and therefore it appears evident that OSA and AD can share complex pathomechanisms, but the sex-based difference in the prevalence and OSA-induced symptoms remains unresolved [1].

One of the first reports on these topics documented a significant association between OSA and AD in women, but not in men [29]. This study underlines the importance of IH, more than sleep fragmentation, in connecting OSA to dementia risk [29]. However, the

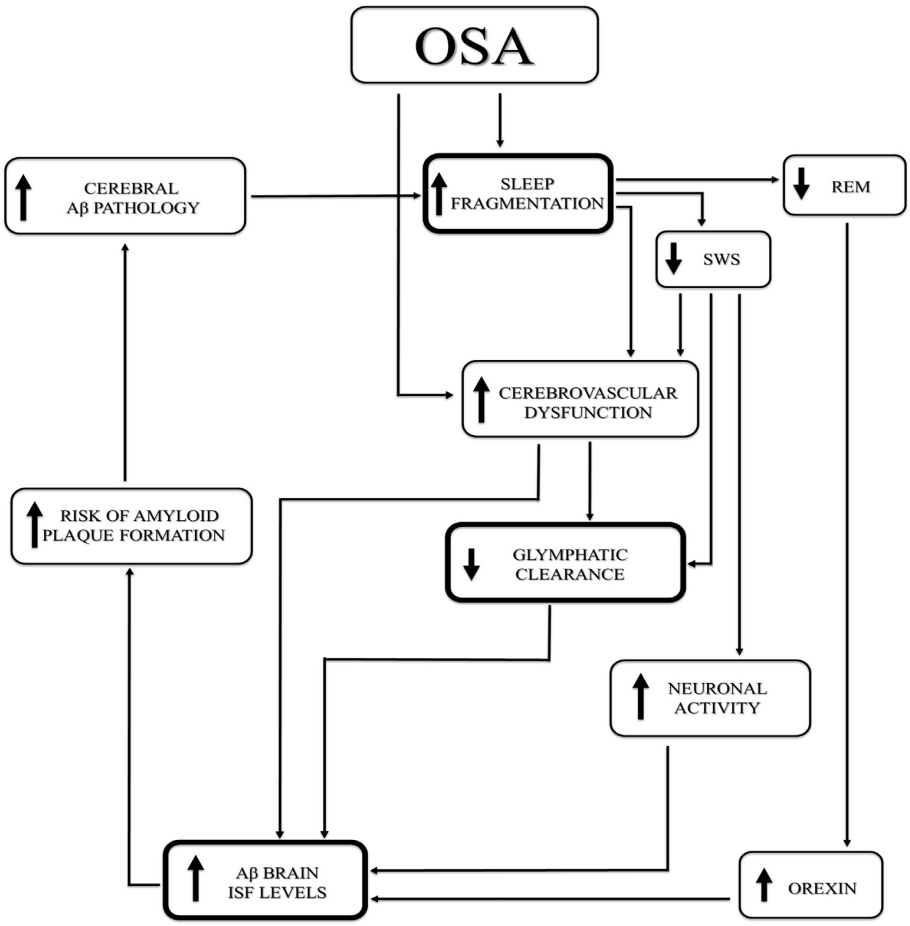

Fig. 2. Schematic diagram of the possible cascade of OSA-induced events involving sleep impairment, brain dynamics, and AD pathology.

beneficial role of sleep in neurodegenerative processes has been widely stated, and sleep fragmentation reduces the effects of the glymphatic system. Women with OSA report insomnia more frequently than men, due to more prolonged partial upper airway obstructions and apnea-hypopnea events during REM, inducing arousals and sleep fragmentation [149,150]. Therefore, in women, the high sleep fragmentation induced by OSA may increase the glymphatic system dysregulation and related risk of neurodegeneration.

The severity of OSA only may not reflect the detrimental effects of apneas and hypopneas on brain health. Accordingly, recent reports documented that AHI is not the best parameter to evaluate OSA severity, in particular in women [150]. The global impact of OSA is indeed completely different in women than in men. Overall, women tend to appear more symptomatic with lower AHI scores compared to men; and report more frequently insomnia [150]. On the other hand, EDS and nocturia are more frequent symptoms related to OSA in men [151]. As a consequence of these differences in clinical presentation, OSA is underestimated in women, with a significant diagnostic delay leading to undertreatment, and less change to prevent consequences [150,151].

Finally, women carrying ApoE4 have a four-fold risk of AD compared to men with the same ApoE genotype. Notably, ApoE4 represents the strongest genetic risk factor for late-onset AD and is associated with AD onset at a younger age [152]. The neuropathological basis is represented by the more prevalent amyloid plaques and NFT documented in female than male patients with AD carrying ApoE4 [152]. Consistently, sleep consolidation has been reported to reduce the effects of ApoE4 on AD neuropathology, and considering the more altered sleep quality in women with OSA, this may justify the increased negative impact of OSA on AD in women than men [152]. However, OSA seems to be a risk factor for AD that is independent of the ApoE4 genotype. Moreover, ApoE4 carriers do not show a higher prevalence of OSA diagnosis [10,33,36]. Notably, Sharma et al. reported that AHI, but not ApoE4, is significantly associated with a longitudinal reduction in CSF $A\beta_{42}$ levels in CN subjects with OSA [10]. Therefore, in patients with OSA, AHI might be a stronger risk factor for cerebral amyloidopathy than the ApoE4 genotype [153].

Considering that previous studies proved that women show worse pathological AD biomarkers changes than men, and that the sex difference was particularly pronounced among individuals with

MCI, it has been stated that females may be more susceptible to the clinical manifestation of AD [154]. However, no study investigating AD biomarkers in patients with OSA identifies differences between men and women.

Hence, although women less frequently present moderate-to-severe OSA than men, they could suffer the adverse effects of OSA more than men. This may contribute to explain the increased frequency of AD in the female population. New studies on OSA as a risk factor for AD should be planned considering the sex-based differences in clinical presentation, health consequences, and difference in the severity indexes of OSA in women than men [155].

Conclusions

Consistent reports have shown that OSA is a risk factor for the pathology, progression, and complications of AD. Studies have reported alterations in AD pathology biomarkers (clinical, biofluid, neuroimaging) in patients with OSA; further, some pathological modifications have been shown to indicate a preclinical or early AD stage. Moreover, OSA co-occurring with AD could worsen or accelerate cognitive decline in patients with AD. Therefore, interventions for improving cognition in patients with AD, including the assessment and management/treatment of OSA, could have a positive effect on the activities of daily living. This could help maintain the patient's independence and reduce the burden of caregivers and related costs. Moreover, in the future, the diagnosis of moderate-severe OSA in patients with SCI and CPAP treatment could permit the restoration of cognitive complaints and possibly stop or reverse the AD pathological cascade, i.e., alterations in the brain Aβ dynamics. This review indicates there is a need for more studies to better understand the potential of screening and treatment of moderate-to-severe OSA in the adult and elderly populations with or without cognitive decline, also focusing on sex differences. Moreover, considering the frequent comorbidity between OSA and SCI, MCI or AD, clinicians working in centers treating (and possibly preventing) dementia should implement their diagnostic work-up by using standardized methods with PSG as a gold standard in order to detect OSA and treat it by involving sleep medicine experts. Hence, the cooperation between sleep medicine and dementia experts may open new frontiers in preventing and delaying the onset of cognitive impairment in the adult and elderly populations.

Practice points

1. Patients with cognitive decline (from SCI to MCI and dementia) should undergo OSA screening since it represents a risk factor for cognitive impairment or cognitive symptom progression.
2. CPAP treatment should be started in MCI and AD patients with comorbid OSA, since it could ameliorate disease progression by modulating the neurodegenerative processes and maintaining the stability of cognitive ability.
3. Sleep medicine and sleep assessment instruments should be considered as diagnostic and potentially therapeutic *armamentarium* for cognitive impairment given the association of OSA diagnosis with the presence of biomarkers consistent with AD pathology from the very early stage of the disease.

Research agenda

1. There is a need for prospective and longitudinal studies to investigate the effects of CPAP treatment on AD biomarkers in patients with OSA.
2. Further, studies should evaluate differences in patients with AD stratified according to the presence/absence of OSA with regard to the neuropsychological profile and cognitive decline rate.
3. There is a need for multimodal studies on AD biomarkers [see A-T-N(-C) classification] in patients with OSA to evaluate a possible longitudinal profile.
4. Although there have been prospective studies on Aβ, there is a need for prospective longitudinal (and therapeutic) studies on plasma tau levels (more feasible than CSF assessments) in patients with OSA, which could further elucidate the pathogenic mechanisms.
5. There is a need for therapeutic studies on the effects of CPAP on cognitive decline in patients with MCI/early stage AD using larger populations (possibly multicenter studies), longer follow-up periods (>one year), and different biomarkers (see above).
6. Most of the studies assessed patients with moderate-to-severe OSA. Further studies should investigate the effect of mild OSA (highly prevalent in the adult-elderly population) and account for the effects of other OSA treatments (e.g., oral appliance therapy).
7. Further studies are needed to assess sex aspects in the relationship among OSA, cognitive decline, and alterations in AD biomarkers, mainly considering the different detrimental effects of apnea-hypopnea events in women compared to men.

Author contributions

Claudio Liguori: conception of the review; manuscript drafting, preparation of tables and figures.

Biancamaria Guarnieri, Michelangelo Maestri: manuscript drafting.

Matteo Spanetta: preparation of tables and figures, manuscript drafting.

Nicola Biagio Mercuri, Enrica Bonanni, Fabio Placidi: critical revision of the manuscript for important intellectual content.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Acknowledgements/Funding sources

All authors have no financial disclosures.

All authors thank the Italian scientific societies AIMS and SINdem for the support in the research strategies for evaluating the interplay between sleep disorders and dementia.

References

[1] Daulatzai MA. Evidence of neurodegeneration in obstructive sleep apnea: relationship between obstructive sleep apnea and cognitive dysfunction in the elderly. J Neurosci Res 2015 Dec;93(12):1778–94.

[2] Polsek D, Gildeh N, Cash D, Winsky-Sommerer R, Williams SCR, Turkheimer F, et al. Obstructive sleep apnoea and Alzheimer's disease: in search of shared pathomechanisms. Neurosci Biobehav Rev 2018 Mar;86:142–9.

[3] Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001 Mar;163(3 Pt 1):608–13.

[4] Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep 1997 Sep;20(9):705–6.

[5] Zamarrón C, Gude F, Otero Y, Alvarez JM, Golpe A, Rodriguez JR. Prevalence of sleep disordered breathing and sleep apnea in 50- to 70-year-old individuals. A Surv Respir 1999;66(4):317–22.

[6] Villaneuva AT, Buchanan PR, Yee BJ, Grunstein RR. Ethnicity and obstructive sleep apnoea. Sleep Med Rev 2005 Dec;9(6):419–36.

[7] Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev 2017 Aug;34:70–81.

[8] Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015 Apr;3(4):310–8.

[9] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. 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 2012 Oct 15;8(5):597–619.

*[10] Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, et al. Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly. A longitudinal study. Am J Respir Crit Care Med 2018 Apr 1;197(7):933–43.

[11] Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008 Feb 15;5(2):136–43.

[12] Floras JS. Hypertension and sleep apnea. Can J Cardiol 2015 Jul;31(7):889–97.

[13] Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the Art review. Chest 2017 Nov;152(5):1070–86.

[14] Ryan S. Adipose tissue inflammation by intermittent hypoxia: mechanistic link between obstructive sleep apnoea and metabolic dysfunction. J Physiol 2017 Apr 15;595(8):2423–30.

[15] Liguori C, Mercuri NB, Izzi F, Romigi A, Cordella A, Piccirilli E, et al. Obstructive sleep apnoea as a risk factor for osteopenia and osteoporosis in the male population. Eur Respir J 2016 Mar;47(3):987–90.

[16] Sharma S, Culebras A. Sleep apnoea and stroke. Stroke Vasc Neurol 2016 Dec 19;1(4):185–91.

[17] Shi L, Chen SJ, Ma MY, Bao YP, Han Y, Wang YM, et al. Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. Sleep Med Rev 2018 Aug;40:4–16.

[18] Ju YE, McLeland JS, Toedebusch CD, Xiong C, Fagan AM, Duntley SP. Sleep quality and preclinical Alzheimer disease. JAMA Neurol 2013;70(5):587–93.

[19] Lucey BP, McCullough A, Landsness EC, Toedebusch CD, McLeland JS, Zaza AM, et al. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. Sci Transl Med 2019 Jan;9(474):11.

[20] Liguori C, Spanetta M, Izzi F, Franchini F, Nuccetelli M, Sancesario GM, et al. Sleep-wake cycle in Alzheimer's disease is associated with tau pathology and orexin dysregulation. J Alzheimers Dis 2020;74(2):501–8.

[21] Molinuevo JL, Rabin LA, Amariglio R, Buckley R, Dubois B, Ellis KA, et al. Implementation of subjective cognitive decline criteria in research studies. Alzheimers Dement 2017 Mar;13(3):296–311.

[22] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011 May;7(3):263–9.

[23] Bubu OM, Andrade AG, Umasabor-Bubu OQ, Hogan MM, Turner AD, de Leon MJ, et al. Obstructive sleep apnea, cognition and Alzheimer's disease: a systematic review integrating three decades of multidisciplinary research. Sleep Med Rev 2020 Apr;50:101250.

[24] Baril AA, Carrier J, Lafrenière A, Warby S, Poirier J, Osorio RS, et al. Biomarkers of dementia in obstructive sleep apnea. Sleep Med Rev 2018 Dec;42:139–48.

[25] Veitch DP, Weiner MW, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. Understanding disease progression and improving Alzheimer's disease clinical trials: recent highlights from the Alzheimer's Disease Neuroimaging Initiative. Alzheimers Dement 2019 Jan;15(1):106–52.

*[26] Guarnieri B, Adorni F, Musicco M, Appollonio I, Bonanni E, Caffarra P, et al. Prevalence of sleep disturbances in mild cognitive impairment and dementing disorders: a multicenter Italian clinical cross-sectional study on 431 patients. Dement Geriatr Cognit Disord 2012;33(1):50–8.

[27] Senaratna CV, Perret JL, Matheson MC, Lodge CJ, Lowe AJ, Cassim R, et al. Validity of the Berlin questionnaire in detecting obstructive sleep apnea: a systematic review and meta-analysis. Sleep Med Rev 2017 Dec;36:116–24.

[28] Bombois S, Derambure P, Pasquier F, Monaca C. Sleep disorders in aging and dementia. J Nutr Health Aging 2010 Mar;14(3):212–7.

[29] Reynolds 3rd CF, Kupfer DJ, Taska LS, Hoch CC, Sewitch DE, Restifo K, et al. Sleep apnea in Alzheimer's dementia: correlation with mental deterioration. J Clin Psychiatr 1985 Jul;46(7):257–61.

[30] Emamian F, Khazaie H, Tahmasian M, Leschziner GD, Morrell MJ, Hsiung GY, et al. The association between obstructive sleep apnea and Alzheimer's disease: a meta-analysis perspective. Front Aging Neurosci 2016 Apr 12;8:78.

[31] Osorio RS, Gumb T, Pirraglia E, Varga AW, Lu SE, Lim J. Sleep-disordered breathing advances cognitive decline in the elderly. Neurology 2015 May 12;84(19):1964–71.

[32] Mubashir T, Abrahamyan L, Niazi A, Piyasena D, Arif AA, Wong J, et al. The prevalence of obstructive sleep apnea in mild cognitive impairment: a systematic review. BMC Neurol 2019 Aug 15;19(1):195.

*[33] Liguori C, Mercuri NB, Izzi F, Romigi A, Cordella A, Sancesario G, et al. Obstructive sleep apnea is associated with early but possibly modificable Alzheimer's disease biomarkers changes. Sleep 2017 May 1;40(5).

[34] Liguori C, Placidi F, Izzi F, Spanetta M, Mercuri NB, Di Pucchio A. Sleep dysregulation, memory impairment, and CSF biomarkers during different levels of neurocognitive functioning in Alzheimer's disease course. Alzheimer's Res Ther 2020 Jan 4;12(1):5.

*[35] Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 2011 Aug 10;306(6):613–9.

[36] Lutsey PL, Misialek JR, Mosley TH, Gottesman RF, Punjabi NM, Shahar E, et al. Sleep characteristics and risk of dementia and Alzheimer's disease: the Atherosclerosis risk in Communities study. Alzheimers Dement 2018 Feb;14(2):157–66.

[37] Pan W, Kastin AJ. Can sleep apnea cause Alzheimer's disease? Neurosci Biobehav Rev 2014 Nov;47:656–69.

[38] Rosenzweig I, Glasser M, Polsek D, Leschziner GD, Williams SC, Morrell MJ. Sleep apnoea and the brain: a complex relationship. Lancet Respir Med 2015 May;3(5):404–14.

[39] Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science 2013 Oct 18;342(6156):373–7.

[40] de la Torre JC. Vascular risk factor detection and control may prevent Alzheimer's disease. Ageing Res Rev 2010 Jul;9(3):218–25.

[41] Gehrman PR, Martin JL, Shochat T, Nolan S, Corey-Bloom J, Ancoli-Israel S. Sleep-disordered breathing and agitation in institutionalized adults with Alzheimer disease. Am J Geriatr Psychiatr 2003 Jul-Aug;11(4):426–33.

[42] O'Hara R, Schröder CM, Kraemer HC, Kryla N, Cao C, Miller E, et al. Nocturnal sleep apnea/hypopnea is associated with lower memory performance in APOE epsilon4 carriers. Neurology 2005 Aug 23;65(4):642–4.

[43] Spira AP, Blackwell T, Stone KL, Redline S, Cauley JA, Ancoli-Israel S, et al. Sleep-disordered breathing and cognition in older women. J Am Geriatr Soc 2008 Jan;56(1):45–50.

[44] Weintraub S, Wicklund AH, Salmon DP. The neuropsychological profile of Alzheimer disease. Cold Spring Harb Perspect Med 2012 Apr;2(4):a006171.

[45] Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL. Blennow K Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014 Jun;13(6):614–29.

[46] Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc 2004 Sep;10(5):772–85.

[47] Beebe DW, Groesz L, Wells C, Nichols A, McGee K. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. Sleep 2003 May 1;26(3):298–307.

[48] Ahuja S, Chen RK, Kam K, Pettibone WD, Osorio RS, Varga AW. Role of normal sleep and sleep apnea in human memory processing. Nat Sci Sleep 2018 Sep 4;10:255–69.

[49] Ferini-Strambi L, Baietto C, Di Gioia MR, Castaldi P, Castronovo C, Zucconi M, et al. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Res Bull 2003 Jun 30;61(1):87–92.

*[50] Torelli F, Moscufo N, Garreffa G, Placidi F, Romigi A, Zannino S, et al. Cognitive profile and brain morphological changes in obstructive sleep apnea. Neuroimage 2011 Jan 15;54(2):787–93.

[51] Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. JAMA Neurol 2017 Oct 1;74(10):1237–45.

[52] Owen JE, BenediktsdÓttir B, Gislason T, Robinson SR. Neuropathological investigation of cell layer thickness and myelination in the hippocampus of people with obstructive sleep apnea. Sleep 2019 Jan 1;42(1).

* The most important references are denoted by an asterisk.

[53] Gaeta AM, Benítez ID, Jorge C, Torres G, Dakterzada F, Minguez O, et al. Prevalence of obstructive sleep apnea in Alzheimer's disease patients. J Neurol 2020 Apr;267(4):1012–22.

[54] Davies CR, Harrington JJ. Impact of obstructive sleep apnea on neurocognitive function and impact of continuous positive Air pressure. Sleep Med Clin 2016 Sep;11(3):287–98.

[55] Kerner NA, Roose SP. Obstructive sleep apnea is linked to depression and cognitive impairment: evidence and potential mechanisms. Am J Geriatr Psychiatr 2016 Jun;24(6):496–508.

[56] Kilpinen R, Saunamäki T, Jehkonen M. Information processing speed in obstructive sleep apnea syndrome: a review. Acta Neurol Scand 2014 Apr;129(4):209–18.

[57] Vaessen TJ, Overeem S, Sitskoorn MM. Cognitive complaints in obstructive sleep apnea. Sleep Med Rev 2015 Feb;19:51–8.

[58] Cross N, Lampit A, Pye J, Grunstein RR, Marshall N, Naismith SL. Is obstructive sleep apnoea related to neuropsychological function in healthy older adults? A systematic review and meta-analysis. Neuropsychol Rev 2017 Dec;27(4):389–402.

[59] Gagnon K, Baril AA, Gagnon JF, Fortin M, Décary A, Lafond C, et al. Cognitive impairment in obstructive sleep apnea. Pathol Biol 2014 Oct;62(5):233–40.

[60] Alchanatis M, Zias N, Deligiorgis N, Amfilochiou A, Dionellis G, Orphanidou D. Sleep apnea-related cognitive deficits and intelligence: an implication of cognitive reserve theory. J Sleep Res 2005 Mar;14(1):69–75.

[61] Olaithe M, Skinner TC, Hillman D, Eastwood PE, Bucks RS. Cognition and nocturnal disturbance in OSA: the importance of accounting for age and premorbid intelligence. Sleep Breath 2015 Mar;19(1):221–30.

[62] Nikodemova M, Finn L, Mignot E, Salzieder N, Peppard PE. Association of sleep disordered breathing and cognitive deficit in APOE ε4 carriers. Sleep 2013 Jun 1;36(6):873–80.

[63] Johnson DA, Lane J, Wang R, Reid M, Djonlagic I, Fitzpatrick AL, et al. Greater cognitive deficits with sleep-disordered breathing among individuals with genetic susceptibility to Alzheimer disease. The multiethnic study of Atherosclerosis. Ann Am Thorac Soc 2017 Nov;14(11):1697–705.

*[64] André C, Rehel S, Kuhn E, Landeau B, Moulinet I, Touron E, et al. Association of sleep-disordered breathing with Alzheimer disease biomarkers in community-dwelling older adults: a secondary analysis of a randomized clinical trial. JAMA Neurol 2020 Mar 23. https://doi.org/10.1001/jamaneurol.2020.0311.

[65] Simrén J, Ashton NJ, Blennow K, Zetterberg H. An update on fluid biomarkers for neurodegenerative diseases: recent success and challenges ahead. Curr Opin Neurobiol 2019 Dec 12;61:29–39.

[66] Fossati S, Ramos Cejudo J, Debure L, Pirraglia E, Sone JY, Li Y, et al. Plasma tau complements CSF tau and P-tau in the diagnosis of Alzheimer's disease. Alzheimers Dement (Amst) 2019 Jun 28;11:483–92.

[67] Ju YE, Finn MB, Sutphen CL, Herries EM, Jerome GM, Ladenson JH, et al. Obstructive sleep apnea decreases central nervous system-derived proteins in the cerebrospinal fluid. Ann Neurol 2016 Jul;80(1):154–9.

[68] Liguori C, Mercuri NB, Nuccetelli M, Izzi F, Cordella A, Bernardini S, et al. Obstructive sleep apnea may induce orexinergic system and cerebral Aβ metabolism dysregulation: is it a further proof for Alzheimer's disease risk? Sleep Med 2019 Apr;56:171–6.

[69] Liguori C, Stefani A, Sancesario G, Sancesario GM, Marciani MG, Pierantozzi M. CSF lactate levels, τ proteins, cognitive decline: a dynamic relationship in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2015 Jun;86(6):655–9.

[70] Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 2009 Nov 13;326(5955):1005–7.

[71] Roh JH, Jiang H, Finn MB, Stewart FR, Mahan TE, Cirrito JR, et al. Potential role of orexin and sleep modulation in the pathogenesis of Alzheimer's disease. J Exp Med 2014;211(13):2487–96.

[72] Naylor E, Aillon DV, Barrett BS, Wilson GS, Johnson DA, Johnson DA, et al. Lactate as a biomarker for sleep. Sleep 2012 Sep 1;35(9):1209–22.

[73] Rempe MJ, Wisor JP. Cerebral lactate dynamics across sleep/wake cycles. Front Comput Neurosci 2015 Jan 14;8:174.

[74] Eidenmüller J, Fath T, Maas T, Pool M, Sontag E, Brandt R. Phosphorylation-mimicking glutamate clusters in the proline-rich region are sufficient to simulate the functional deficiencies of hyperphosphorylated tau protein. Biochem J 2001 Aug 1;357(Pt 3):759–67.

[75] Maas T, Eidenmüller J, Brandt R. Interaction of tau with the neural membrane cortex is regulated by phosphorylation at sites that are modified in paired helical filaments. J Biol Chem 2000 May 26;275(21):15733–40.

[76] Šimić G, Babić Leko M, Wray S, Harrington CR, Delalle I, Jovanov-Milošević N, et al. Monoaminergic neuropathology in Alzheimer's disease. Prog Neurobiol 2017 Apr;151:101–38.

[77] Osorio RS, Ayappa I, Mantua J, Gumb T, Varga A, Mooney AM, et al. Interaction between sleep-disordered breathing and apolipoprotein E genotype on cerebrospinal fluid biomarkers for Alzheimer's disease in cognitively normal elderly individuals. Neurobiol Aging 2014 Jun;35(6):1318–24.

[78] Bubu OM, Pirraglia E, Andrade AG, Sharma RA, Gimenez-Badia S, Umasabor-Bubu OQ, et al. Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes. Sleep 2019 Jun 11;42(6).

[79] Hampel H, O'Bryant SE, Molinuevo JL, Zetterberg H, Masters CL, Lista S, et al. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. Nat Rev Neurol 2018 Nov;14(11):639–52.

[80] Zetterberg H. Applying fluid biomarkers to Alzheimer's disease. Am J Physiol Cell Physiol 2017 Jul 1;313(1):C3–10.

[81] Bu XL, Liu YH, Wang QH, Jiao SS, Zeng F, Yao XQ, et al. Serum amyloid-beta levels are increased in patients with obstructive sleep apnea syndrome. Sci Rep 2015 Sep 9;5:13917.

[82] Motamedi V, Kanefsky R, Matsangas P, Mithani S, Jeromin A, Brock MS, et al. Elevated tau and interleukin-6 concentrations in adults with obstructive sleep apnea. Sleep Med 2018 Mar;43:71–6.

[83] Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O. Cerebrospinal fluid levels of Aβ 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Arch Gen Psychiatr 2012 Jan;69(1):98–106.

[84] Braak H, Zetterberg H, Del Tredici K, Blennow K. Intraneuronal tau aggregation precedes diffuse plaque deposition, but amyloid-β changes occur before increases of tau in cerebrospinal fluid. Acta Neuropathol 2013 Nov;126(5):631–41.

[85] Selkoe DJ. Alzheimer's disease: a central role for amyloid. J Neuropathol Exp Neurol 1994 Sep;53(5):438–47.

[86] Shiota S, Takekawa H, Matsumoto SE, Takeda K, Nurwidya F, Yoshioka Y. Chronic intermittent hypoxia/reoxygenation facilitate amyloid-β generation in mice. J Alzheimers Dis JAD 2013;37(2):325–33.

[87] Ooms S, Overeem S, Besse K, Rikkert MO, Verbeek M, Claassen JA. Effect of 1 night of total sleep deprivation on cerebrospinal fluid Aβ 42 in healthy middle-aged men: a randomized clinical trial. JAMA Neurol 2014;71(8):971–7.

[88] Chen GJ, Xu J, Lahousse SA, Caggiano NL, de la Monte SM. Transient hypoxia causes Alzheimer-type molecular and biochemical abnormalities in cortical neurons: potential strategies for neuroprotection. J Alzheimers Dis 2003 Jun;5(3):209–28.

[89] Egashira N, Iwasaki K, Ishibashi M, Hatip-Al-Khatib I, Wolozin B, Mishima K, et al. Hypoxia enhances beta-amyloid-induced apoptosis in rat cultured hippocampal neurons. Jpn J Pharmacol 2002 Dec;90(4):321–7.

[90] Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016 Jun;15(7):673–84.

[91] Jack Jr CR, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 2016 Aug 2;87(5):539–47.

[92] Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature 2018 Feb 8;554(7691):249–54.

[93] Liguori C, Romigi A, Mercuri NB, Nuccetelli M, Izzi F, Albanese M, et al. Cerebrospinal-fluid orexin levels and daytime somnolence in frontotemporal dementia. J Neurol 2014 Sep;261(9):1832–6.

[94] Kanbayashi T, Inoue Y, Kawanishi K, Takasaki H, Aizawa R, Takahashi K, et al. CSF hypocretin measures in patients with obstructive sleep apnea. J Sleep Res 2003 Dec;12(4):339–41.

[95] Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005 Oct 27;437(7063):1257–63.

[96] Pedrazzoli M, D'Almeida V, Martins PJ, Machado RB, Ling L, Nishino S, et al. Increased hypocretin-1 levels in cerebrospinal fluid after REM sleep deprivation. Brain Res 2004 Jan 2;995(1):1–6.

[97] Williams RH, Jensen LT, Verkhratsky A, Fugger L, Burdakov D. Control of hypothalamic orexin neurons by acid and CO2. Proc Natl Acad Sci U S A 2007 Jun 19;104(25):10685–90.

[98] Sunanaga J, Deng BS, Zhang W, Kanmura Y, Kuwaki T. CO2 activates orexin-containing neurons in mice. Respir Physiol Neurobiol 2009 May 15;166(3):184–6.

[99] Shi Y, Chen L, Chen T, Li L, Dai J, Lui S, et al. A meta-analysis of voxel-based brain morphometry studies in obstructive sleep apnea. Sci Rep 2017 Aug 30;7(1):10095.

[100] Tahmasian M, Rosenzweig I, Eickhoff SB, Sepehry AA, Laird AR, Fox PT, et al. Structural and functional neural adaptations in obstructive sleep apnea: an activation likelihood estimation meta-analysis. Neurosci Biobehav Rev 2016 Jun;65:142–56.

[101] Weng HH, Tsai YH, Chen CF, Lin YC, Yang CT, Tsai YH, et al. Mapping gray matter reductions in obstructive sleep apnea: an activation likelihood estimation meta-analysis. Sleep 2014 Jan 1;37(1):167–75.

[102] Huang X, Tang S, Lyu X, Yang C, Chen X. Structural and functional brain alterations in obstructive sleep apnea: a multimodal meta-analysis. Sleep Med 2019 Feb;54:195–204.

[103] Yeung AWK. Morphometric and functional connectivity changes in the brain of patients with obstructive sleep apnea: a meta-analysis. J Sleep Res 2019 Dec;28(6):e12857.

[104] Baril AA, Gagnon K, Descoteaux M, Bedetti C, Chami S, Sanchez E, et al. Cerebral white matter diffusion properties and free-water with

obstructive sleep apnea severity in older adults. Hum Brain Mapp 2020 Mar 13. https://doi.org/10.1002/hbm.24971.
*[105] Baril AA, Gagnon K, Brayet P, Montplaisir J, De Beaumont L, Carrier J, et al. Gray matter hypertrophy and thickening with obstructive sleep apnea in middle-aged and older adults. Am J Respir Crit Care Med 2017 Jun 1;195(11):1509–18.
[106] Cross NE, Memarian N, Duffy SL, Paquola C, LaMonica H, D'Rozario A, et al. Structural brain correlates of obstructive sleep apnoea in older adults at risk for dementia. Eur Respir J 2018 Jul 4;52(1).
[107] Celle S, Boutet C, Annweiler C, Barthélémy JC, Roche F. Sleep apnoea in the asymptomatic elderly: a real issue for the brain? Eur Respir J 2018 Jun 14;51(6).
[108] Chiba Y, Fujishiro H, Iseki E, Kasanuki K, Sato K. The cingulate island sign in patients with dementia with Lewy bodies or Alzheimer's disease: a direct comparison between 18F-FDG PET and 123I-IMP SPECT. Neurosci Lett 2018 Sep 14;683:168–73.
[109] Dani A, Pietrini P, Furey M, Freo U, Raphaelson M, Alexander GE, et al. Patients with sleep apnea syndrome (SAS) show neuropsychological impairment and regional cerebral glucose metabolic deficits: a pre-treatment positron emission tomography (PET) study. J Sleep Res 1996;5(Suppl. 1):43.
[110] Yaouhi K, Bertran F, Clochon P, Mézenge F, Denise P, Foret J, et al. A combined neuropsychological and brain imaging study of obstructive sleep apnea. J Sleep Res 2009 Mar;18(1):36–48.
[111] Ju G, Yoon IY, Lee SD, Kim YK, Yoon E, Kim JW. Modest changes in cerebral glucose metabolism in patients with sleep apnea syndrome after continuous positive airway pressure treatment. Respiration 2012;84(3):212–8.
[112] Mattsson N, Insel PS, Donohue M, Jagust W, Sperling R, Aisen P, et al. Predicting reduction of cerebrospinal fluid Aβ 42 in cognitively healthy controls. JAMA Neurol 2015 May;72(5):554–60.
[113] Yun CH, Lee HY, Lee SK, Kim H, Seo HS, Bang SA, et al. Amyloid burden in obstructive sleep apnea. J Alzheimers Dis 2017;59(1):21–9.
*[114] Elias A, Cummins T, Tyrrell R, Lamb F, Dore V, Williams R, et al. Risk of Alzheimer's disease in obstructive sleep apnea syndrome: amyloid-β and tau imaging. J Alzheimers Dis 2018;66(2):733–41.
[115] Andrade AG, Bubu OM, Varga AW, Osorio RS. The relationship between obstructive sleep apnea and Alzheimer's disease. J Alzheimers Dis 2018;64(s1):S255–70.
[116] Hogan M, Shim A, Umasabor-Bubu O, Fahad M, Bubu O. Obstructive sleep apnea is associated with longitudinal increases in amyloid burden in elderly mild cognitive impairment individuals. Am J Undergrad Res 2019;15(4):71–7.
[117] Carvalho DZ, St Louis EK, Knopman DS, Boeve BF, Lowe VJ, Roberts RO, et al. Association of excessive daytime sleepiness with longitudinal Aβ accumulation in elderly persons without dementia. JAMA Neurol 2018 Jun 1;75(6):672–80.
[118] Spira AP, An Y, Wu MN, Owusu JT, Simonsick EM, Bilgel M, et al. Excessive daytime sleepiness and napping in cognitively normal adults: associations with subsequent amyloid deposition measured by PiB PET. Sleep 2018 Oct 1;41(10).
[119] Pack AI, Dinges DF, Gehrman PR, Staley B, Pack FM, Maislin G. Risk factors for excessive sleepiness in older adults. Ann Neurol 2006 Jun;59(6):893–904.
[120] Ohayon MM, Mahowald MW, Dauvilliers Y, Krystal AD, Léger D. Prevalence and comorbidity of nocturnal wandering in the U.S. adult general population. Neurology 2012 May 15;78(20):1583–9.
[121] Jaussent I, Morin CM, Ivers H, Dauvilliers Y. Incidence, worsening and risk factors of daytime sleepiness in a population-based 5-year longitudinal study. Sci Rep 2017 May 2;7(1):1372.
[122] Hudgel DW. Critical review: CPAP and weight management of obstructive sleep apnea cardiovascular co-morbidities. Sleep Med Rev 2018 Feb;37:14–23.
[123] Ferini-Strambi L, Marelli S, Galbiati A, Castronovo C. Effects of continuous positive airway pressure on cognition and neuroimaging data in sleep apnea. Int J Psychophysiol 2013 Aug;89(2):203–12.
[124] Zimmerman ME, Arnedt JT, Stanchina M, Millman RP, Aloia MS. Normalization of memory performance and positive airway pressure adherence in memory-impaired patients with obstructive sleep apnea. Chest 2006 Dec;130(6):1772–8.
[125] Ancoli-Israel S, Palmer BW, Cooke JR, Corey-Bloom J, Fiorentino L, Natarajan L, et al. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. J Am Geriatr Soc 2008 Nov;56(11):2076–81.
[126] Cooke JR, Ayalon L, Palmer BW, Loredo JS, Corey-Bloom J, Natarajan L, et al. 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 2009 Aug 15;5(4):305–9.
[127] Troussière AC, Charley CM, Salleron J, Richard F, Delbeuck X, Derambure P, et al. Treatment of sleep apnoea syndrome decreases cognitive decline in patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2014 Dec;85(12):1405–8.
[128] Crawford-Achour E, Dauphinot V, Martin MS, Tardy M, Gonthier R, Barthelemy JC, et al. Protective effect of long-term CPAP therapy on cognitive performance in elderly patients with severe OSA: the PROOF study. J Clin Sleep Med 2015 Apr 15;11(5):519–24.
*[129] Richards KC, Gooneratne N, Dicicco B, Hanlon A, Moelter S, Onen F, et al. CPAP adherence may slow 1-year cognitive decline in older adults with mild cognitive impairment and apnea. J Am Geriatr Soc 2019 Mar;67(3):558–64.
[130] Maestri M, Liguori C, Bonanni E, Guarnieri B. PAP use in mild cognitive impairment to delay progression to dementia. J Clin Sleep Med 2020 Aug 15;16(8):1397. https://doi.org/10.5664/jcsm.8536.
[131] Liguori C, Chiaravalloti A, Izzi F, Nuccetelli M, Bernardini S, Schillaci O, et al. Sleep apnoeas may represent a reversible risk factor for amyloid-β pathology. Brain 2017 Dec 1;140(12):e75.
[132] Ju YS, Zangrilli M, Finn MB, Fagan AM, Holtzman DM. Obstructive sleep apnea treatment, slow wave activity, and amyloid-β. Ann Neurol 2019 Feb;85(2):291–5.
[133] O'Donoghue FJ, Briellmann RS, Rochford PD, Abbott DF, Pell GS, Chan CH, et al. Cerebral structural changes in severe obstructive sleep apnea. Am J Respir Crit Care Med 2005 May 15;171(10):1185–90.
[134] Canessa N, Castronovo V, Cappa SF, Aloia MS, Marelli S, Falini A, et al. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. Am J Respir Crit Care Med 2011 May 15;183(10):1419–26.
[135] Huynh NT, Prilipko O, Kushida CA, Guilleminault C. Volumetric brain morphometry changes in patients with obstructive sleep apnea syndrome: effects of CPAP treatment and literature review. Front Neurol 2014 Apr 29;5:58.
*[136] Kim H, Joo E, Suh S, Kim JH, Kim ST, Hong SB. Effects of long-term treatment on brain volume in patients with obstructive sleep apnea syndrome. Hum Brain Mapp 2016 Jan;37(1):395–409.
[137] Castronovo V, Scifo P, Castellano A, Aloia MS, Iadanza A, Marelli S, et al. White matter integrity in obstructive sleep apnea before and after treatment. Sleep 2014 Sep 1;37(9):1465–75.
[138] Shokri-Kojori E, Wang GJ, Wiers CE, Demiral SB, Guo M, Kim SW, et al. Aβ accumulation in the human brain after one night of sleep deprivation. Proc Natl Acad Sci U S A 2018 Apr 24;115(17):4483–8.
[139] Wostyn P, Van Dam D, Audenaert K, De Deyn PP. Do repetitive Valsalva maneuvers reduce glymphatic clearance? Ann Neurol 2017 Feb;81(2):322.
[140] Liu H, Qiu H, Yang J, Ni J, Le W. Chronic hypoxia facilitates Alzheimer's disease through demethylation of γ-secretase by downregulating DNA methyltransferase 3b. Alzheimers Dement 2016 Feb;12(2):130–43.
[141] Salminen A, Kauppinen A, Kaarniranta K. Hypoxia/ischemia activate processing of Amyloid Precursor Protein: impact of vascular dysfunction in the pathogenesis of Alzheimer's disease. J Neurochem 2017 Feb;140(4):536–49.
[142] Mander BA, Marks SM, Vogel JW, Rao V, Lu B, Saletin JM, et al. Aβ disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. Nat Neurosci 2015 Jul;18(7):1051–7.
[143] Varga AW, Wohlleber ME, Giménez S, Romero S, Alonso JF, Ducca EL, et al. Reduced slow-wave sleep is associated with high cerebrospinal fluid Aβ42 levels in cognitively normal elderly. Sleep 2016 Nov 1;39(11):2041–8.
[144] Mallampalli MP, Carter CL. Exploring sex and gender differences in sleep health: a Society for Women's Health Research Report. J Womens Health (Larchmt). 2014 Jul;23(7):553–62.
[145] Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clin Epidemiol 2014 Jan 8;6:37–48.
[146] Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis 2015 Aug;7(8):1311–22.
[147] Koo P, McCool FD, Hale L, Stone K, Eaton CB. Association of obstructive sleep apnea risk factors with nocturnal enuresis in postmenopausal women. Menopause 2016 Feb;23(2):175–82.
[148] Christensen A, Pike CJ. Menopause, obesity and inflammation: interactive risk factors for Alzheimer's disease. Front Aging Neurosci 2015 Jul 7;7:130.
[149] Won CH, Reid M, Sofer T, Azarbarzin A, Purcell S, White D, et al. Sex differences in obstructive sleep apnea phenotypes, the multi-ethnic study of Atherosclerosis. Sleep 2019 Nov 5. https://doi.org/10.1093/sleep/zsz274. pii: zsz274.
[150] Bonsignore MR, Saaresranta T, Riha RL. Sex differences in obstructive sleep apnoea. Eur Respir Rev 2019 Nov 6;28(154).
[151] Guarnieri B. Sleep disorders and cognitive alterations in women. Maturitas 2019 Aug;126:25–7.
[152] Yesavage JA, Friedman L, Kraemer H, Tinklenberg JR, Salehi A, Noda A, et al. Sleep/wake disruption in Alzheimer's disease: APOE status and longitudinal course. J Geriatr Psychiatr Neurol 2004 Mar;17(1):20–4.
[153] Liguori C, Placidi F. Is it time to consider obstructive sleep apnea syndrome a risk factor for Alzheimer's disease? Am J Respir Crit Care Med 2018 Apr 1;197(7):855–6.
[154] Koran MEI, Wagener M, Hohman TJ, Alzheimer's Neuroimaging Initiative. Sex differences in the association between AD biomarkers and cognitive decline. Brain Imag Behav 2017 Feb;11(1):205–13.
[155] Ferretti MT, Martinkova J, Biskup E, Benke T, Gialdini G, Nedelska Z, et al. Sex and gender differences in Alzheimer's disease: current challenges and implications for clinical practice. Eur J Neurol 2020 Jun;27(6):928–43.