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*Review*

# Biomarkers in Obstructive Sleep Apnoea: Predicting Neurodegenerative Risk and Treatment-Responsive Vulnerability

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**Abstract**

Background: Obstructive sleep apnoea (OSA) is increasingly associated with earlier onset and accelerated trajectories of neurodegenerative change. Mechanistically, this relationship is thought to reflect convergent pathways spanning intermittent hypoxia. Biomarker profiling offers a pragmatic route to interrogate these processes in vivo, providing quantitative indices for risk stratification and for monitoring the biological response to OSA therapy in the context of cognitive decline prevention. Objectives: The present study undertakes a scoping review on the mechanistic links between OSA and neurodegeneration, as well as the utility of biomarkers for risk stratification and monitoring efficacy of treatment to mitigate cognitive decline. Methods: A literature search was conducted using PubMed, Scopus, Embase and Cochrane from January 2000 to February 2026. Search terms included "Obstructive sleep apnoea", "Continuous Positive Airway Pressure", "Uvulopalatopharyngoplasty", "Biomarkers", "Genomics", "Alzheimer Disease" and "Parkinson Disease". We included all studies that analysed biomarker changes in OSA patients and/or the effect of CPAP on biomarkers. Studies with only cognitively impaired cohorts, editorials, opinion pieces, conference abstracts, non-human studies, and non-English studies were excluded. Results: A total of 59 unique studies were included. Forty of them analysed biomarkers involved in the pathophysiology behind neurodegeneration in OSA patients, while 26 described the changes in biomarkers post therapy. Notably, 15 studies were included in both aspects. Lastly, eight studies explored novel applications of multiomics technologies.

**Keywords:** Obstructive Sleep Apnea; biomarkers; cognitive impairment; Continuous Positive Airway Pressure; Parkinson's disease; Alzheimer's disease

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## 1. Introduction

Obstructive sleep apnoea (OSA) is highly prevalent, with global modelling estimates indicating that approximately 936 million adults aged 30–69 years meet the diagnostic criteria for OSA [1], highlighting a substantial yet under-recognised population health burden. Emerging evidence also suggests a bidirectional association between OSA and neurodegenerative diseases [2], particularly in untreated and elderly populations. The pathophysiological cascade linking OSA to neurodegeneration is complex and multifactorial, involving chronic intermittent hypoxia (CIH)-induced oxidative stress, systemic inflammation, disruption of the blood–brain barrier (BBB) and subsequent accumulation of neurotoxic proteins such as alpha-synuclein and amyloid-beta (Aβ) [3].

Continuous positive airway pressure (CPAP) therapy, the cornerstone of OSA management, has the potential to attenuate early cognitive decline and neurodegeneration [4]. This opportunity for early intervention emphasises the need for timely detection of OSA. Consequently, the measurement of candidate biomarkers may facilitate the identification of OSA patients at an increased risk of neurodegenerative conditions and enable the monitoring of therapeutic efficacy.

Currently, there is limited literature illustrating the changes in biomarkers in OSA patients and their correlation to cognitive decline. Given the broad and complex link between OSA and neurodegeneration, this scoping review aims to describe biomarker alterations in OSA, their mechanistic implications in neurodegeneration and changes post therapy. Additionally, we discuss the potential of novel multiomics approaches in advancing this field towards precision therapy.

## 2. Methods

This review has been registered on the Open Science Framework (OSF; registration number: xv72r) and its reporting has been done in alignment with the PRISMA extension for scoping reviews (PRISMA-ScR) guidelines. The PRISMA checklist can be found in Supplementary Table S1.

*Search Strategy*

A literature search was conducted using PubMed, Scopus, Embase and Cochrane from January 2000 to February 2026. Search terms included "Obstructive sleep apnoea", "Continuous Positive Airway Pressure", "Uvulopalatopharyngoplasty", "Biomarkers", "Genomics", "Alzheimer Disease" and "Parkinson Disease". We included all studies that analysed biomarker changes in OSA patients and/or the effect of CPAP on biomarkers. Systematic reviews, as well as studies with cognitively impaired cohorts, clinical trials (including randomised and non-randomised clinical trials), editorials, opinion pieces, conference abstracts, non-human studies, and non-English studies were excluded. The full search strategy can be found in Supplementary Table S2.

All records retrieved from the databases were imported into reference management software (Covidence, 2026), and duplicates were removed. A total of 450 records were identified, of which 217 duplicates were removed, leaving 233 records for title and abstract screening. One hundred and twenty-six records were excluded as they did not meet the eligibility criteria.

One hundred and seven full-text articles were subsequently retrieved and assessed for eligibility. Of these, 64 articles were excluded, with reasons including: review articles (n = 30), abstract only (n = 13), study cohort had cognitive impairments (n = 5), non-human studies (n = 4), lack of mention of biomarkers (n = 3), non-English studies (n = 3), wrong outcomes (n = 5), clinical trial (n = 1). Secondary literature such as systematic reviews or meta-analyses meeting our inclusion criteria were excluded (n = 30); however, their reference lists were screened to identify additional eligible primary studies. We screened the reference list of 11 systematic reviews that fit our inclusion criteria and identified 16 new primary studies that were subsequently included in our scoping review. The final scoping review included 59 unique primary studies (Figure 1).

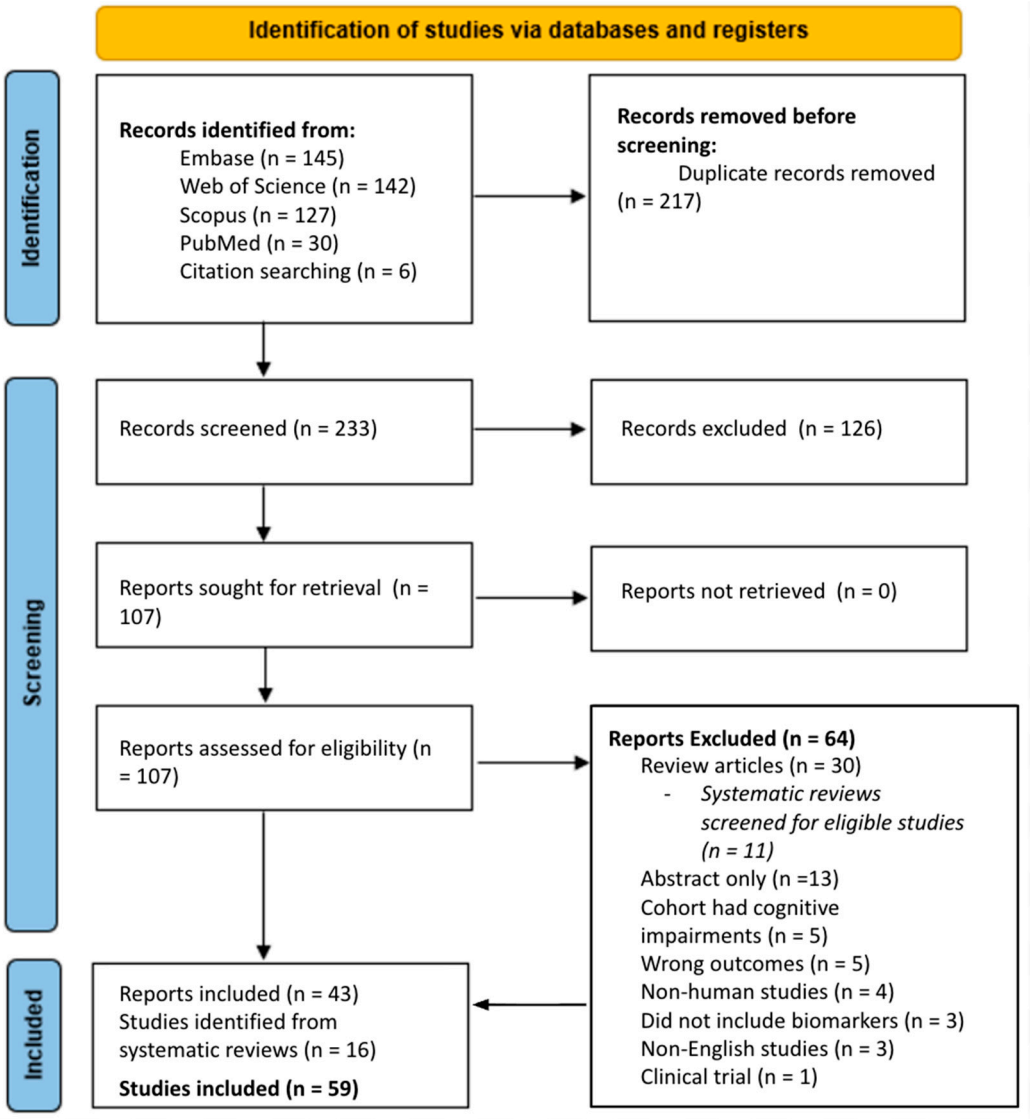



**Figure 1.** PRISMA flow diagram.

Title/abstract and full-text screening were performed independently by the two reviewers Chen Meng Yee (CMY) and Wang Jia Dong James (WJDJ). Data about article characteristics, number of participants and main study outcomes were extracted by CMY into a data extraction form and verified by WJDJ. Disagreements at all stages were resolved through discussion between the two reviewers.

## 3. Results

The studies were grouped based on their main outcomes and classified into three groups: (1) biomarker alterations and mechanistic links between OSA and neurodegeneration, (2) biomarker alterations after therapeutic intervention in OSA, (3) multiomics studies. We summarised the population and study design for each group, along with the broad findings.

A total of 59 unique primary studies were included. Forty of them analysed biomarkers involved in the pathophysiology behind neurodegeneration in OSA patients (Table 1 and Table 2), while 26 described the changes in biomarkers post therapy (Tables 3 and 4). Notably, 15 studies (highlighted in grey) were included in both aspects. Lastly, eight studies explored novel applications of multiomics technologies in this field (Table 5).

OSA has been hypothesised to be linked to the development of cognitive impairment, in particular Alzheimer's dementia (AD), as well as Parkinson's disease (PD) [5]. OSA

was also associated with a higher prevalence of mild cognitive impairment (MCI), with evidence of a severity–prevalence gradient, whereby greater OSA severity corresponded to a higher MCI burden [6]. Beyond cognition, OSA has been implicated in the development and progression of cardiovascular disease [7], obesity [8], and psychiatric disorders [9]—conditions that themselves are associated with elevated neurodegenerative risk. Other shared, non-modifiable risk factors between the two diseases include older age, male sex, family history, and potential genetic susceptibility [10].

Several studies have proposed potential mechanisms by which OSA may contribute to neurodegeneration at a cellular level. Broadly, these involve a complex interplay [11] between systemic inflammation, vascular and endothelial injury, blood–brain barrier (BBB) and glymphatic dysfunction, as well as structural and functional changes within the brain (Figure 2). Existing literature (Table 1) has demonstrated pathological alterations in these potential biomarker levels in patients with OSA, which correlate with measures of OSA severity and cognitive decline.

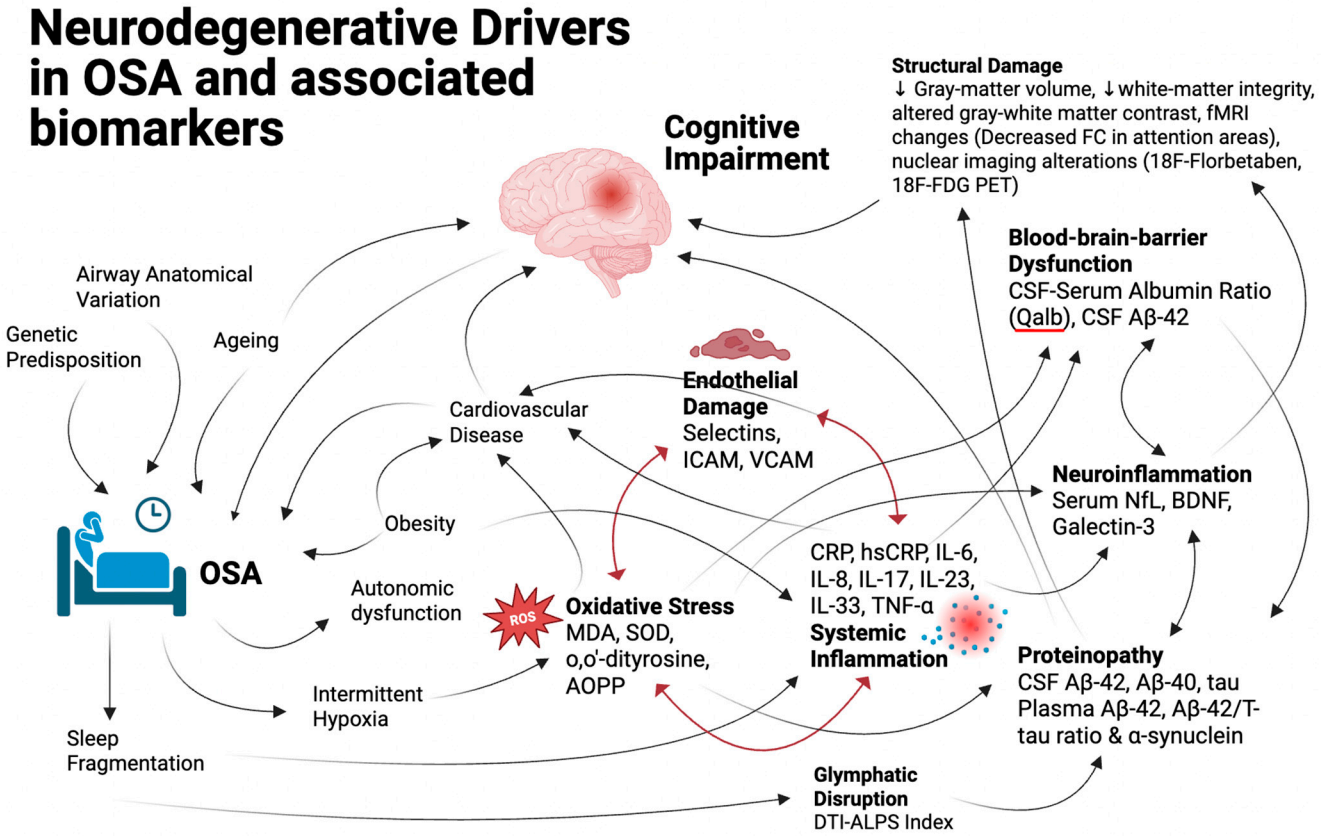



**Figure 2.** Pathophysiology of neurodegeneration in OSA and associated measurable biomarkers. (Created in BioRender. Chen, J. https://BioRender.com/jatxmy1 (accessed on 13 February 2026)). CSF: Cerebrospinal fluid, MDA: Malondialdehyde, SOD: Superoxide dismutase, AOPP: Advanced oxidation protein product, Aβ: Amyloid-beta, ICAM: Intercellular adhesion molecule, VCAM: Vascular cell adhesion molecule, DLTI-ALPS: Diffusion tensor image analysis along the perivascular space, CRP: C-reactive protein, hsCRP: High-sensitivity C-reactive protein, IL: Interleukin, TNF-α: Tumour necrosis factor-alpha, fMRI: Functional magnetic resonance imaging, FC: Functional connectivity, NFL: Neurofilament light chain, BDNF: Brain-derived neurotrophic factor, Qalb: CSF-to-plasma-albumin ratio.

**Table 1.** Studies demonstrating alterations in biomarkers in OSA patients with links to neurodegeneration, endothelial damage, reactive oxygen species and systemic inflammation. (Highlighted rows indicate studies which presented both biomarker alterations in OSA patients compared to controls, as well as changes post CPAP, "↑", "↓" and "-" represent an increase, decrease and unchanged level of each biomarker, respectively).

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Studies about Neuroinflammation (n = 20) | | | | | |
| Liguori et al. 2017 [12] | Obstructive Sleep Apnea is Associated With Early but Possibly Modifiable Alzheimer's Disease Biomarkers Changes | Longitudinal | 50 | • CSF Aβ42 ↓<br>• CSF lactate ↑ | • OSA patients showed lower CSF Aβ42 concentrations, higher CSF lactate levels, and higher t-tau/Aβ42 ratio compared to controls and OSA-CPAP patients.<br>• Lower CSF Aβ42 levels were associated with hypoxia measures (mean $SaO_2$ levels: r = 0.62, $p$ = 0.001) and lower cognitive scores (I-RAVL: r = 0.79, $p < 0.0001$; D-RAVL: r = −0.75, $p < 0.0001$; Raven: r = 0.70, $p$ = 0.0001).<br>• CSF t-tau was associated with PSG indices (total sleep time: r = −0.77, $p < 0.0001$; sleep efficiency: r = −0.66, $p < 0.001$; wake after sleep onset: r = 0.60, $p$ = 0.001). |
| Osorio et al. 2014 [13] | The interaction between sleep-disordered breathing and apolipoprotein E genotype on cerebrospinal fluid biomarkers for Alzheimer's disease in cognitively normal elderly individuals. | Case–control | 95 | • CSF Aβ42 –<br>• CSF p-tau –<br>• CSF t-tau – | • There were no significant differences in CSF Aβ42 (619.4 ± 252.3 vs. 607.1 ± 209.4, $p > 0.05$), $p$-tau (46.4 ± 18.6 vs. 39.3 ± 14.6, $p > 0.05$) and t-tau (289.1 ± 130.0 vs. 250.6 ± 115.7, $p > 0.05$) levels between OSA and healthy adults.<br>• AHI4% (AHI with hypopnoeas restricted to respiratory events associated with 4% desaturation) was poorly correlated with CSF Aβ42 (r = 0.07, $p$ = 0.52). |
| Sharma et al. 2018 [14] | Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly: A Longitudinal Study. | Longitudinal | 208 | • CSF Aβ42 –<br>• CSF p-tau –<br>• CSF t-tau – | • There were no significant differences between CSF Aβ42 (657.48 ± 224.79 vs. 681.88 ± 243.18, $p > 0.05$) and t-tau (40.97 [31.71,49] vs. 42.50 [31.5,52.05], $p > 0.05$) between OSA and healthy elderly.<br>• Significant correlations were observed between longitudinal change in CSF Aβ42 levels and AHI (ρ = −0.24, $p < 0.05$). |
| Ju et al. 2016 [15] | Obstructive Sleep Apnea decreases Central NervousSystem–Derived Proteins in the Cerebrospinal Fluid. | Case–control | 41 | • CSF Aβ42 ↓<br>• CSF Aβ40 ↓<br>• CSF VILIP-1 ↓<br>• CSF Neurogranin ↓<br>• CSF p-tau –<br>• CSF tau – | • OSA patients had significantly lowered CSF Aβ40 (7900 ± 2483 vs. 11,208 ± 3420, $p$ = 0.003), Aβ42 (717 ± 143 vs. 914 ± 224, $p$ = 0.013), visinin-like protein 1 (VILIP-1) (104 ± 42 vs. 144 ± 52, $p$ = 0.040) and neurogranin (1330 ± 814 vs. 2199 ± 1135, $p$ = 0.039).<br>• CSF tau (167 ± 80 vs. 221 ± 92, $p$ = 0.098) and pTau181 (32 ± 13 vs. 42 ± 14, $p$ = 0.054) were unchanged. |

**Table 1.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Bubu et al. 2019 [16] | Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes | Longitudinal | 1639 | • CSF Aβ42 –<br>• CSF t-tau –<br>• CSF p-tau – | • In cognitively normal adults with OSA, there was no significant difference in CSF Aβ42, t-tau or p-tau compared to healthy adults.<br>• OSA patients experienced faster annual decreases in CSF Aβ42 levels as well as increases in CSF t-tau and p-tau. |
| Fernandes et al. 2022 [17] | 18F-FDG PET, cognitive functioning, and CSF biomarkers in patients with obstructive sleep apnoea before and after continuous positive airway pressure treatment. | Prospective cohort with longitudinal intervention | 68 | • CSF Aβ42 ↓<br>• CSF p-tau ↑<br>• Cortical glucose consumption ↓ | • OSA patients showed lower CSF Aβ42 and higher p-tau CSF levels than controls.<br>• CSF t-tau and p-tau were significantly correlated with reduced 18F-FDG uptake across different Broadman areas (bilateral praecuneus, posterior cingulate cortex, and frontal areas) (all $p < 0.03$).<br>• No significant correlations were observed between CSF levels and cognitive performance.<br>• OSA patients showed an improvement in cognition and a global increase in cerebral 18F-FDG uptake after CPAP (across all cortical regions $p < 0.0001$). |
| Fernandes et al. 2025 [18] | Persistent blood-brain barrier dysregulation in patients with obstructive sleep apnea following long-term continuous positive airway pressure treatment. | Longitudinal | 75 | • Qalb ↑<br>• CSF Aβ42 ↓ | • Moderate-severe OSA patients had higher Qalb.<br>• OSA patients had lower CSF Aβ42 levels ($p < 0.05$) compared to controls.<br>• CPAP treated patients had significantly higher CSF Aβ 42 levels.<br>• In OSA patients who exhibited pathological levels of CSF biomarkers, CPAP treatment did not lead to significant improvement in Qalb compared to controls (all $p > 0.05$). |
| Owen et al. 2021 [19] | Alzheimer's disease neuropathology in the hippocampus and brainstem of people with obstructive sleep apnea. | Post mortem case series | 34 | • Aβ plaques ↑<br>• Neurofibrillary tangles ↑ | • OSA severity was a significant predictor of Aβ plaque and neurofibrillary tangle burden in the hippocampus. |
| Elias et al. 2018 [20] | Risk of Alzheimer's disease in obstructive sleep apnea syndrome: Amyloid-beta and tau imaging. | Cross-sectional (with treatment group) | 119 | • 18-F AV1451 (tau) –<br>• 18F-florbetaben (Aβ) ↑ | • There was no significant difference (SUVR) in 18F-AV1451 (tau) uptake between the two groups.<br>• Cortical uptake of 18F-florbetaben (Aβ) was higher in the OSA group than in the control group.<br>• The use of CPAP had no effect on cognitive or amyloid PET findings. |

**Table 1.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Yla-Herttuala et al. 2021 [21] | Severe Obstructive Sleep Apnea and Increased Cortical Amyloid-beta Deposition. | Cross-sectional | 19 | • [11C]-PiB-PET (Aβ) ↑ | • [11C]-PiB-PET revealed evidence of statistically significant increased Aβ uptake. |
| Sun et al. 2022 [22] | Altered amyloid-beta and tau proteins in neural-derived plasma exosomes in obstructive sleep apnea. | Cross-sectional with longitudinal cohort | 122 | • Exosome Aβ42 ↑ | • Levels of Aβ42 in neuronal-derived exosomes were significantly higher in OSA patients compared to controls, but not for t-tau and *p*-tau.<br>• Levels of Aβ42 (r = 0.53, $p < 0.001$), t-tau (r = 0.44, $p < 0.001$), and P-T181-tau (r = 0.4, $p < 0.001$) in neuronal-derived exosomes were correlated with MoCA scores.<br>• Levels of Aβ42, t-tau, and P-T181-tau after 1 year of CPAP intervention were significantly lower than those at baseline. |
| Madaeva et al. 2019 [23] | Plasma Amiloid β42 in Patients with Obstructive Sleep Apnea before and after CPAP-Therapy: Pilot Study. | Prospective | 24 | • Plasma Aβ42 ↓ | • OSA patients had lower plasma Aβ42 levels at baseline. After CPAP, levels increased to match controls.<br>• Treated patients had an increase in short-wave-sleep (SWS) duration. |
| Kong et al. 2021 [24] | Biomarkers of Alzheimer's disease in severe obstructive sleep apnea–hypopnea syndrome in the Chinese population. | Case–control | 51 | • Plasma Aβ42 –<br>• Plasma Aβ40 ↑<br>• Plasma p-tau ↑<br>• Plasma t-tau ↑ | • The plasma levels of Aβ40 (29.24 ± 32.52 vs. 13.18 ± 10.78, $p = 0.049$), t-tau (11.88 ± 7.05 vs. 7.64 ± 4.17, $p = 0.037$), p-tau (26.31 ± 14.41 vs. 17.34 ± 9.12, $p = 0.027$) in patients with severe OSA were significantly higher than those in the control group.<br>• Aβ42, Aβ40, t-tau, and p-tau were significantly negatively correlated with mean oxygen saturation, low oxygen saturation and Mini-Mental State examination scale scores and positively correlated with oxygen desaturation index (all $p < 0.05$). |
| Przybylska-Kuć et al. 2019 [25] | Obstructive sleep apnea may increase the risk of Alzheimer's disease. | Cross-sectional | 112 | • Serum Aβ42 –<br>• Serum Aβ40 ↑ | • Serum Aβ40 concentrations in OSA patients were significantly higher compared with healthy adults (191.1 vs. 76.9, $p < 0.05$).<br>• Aβ40 levels correlated with AHI (r= 0.45, $p < 0.05$), mean $SaO_2$ (r = −0.28, $p < 0.05$), ST90% (r = 0.41, $p < 0.05$) and ODI (r = 0.46, $p < 0.05$).<br>• There were no differences in Aβ 42 concentration between the groups. |

**Table 1.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Bu et al. 2015 [26] | Serum amyloid-beta levels are increased in patients with obstructive sleep apnea syndrome | Case–control | 94 | • Serum Aβ42 ↑<br>• Serum Aβ40 ↑<br>• Serum total tau –<br>• Serum P-tau181 ↑ | • There were elevated levels of serum Aβ 40 (107.54 ± 65.77 vs. 71.58 ± 34.70, $p = 0.003$), Aβ 42 (86.37 ± 61.14 vs. 50.91 ± 26.93, $p = 0.006$) and P-tau181 levels (42.03 ± 21.58 vs. 30.56 ± 17.30, $p = 0.003$) in OSA patients.<br>• No differences in the serum total tau levels between the groups were found (45.40 ± 34.24 vs. 40.49 ± 24.61, $p = 0.753$).<br>• There were correlations between the levels of these markers and OSA indices. Serum Aβ40 (AHI: r = 0.333, $p = 0.029$; ODI: r = 0.507, $p = 0.003$; mean $SaO_2$: r = − 0.429, $p = 0.011$). Serum Aβ 42 (AHI: r = 0.313, $p = 0.041$; ODI: r = 0.517, $p = 0.002$; mean $SaO_2$: r = −0.358, $p = 0.038$). |
| Zhou et al. 2025 [27] | Association between serum α-synuclein levels and neurocognitive deficits in patients with obstructive sleep apnea: A case-control study. | Cross-sectional | 108 | • Serum α-synuclein ↑ | • Serum α-synuclein levels were significantly elevated in OSA patients and independently associated with cognitive impairment in OSA (MMSE: β = −0.459, 95% CI: −0.725 to −0.182, $p = 0.005$; MoCA: β = 0.443, 95% CI: −0.135 to 0.624, $p = 0.159$).<br>• ROC analysis revealed a strong predictive value of α-synuclein for cognitive deficits (AUC = 0.892, 95% CI: 0.830–0.954). |
| Svatikova et al. 2003 [28] | Serum amyloid A in obstructive sleep apnea. | Cross-sectional | 10 | • Plasma serum amyloid-A ↑ | • Plasma SAA levels are more than 2-fold greater (18.8 ± 2.6 versus 7.2 ± 2.6, $p = 0.005$) in patients with moderate-to-severe OSA compared with subjects with mild OSA or healthy controls.<br>• There was a significant positive correlation between SAA and AHI (r = 0.40, $p = 0.03$). |
| Zong et al. 2023 [29] | Involvement of Galectin-3 in neurocognitive impairment in obstructive sleep apnea via regulating inflammation and oxidative stress through NLRP3. | Prospective | 47 | • Serum Galectin-3 ↑<br>• Pro-inflammatory markers (IL-1β, IL-8) ↑<br>• Oxidative stress (MDA) ↑<br>• Antioxidants (SOD, CAT) ↓ | • Serum galectin-3 level in severe OSA patients was higher than those in mild–moderate OSA patients and those in the healthy controls.<br>• Serum galectin-3 levels were significantly correlated with PSG indices (AHI: r = 0.738, $p < 0.001$; ODI: r = 0.704, $p < 0.001$; $LSaO_2$: r = −0.426, $p < 0.001$; $MSaO_2$: r = −0.315, $p = 0.011$) and poorer MoCA scores (r = −0.575, $p < 0.001$).<br>• Alterations in serum IL-1β, IL-8, MDA, SOD and CAT were significantly correlated with poorer PSG indices (AHI, $LSaO_2$ and $MSaO_2$) and MoCA scores.<br>• CPAP treatment in severe OSA patients (mean AHI 51.6 ± 17.4) for 12 weeks significantly reduced the levels of galectin-3 ($p < 0.001$). |

**Table 1.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Shi et al. 2022 [30] | Serum neurofilament light reflects cognitive dysfunctions in children with obstructive sleep apnea. | Case–control | 105 | • Serum NfL ↑<br>• Serum tau – | • OSA children had significantly higher serum NfL levels (31.68 [27.29–36.07] vs. 19.13 [17.32–20.95], $p < 0.001$). Serum tau was unchanged ($p = 0.172$).<br>• NfL was correlated with AHI ($r = 0.647$, $p < 0.001$), ODI ($r = 0.452$, $p < 0.001$), mean $SaO_2$ ($r = -0.430$, $p < 0.001$) and cognitive dysfunction (full-scale IQ: $r = -0.388$, $p < 0.001$).<br>• Serum NfL had an AUC of 0.816 (95% CI: 0.736–0.897, $p < 0.001$) in predicting OSA. |
| Staats et al. 2005 [31] | Regulation of brain-derived neurotrophic factor (BDNF) during sleep apnoea treatment. | Cross-sectional (with treatment group) | 17 | • Serum and plasma BDNF – | • Patients with untreated OSA have normal serum and plasma BDNF levels.<br>• No correlations were observed between BDNF and OSA indices (ESS and RDI) (all $p > 0.05$).<br>• CPAP treatment is associated with a rapid decrease in serum and plasma BDNF levels and remained below baseline. |
| P. Li et al. 2022 [32] | The Effects of CPAP Treatment on Resting-State Network Centrality in Obstructive Sleep Apnea Patients. | Longitudinal | 42 | • Pre-CPAP OSA patients showed increased voxel-level degree centrality (DC) values in the bilateral cerebellar posterior lobes (CPLs) and decreased DC values in the right superior temporal gyrus, left superior frontal gyrus and right middle frontal gyrus.<br>• MoCA scores were positively correlated with the DC value of several areas (CPL: $r = 0.45$, $p = 0.039$; middle temporal gyrus: $r = 0.504$, $p = 0.020$; superior temporal gyrus: $r = 0.48$, $p = 0.028$; precentral gyrus: $r = 0.467$, $p = 0.033$; paracentral lobule: $r = 0.512$, $p = 0.018$).<br>• Post-CPAP OSA patients showed reduced DC values in the bilateral CPL and increased DC values in several brain regions in the frontal, temporal, and insular lobes. | |
| Studies about Neuroimaging (n = 8) | | | | | |
| L. Li et al. 2025 [33] | Functional Connectivity Changes in Primary Motor Cortex Subregions of Patients With Obstructive Sleep Apnea. | Cross-sectional | 130 | • Functional connectivity (FC) ↓ | • OSA significantly impacts brain functional networks.<br>• Various FCs between brain regions were significantly correlated with OSA indices and neurodegeneration measures. In particular, FC between the left A6cvl and left MFG was negatively correlated with AHI ($r = -0.259$, $p = 0.044$), ODI ($r = -0.320$, $p = 0.012$) and MoCA scores ($r = -0.350$, $p = 0.006$). |

**Table 1.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Kim et al. 2013 [34] | Obstructive Sleep Apnea as a Risk Factor for Cerebral White Matter Change in a Middle-Aged and Older General Population. | Cross-sectional | 503 | • White-matter change ↑ | • After adjusting for possible confounders, moderate–severe OSA was significantly associated with presence of WMC.<br>• The number of WMC was positively correlated with AHI (r = 0.17, $p$ = 0.0001). |
| Ylä-Herttuala et al. 2022 [35] | Decreased Gray—White Matter Contrast of [11C]-PiB Uptake in Cognitively Unimpaired Subjects with Severe Obstructive Sleep Apnea. | Case–control | 19 | • Grey–white-matter contrast ↓ | • Static [11C]-PiB PET uptake showed significantly decreased GM-WM contrast in 5/14 OSA patients and was associated with smoking and higher AHI.<br>• GM-WM contrast was also correlated with AHI (r = 0.539, $p$ = 0.017).<br>• Dynamic studies noted alterations in trace accumulation in the late phase of tracer kinetics, potentially related to glymphatic dysfunction and altered clearance. |
| Lee et al. 2022 [36] | Glymphatic system dysfunction in obstructive sleep apnea evidenced by DTI-ALPS. | Case–control | 24 | • DTI-ALPS index ↓ | • DTI-ALPS in patients with OSA was significantly lower than that in healthy controls (1.30450 vs. 1.61600, $p$ = 0.0006).<br>• DTI-ALPS index negatively correlated with AHI (r = 0.427, $p$ = 0.042) and oxygen desaturation index (r = 0.497, $p$ = 0.036) during non-REM sleep. These correlations were not present in REM sleep. Glymphatic system dysfunction could be correlated with non-REM sleep disruption rather than REM sleep. |
| Xiong et al. 2024 [37] | Resting-state fMRI network efficiency as a mediator in the relationship between the glymphatic system and cognitive function in obstructive sleep apnea hypopnea syndrome: Insights from a DTI-ALPS investigation | Cross-sectional | 31 | • DTI-ALPS index ↓ | • OSA patients had significantly lower ALPS index (1.268 vs. 1.431, $p < 0.0001$).<br>• There was a negative correlation with AHI (r = −0.389, $p$ = 0.031) as well as moderate positive correlation with MoCA scores (r = 0.525, $p$ = 0.002). |
| Roy et al. 2022 [38] | Impaired Glymphatic System Actions in Obstructive Sleep Apnea Adults | Case–control | 121 | • DTI-ALPS index ↓ | • DLTI-ALPS index was significantly lower in OSA patients (1.34 ± 0.11 vs. 1.38 ± 0.11, $p$ = 0.03). |

**Table 1.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Lin et al. 2024 [39] | Association of MRI Indexes of the Perivascular Space Network and Cognitive Impairment in Patients with Obstructive Sleep Apnea | Prospective | 105 | • DTI-ALPS index ↓ | • Both the mild OSA group (1.7 ± 0.3) and the moderate OSA group (1.7 ± 0.4) exhibited lower mean DTI-ALPS than the HCs (2.1 ± 0.4; both $p < 0.001$).<br>• DLTI-ALPS index significantly correlated with AHI (r = −0.50, $p < 0.001$), ODI (r = −0.48, $p < 0.001$), and ESS score (r = −0.48, $p < 0.001$).<br>• 15 patients had improved DLTI-ALPS index ($p < 0.001$) after uvulopalatopharyngoplasty (median 4.9 months post operatively). |
| Studies about Oxidative Stress (n = 2) | | | | | |
| Jordan et al. 2006 [40] | Evaluation of oxidative stress measurements in obstructive sleep apnea syndrome. | Longitudinal | 25 | • SOD ↓<br>• Urinary 8-OHdg ↑ | • MDA concentrations correlated with a duration of nocturnal desaturation below 85%.<br>• o,o′-dityrosine levels decreased after therapy as a function of baseline concentrations. |
| Sales et al. 2013 [41] | Cognition and biomarkers of oxidative stress in obstructive sleep apnea. | Cross-sectional | 14 | • Vitamin E ↓<br>• Plasma folate ↓<br>• SOD ↓<br>• Homocysteine ↑ | • OSA patients had lower levels of vitamin E (12.8 ± 3.6 vs. 19.1 ± 6.7, $p = 0.005$), SOD (10 ± 2.9 vs. 14.4 ± 2.3, $p = 0.001$) and plasma folate (4.8 ± 2.3 vs. 9.3 ± 2.8, $p < 0.001$), as well as higher concentrations of homocysteine (16.7 ± 8.0 vs. 10.7 ± 2.9, $p = 0.02$).<br>• Vitamin E levels were related to performance in the backward digit span task (F = 15.9; $p = 0.002$). A relationship between SOD concentrations and executive non-perseveration errors in the Wisconsin Card Sorting Test (F = 7.9; $p = 0.01$) was also observed. |
| Studies about Systemic Inflammation (n = 10) | | | | | |
| Wu et al. 2016 [42] | Effect of CPAP therapy on C-reactive protein and cognitive impairment in patients with obstructive sleep apnea hypopnea syndrome. | Prospective | 178 | • hsCRP ↑ | • hsCRP concentration was higher in the moderate-to-severe OSA group (mod–severe OSA: 2.71 ± 1.80 mg/L, healthy/mild OSA: 1.00 ± 1.28 mg/L, $p < 0.001$).<br>• hsCRP correlated with parameters of overnight hypoxia (AHI: r = 0.307, $p < 0.01$; ST90: r = 0.209, $p < 0.05$) and significantly improved (1.04 ± 0.94 vs. 2.90 ± 1.68, $p < 0.001$) after CPAP treatment. |

**Table 1.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Bozic et al. 2018 [43] | Adropin and Inflammation Biomarker Levels in Male Patients With Obstructive Sleep Apnea: A Link With Glucose Metabolism and Sleep Parameters. | Case–control | 75 | • Adropin ↓<br>• IL-6 ↑<br>• TNF-α ↑<br>• hs-CRP ↑ | • Plasma adropin levels were significantly lower in the severe OSA group in comparison with the moderate and control groups (4.50 ± 1.45 vs. 6.55 ± 1.68 vs. 8.15 ± 1.79, $p < 0.001$). In the severe OSA group, plasma IL-6 (3.58 ± 1.55 vs. 1.26 ± 0.69, $p < 0.001$), TNF-α (8.67 ± 2.41 vs. 2.35 ± 1.25, $p < 0.001$) and hs-CRP ($p < 0.001$) were different when compared with controls.<br>• Plasma adropin was negatively correlated with AHI (r = −0.615, $p < 0.001$) and ODI (r = −0.573, $p < 0.001$).<br>• ROC analysis showed that AUC for plasma adropin levels in excluding OSA was 0.831 (95% CI 0.737–0.925, $p < 0.001$). |
| Bouloukaki et al. 2017 [44] | Evaluation of Inflammatory Markers in a Large Sample of Obstructive Sleep Apnea Patients without Comorbidities. | Case–control | 1053 | • hs-CRP ↑<br>• Fibrinogen ↑<br>• ESR -<br>• Uric acid ↑ | • OSA patients had significantly higher hs-CRP ($p = 0.002$) and fibrinogen ($p = 0.009$) levels.<br>• Uric acid levels were significantly different between all groups ($p < 0.001$), apart from mild versus moderate group ($p = 0.12$).<br>• There were no significant differences between all groups for ESR ($p > 0.05$).<br>• All biomarkers were strongly associated with AHI, ODI, and minimum $SaO_2$ and mean $SaO_2$) (all $p < 0.001$). |
| Koppu et al. 2023 [45] | Assessment of Clinical and Biochemical Associations in Obstructive Sleep Apnea: An Institutional Experience. | Cross-sectional | 80 | • CRP, IL-6, TNF-α ↑ | • OSA patients had elevated levels of inflammatory markers, such as CRP, TNF-α and IL-6. |
| Motamedi et al. 2018 [46] | Elevated tau and interleukin-6 concentrations in adults with obstructive sleep apnea. | Cross-sectional | 74 | • Plasma tau ↑<br>• IL-6 ↑ | • Plasma tau and IL-6 concentrations were elevated in participants with moderate–severe OSA compared to those with mild OSA or healthy controls.<br>• Tau concentrations significantly correlated with the AHI (r = 0.342, $p = 0.004$) and maximum desaturation during sleep (r = 0.293, $p = 0.02$). |

**Table 1.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Shen et al. 2023 [47] | IL-33/ST2 mediating systemic inflammation and neuroinflammation through NF-kB participated in the neurocognitive impairment in obstructive sleep apnea. | Cross-sectional with longitudinal cohort | 21 | • IL-6, IL-8, IL-33, ST2, p65NF-κB ↑ | • Levels of serum IL-6 and IL-8 as well as protein levels of IL-33, ST2 and p65NF-κB in OSA patients were significantly elevated compared to the control group.<br>• IL-6 ($r = -0.35$, $p < 0.05$), IL-8 ($r = -0.49$, $p < 0.01$), IL-33 ($r = -0.57$, $p < 0.01$), ST2 ($r = -0.69$, $p < 0.01$) and p65NF-κB ($r = -0.57$, $p < 0.01$) levels were negatively correlated with MoCA scores.<br>• These levels significantly decreased after 1 year of adherent CPAP. |
| Y. Wang et al. 2021 [48] | Patients with obstructive sleep apnea have suppressed levels of soluble cytokine receptors involved in neurodegenerative disease, but normal levels with airways therapy. | Cross-sectional (with treatment group) | 46 | • Soluble cytokine receptors ↓ | • Untreated OSA patients show significantly reduced (twofold to sevenfold) serum levels of four key soluble cytokine receptors (gp130, IL6R, TNFR1, and TNFR2) which are associated with neurodegenerative disease.<br>• CPAP led to significantly higher levels of these soluble cytokine receptors. |
| M. Li et al. 2023 [49] | Complement protein levels in serum astrocyte-derived exosomes are associated with cognitive impairment in obstructive sleep apnea. | Cross-sectional | 212 | • C3b, C5b-9 ↑ | • C3b and C5b-9 were elevated in OSA patients compared to controls and independently associated with cognitive impairment. (C3b: OR = 3.619, 95% CI 1.666–7.858, $p = 0.001$; C5b: OR = 1.590, 95% CI 1.357–1.863, $p < 0.001$).<br>• Pearson's correlation analysis showed that the severity of OSA (AHI, ODI, mean $SaO_2$, and ST90) was not associated with complement protein levels. |
| M. Li et al. 2024 [50] | Mitochondrial dysfunction is associated with cognitive impairment in adults with OSA without dementia. | Cross-sectional with longitudinal cohort | 268 | • Mitochondrial proteins (humanin, MOTS-c, NRGN) ↑ | • The odds of cognitive impairment in patients with OSA were higher with higher NDE levels of humanin ($\beta = -0.505$, SE = 0.048, $p < 0.001$), MOTS-c ($\beta = -0.580$, SE = 0.001, $p < 0.001$), and NRGN ($\beta = -0.585$, SE = 0.553, $p < 0.001$), after adjusting for age, sex, education, vascular risk factors.<br>• There was an AUC of 0.905 for humanin, 0.873 for MOTS-c, and 0.934 for NRGN to predict MCI in OSA patients without dementia.<br>• These levels decreased after CPAP therapy. |

**Table 1.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Key Findings |
|---|---|---|---|---|---|
| Xue et al. 2023 [51] | Neuronal glutamate transporters are associated with cognitive impairment in obstructive sleep apnea patients without dementia. | Longitudinal | 317 | • Plasma NDE EAAT2 ↑ | • Plasma NDEs EAAT2 level was significantly higher in OSA patients and correlated with poorer PSG indices (mean $SaO_2$: r = −0.141, $p$ = 0.025), and cognitive impairment (MoCA: r = −0.480, $p$ < 0.001).<br>• After adjusting for age, sex, education, hypertension, diabetes mellitus, hyperlipidemia, HAMD scores, and AHI, it was independently associated with a higher risk of MCI (OR = 2.741, 95% CI = 2.085–3.065, $p$ < 0.001).<br>• One year after CPAP treatment, plasma NDEs EAAT2 level was significantly lower. |

### 3.1. Oxidative Stress

Two studies examined changes in markers of oxidative stress in OSA. OSA increases oxidative stress primarily through recurrent cycles of intermittent hypoxia and reoxygenation, analogous to repeated ischaemia–reperfusion injury. Excess reactive oxygen species (ROS) are generated via mitochondrial dysfunction as well as the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthase (NOS) [52]. The resulting lipid peroxidation, protein oxidation and DNA damage promote direct neuronal injury, pathological protein aggregation [53] and microglial activation [54], thereby contributing to neurodegeneration.

In a longitudinal study of 25 patients with sleep-related breathing disorders [40], the team quantified multiple oxidative stress markers in blood and urine before and after CPAP therapy and examined correlations with objective indices of OSA severity: duration of nocturnal desaturation below 90% (ST90) and 85% (ST85), apnea–hypopnea index (AHI) as well as arterial oxygen saturation ($SaO_2$). Elevated plasma malondialdehyde (MDA), a terminal product of polyunsaturated fatty acid peroxidation, was identified in individuals with CIH and proposed as a promising marker of ROS activity. MDA levels correlated significantly with markers of overnight hypoxia (ST90: r = 0.59, $p$ < 0.05; ST85: r = 0.77, $p$ < 0.0005).

Urinary o,o'-dityrosine, a stable end-product of selective proteolysis, and 8-hydroxy-2-deoxyguanosine, a marker of oxidative DNA damage, could serve as non-invasive indices for clinical monitoring. o,o'-dityrosine showed potential as a marker of CPAP efficacy (r = 0.61, $p$ < 0.05), whereas 8-hydroxy-2-deoxyguanosine reflected oxidative stress and hypoxia (ST90: r = 0.5, $p$ < 0.05 & ST85 r = 0.4, $p$ = 0.064), although its utility is limited due to influences by alterations in renal function. Other oxidative stress markers, such as superoxide dismutase (SOD) and glutathione derivatives, showed inconsistent relationships with hypoxic burden and/or CPAP therapy, limiting their suitability for OSA-specific biomarker panels. Future studies are needed to determine whether CPAP-induced normalisation of these markers can attenuate cognitive decline in OSA patients.

### 3.2. Systemic Inflammation

Ten studies analysed the changes in inflammatory markers in OSA patients. Systemic inflammation is a major contributor to neurodegeneration in OSA, mediated by

complex interactions among multiple cytokines and signalling pathways [55]. A key consequence is the disruption of the BBB. Cytokines such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) are heavily implicated. TNF-α binds TNFR1 receptors on brain microvascular endothelial cells (BMECs), activating NF-κB and disrupting tight junctions. IL-1β acts synergistically by activating astrocytes via NF-κB and JNK pathways, promoting further cytokine release and vascular endothelial growth factor-A (VEGF-A) production, which directly increases BBB permeability. IL-6 complexes with soluble IL-6 receptors (sIL-6R) and binds glycoprotein 130 (gp130) on BMECs, thereby further compromising BBB integrity. Additional cytokines serve as downstream mediators of neuroinflammation by promoting leukocyte recruitment and adhesion within the central nervous system.

Although numerous studies have documented elevated levels of circulating cytokines in OSA, relatively few have directly linked these alterations to cognitive outcomes. Wu et al. observed significantly higher hsCRP levels in adults with moderate-to-severe OSA (AHI $\geq$ 15) compared to healthy or mild OSA subjects (AHI 0–15) (moderate–severe OSA: 2.71 $\pm$ 1.80 mg/L, healthy/mild OSA: 1.00 $\pm$ 1.28 mg/L, $p < 0.001$) [42]. After adjustment for confounders, hsCRP remained strongly correlated with measures of hypoxia, including AHI (r = 0.307, $p < 0.01$), ST90 (r = 0.209, $p < 0.05$), oxygen desaturation index (ODI; r = 0.324, $p < 0.01$) and $SaO_2$ (r = $-0.282$, $p < 0.01$), as well as lower Montreal Cognitive Assessment (MoCA) scores (r = $-0.371$, $p < 0.01$).

TNF-α is another crucial pro-inflammatory cytokine in sleep regulation, acting via NF-κB to upregulate adenosine A1 receptor, cyclooxygenase-2, and NOS. Its release is also modulated by other cytokines, T cell activation, and autoregulatory TNF-α signalling, establishing a positive feedback loop that amplifies neuroinflammation. Bozic et al. revealed significantly raised TNF-α levels in OSA patients (8.67 $\pm$ 2.41 vs. 2.35 $\pm$ 1.25, $p < 0.001$), alongside plasma adropin, IL-6 and hsCRP [43]. Notably, none of the included studies observed any correlation between TNF-α and measures of OSA severity or neurodegeneration.

On top of hsCRP and TNF-α, comparable associations have been reported for other inflammatory markers, including IL-6, IL-8, IL-33 [47], mitochondrial proteins [50], soluble cytokine receptors [48] and complement proteins. Collectively, these biomarkers have the potential to predict cognitive decline in OSA patients, but longitudinal validation is required.

## 4. Neuroinflammation

The brain's high metabolic demand renders it particularly vulnerable to hypoxia. The BBB, once considered impermeable to peripheral inflammation, is now recognised as a conduit for pro-inflammatory cytokines that induce neuronal and glial injury [56]. This, in turn, amplifies the release of inflammatory mediators, exacerbating BBB disruption and perpetuating a vicious cycle of neuroinflammation. Neurodegenerative processes are characterised by accumulation of tau and amyloid-β (Aβ), potentially driven by hypoxia-induced upregulation of protein production, oxidative stress and impaired glymphatic clearance. Although CSF levels of neurotoxic proteins remain the diagnostic gold standard in AD, plasma tau and neurofilament light chain (NfL) have also emerged as promising, less invasive biomarkers of neurodegeneration [57]. A total of 20 studies examined these changes, with majority of the studies focusing on Aβ, tau and NfL.

### *4.1. Amyloid-β, T-Tau and P-Tau*

AD neuropathology implicates the formation of extracellular amyloid plaques comprising primarily Aβ42 and Aβ40 derived from amyloid precursor protein (APP) via β/γ-secretase and intracellular neurofibrillary tangles containing hyperphosphorylated

tau. Measurements of CSF and/or plasma concentrations of these proteins therefore may identify preclinical AD.

In a longitudinal study of 50 OSA patients, Liguori et al. reported significantly lower CSF Aβ42 levels in OSA patients compared with controls (484 pg/mL [159.90] vs. 888.40 pg/mL [147.88], $p < 0.001$) [12]. A similar trend was observed with CSF t-tau/Aβ42 ratios (0.67 [0.58] vs. 0.25 [0.08], $p < 0.01$), with 64% and 46% of OSA patients meeting pathological thresholds for CSF Aβ42 (<500 pg/mL) and t-tau/Aβ42 (>0.52) respectively, while no controls exceeded cut-offs. CSF Aβ42 levels were positively correlated with mean $SaO_2$ (r = 0.62, $p = 0.001$), suggesting that CIH promotes amyloid deposition.

Consistent findings were observed in a larger longitudinal cohort of 1639 OSA patients, in whom Bubu et al. documented an accelerated decline in CSF Aβ42 (B = −2.71, 95% CI = −3.11 to −2.35, $p < 0.0001$) as well as increases in CSF p-tau (B = 1.21, 95% CI = 1.02 to 1.42, $p < 0.0001$) and t-tau (B = 3.68, 95% CI = 3.31 to 4.07 $p < 0.0001$) relative to controls, indicating faster progression towards MCI and AD in OSA [16].

Although CSF Aβ42 and tau appear to be useful AD biomarkers in OSA, they are unlikely to be sufficient as standalone diagnostic tools. Their use in isolation may signal preclinical AD pathology but lacks specificity. Moreover, potentially more informative composite measures, such as Aβ42/Aβ40 ratios [58], have not been systematically evaluated in OSA, despite their established prognostic value in MCI. Further studies utilising these ratios will be essential to refine the association between OSA, AD-related pathology, and neuroinflammation.

### *4.2. Neurofilament Light Chain (NfL) and Brain-Derived Neurotrophic Factor (BDNF)*

Neurofilament light chain (NfL), a neuron-specific protein released after axonal injury, diffuses into the CSF and subsequently blood, providing a sensitive marker of neuroaxonal damage. Additionally, brain-derived neurotrophic factor (BDNF) is a neurotrophin that is upregulated during neuroinflammation and involved in neuronal survival and synaptic plasticity [59]. Shi et al. identified that serum NfL levels in 105 OSA children were significantly elevated (31.68 pg/mL [27.29–36.07] vs. 19.13 pg/mL [17.32–20.95], $p < 0.001$) and correlated with disease severity (AHI: r = 0.647, $p < 0.001$; ODI: r = 0.452, $p < 0.001$); mean $SaO_2$: r =−0.430, $p < 0.001$). Raised serum NfL also led to poorer cognitive function across multiple IQ domains (verbal: r = −0.447, performance: r = −0.480, full-scale: r = −0.388; all $p < 0.001$). NfL demonstrated good sensitivity and specificity as an accessible diagnostic marker of OSA (AUC = 0.816, 95% CI: 0.736–0.897, $p < 0.001$) [30]. OSA patients may have poorer cognitive function which could be induced by CIH, sleep fragmentation and inflammatory activation leading to axonal and neuronal damage, as demonstrated by raised NfL levels.

The only study included on BDNF by Staats et al. reported no differences in serum or plasma BDNF between OSA patients and controls. There were also no significant correlations between BDNF levels and the respiratory disturbance index (RDI) (serum BDNF: r = 0.32, $p = 0.27$; plasma BDNF: r = 0.39, $p = 0.19$) or the ESS (serum BDNF: r = 0.14, $p = 0.62$; plasma BDNF: r = 0.10, $p = 0.73$) [31]. Overall, CIH-induced alterations in circulating BDNF remain unclear, and longitudinal studies are needed to define its trajectory and potential role in neurodegeneration.

### *4.3. α-Synuclein*

α-Synuclein is implicated in multiple synucleinopathies, including PD, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), where aggregation of misfolded α-synuclein monomers into insoluble oligomers and fibrils drives neurodegeneration and microglial/astrocytic activation [60]. Evidence linking circulating α-synuclein

to neurocognitive impairment in OSA remains limited. In a recent case–control cohort, Zhou et al. studied 108 untreated OSA patients and 100 matched controls and found significantly higher serum α-synuclein levels in OSA patients (385.62 ± 125.47 pg/mL vs. 215.30 ± 78.65 pg/mL, $p < 0.001$). Elevated α-synuclein levels were independently associated with neurocognitive deficits after adjustment for age, sex, BMI, vascular risk factors and education (MMSE: β = −0.459, 95% CI: −0.725 to −0.182, $p = 0.005$). ROC analysis showed excellent discrimination of cognitive impairment (AUC = 0.892, 95% CI: 0.830 to 0.954) [27]. These findings suggest serum α-synuclein may be a promising biomarker for OSA-related cognitive risk, warranting longitudinal validation.

### *4.4. Galectin-3*

Galectin-3 (Gal-3) is a β-galactoside-binding lectin upregulated in activated microglia and macrophages in the CNS during various neurological diseases. It has been increasingly recognised as a mediator of neuroinflammation and a biomarker linked to AD, PD and frontotemporal dementia [61]. In a longitudinal cohort of 47 newly diagnosed OSA patients, Zong et al. observed higher serum Gal-3 levels in severe OSA (2.31 ± 0.43 ng/mL) compared to mild–moderate OSA (1.87 ± 0.32 ng/ mL, $p < 0.001$) and healthy controls (1.56 ± 0.22 ng/mL, $p < 0.001$). Gal-3 levels correlated positively with AHI (r = 0.738, $p < 0.001$) and ODI (r = 0.704, $p < 0.001$) and inversely with lowest oxygen saturation (r =−0.426, $p < 0.001$) and mean oxygen saturation (r =−0.315, $p = 0.01$). Importantly, higher Gal-3 was associated with worse MoCA performance (r = −0.575, $p < 0.001$). After 12 weeks of CPAP, Gal-3 levels declined significantly (1.73 ± 0.22 ng/mL, $p < 0.001$), suggesting partial reversibility with treatment [29]. Despite its promise as a marker of neuroinflammation, mechanistic studies in both animal models and human cohorts are needed to clarify the links behind Gal-3 and OSA-related cognitive dysfunction.

In summary, multiple studies outline the mechanistic hypotheses behind CIH and neurodegeneration. BBB disruption and subsequent neuroinflammation appear to create a milieu for accumulation of pathological proteins, as reflected in altered Aβ42 and α-synuclein profiles. Positive associations between CSF Aβ, as well as serum NfL, Gal-3, and hypoxic parameters further suggests that axonal injury and neuroinflammation scale with OSA severity. While compensatory markers such as BDNF remain incompletely characterised and require further investigation, the overall data position OSA as a potentially associated modifiable contributor to neurodegenerative risk. In future, plasma and CSF biomarkers could enable early risk stratification and targeted intervention in OSA to preserve neurological function in individuals with OSA. However, further longitudinal studies are needed to accomplish this.

### *4.5. Neuroimaging*

OSA is linked to widespread structural and functional brain changes detectable across multiple neuroimaging techniques, as evidenced by 8 studies. Structural MRI consistently showed reduced grey-matter volume in regions central to attention processing, including the frontal, temporal and parietal lobes, as well as the hippocampus, basal ganglia, thalamus and cerebellum, with a predominance in the right hemisphere. Resting state functional-MRI (fMRI) studies similarly reported reduced or disrupted functional connectivity (FC) within core attention-related networks, with connectivity measures correlating with indices of OSA severity [33]. Perfusion imaging further demonstrated reduced cerebral blood flow and volume, particularly in bilateral parietal and prefrontal cortices, with hypoperfusion linked to intermittent hypoxia and sleep fragmentation.

Diffusion tensor imaging (DTI) revealed lower fractional anisotropy (FA) and higher mean and radial diffusivity in the corpus callosum, as well as the prefrontal, premotor

and supplementary motor cortices, indicating the link between compromised white-matter integrity and impaired sustained attention and prospective memory [32].

Complementing these findings, a cross-sectional study of 503 adults from the Korean Genome and Epidemiology Study by Kim et al. also revealed that OSA severity was strongly associated with white-matter change (WMC) (no OSA: 33.56%, mild: 42.86%, moderate–severe: 62.26%, $p < 0.0001$), predominantly in the frontal lobes. AHI correlated positively with white-matter lesion burden (r = 0.17, $p = 0.0001$) [34]. Collectively, these observations suggest that OSA may promote cerebral small vessel disease through intermittent hypoxia, systemic inflammation and haemodynamic instability [62]. In multivariate logistic regression adjusting for demographic and vascular risk factors, moderate–severe OSA was associated with approximately twofold increased odds of white-matter lesions (OR = 2.08, 95% CI: 1.05 to 4.13), whereas mild OSA showed no such association, implying that severe OSA may drive cerebrovascular injury and that timely interventions could mitigate these insults.

Advances in nuclear imaging now allow in vivo visualisation of neurodegenerative proteins via radioligand uptake. In a cross-sectional cohort of 119 male veterans, Elias et al. utilised 18F-florbetaben and 18F-AV1451 to target Aβ and tau aggregates respectively. Compared to controls, OSA patients exhibited higher cortical amyloid standardised uptake value ratio (SUVR) with 18F-florbetaben (1.35 ± 0.21 vs. 1.27 ± 0.16, 95% CI =−0.14 to −0.003, $p = 0.04$) and showed impairments in visual attention and processing speed on neuropsychological testing (Trail Marking Test A: 41.81 ± 12.54 s vs. 35.63 ± 11.69 s, $p = 0.03$; Trail Marking Test B: 126.70 ± 82.47 s vs. 97.95 ± 33.79 s, $p = 0.03$) [20].

This association was moderated by both APOE ε4 genotype and BMI. The OSA group contained a higher proportion of APOE ε4 carriers (34.2% vs. 15.9%, $\chi 2 = 4.53$, $p = 0.03$), who also demonstrated elevated amyloid relative to controls (1.41 ± 0.21 vs. 1.27 ± 0.17, $p = 0.02$). In multivariable regression, OSA was no longer a significant predictor of 18F-florbetaben uptake when APOE ε4 carriers and BMI were added to the model ($R^2 = 0.145$, $p = 0.971$), whereas APOE ε4 ($p = 0.037$) and BMI ($p = 0.01$) remained significant, indicating that APOE ε4 exerts a stronger influence on Aβ burden than OSA alone. Nonetheless, in individuals with both risk factors, CIH and genetic vulnerability may act together to accelerate amyloid accumulation [63].

In contrast, tau PET with 18F-AV1451 tracer revealed no significant group differences in tau SUVR across mesial temporal, neocortical, or temporoparietal regions (mesial temporal: 1.24 ± 0.14 vs. 1.19 ± 0.12, $p = 0.09$; neocortical: 1.18 ± 0.10 vs. 1.15 ± 0.08, $p = 0.14$; temporoparietal: 1.20 ± 0.10 vs. 1.17 ± 0.09, $p = 0.11$). As cortical tau accumulation typically follows prolonged Aβ deposition, cognitively intact, preclinical individuals with OSA may not yet display pathological tau levels. Even so, the capacity to detect increased Aβ load in OSA underscores the importance of recognition and intervention to interrupt the amyloid cascade [64] and mitigate the eventual AD risk.

Extending these insights, Ylä-Herttuala et al. demonstrated globally decreased grey-to-white-matter (GM-WM) contrast in [11C]-PiB uptake. Dynamic PET analysis reflected altered late-phase tracer kinetics (11.1 ± 5.5 vs. −14.9 ± 5.3, $p = 0.017$), implicating glymphatic dysfunction as a plausible mechanism. Patients with abnormal SUVR also had substantially higher AHI (79.0 ± 17.9 vs. 45.4 ± 11.0, $p = 0.001$), reinforcing the association between OSA severity and amyloid pathology [35].

To date, most studies have focused on individual biomarker modalities in isolation. However, comprehensive understanding of OSA-related neurodegeneration requires integrated, multimodal assessment within the same cohort. Addressing this, Fernandes et al. evaluated CSF AD biomarkers, cerebral glucose metabolism via 18F-fuoro-2-deoxy-

d-glucose (18F-FDG) PET and cognitive outcomes in patients with moderate–severe OSA (mean AHI 44.52 ± 20.46). OSA participants demonstrated significantly lower global cognition (MMSE: 25.87 ± 2.63 vs. 28.08 ± 0.9, $p = 0.001$), reduced CSF Aβ42 (622.78 ± 211.96 pg/mL vs. 921.96 ± 69.55 pg/mL, $p = 0.002$) and elevated CSF p-tau (62.34 ± 49.37 pg/mL vs. 32.75 ± 5.21 pg/mL, $p = 0.001$) relative to controls [17].

Neuroimaging further revealed reduced 18F-FDG uptake in the bilateral praecuneus (BA 7), posterior cingulate cortex (BA 23), and frontal areas (BA8-10) (cluster level FWE corrected $p < 0.05$). These hypometabolic changes correlated positively with CSF p-tau and t-tau (all $p < 0.003$), directly linking AD-like proteinopathy to functional brain impairment. This work provides strong evidence that moderate–severe OSA is associated with a multimodal biomarker profile that is indistinguishable from preclinical AD, encompassing objective cognitive deficits, CSF protein abnormalities, and functional imaging changes.

## 5. Blood–Brain-Barrier (BBB) Disruption

BBB disruption represents another key mechanistic link between OSA and neurodegeneration. The BBB maintains central nervous system (CNS) homeostasis by tightly regulating molecular exchange between blood and brain. As noted above, intermittent hypoxia in OSA induces vascular endothelial injury and upregulation of pro-inflammatory cytokines, compromising tight-junction integrity [65], increasing BBB permeability and permitting the entry of neurotoxic and inflammatory mediators. This promotes a self-perpetuating cycle of immune cell infiltration, glial activation, and progressive neuronal damage.

Biomarker-based assessment of BBB disruption remains limited. Promising candidates include the CSF-to-plasma-albumin ratio (Qalb) [66], a widely used index of BBB integrity, and CSF Aβ42 levels. In a recent retrospective study, Fernandes et al. found significantly higher Qalb levels in moderate-to-severe OSA patients compared to healthy controls ($p = 0.026$), with similarly elevated Qalb in patients treated with CPAP for at least twelve months ($p = 0.044$). Qalb did not differ between untreated and CPAP-treated OSA, suggesting partial or absent reversibility of BBB dysfunction. Subgroup analysis showed that 52.6% (20/38) of moderate–severe OSA patients exhibited pathological CSF Aβ42 levels, while 31.6% (12/38) demonstrated high Qalb values. There was no significant difference between Qalb levels in patients with (7.25 ± 2.47) and without (8.50 ± 9.06) pathological CSF Aβ42 levels, indicating that BBB impairment in OSA may occur independently of overt Aβ pathology [18].

These findings are consistent with the hypothesis that CIH-mediated BBB compromise may contribute to OSA-related neurodegeneration. Elevated QAlb in untreated, moderate–severe OSA provides direct evidence of increased BBB permeability, and its persistence despite CPAP raises concern that BBB injury may only be partially reversible or reflect cumulative injury that may not be reversed by delayed intervention. Future longitudinal studies combining multiple biomarkers are required to clarify the temporal relationship between BBB dysfunction and proteinopathy and determine whether such panels can identify OSA patients at greatest risk of cognitive decline.

## 6. Glymphatic Dysfunction

The glymphatic system is essential for the clearance of soluble proteins and metabolic waste, mediating fluid and solute exchange across the brain parenchyma, and facilitating removal of Aβ and tau [67]. Glymphatic activity is maximal during non-rapid eye movement (NREM) sleep; thus, recurrent apnoeic events and sleep fragmentation in OSA are expected to impair CSF–interstitial fluid exchange and clearance of these proteins [68], accelerating their aggregation within the brain. Glymphatic dysfunction has been implicated in several neurodegenerative disorders, including AD and vascular dementia.

Diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) is a novel MRI technique for assessing glymphatic function. A lower DTI-ALPS index reflects reduced water diffusivity along perivascular spaces, indicating impaired glymphatic activity, and has been associated with cognitive dysfunction [69]. Notably, the present review included four primary studies on DTI-ALPS [36–39]. Across all studies, DTI-ALPS was significantly reduced in OSA patients and strongly correlated with indices of OSA severity as well as cognitive function. In particular, Lee et al. demonstrated in a case–control study involving 24 participants that the DTI-ALPS index was only correlated with poorer PSG indices during the NREM phase of sleep (AHI: r = 0.427, $p$ = 0.042; ODI: r = 0.497, $p$ = 0.036) but not REM sleep, suggesting that glymphatic impairment in OSA is driven primarily by the disruption of NREM-predominant clearance activity [36]. Current literature supports this, with studies demonstrating greater slow-wave activity in the N3 sleep stage, which correlates with greater CSF flow across periventricular areas [70,71]. Overall, these findings position the DTI-ALPS index as a biomarker that highlights the presence glymphatic disruption in OSA patients, as well as the downstream neurocognitive decline.

Future research should prioritise elucidating the precise mechanisms by which OSA may disrupt glymphatic function, delineating the effects of OSA treatment on glymphatic clearance and cognitive outcomes, and establishing the DTI-ALPS index as a prognostic biomarker for cognitive decline in OSA. The application of emerging advanced neuroimaging techniques may further complement DTI-ALPS and enable more accurate quantification of glymphatic activity.

Overall, multiple neuroimaging studies indicate that OSA is associated with a multifaceted pattern of brain injury spanning from structural atrophy to white-matter damage, network dysfunction, and molecular pathology. These findings support several mechanistic pathways by which OSA may promote neurodegeneration, including small-vessel disease, accumulation of neurotoxic proteins, and interactions with genetic vulnerability such as ApoE e4. Importantly, evidence from longitudinal and treatment studies suggests that at least some functional abnormalities and amyloid changes may be partially reversible with early diagnosis and effective OSA management.

The distribution of studies across the four thematic areas reveals important patterns in the current evidence linking OSA to neurodegeneration (Table 2). Neuroinflammation emerged as the most extensively studied theme, encompassing 20 studies which analysed the alterations across a wide range of biomarkers. This breadth reflects the field's recognition of neuroinflammation as a central mechanistic pathway. This is complemented by the neuroimaging studies (n = 8) which provide direct in vivo evidence of brain pathology. Systemic inflammation was the next most represented theme (n = 10), spanning a wide range of inflammatory markers. Oxidative stress remains largely unexplored, especially given the established role of intermittent hypoxia in generating reactive oxygen species (n = 2).

**Table 2.** Summary of studies examining biomarker alterations in OSA, overall direction of change and correlation with PSG markers and neurodegeneration. ("↑", "↓" and "-" represent an increase, decrease and unchanged level of each biomarker, respectively., "+" indicates correlation, "N.S" indicates "not stated").

| Neuroinflammation (20 Studies) | Direction of Change | Correlation with OSA Severity | Correlation with Neurodegeneration |
|---|---|---|---|
| CSF Aβ42 (n = 7) | ↓ (4 ↓, 3 -) | + | + |
| CSF Aβ40 (n = 1) | ↓ | N.S | N.S |
| CSF p-tau (n = 5) | -(4 -, 1 ↑) | + | N.S |
| CSF t-tau (n = 4) | - | + | + |
| CSF t-tau/Aβ42 ratio (n = 1) | ↑ | N.S | N.S |
| CSF lactate (n = 1) | ↑ | + | N.S |
| CSF VILIP-1 | ↓ | N.S | N.S |
| CSF neurogranin | ↓ | N.S | N.S |
| Aβ plaques (n = 1) | ↑ | + | N.S |
| Neurofibrillary tangles (n = 1) | ↑ | N.S | N.S |
| Plasma p-tau (n = 1) | ↑ | + | + |
| Plasma t-tau (n = 1) | ↑ | + | + |
| Plasma Aβ42 (n = 2) | 1 ↓, 1- | + | + |
| Plasma Aβ40 (n = 1) | ↑ | + | + |
| Plasma/serum amyloid-A (n = 1) | ↑ | N.S | N.S |
| Plasma/serum BDNF (n = 1) | - | + | N.S |
| Exosome Aβ42 (n = 1) | ↑ | N.S | + |
| Serum NfL (n = 1) | ↑ | + | + |
| Serum Aβ42 (n = 2) | 1 ↑, 1- | + | + |
| Serum Aβ40 (n = 2) | ↑ | + | + |
| Serum total tau (n = 2) | - | N.S | N.S |
| Serum p-tau181 (n = 1) | ↑ | N.S | N.S |
| Serum α-synuclein (n = 1) | ↑ | Not significant | + |
| Serum galectin-3 (n = 1) | ↑ | + | + |
| **Neuroimaging (8 Studies)** | **Direction of Change** | **Correlation with OSA Severity** | **Correlation with Neurodegeneration** |
| DTI-ALPS index (n = 4) | ↓ | + | + |
| Tau-PET (n = 1) | - | Not significant | N.S |
| Aβ-PET (n = 2) | ↑ | Not significant | N.S |
| Qalb (n = 1) | ↑ | N.S | N.S |
| White-matter change (n = 1) | ↑ | + | N.S |
| GW-matter contrast (n = 1) | ↓ | + | N.S |
| Functional connectivity (n =2) | ↓ | + | + |
| **Systemic Inflammation (10 Studies)** | **Direction of Change** | **Correlation with OSA Severity** | **Correlation with Neurodegeneration** |
| IL-6 (n = 4) | ↑ | N.S | + |
| CRP/hsCRP (n = 4) | ↑ | + | N.S |
| IL-8 (n = 2) | ↑ | + | + |
| TNF-alpha (n = 2) | ↑ | N.S | N.S |
| Soluble cytokine receptors (n = 1) | ↓ | N.S | N.S |
| Complement proteins (n = 1) | ↑ | Not significant | + |
| IL-1β (n = 1) | ↑ | + | + |
| IL-33 (n = 1) | ↑ | N.S | + |
| Fibrinogen (n = 1) | ↑ | + | N.S |
| Uric acid (n = 1) | ↑ | + | N.S |
| ESR (n = 1) | - | N.S | N.S |
| Adropin (n = 1) | ↓ | + | N.S |
| Plasma NDE EAAT2 (n = 1) | ↑ | + | + |
| Mitochondrial proteins (n = 1) | ↑ | N.S | + |
| **Oxidative Stress (2 Studies)** | **Direction of Change** | **Correlation with OSA Severity** | **Correlation with Neurodegeneration** |
| SOD (n = 3) ** | ↓ | + | **+** |
| Urinary 8-OHdg (n = 1) | ↑ | **+** | N.S |
| MDA (n = 1) | ↑ | + | +/Not significant |
| CAT (n = 1) | ↓ | + | + |
| Vitamin E (n = 1) | ↓ | N.S | + |
| Plasma folate (n = 1) | ↓ | N.S | N.S |
| Homocysteine (n = 1) | ↑ | N.S | N.S |

** One study on neuroinflammation also analysed alterations in SOD, MDA and CAT.

## 7. Biomarker Changes After Therapeutic Interventions

Given the strengthening association between OSA and neurodegenerative pathology, and the established efficacy of interventions such as continuous positive airway pressure (CPAP), the next step is to determine whether these therapies can attenuate or reverse neurodegenerative processes. It is also crucial to assess whether clinical improvements parallel normalisation of circulating biomarkers. This section therefore summarises the available

evidence (Table 3) on the influence of CPAP and surgical interventions on biomarkers of inflammation, endothelial dysfunction, and neurotoxicity, with particular emphasis on the time course, magnitude, and clinical correlates of these changes.

**Table 3.** Studies demonstrating alterations in biomarkers in OSA patients post therapy. Rows with background color indicate studies which presented biomarker alterations in OSA patients compared to controls, as well as changes post CPAP. ("↑", "↓" and "-" represent an increase, decrease and unchanged level of each biomarker, respectively. AHI: Apnea–hypopnea index, ESS: Epworth Sleepiness Scale, N.S: Not stated).

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Treatment Details | Key Findings |
|---|---|---|---|---|---|---|
| Effect of CPAP on biomarkers (n = 24) | | | | | | |
| Elias et al. 2018 [20] | Risk of Alzheimer's disease in obstructive sleep apnea syndrome: Amyloid-beta and tau imaging. | Cross-sectional (with treatment group) | 119 | • 18F-florbetaben (Aβ) – | • Duration: N.S<br>• Adherence: N.S<br>• Residual AHI: N.S<br>• Oxygenation: N.S | • The use of CPAP had no effect on cognitive or amyloid PET findings. |
| Sehr et al. 2024 [72] | Effects of obstructive sleep apnea treatment on neurodegenerative biomarker neurofilament light chain and cognitive performance. | Longitudinal | 20 | • Serum NfL – | • Duration: 9 months<br>• Adherence: ≥4 h per night<br>• Residual AHI: <10/hour ($p$ value N.S)<br>• Oxygenation: N.S<br>• ESS: Improved ($p$ = 0.01) | • At 2 and 9 months after initiation of CPAP therapy, serum NfL remained stable in patients with effective OSA treatment (9.25 [4.44] vs. 10.30 [5.19], $p$ = 0.347).<br>• Cognitive measures were unchanged. (MoCA: 28.30 (2.36) vs. 28.30 (1.83), $p$ = 1.00). |
| Staats et al. 2005 [31] | Regulation of brain-derived neurotrophic factor (BDNF) during sleep apnoea treatment. | Cross-sectional (with treatment group) | 17 | • Serum and plasma BDNF ↓ | • Duration: 3 months<br>• Adherence: ≥4 h per night<br>• Residual AHI: N.S<br>• Oxygenation: Improved ($p$ value N.S)<br>• ESS: Improved ($p$ value N.S) | • CPAP treatment is associated with a rapid decrease in serum and plasma BDNF levels. |
| Zong et al. 2023 [29] | Involvement of Galectin-3 in neurocognitive impairment in obstructive sleep apnea via regulating inflammation and oxidative stress through NLRP3. | Longitudinal | 47 | • Serum galectin-3 ↓ | • Duration: 12 weeks<br>• Adherence: ≥4 h per night<br>• Residual AHI: Improved ($p < 0.001$)<br>• Oxygenation: Improved ($p < 0.001$)<br>• ESS: Improved ($p < 0.001$) | • CPAP treatment for 12 weeks effectively reduced the levels of galectin-3 (1.73 ± 0.22 ng/mL vs. 2.31 ± 0.43 ng/mL, $p < 0.001$) and improved cognitive function. |
| Liguori et al. 2017 [12] | Obstructive Sleep Apnea is Associated With Early but Possibly Modifiable Alzheimer's Disease Biomarkers Changes. | Longitudinal | 50 | • CSF Aβ42 ↑<br>• CSF lactate, t-tau/Aβ42 ratio ↓ | • Duration: 1 year<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: Improved ($p < 0.0001$)<br>• Oxygenation: Improved ($p < 0.01$) | • CPAP-treated patients had significantly lower CSF lactate (1.70 [0.18] vs. 2.21 [0.48], $p < 0.001$), and t-tau/Aβ42 ratio (0.27 [0.13] vs. 0.67 [0.58], $p < 0.001$) than untreated patients. They had significantly higher Aβ42 levels (881.40 [174.33] vs. 484.00 [159.90], $p < 0.001$). |

**Table 3.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Treatment Details | Key Findings |
|---|---|---|---|---|---|---|
| W.-T. Liu et al. 2023 [73] | Continuous Positive Airway Pressure Reduces Plasma Neurochemical Levels in Patients with OSA: A Pilot Study. | Prospective | 30 | • Plasma t-tau, t-tau-Aβ42, Aβ42/T-tau ratio ↓<br>• Plasma Aβ42 – | • Duration: 3 months<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: Improved ($p$ value N.S)<br>• Oxygenation: N.S<br>• ESS: Improved ($p < 0.05$) | • There were significant decreases in the level of plasma t-tau (22.47 ± 2.38 vs. 24.69 ± 5.26, $p < 0.05$), product of t-tau-Aβ42 (368.21 ± 46.21 vs. 412.56 ± 117.73, $p < 0.05$) as well as the Aβ42/T-tau ratio (0.73 ± 0.07 vs. 0.69 ± 0.09, $p < 0.01$).<br>• There was minimal change to plasma Aβ42 post CPAP (16.36 ± 0.43 vs. 16.53 ± 1.06, $p = 0.73$). |
| Sun et al. 2022 [22] | Altered amyloid-beta and tau proteins in neural-derived plasma exosomes in obstructive sleep apnea. | Cross-sectional with longitudinal cohort | 122 | • Exosome Aβ42, t-tau, P-T181-tau ↓ | • Duration: 1 year<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: <5 per hour ($p$ value N.S)<br>• Oxygenation: N.S<br>• ESS: Improved ($p = 0.01$) | • Levels of Aβ42 (2.83 ± 0.31 vs. 3.54 ± 0.52, $p = 0.001$), t-tau (143.33 ± 22.62 vs. 179.58 ± 38.51, $p = 0.012$), and P-T181-tau (40.83 ± 9.06 vs. 51.33 ± 13.13, $p = 0.034$) after 1 year of CPAP intervention were significantly lower than those at baseline.<br>• Post-CPAP patients had better MoCA scores (26.17 ± 1.47 vs. 23.75 ± 2.56, $p = 0.01$). |
| Madaeva et al. 2019 [23] | Plasma Amiloid β42 in Patients with Obstructive Sleep Apnea before and after CPAP-Therapy: Pilot Study. | Prospective | 24 | • Plasma Aβ42 ↑ | • Duration: 3 months<br>• Adherence: ≥4 h per night<br>• Residual AHI: Improved ($p < 0.05$)<br>• Oxygenation: Improved ($p < 0.05$) | • OSA patients had lower plasma Aβ42 levels at baseline. After CPAP, levels increased compared to baseline ($p = 0.041$) and were comparable to controls ($p > 0.05$).<br>• Treated patients had an increase in short-wave-sleep (SWS) duration. |
| Ju et al. 2019 [74] | Treatment of obstructive sleep apnea restores the relationship between slow wave activity and amyloid-beta. | Longitudinal | 18 | • CSF Aβ42 –<br>• CSF Aβ40 –<br>• CSF tau – | • Duration: 4 months<br>• Adherence: ≥4 h per night<br>• Residual AHI: Improved ($p < 0.001$)<br>• Oxygenation: Improved ($p < 0.007$) | • There were no significant changes in CSF Aβ42 (987 ± 329 vs. 977 ± 319, $p = 0.733$), Aβ40 (12,059 ± 3560 vs. 12,033 ± 3972, $p = 0.944$) or tau (182 ± 102 vs. 184 ± 96, $p = 0.602$) levels after CPAP treatment.<br>• After CPAP treatment, higher slow-wave activity is significantly correlated with lower CSF Aβ. |

**Table 3.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Treatment Details | Key Findings |
|---|---|---|---|---|---|---|
| Fernandes et al. 2025 [18] | Persistent blood-brain barrier dysregulation in patients with obstructive sleep apnea following long-term continuous positive airway pressure treatment. | Longitudinal | 75 | • Qalb –<br>• CSF Aβ42 ↑ | • Duration: 1 year<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: Improved (*p* value N.S)<br>• Oxygenation: N.S | • CPAP-treated patients had significantly higher CSF Aβ 42 levels (846.50 vs. 485.00, $p < 0.001$).<br>• Qalb levels remained unchanged.<br>• In OSA patients who exhibited pathological levels of CSF biomarkers, CPAP treatment did not lead to significant improvement in Qalb compared to controls (all $p > 0.05$). |
| Fernandes et al. 2022 [17] | 18F-FDG PET, cognitive functioning, and CSF biomarkers in patients with obstructive sleep apnoea before and after continuous positive airway pressure treatment. | Prospective cohort with longitudinal intervention | 68 | • 18-FDG PET uptake ↑ | • Duration: 1 year<br>• **Adherence: N.S**<br>• Residual AHI: Improved ($p = 0.003$)<br>• Oxygenation: N.S | • CPAP patients showed an improvement in cognition (MMSE: 27.58 ± 1.88 vs. 26.17 ± 2.69, $p > 0.05$) and a significant increase in cerebral 18F-FDG uptake in the right and left frontal areas and left parietal lobe (BA 4, BA 6, BA 10) (all $p < 0.0001$). |
| Long et al. 2023 [75] | Functional Connectivity Changes in the Insular Subregions of Patients with Obstructive Sleep Apnea after 6 Months of Continuous Positive Airway Pressure Treatment. | Longitudinal | 36 | • Functional connectivity ↑ | • Duration: 6 months<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: Improved ($p < 0.001$)<br>• Oxygenation: N.S<br>• ESS: Improved ($p = 0.028$) | • CPAP-treated patients showed increased FC from the right ventral anterior insula to the bilateral superior frontal gyrus and bilateral middle frontal gyrus as well as from the left posterior insula to the left middle temporal gyrus and left inferior temporal gyrus.<br>• CPAP patients had improved cognitive outcomes (MoCA: 25.4 ± 3.18 vs. 25 [20,26], $p = 0.012$). |
| M. Li et al. 2022 [76] | Paroxysmal slow wave events are associated with cognitive impairment in patients with obstructive sleep apnea. | Longitudinal | 339 | • PSWE events | • Duration: 1 year<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: <5 per hour (*p* value N.S)<br>• Oxygenation: N.S<br>• ESS: Improved ($p < 0.001$) | • Paroxysmal slow-wave events (PSWEs) were negatively correlated with global cognitive performance and cognitive subdomains.<br>• After 1 year of CPAP treatment, the total PSWEs decreased significantly (3.1 [2.5] vs. 3.5 [3.2], $p < 0.001$), and MoCA scores (24.44 ± 3.06 vs. 24.04 ± 3.36, $p = 0.039$) were improved compared with baseline. |

**Table 3.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Treatment Details | Key Findings |
|---|---|---|---|---|---|---|
| Shiota et al. 2014 [77] | Effect of continuous positive airway pressure on regional cerebral blood flow during wakefulness in obstructive sleep apnea. | Prospective | 24 | • rCBF ↑ | • Duration: 6 months<br>• Adherence: ≥4 h per night, ≥80% per month<br>• Residual AHI: Improved (*p* value N.S)<br>• Oxygenation: Improved (*p* value N.S) | • Patients with OSA before CPAP treatment showed a significantly lower regional cerebral blood flow (rCBF) in the frontal lobe.<br>• After the treatment, no difference in rCBF was observed between the good CPAP compliance group and the controls. |
| Kim et al. 2016 [78] | Effects of Long-Term Treatment on Brain Volume in Patients With Obstructive Sleep Apnea Syndrome. | Longitudinal | 80 | • Brain volume ↑ | • Duration: 8–44 months<br>• Adherence: ≥4 h per night, ≥70% of all nights<br>• Residual AHI: N.S<br>• Oxygenation: N.S | • There was increased brain volume following CPAP treatment.<br>• Volume increase was correlated with longer treatment in the cortical areas that largely overlapped with the initial atrophy. |
| P. Li et al. 2022 [32] | The Effects of CPAP Treatment on Resting-State Network Centrality in Obstructive Sleep Apnea Patients. | Longitudinal | 42 | • Functional connectivity - | • Duration: 1 month<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: Improved ($p < 0.001$)<br>• Oxygenation: N.S<br>• ESS: Improved ($p = 0.007$) | • Post-CPAP OSA patients showed reduced DC values in the bilateral CPL and increased DC values in several brain regions in the frontal, temporal, and insular lobes. |
| Schiza et al. 2010 [79] | C-reactive protein evolution in obstructive sleep apnoea patients under CPAP therapy. | Longitudinal | 528 | • CRP ↓ | • Duration: 1 year<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: N.S<br>• Oxygenation: N.S | • A significant reduction in CRP levels was observed after CPAP therapy ($0.31 \pm 0.29$ vs. $0.74 \pm 0.62$, $p < 0.001$).<br>• Significant correlations were noted between CRP values and AHI ($p < 0.0001$, rho = 0.54), ODI ($p < 0.0001$, rho = 0.52), mean $SaO_2$ ($p < 0.0001$, rho = 0.48) and $SaO_2$ nadir during sleep ($p < 0.0001$, rho = 0.53).<br>• CRP reduction plateaued at 6 months of CPAP ($p > 0.05$ when compared to 12 months after CPAP). |

**Table 3.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Treatment Details | Key Findings |
|---|---|---|---|---|---|---|
| Wu et al. 2016 [42] | Effect of CPAP therapy on C-reactive protein and cognitive impairment in patients with obstructive sleep apnea hypopnea syndrome. | Prospective | 178 | • hsCRP ↓ | • Duration: 6 months<br>• **Adherence: >20 h per week**<br>• Residual AHI: N.S<br>• Oxygenation: N.S<br>• ESS: Improved ($p < 0.001$) | • hsCRP levels significantly improved (1.04 ± 0.94 vs. 2.90 ± 1.68, $p < 0.001$) after CPAP treatment.<br>• CPAP patients had improved cognitive function (MoCA: 27.37 ± 2.32 vs. 26.18 ± 2.14, $p < 0.001$; MMSE: 28.7 ± 1.26 vs. 28.33 ± 3.21, $p = 0.236$). |
| Shen et al. 2023 [47] | IL-33/ST2 mediating systemic inflammation and neuroinflammation through NF-kB participated in the neurocognitive impairment in obstructive sleep apnea. | Cross-sectional with longitudinal cohort | 21 | • IL-6, IL-8, IL-33, ST2, p65NF-κB ↓ | • Duration: 1 year<br>• Adherence: ≥4 h per night, ≥70% of all nights<br>• Residual AHI: Improved ($p < 0.001$)<br>• Oxygenation: Improved ($p < 0.001$)<br>• ESS: Improved ($p < 0.001$) | • Levels of IL-6 (7.58 ± 1.16 vs. 8.71 ± 1.87, $p < 0.05$), IL-8 (246.70 ± 27.38 vs. 272.30 ± 29.14, $p < 0.05$), IL-33 (values N.S, $p < 0.05$), ST2 (values N.S, $p < 0.05$) and p65NF-κB (values N.S, $p < 0.05$) significantly decreased after 12 weeks of CPAP.<br>• CPAP patients had improved MoCA and MMSE scores (both $p < 0.01$). |
| Steiropoulos et al. 2009 [80] | Long-Term Effect of Continuous Positive Airway Pressure Therapy on Inflammation Markers of Patients with Obstructive Sleep Apnea Syndrome. | Longitudinal | 52 | • TNF-α ↓<br>• Uric acid ↓<br>• IL-6 - | • Duration: 6 months<br>• Adherence: ≥ 4 h per night<br>• Residual AHI: N.S<br>• Oxygenation: N.S | • Levels of TNF-α (8.41 ± 5.7 vs. 5.72 ± 4.91, $p = 0.001$), uric acid (8.79 ± 1.48 vs. 6.2 ± 1.37, $p < 0.001$) decreased significantly after 6 months of good compliance to CPAP treatment.<br>• In contrast, IL-6 levels showed no significant change (2.71 ± 1.27 vs. 2.46 ± 1.08 $p = 0.266$). |
| M. Li et al. 2024 [50] | Mitochondrial dysfunction is associated with cognitive impairment in adults with OSA without dementia. | Cross-sectional with longitudinal cohort | 268 | • Mitochondrial proteins (humanin, MOTS-c, NRGN) ↓ | • Duration: 1 year<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: <5 events/hour ($p$ value N.S)<br>• Oxygenation: N.S | • NDE levels of humanin (8.78 ± 6.41 vs. 9.66 ± 7.32, $p = 0.002$), MOTS-c (235.36 ± 156.52 vs. 265.40 ± 176.43, $p = 0.001$), and NRGN (0.61 ± 0.48 vs. 0.67 ± 0.53, $p = 0.006$) decreased significantly after CPAP therapy.<br>• CPAP therapy led to improved MoCA scores (25.23 ± 2.76 vs. 24.86 ± 2.92, $p = 0.029$). |

**Table 3.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Treatment Details | Key Findings |
|---|---|---|---|---|---|---|
| Ildiz et al. 2025 [81] | The relationship between disease severity, treatment adherence, inflammation, and neurocognitive functions in patients with obstructive sleep apnea syndrome. | Longitudinal | 155 | • PDW, PLR, NLR ↓ | • Duration: 3 months<br>• Adherence: ≥4 h per night<br>• Residual AHI: N.S<br>• Oxygenation: N.S<br>• ESS: Improved ($p < 0.001$) | • Treated individuals had significantly lower platelet distribution width (PDW) (11.6 [10.6–13] vs. 13.6 [11.4–16], $p = 0.011$), platelet-to-lymphocyte ratio (PLR) (104.71 [90.34–123.10] vs. 120.34 [96.63–149.66], $p = 0.045$), and neutrophil-to-lymphocyte ratio (NLR) (1.83 [1.33–2.13] vs. 2.14 [1.62–2.56], $p = 0.039$) compared to untreated patients.<br>• Cognitive scores did not improve significantly after CPAP (MMSE: 27.02 ± 1.96 vs. 26.88 ± 1.97, $p = 0.708$; MoCA: 24.22 ± 2.52 vs. 23.74 ± 2.99, $p = 0.394$). |
| Y. Wang et al. 2021 [48] | Patients with obstructive sleep apnea have suppressed levels of soluble cytokine receptors involved in neurodegenerative disease, but normal levels with airways therapy. | Cross-sectional (with treatment group) | 46 | • Soluble cytokine receptors ↑ | • Duration: 6 months<br>• **Adherence: N.S**<br>• Residual AHI: N.S<br>• Oxygenation: Improved ($p$ value N.S)<br>• ESS: Improved ($p$ value N.S) | • Untreated OSA patients show significantly reduced (twofold to sevenfold) serum levels of gp130, IL6R, TNFR1, and TNFR2, which are associated with neurodegenerative disease (all $p < 0.0001$).<br>• CPAP led to significantly higher levels of these soluble cytokine receptors (all $p < 0.0001$). |
| Xue et al. 2023 [51] | Neuronal glutamate transporters are associated with cognitive impairment in obstructive sleep apnea patients without dementia. | Longitudinal | 317 | • Plasma NDE EAAT2 ↓ | • Duration: 1 year<br>• Adherence: ≥4 h per night, ≥5 nights per week<br>• Residual AHI: <5 events/hour ($p$ value N.S)<br>• Oxygenation: N.S | • Plasma NDE EAAT2 level was significantly higher in OSA patients and significantly associated with cognitive impairment.<br>• CPAP treatment led to significantly lower plasma NDE EAAT2 levels (2.985 [6.192] vs. 2.754 [6.009], $p = 0.019$).<br>• Changes to plasma NDE levels of EAAT2 were significantly negatively correlated to MoCA alteration (r = −0.52, $p = 0.009$) |

**Table 3.** *Cont.*

| Author, Year | Title of Study | Study Design | Sample Size (n) | Biomarkers Studied | Treatment Details | Key Findings |
|---|---|---|---|---|---|---|
| Effect of surgery on biomarkers (n = 2) | | | | | | |
| Kong et al. 2023 [82] | Alzheimer's disease biomarkers in patients with obstructive sleep apnea hypopnea syndrome and effects of surgery: A prospective cohort study. | Prospective | 27 | • Plasma Aβ42, Aβ40, t-tau and p-tau ↓ | • 6 months post uvulopalatopharyngoplasty (UPPP) | • Plasma Aβ42 (0.23 ± 0.17 vs. 0.20 ± 0.16, $p = 0.0001$), Aβ40 (23.52 ± 24.46 vs. 29.24 ± 32.52, $p = 0.0046$), t-tau (8.88 ± 6.21 vs. 11.88 ± 7.05, $p = 0.0001$) and p-tau (20.43 ± 10.50 vs. 26.31 ± 14.41, $p = 0.0001$) decreased significantly at 6 months post operation.<br>• All biomarkers negatively correlated with MMSE scores (all $p < 0.05$).<br>• Postoperative patients had improved MMSE scores (29.07 ± 1.78 vs. 27.14 ± 1.65, $p = 0.0001$). |
| Lin et al. 2024 [39] | Association of MRI Indexes of the Perivascular Space Network and Cognitive Impairment in Patients with Obstructive Sleep Apnea. | Prospective | 15 | • DLTI-ALPS index ↑ | • 4.9 months post uvulopalatopharyngoplasty (UPPP) | • 15 patients had improved DLTI-ALPS index ($p < 0.001$) after uvulopalatopharyngoplasty (median 4.9 months postoperatively). |

A key methodological consideration in interpreting biomarker changes post CPAP is whether treatment was objectively effective. Across included studies, there was minimal heterogeneity in the definition of CPAP adherence. Where available, we report objective adherence (hours of use per night), therapy duration, residual AHI, and indices of oxygenation improvement for each study. Subjective improvement (Epworth Sleepiness Scale, ESS) was also reported, where available.

CPAP has been the cornerstone of OSA management and has consistently demonstrated substantial reductions in disease severity as well as all-cause mortality [83,84]. It achieves therapeutic effect by reducing upper airway resistance through the prevention of sleep-induced airway collapse and promotion of airway dilatation, with potential mechanoreceptor stimulation leading to increased pharyngeal muscle tone [85]. CPAP has also been hypothesised to potentially lead to clinically meaningful recovery of cognitive function [86]. A total of 26 studies were included.

### *7.1. Markers of Inflammation*

Eight studies analysed the levels of serum inflammatory cytokines in patients post CPAP and demonstrated consistent reductions across a broad spectrum of biomarkers.

CRP represents a promising marker for monitoring CPAP efficacy. Schiza et al. demonstrated significant reduction in CRP levels (0.31 ± 0.29 vs. 0.74 ± 0.62, $p < 0.001$) after 1 year of effective CPAP therapy (≥4 h CPAP use/night, >5 days per week). Notably, CRP levels plateaued at 6 months, despite continued adherence to CPAP over 1 year, which could indicate that the therapeutic effects of CPAP require at least 6 months of continued adherence to treatment [79]. Similarly, Wu et al. reported that six months of adherent (≥4 h per night) CPAP led to significant reductions in hsCRP (1.04 ± 0.94 mg/L vs. 2.90 ± 1.68 mg/L, $p < 0.001$), achieving levels comparable to those seen in healthy individuals or patients with mild OSA (1.00 ± 1.28 mg/L). They also reported improved MoCA scores (27.37 ± 2.32

vs. 26.18 ± 2.14, $p < 0.001$), which may link inflammatory normalisation to cognitive improvement [42].

Shen et al. demonstrated that 1 year (≥4 h CPAP use/night) CPAP use significantly reduced levels of IL-6, IL-8, IL-33, ST2 and p65NF-κB—a pathway directly implicated in neuroinflammation via NF-κB signalling—with parallel improvements in both MMSE and MoCA scores [47]. Similarly, Steiropoulos et al. demonstrated significant reductions in TNF-α (8.41 ± 5.7 vs. 5.72 ± 4.91 pg/mL, $p = 0.001$) and uric acid (8.79 ± 1.48 vs. 6.2 ± 1.37 mg/dL, $p < 0.001$), although IL-6 levels remained unchanged, highlighting the heterogeneity of cytokine responses to treatment [80]. Collectively, the evidence presented demonstrates that CPAP therapy is associated with reductions in systemic inflammation, as reflected by the consistent reductions in multiple pro-inflammatory cytokines across studies. Given the established role of inflammatory mediators in the pathogenesis of cardiovascular disease [87] and their contribution to increased morbidity and mortality [88], the benefits of effective long-term CPAP are likely to extend beyond mitigating neurodegeneration.

Nonetheless, it is important to recognise that levels of circulating inflammatory markers are strongly influenced by age, BMI and comorbidities, therefore stringent adjustment for these confounders is essential in future work. Longer-term follow-up studies are also required to determine the durability of these anti-inflammatory effects and their direct relationship to subsequent cognitive outcomes in the OSA population.

### *7.2. Neurotoxic Proteins*

Ten studies examined the impact of CPAP on circulating and CSF levels of neurotoxic proteins with heterogeneous results. Our included studies demonstrated that levels of CSF Aβ42 increased while the t-tau/CSF Aβ42, CSF tau and CSF lactate decreased following CPAP. In contrast, plasma Aβ42 responses were variable. Madaeva et al. reported a significant improvement in plasma Aβ42 ($p = 0.041$) in OSA patients after three months of CPAP, with posttreatment levels being comparable to healthy controls despite being lower at baseline ($p = 0.024$) [23]. Conversely, Liu et al. observed only minimal, non-significant changes in plasma Aβ42 (16.36 ± 0.43 vs. 16.53 ± 1.06, $p = 0.73$) [73]. Notably, in Madaeva et al. CPAP was associated with a 56% increase in the slow-wave-sleep (SWS) duration ($p < 0.05$), leading the authors to hypothesise that SWS restoration by CPAP may enhance clearance of neurotoxic products. This aligns with findings from other studies [74] reporting significant inverse correlations between SWS activity and CSF Aβ40 and Aβ42.

Overall, CSF concentrations of neurotoxic proteins remain the most robust biomarkers of neurodegeneration, and current evidence hypothesises that CPAP may enhance cerebral waste clearance and glymphatic function. By contrast, plasma Aβ42 is a less reliable index of neurodegeneration given its propensity to bind to plasma and membrane proteins [89,90] and its non-linear trajectory relative to cognitive decline [91].

Serum NfL represents another biomarker of neurotoxicity. Despite evidence of elevated serum NfL levels in OSA patients, there is limited evidence demonstrating its change after CPAP treatment. Sehr et al. classified OSA patients undergoing CPAP therapy into two groups based on treatment effectiveness, which was measured by sufficient adherence and normalisation of AHI. They found that, with effective and adherent CPAP therapy, OSA patients had stable age-adjusted serum NfL levels during follow-up at 2 and 9 months (baseline: 9.3 pg $mL^{-1}$, 2 months: 10.6 pg $mL^{-1}$, 9 months: 10.3 pg $mL^{-1}$, $p = 0.347$). In comparison, ineffective treatment resulted in significant increase in serum NfL (baseline: 11.0 pg $mL^{-1}$; 2 months: 11.4 pg $mL^{-1}$; 9 months: 14.1 pg $mL^{-1}$, $p < 0.001$) [72]. Therefore, serum NfL could be a promising biomarker for monitoring the efficacy of CPAP therapy, and rigorous studies with larger cohorts are required to validate these findings.

### 7.3. Neuroimaging

Eight studies examined the alterations in neuroimaging findings post CPAP. Neuroimaging evidence consistently indicates substantial neuroplastic potential in OSA patients. Kim et al. reported that CPAP-treated patients exhibited increased global cortical volume (all areas corrected $p$ values < 0.05), with longer treatment durations associated with more widespread volumetric gains (all corrected $p$ values < 0.05) [78]. Other studies demonstrated that CPAP-related improvements across multiple neuroimaging modalities, alongside partial reversal of cognitive deficits in several domains, although findings remain heterogeneous.

## 8. Surgical Interventions

Surgical treatment may be considered for OSA patients with correctable anatomical abnormalities, or as a last resort for those who are intolerant or non-adherent to CPAP. A wide range of procedures target different levels of upper airway obstruction, thus accurate preoperative assessment with sleep endoscopy and/or imaging is essential. Uvulopalatopharyngoplasty (UPPP) is currently the most performed surgery, but long-term outcomes in patients post UPPP are mixed. A meta-analysis by He et al. reported significant short-term (<1 year) improvements in objective indices (AHI decreased by 37.3%, $p = 0.028$; ODI decreased 44.6%, $p < 0.001$; and ST90 decreased 37.5%, $p < 0.001$). However, these indices did not show sustained improvements at longer-term follow-up (≥34 months) [92].

The present review included two studies that analysed biomarker alterations post UPPP. Kong et al. conducted a prospective study of 27 patients six months after UPPP. The team observed significant reductions in plasma Aβ42 (0.23 ± 0.17 vs. 0.20 ± 0.16, $p = 0.0001$), Aβ40 (29.24 ± 32.52 vs. 23.52 ± 24.46, $p = 0.0046$), t-tau (11.88 ± 7.05 vs. 8.88 ± 6.21, $p = 0.0001$) and p-tau (26.31 ± 14.41 vs. 20.43 ± 10.50, $p = 0.0001$) [82]. Complementing these findings, Lin et al. demonstrated significant improvements in DTI-ALPS in a subset of 15 OSA patients ($p < 0.001$, median 4.9 months postoperatively) [39], suggesting that surgical restoration of upper airway patency may enhance glymphatic clearance alongside reductions in markers of cerebral proteinopathy.

Overall, surgical interventions such as UPPP, despite variable long-term efficacy on respiratory indices, appear to confer short-term reductions in plasma biomarkers of neurodegeneration, which may help to attenuate disease progression. However, both studies are limited by small surgical subgroup sizes, short follow-up durations and the absence of long-term biomarker trajectories. Furthermore, given the mixed long-term efficacy of UPPP on respiratory indices beyond one year as demonstrated by He et al., it remains unclear whether short-term biomarker improvements translate into sustained neuroprotective benefits. Therefore, further longitudinal studies with larger cohorts and extended follow-up durations are needed to establish the long-term neuroprotective benefits of surgical intervention in OSA.

A synthesis of the included studies reveals that therapeutic intervention in OSA, predominantly CPAP, can modulate a broad spectrum of biomarkers across multiple pathophysiological domains (Table 4). Neuroinflammation was the most extensively investigated domain (n = 10), followed by systemic inflammation (n = 8). Lastly, neuroimaging studies (n = 8) provide direct evidence of treatment-induced structural and functional improvements. Notably, the absence of oxidative stress markers, as well as the heterogeneity of studied biomarkers, highlights the importance of future longitudinal investigations.

**Table 4.** Alterations in biomarkers post therapy. ("↑", "↓" and "-" represent an increase, decrease and unchanged level of each biomarker, respectively.)

| Neuroinflammation (n = 10) | Neuroimaging (n = 8) | Systemic Inflammation (n = 8) |
|---|---|---|
| CSF Aβ42 (n = 3) ↑ (2 ↑, 1 -)<br>CSF t-tau (n = 1) –<br>CSF t-tau/Aβ42 ratio (n = 1) ↓<br>CSF lactate (n = 1) ↓Plasma Aβ42 (n = 2) 1 ↑, 1-<br>Plasma t-tau (n = 2) ↓<br>Plasma p-tau (n = 1) ↓<br>Plasma t-tau/Aβ42 ratio (n = 1) ↓<br>Plasma Aβ40 (n = 1) ↓<br>Serum BDNF (n = 1) ↓<br>Serum NfL (n = 1) -<br>Serum galectin-3 (n = 1) ↓<br>Exosome Aβ42, T-tau, P-T181-tau (n = 1) ↓ | PET-18F FDG (n = 1) ↑<br>PET Aβ (n = 1) ↑<br>Qalb (n = 1) -<br>Brain volume (n = 1) ↑<br>Functional connectivity (n = 2) 1 ↑, 1-<br>Cerebral blood flow (n = 1) ↑<br>DTI-ALPS index (n = 1) ↑ | CRP (n = 2) ↓<br>IL-6 (n = 2) 1 ↓, 1 -<br>IL-8 (n = 1) ↓<br>IL-33 (n = 1) ↓<br>TNF-alpha (n =1) ↓<br>Soluble cytokine receptors (n = 1) ↑<br>Uric acid (n = 1) ↓<br>PDW, PLR, NLR (n =1) ↓<br>Plasma NDE EAAT2 (n = 1) ↓<br>Mitochondrial proteins (n = 1) ↓ |

## 9. Multiomics Technologies

Most studies to date have adopted a single-marker or limited-panel approach. Given the complex, multifactorial pathophysiology linking OSA to neurodegeneration, this approach is inherently limited. Multiomics technologies enable the visualisation of OSA pathophysiology across the biological spectrum through the analysis of genes (genomics), RNA transcripts (transcriptomics), proteins (proteomics) and epigenetic modifications (epigenomics).

These integrated pathway analyses offer an unprecedented ability to delineate the entire molecular landscape of OSA, identify novel biomarkers with high diagnostic accuracy, and elucidate the links between CIH and neurodegenerative outcomes. This may in turn improve risk stratification, therapeutic monitoring, and understanding of disease mechanisms. Recent advances have begun to establish this framework, although direct links to neurodegenerative pathologies have yet to be demonstrated. Eight studies were included, highlighting these advances (Table 5).

**Table 5.** Studies involving multiomics technologies in the study of OSA pathophysiology and therapy.

| Author, Year | Title of Study | Key Findings |
|---|---|---|
| J. Li et al. 2024) [93] | Advances in non-coding RNA as a biomarker for obstructive sleep apnoea hypoventilation syndrome. | • Specific ncRNAs can be used as reference indicators for accurate diagnosis of OSA.<br>• ncRNAs have potential to be biomarkers for combined OSA and health issues. |
| H.-Y. Li et al. 2019 [94] | Alterations in Alzheimer's Disease-Associated Gene Expression in Severe Obstructive Sleep Apnea Patients. | • The expressions of CCL2, IL-6, CXCL8, HLA-A, and IL1RN in the patients with severe OSA were significantly different from those in the patients with non-severe OSA. |
| Cortese et al. 2022 [95] | Epigenetic age acceleration in obstructive sleep apnoea is reversible with adherent treatment. | • OSA-induced perturbations promote biological age acceleration, which are partially reversible when adherent and effective treatment of OSA is implemented. |

**Table 5.** *Cont.*

| Author, Year | Title of Study | Key Findings |
| --- | --- | --- |
| Fan et al. 2021 [96] | Identification of key genes and immune infiltration modulated by CPAP in obstructive sleep apnea by integrated bioinformatics analysis. | • Eleven genes were identified to be differentially expressed in OSA patients.<br>• They were used to construct a random forest model to predict therapeutic efficacy of CPAP in OSA with a good performance with AUC of 0.92.<br>• Further studies of the immune cell networks revealed that monocytes were found to be related to the remission of OSA and partially correlated with the hub genes identified. |
| E. Zhou et al. 2025 [97] | Identifying and validating immunological biomarkers in obstructive sleep apnea through bioinformatics analysis. | • Identified 175 differentially expressed genes (DEGs) from a dataset which contained visceral adipose tissue samples of 10 OSA patients and 8 controls.<br>• Memory B cells, mast cells resting, and dendritic cells resting were the predominant immune cells related to DEIRGs.<br>• Identified 128 miRNAs, 40 transcription factors, and 172 drugs/compounds that interacted with the DEIRGs.<br>• IL-33, EIF2AK2, IL10RB, and ANGPTL1 were also upregulated in clinical OSA samples. |
| Q. Liu et al. 2025 [98] | Preliminary evidence of immune infiltration and neutrophil degranulation in peripheral blood of non-obese OSA patients related to cognitive decline. | • The relative expression of DEFA4 was significantly correlated with the MoCA score and sleep parameters.<br>• Biomarkers representative of neutrophils' activation were elevated significantly in the OSA group. |
| Ou et al. 2024 [99] | TDP43/HDAC6/Prdx1 signaling pathway participated in the cognitive impairment of obstructive sleep apnea via regulating inflammation and oxidative stress. | • Expression of TDP-43 and HDAC6 was increased in subjects with OSA, whereas Prdx1 expression was decreased.<br>• These alterations were reversed after 12 weeks of CPAP treatment.<br>• Protein expression of TDP-43 and HDAC6 was negatively correlated with MoCA scores in patients with OSA, while Prdx1 expression exhibited the opposite trend. |
| Cederberg et al. 2022 [100] | Proteomic Biomarkers of the Apnea Hypopnea Index and Obstructive Sleep Apnea: Insights into the Pathophysiology of Presence, Severity, and Treatment Response. | • 84 proteins (47 positively, 37 negatively) associated with AHI, 5 of which were noted to be significantly decreased following CPAP/PAP treatment.<br>• 69 differentially expressed proteins (DEPs) between different OSA severity groups.<br>• These DEPs yielded a specificity of 63.3% and sensitivity of 73.9% in predicting OSA severity (AUC = 0.74). |

### 9.1. Transcriptomics

The investigation of non-coding RNAs (ncRNA) has revealed considerable potential diagnostic and therapeutic monitoring biomarkers. ncRNAs participate in diverse biological processes, including regulation of gene expression, epigenetic modifications, and oncogenesis, and their dysregulation has been associated with multiple diseases [101].

Specific gene expression signatures have been identified that differentiate OSA severity and implicate immune–inflammatory pathways. Li et al. demonstrated that severe OSA is associated with altered expression of AD-related genes, including the downregulation of CCL2, CXCL8, HLA-A and IL-6 and upregulation of IL1RN [94]. Liu et at. applied similar methods and demonstrated that the expression of immune-related differentially expressed genes (DEG), particularly DEFA4, was significantly correlated with MoCA score ($r = -0.58$, $p = 0.041$) and indices of OSA severity such as AHI ($r = 0.636$, $p = 0.022$) [98]. DEG levels may therefore have prognostic value for OSA severity in newly diagnosed patients. They also reported no significant difference in DEG profiles before and after CPAP therapy, although further longitudinal studies are required to validate this.

Building on this work, Li et al. identified 11 different miRNAs established in the diagnosis of OSA, with multi-ncRNA panels yielding improved specificity and sensitivity. Notably, the combination of miR-145-5p and let-7d-5p exhibited 93% sensitivity and 100% specificity (AUC = 0.951, 95% CI: 0.856 to 1.00). The study also reported the involvement of more than 35 ncRNAs in various OSA-related complications and delineated their roles in pathophysiology [93]. Therefore, the utility of ncRNA may extend beyond OSA-related neurodegeneration to the monitoring of related complications.

### 9.2. Epigenomics

Beyond the transcriptome, the epigenome constitutes an additional critical layer of regulation. There is increasing interest in epigenetic ageing [102], typically assessed via DNA methylation, and its relationship to disease. Epigenetic age acceleration has been associated with increased risk and progression of AD [103] and other neurodegenerative diseases [104], potentially via disrupted gene regulation and chronic inflammation [105]. Importantly, adverse epigenetic modifications may be reversible with epigenetic regulators, which could be exploited as targeted therapies in OSA. A novel study by Cortese et al. reported a significant deceleration of epigenetic age after one year of adherent CPAP therapy, relative to both pretreatment values and healthy controls [95].

### 9.3. Proteomics

Proteomics involves the systemic identification and quantification of proteins expressed by cells via mass spectrometry and the mapping of their changes, modifications and interactions to elucidate disease mechanisms and treatment effects. Cederberg et al. studied proteins cross-sectionally associated with the presence and severity of OSA in a cohort of 1391 patients. Across all participants, 84 proteins were associated with AHI (47 positively, 37 negatively), while 69 differentially expressed proteins (DEPs) were identified when comparing groups of different OSA severity. Subsequent analyses revealed 10 proteins that were significant markers of AHI and eight DEPs that discriminated moderate-to-severe OSA, yielding a specificity of 63.3% and sensitivity of 73.9% in predicting OSA severity (AUC = 0.74). Post CPAP, levels of five proteins were significantly reduced and mapped to pathways related to blood coagulation, inflammatory response, fibrinolysis, and plasminogen activation [100]. These findings suggest that protein-based biomarkers may have clinical utility in prognosticating OSA severity and monitoring treatment response, while also providing mechanistic insights into physiological alterations in OSA.

Current multiomic studies in OSA patients converge on pathways involving oxidative stress, inflammation, endothelial dysfunction and metabolic stress, all of which are recognised drivers of neurodegeneration and correspond to measurable biomarkers described earlier. In the long term, integration of heterogeneous datasets within multiomics frameworks represents a promising research direction. Such approaches may elucidate mechanistic links between OSA and neurodegeneration at a molecular level and in turn enable the development of biomarker panels for research-based risk stratification. However, direct clinical translation remains a distant goal that will require robust longitudinal validation and standardisation of methodologies.

### *9.4. Multiomics Integration in Predictive Models*

Beyond biomarker discovery, transcriptomic studies have demonstrated the potential of DEG-based approaches to inform predictive models for diagnostic and treatment response. Fan et al. identified 11 key hub genes with altered expression following CPAP treatment and utilised them to construct a random forest model that predicted treatment response with an AUC of 0.92. They further demonstrated that CPAP therapy modulated immune cell infiltration, particularly monocytes, which correlated with hub genes such as CD22 and ESAM [96].

Multiomics also offers a rich platform for biomarker discovery and therapeutic target identification. Building on prior work, Zhou et al. identified 175 DEGs with high diagnostic accuracy, including IL10RB and SLC40A1 (both AUC = 0.9). These genes were implicated in cytokine-mediated signalling, inflammatory response, and adaptive immunity. After validating these findings in independent clinical samples, the authors constructed comprehensive regulatory networks that identified 128 miRNAs, 40 transcription factors and 172 potential drug compounds that interacted with the DEIRGs, providing a substantial resource for future studies of pathogenesis and therapeutics [97]. Therefore, the integration of these predictive models with hypothesised neurodegenerative markers such as CSF Aβ42, serum NfL and the DTI-ALPS within large deeply phenotyped cohorts would be the next step towards potentially clinically actionable risk-stratification tools for OSA-related neurodegeneration.

### *9.5. Future Directions of Multiomics Technologies*

As elucidated above, the priority is harmonised, deep phenotyping that moves beyond severity labels to mechanistically aligned exposure metrics. Future cohorts should incorporate repeated sleep assessments and a broader panel of physiologic features—hypoxic burden, arousal burden, sleep fragmentation, REM-related vulnerability, and autonomic signatures—paired with time-locked biospecimen collection to address temporal variability. Embedding causal frameworks (e.g., target-trial emulation in observational datasets, mediation analyses to test vascular/BBB pathways, and genetics-informed approaches where feasible) would help separate correlation from mechanism and clarify whether biomarker changes represent upstream drivers, downstream injury markers, or epiphenomena.

On the translational front, the next step is to evaluate biomarker-guided care pathways rather than biomarkers in isolation. Pragmatic trials could evaluate whether risk-enriched strategies such as using baseline biomarker profiles to intensify CPAP adherence support, escalate to alternative therapies, or trigger neuroimaging/CSF confirmation could improve cognitive trajectories compared with standard care. Parallel implementation work should define feasible “minimal panels” for routine practice, establish clinically actionable thresholds, and quantify incremental benefit using decision-analytic methods, ensuring that precision approaches remain scalable and equitable across real-world OSA populations.

## 10. Limitations and Future Directions

### 10.1. Summary of Evidence

In this scoping review, we identified a total of 59 unique primary studies. Forty of them analysed biomarkers involved in the pathophysiology behind neurodegeneration in OSA patients, while 26 described the changes in biomarkers post therapy. Notably, 15 studies were included in both aspects. Lastly, eight studies explored novel applications of multiomics technologies in this field. Currently, measurements of biomarkers emerge as promising markers of neurodegenerative risk in OSA patients, but several significant limitations must be acknowledged before these findings can be translated into practical clinical practice.

### 10.2. Limitations

First, substantial heterogeneity within study populations is a major concern. Many studies include small sample sizes and inadequately control for potent confounders such as age, genetic susceptibility, obesity, and comorbidities, which independently influence both OSA severity and circulating biomarker levels. Elevated markers may therefore reflect a chronic pro-inflammatory state driven by comorbid conditions rather than hypoxia-induced dysregulation attributable to OSA. Moreover, OSA itself is heterogeneous, yet most work solely relies on AHI-based severity categories. As demonstrated by Jordan et al., biomarkers such as MDA and urinary 8-OHdG correlated more strongly with nocturnal hypoxemia (e.g., ST90, ST85) than AHI alone, underscoring the need for refined studies that better quantify hypoxic burden across phenotypes, symptom profiles and comorbidity clusters. At present, significant heterogeneity and limited standardisation across cohorts substantially restrict the clinical utility of biomarkers for predicting neurodegeneration reliably.

Second, the predominance of cross-sectional designs limits causal inference. While associations between OSA severity and biomarker levels are well-established, it remains unclear whether OSA directly drives these changes or whether they share common upstream risk factors. Longitudinal studies with extended follow-up are scarce but essential. Existing data on the reversibility of neurodegeneration-related biomarkers with OSA treatment are promising but mixed: CPAP therapy consistently reduces inflammatory markers such as IL-6 and hsCRP, whereas persistent elevation of Qalb after 12 months of CPAP may suggest that some neurological injuries may be irreversible. Currently, long-term biomarker trajectories after intervention, particularly following surgical treatments, remain poorly characterised. Robust longitudinal cohorts are therefore needed to establish temporal relationships between cumulative CIH exposure, biomarker accumulation, as well as posttreatment alterations.

Third, the invasiveness and feasibility of biomarker measurements pose barriers to implementation. Current evidence spans a spectrum of sampling methods, each with trade-offs between pathophysiologic specificity and clinical practicality. Urinary markers such as 8-OHdG and o,o'-dityrosine are minimally invasive and well suited for routine in-clinic collection and large-scale screening, but their levels are influenced by systemic diseases and renal function. Plasma biomarkers provide a compelling intermediate option and circulating biomarkers such as TNF-α correlate strongly with OSA severity. Advances in ultra-sensitive assays have also enabled detection of brain-derived neuroinflammatory proteins (e.g., α-synuclein, Gal-3) in serum. However, blood-based biomarkers remain susceptible to confounding by comorbid conditions, which may limit their specificity for neurodegeneration in OSA. Neuroimaging offers direct visualisation of structural, functional and molecular brain changes without requiring fluid sampling. Modalities such as DTI-ALPS and PET with radioligands such as [11C]-PiB can provide reliable quantification of protein aggregation and thus serve as a direct measure of neurodegenerative pathology.

Nonetheless, their use for routine screening or serial monitoring remains constrained due to costs, availability, and logistical complexity.

A further limitation is exposure misclassification—both at the level of OSA phenotyping and treatment quantification. Across cohorts, OSA is variably defined (PSG vs. home testing; differing hypopnoea criteria and desaturation thresholds), with substantial night-to-night variability that is rarely captured by single-timepoint assessments. This variability is clinically meaningful in phenotypes such as REM-predominant or positional OSA, where AHI may underrepresent cumulative neurobiological stress. Likewise, "treated OSA" is often operationalised as CPAP prescription or self-reported use, rather than objective adherence, residual AHI, or restoration of sleep architecture—introducing dilution bias when biomarker trajectories are interpreted as treatment effects.

Finally, interpretive ambiguity persists in distinguishing reversible functional perturbation from established neurodegenerative injury. Many candidate biomarkers are sensitive to acute sleep loss, circadian variation, and systemic metabolic or inflammatory states, complicating attribution to brain-specific pathology in OSA. Moreover, cognitive outcomes are frequently limited to screening instruments or short-term neuropsychological change, rather than adjudicated incident MCI/dementia or biomarker-confirmed disease progression. Without anchoring biomarker change to clinically consequential endpoints, it remains difficult to define what constitutes a "meaningful" biomarker response—particularly in scenarios where markers (e.g., QAlb) persist despite CPAP.

### *10.3. Future Directions*

Future research should move beyond predominantly cross-sectional, AHI-centred analyses toward large, deeply phenotyped longitudinal cohorts with standardised OSA definitions and repeated measures of biologically relevant exposure, including hypoxic burden, sleep fragmentation, REM-related vulnerability, and night-to-night variability. Treatment effects should likewise be characterised using objective adherence, residual disease burden, and recovery of sleep architecture, rather than treatment prescription alone. Biomarker studies are best advanced through multimodal, temporally aligned designs that integrate blood- and urine-based markers with CSF and neuroimaging in nested subcohorts, while incorporating multiomics platforms to delineate mechanistic pathways and trajectory-specific signatures. These frameworks should be anchored to clinically meaningful outcomes, including incident MCI or dementia, adjudicated cognitive decline, and biomarker-supported neurodegenerative progression. In parallel, causal-analytic approaches, including mediation analyses and target-trial emulation where appropriate, will be important to distinguish reversible physiological perturbation from established neural injury, define clinically meaningful treatment-responsive biomarker change, and identify patient subgroups most likely to benefit from early intervention. Ultimately, translational progress will depend on validating scalable minimal biomarker panels with clear thresholds and demonstrable incremental predictive value beyond routine clinical variables, enabling equitable implementation of biomarker-guided risk stratification in clinical practice.

## 11. Conclusions

The evidence mapped in this scoping review is consistent with OSA contributing to neurodegenerative risk. The convergence of evidence across multiple mechanistic pathways and biomarker platforms underscores the potential for biomarkers to serve as research tools with potential future clinical utility, pending longitudinal validation. Furthermore, the emergence of multiomics technologies raises the possibility that future research may benefit from integrated multimodal approaches that comprehensively characterise the

molecular complexity of OSA pathophysiology. Future rigorous longitudinal studies in deeply phenotyped cohorts, incorporating standardised exposure metrics and multiomics integration, are needed to validate the reliability, generalisability and clinical utility of biomarker panels in this field. The current body of evidence established in this scoping review provides a framework for future longitudinal studies but is insufficient to support the routine clinical use of any biomarker for neurodegenerative risk stratification in OSA at this time.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jor6030014/s1, Table S1: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist; Table S2: Literature search. Reference [106] is cited in the supplementary materials.

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