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Title: Biomarkers of dementia in obstructive sleep apnea

Authors: Andrée-Ann Baril[1,2], Julie Carrier[1,3], Alexandre Lafrenière[1,3], Simon Warby[1,2], Judes Poirier[4,5], Ricardo S. Osorio[6], Najib Ayas[7,8], Marie-Pierre Dubé[9,10], Dominique Petit[1], Nadia Gosselin[1,3], on behalf of the Canadian Sleep and Circadian Network

Authors' affiliations:
1. Center for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, Canada
2. Department of Psychiatry, Faculty of Medicine, Université de Montréal, Montreal, Canada
3. Department of Psychology, Université de Montréal, Montreal, Canada
4. Centre for Studies on Prevention of Alzheimer's disease, Douglas Institute, Verdun, Canada
5. Department of Psychiatry and Medicine, McGill University, Montreal, Canada
6. Department of Psychiatry, Center for Brain Health, NYU Langone Medical Center, New York City, United-States
7. Division of Critical Care Medicine, Faculty of Medicine, University of British Columbia, Vancouver, Canada
8. Center for Health Evaluation & Outcomes Sciences, St. Paul Hospital, Vancouver, Canada
9. Department of Medicine, Faculty of Medicine, Université de Montréal, Montreal, Canada
10. Beaulieu-Saucier Pharmacogenomics Center, Montreal Heart Institute, Montreal, Canada

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Corresponding author:
Nadia Gosselin, PhD
Center for Advanced Research in Sleep Medicine
Hôpital du Sacré-Cœur de Montréal
5400 boul. Gouin Ouest, local E-0330
Montréal, Québec Canada H4J 1C5
Tel: 514-338-2222 ext. 7717
Fax: 514-338-3893
nadia.gosselin@umontreal.ca

Summary

Epidemiologic and mechanistic evidence is increasingly supporting the notion that obstructive sleep apnea is a risk factor for dementia. Hence, the identification of patients at risk of cognitive decline due to obstructive sleep apnea may significantly improve preventive strategies and treatment decision-making. Cerebrospinal fluid and blood biomarkers obtained through genomic, proteomic and metabolomic approaches are improving the ability to predict incident dementia. Therefore, fluid biomarkers have the potential to predict vulnerability to neurodegeneration in individuals with obstructive sleep apnea, as well as deepen our understanding of pathophysiological processes linking obstructive sleep apnea and dementia. Many fluid biomarkers linked to Alzheimer's disease and vascular dementia show abnormal levels in individuals with obstructive sleep apnea, suggesting that these conditions share common underlying mechanisms, including amyloid and tau protein neuropathology, inflammation, oxidative stress, and metabolic disturbances. Markers of these processes include amyloid-β, tau proteins, inflammatory cytokines, acute-phase proteins, antioxydants and oxidized products, homocysteine and clusterin (apolipoprotein J). Thus, these biomarkers may have the ability to identify adults with obstructive sleep apnea at high risk of dementia and provide an opportunity for therapeutic intervention. Large cohort studies are necessary to establish a specific fluid biomarker panel linking obstructive sleep apnea to dementia risk.

Glossary of terms

All-cause dementia

Presence of dementia regardless of subtypes, such as Alzheimer's disease, vascular dementia and others;

Mild cognitive impairment

Objective cognitive impairment that is more severe that is expected for normal aging, but has no or only a minimal impact on activities of the daily living. Mild cognitive impairment can be considered a prodromal stage of Alzheimer's disease, although it can be caused by other conditions such as vascular and psychiatric diseases. Moreover, it can lead to other type of dementias than Alzheimer's disease, remain stable or even return to normal cognitive functioning;

Omics

Large-scale evaluation of biomarkers by molecule types, generally in a discovery-based approach, including genomics, proteomics, and metabolomics;

Preclinical and prodromal Alzheimer's disease

The preclinical stage corresponds to cognitively normal individuals who will later develop Alzheimer's disease while the prodromal stage corresponds to individuals with mild cognitive impairment who will later develop Alzheimer's disease. These stages can be identified longitudinally and may also be of interest in other type of dementias. Moreover, recent recommendations suggest that identifying preclinical and prodromal Alzheimer's disease is possible at a single time point when abnormal biomarkers levels that are highly suggestive of Alzheimer's disease pathology are present.

Abbreviations

8-OHdg – 8-hydroxy-2-desoxyguanosine

ABCA7 – ATP-binding cassette transporter A

AQP4 – aquaporin 4

APOE – apolipoprotein

APP – amyloid-β precursor protein

Aβ – amyloid-β

ACT – α1-antichymotrypsin

AD – Alzheimer's disease

BBB – blood-brain barrier

BIN1 – bridging integrator 1

CLU (or APOJ) – clusterin

CPAP – continuous positive airway pressure

CR1 – complement component receptor 1

hsCRP – high-sensitivity c-reactive protein

CSF – cerebrospinal fluid

FERMT2 – fermitin family member 2

HLA – major histocompatibility complex

HDL-C – high-density lipoprotein cholesterol

ICAM-1 – intercellular adhesion molecule 1

IL – interleukins

IFN – interferon

MCI – mild cognitive impairment

MDA – malondialdehyde

MTHFR – 5,10-methylenetetrahydrofolate reductase

OSA – obstructive sleep apnea

PS – polygenic score

PET –positron emission tomography

PICALM – phosphatidylinositol-binding clathrin assembly molecule

SOD – superoxide dismutase

SORL1 – sortilin-related receptor 1

TGF-β1 – transforming growth factor β1

TNF-α – tumor necrosis factor α

VCAM-1 – vascular cellular adhesion molecule 1

VaD – vascular dementia

VILIP-1 – visinin-like protein 1

YKL-40 – chitinase-3-like protein 1

1. Introduction

Approximately 36 million people worldwide have dementia and this number is expected to reach 115 million in 2050 [1]. Alzheimer's disease (AD) is the most common type of dementia and is characterized by the aggregation of extracellular amyloid-β (Aβ) and intracellular hyperphosphorylation of tau proteins, leading to amyloid plaques and neurofibrillary tangles respectively [2]. Vascular dementia (VaD) is the second most common type of dementia and is caused by cerebrovascular events [3]. About 20% of dementia cases are mixed, with the presence of both AD and VaD pathophysiological processes [4]. Mild cognitive impairment (MCI) is the presence of cognitive decline with no or mild functional impact that can evolve over time towards dementia [5]. MCI that eventually becomes dementia is called prodromal dementia, although novel recommendations suggest that identifying prodromal dementia is possible at a given point when MCI is combined with abnormal biomarkers levels highly suggestive of dementia pathology [5]. Since the neuropathological process starts years before the clinical manifestations of AD and VaD [6], one of the most important targets is preclinical dementia, i.e., cognitively normal individuals who will later develop dementia. Current research efforts aim to identify preclinical dementia in order to eventually apply disease modifying-therapy [5].

Dementia biomarkers that enable the identification of individuals at risk of dementia are receiving increasing attention. They are biological indicators of risk, or progression towards neurodegenerative processes, and are useful because early diagnosis is central to dementia research and clinical screening [7]. Neuroimaging biomarkers that measure brain atrophy, reduced brain glucose metabolism, or amyloid plaques can detect changes up to 15 years before dementia onset [6], but they have limited availability and are expensive. Cognitive assessment is easy and accessible, but cognitive impairment occurs later in the course of the disease [6]. Fluid biomarkers of dementia are a great

alternative to neuroimaging and cognitive biomarkers: they are inexpensive and have the potential to be easily implemented in large cohort studies or used for screening dementia risk in older individuals.

Targeting modifiable risk factors are of outmost importance to reduce the occurrence and progression of dementia. An emerging modifiable risk factor for dementia is obstructive sleep apnea (OSA), which is characterized by respiratory obstructions during sleep [8]. Recently, several cohort studies and a meta-analysis have identified OSA as a risk factor for cognitive decline starting at an earlier age, as well as for MCI and all-cause dementia [9-14]. This review will mainly focus on AD and VaD, because they are the two most common causes of dementia. Moreover, epidemiological and mechanistic evidence suggests a relationship between these two types of dementia and OSA. Because continuous positive airway pressure (CPAP) effectively treats OSA [15], it is a modifiable risk factor of dementia. CPAP may delay the onset of cognitive decline [13], although results on the cognitive effects of CPAP in middle-aged individuals are inconsistent [16]. Some studies showed that CPAP improves neuropsychological functioning over a few weeks [17] and slows the rate of cognitive decline over three years [18] in patients with both AD and OSA. CPAP also improved cognition in stroke patients [19]. With a prevalence in the elderly that reaches over 50% in some studies [20], OSA could become an important target to prevent dementia.

Many pathophysiological mechanisms have been proposed to explain the relationship between OSA and dementia (see Figure 1). First, recent evidence suggests that the consequences of OSA, namely disturbed sleep and intermittent hypoxia, may induce AD neuropathology. Combined $A\beta$ and tau pathology seems to play a causative role in AD [5]. Thus, processes leading to increased $A\beta$ generation and deposition in the brain, reduced $A\beta$ clearance to the cerebrospinal fluid (CSF), as well as tau hyperphosphorylation may play a role in the pathogenesis of AD. Disrupted slow-wave sleep in healthy adults was associated with increased $A\beta$ levels in the CSF [21], suggesting that disturbed sleep may lead to $A\beta$ generation. Moreover, an innovative animal model demonstrated that sleep plays an

important role in the Aβ clearance by enlarging the interstitial space [22], which suggests that disturbed sleep in OSA may lead to reduced Aβ clearance. In addition, studies identified multiple pathways linking hypoxia/ischemia with Aβ deposition in the brain (see [23] for a review). Hypoxia/ischemia increases Aβ generation by affecting its precursor, Aβ precursor protein (APP). Hypoxia/ischemia increases APP production and cleavage into Aβ, and reduces the activity of neuroprotective enzymes that act on APP [23]. In addition, a few studies suggest that both sleep disruption and chronic hypoxia increase tau protein levels and their hyperphosphorylation [21, 24-26].

It is likely that OSA also plays an indirect role in the development of dementia by increasing the incidence of cardiovascular and metabolic diseases, including hypertension, obesity, metabolic syndrome, stroke and diabetes [27], which are themselves independent risk factors of dementia [3, 28]. Moreover, sleep fragmentation and intermittent hypoxia in OSA both induce inflammation, oxidative stress, mitochondrial dysfunction, endothelial dysfunction, and metabolic deregulation [29], which have all been proposed to foster the development of AD and VaD [30, 31] (see Figure 1).

This theoretical review aims to identify the most promising fluid biomarkers of dementia that should be included in future large research cohorts of individuals with OSA. Ultimately, a panel of fluid biomarkers could improve direct patient care significantly by identifying adults with OSA at higher risk of developing dementia, and could be useful to unravel the pathophysiological mechanisms linking OSA to dementia. To achieve this goal, we first present the most promising candidate biomarkers of dementia that emerged from the recent literature. We present evidence on CSF and blood biomarkers of AD and VaD, including those from genomics, proteomics, and metabolomics. When possible, we also present the corresponding findings of these biomarkers in the OSA population. Finally, we propose a research agenda for testing fluid biomarkers of dementia in OSA.

2. Genomics

2.1. Genetics of dementia

Usually using blood samples, genetic and genome-wide association studies investigate specific polymorphisms, which are the occurrence of different alleles in the population. The most important and well-established genetic risk factor for sporadic AD is the *apolipoprotein E4 (APOE4)* allele (see [32] for a review), which was first described in the early 90's [33]. AD risk is increased by 300% for one *APOE4* allele and 1500% for two *APOE4* alleles, while the *APOE2* allele is protective [32]. APOE is involved in lipid transport and membrane integrity in the brain as well as in Aβ degradation [34].

Although none are associated with AD as strongly as *APOE*, several other polymorphisms modify the incidence of AD, including *clusterin (CLU), sortilin-related receptor-1 (SORL1), complement component receptor 1 (CR1), ATP-binding cassette transporter A (ABCA7), fermitin family member 2 (FERMT2), major histocompatibility complex class II (HLA-DRB5, HLA-DRB1), bridging integrator 1 (BIN1),* and *phosphatidylinositol-binding clathrin assembly molecule (PICALM)* [32]. These genes affect the risk for AD by about 10-20% each, and they code for proteins involved in Aβ production and clearance, tau toxicity, endosomal vesicle cycling, lipid transport, and the immune response. Recently, polymorphisms of the *aquaporin 4 (AQP4)* gene were investigated in relationship with AD risk. This gene codes for a water channel involved in the clearance of products via the so-called glymphatic system. *AQP4* polymorphisms modified the rate of cognitive decline after AD diagnosis in one study, and moderated the relationship between sleep quality and Aβ burden measured with PET imaging in another [35, 36]. In the context of recent discoveries linking sleep quality to Aβ clearance in the interstitial fluid [22], more studies are needed to better define how *AQP4* polymorphisms are involved in the relationship between sleep disruption and the incidence of dementia.

Because many polymorphisms are now linked to incident AD, genetic susceptibility to dementia for a given individual can be computed with a polygenic score (PS). The risk of developing AD and the

age of onset can be predicted with a PS combining 31 polymorphisms, which correlates with several other biomarkers of AD, including CSF Aβ and tau protein levels [37]. A PS computed with thousands of polymorphisms has high predictive accuracy for AD even when the most common polymorphisms such as *APOE* are not included [38], suggesting that the genetic susceptibility to AD includes a large number of genes with only a small risk associated to each individually.

VaD risk is increased by the *APOE4* allele as well as by other specific genetic polymorphisms, including *5,10-methylenetetrahydrofolate reductase (MTHFR)*, which is involved in homocysteine conversion, as well as *TNF-α* and *transforming growth factor β1 (TGF-β1),* which are cytokines involved in the immune response (see [39] for a review). Genes increasing the risk of stroke have also the potential to modify the risk of VaD [39]. Ischemic stroke can be predicted with a PS computed with thousands of polymorphisms [40]. Moreover, a PS computed with polymorphisms that are associated with stroke correlated with cognitive abilities in adults without stroke [41].

2.2. Dementia genetics factors in OSA

Multiple genes were associated with the presence of OSA and its severity [42]. However, very few of them have been linked to incident dementia. Looking at genes related to dementia risk, recent meta-analyses concluded that there is no association between *APOE* polymorphism and the presence of OSA [43, 44]. However, the *APOE4* allele may interact with OSA to worsen cognitive performance: OSA severity was associated with worse memory, attention, executive functioning as well as worse global cognition only in *APOE4* carriers [45-48]. Polymorphisms of *TNF-α* and *interleukin-6 (IL-6)*, which code for inflammatory cytokines, as well as *HLA-DRB1* have all been associated with the presence of OSA [43, 49-51], although how inflammation may lead to OSA remains to be clarified.

3. CSF biomarkers

3.1. CSF biomarkers of dementia

CSF biomarkers that are directly related to AD neuropathology can be used to diagnose probable AD (see [52, 53] for reviews). Low CSF $A\beta_{42}$ levels and $A\beta_{42/40}$ ratio are the signature of AD and probably result in the increased brain deposition of $A\beta$ in the form of amyloid plaques [52, 53]. Low CSF $A\beta_{42}$ levels are also observed in the preclinical stages of AD (i.e., cognitively normal adults who will later develop AD) [53], suggesting that $A\beta$ deposition is a very early process. Low CSF $A\beta_{42}$ levels can also be observed in VaD, but they are less marked than in AD [54]. On the other hand, most reports show no $A\beta_{40}$ level changes in AD patients [52].

High CSF tau levels also have high sensitivity and specificity for AD and prodromal AD, but were often reported as unchanged in preclinical AD [52]. Increased CSF tau levels may occur later than the $A\beta$ changes in the neurodegenerative process [53], which has been confirmed with recent work using positron emission tomography (PET) markers [55]. While CSF total tau levels are elevated in both AD and VaD, phosphorylated tau levels are more specific to AD and can be useful to discriminate between these two types of dementia [52, 53].

Although CSF $A\beta_{42}$, $A\beta_{42/40}$ ratio and tau levels are increasingly recognized as established biomarkers for dementia, cut-off values to diagnose AD remain variable across studies and assays [56]. Values for AD diagnosis vary between <480 and 640 pg/ml for $A\beta_{42}$ levels and between >250 and 375 g/ml for total tau levels [57]. Regarding the $A\beta_{42/40}$ ratio, recent studies suggest a cut-off value between <0.05 and 0.06 [58, 59].

In addition to biomarkers representing AD neuropathology, novel and promising CSF biomarkers have recently emerged in the literature. Lactate accumulation in the CSF, hypothesized to represent mitochondrial dysfunction, was evidenced in AD patients compared to controls and VaD patients [60]. Chitinase-3-like protein 1 (YKL-40) and visinin-like protein 1 (VILIP-1), which are markers of

inflammation and neuronal injury respectively, are other promising CSF biomarkers of AD. Although only YKL-40 is high in MCI and AD patients, high levels of both YKL-40 and VILIP-1 were shown to predict conversion from MCI to AD [61].

3.2. CSF biomarkers in OSA

Adults with OSA had low CSF $A\beta_{40,}$ $A\beta_{42}$ and VILIP-1 levels, but unchanged CSF tau levels were found [62]. In a recent study in which all subjects reported subjective cognitive impairment, those with OSA exhibited lower CSF $A\beta_{42}$ levels, a higher tau/$A\beta_{42}$ ratio, a higher lactate level, but no tau level changes when compared to controls and OSA patients treated with CPAP [63]. A case-report of a 57-year-old man with severe OSA and subjective cognitive impairment showed abnormal low CSF levels of $A\beta_{42}$ and $A\beta_{42/40}$ (<500 pg/ml and <0.06) and high total tau/$A\beta_{42}$ ratio levels (>0.52) that were normalized with a one-year treatment with CPAP [64]. In the largest cross-sectional and only longitudinal study to date performed in cognitively normal elderly, OSA severity indices were not associated with CSF $A\beta_{42}$ levels at cross-section but correlated with annual rates of CSF $A\beta_{42}$ level decrease over the two-year follow-up [65], which would be consistent with increases in amyloid burden over time. Interestingly, the decrease in the annual rate of CSF $A\beta_{42}$ in association with OSA severity was larger than what would be predicted by the *APOE4* allele alone. Overall, most of these recent reports performed in subjects aged 50-70 years suggest that OSA is associated with low CSF $A\beta_{42}$ levels as would be expected in the preclinical stages of dementia.

4. Blood-based proteomic biomarkers of AD neuropathology

4.1. Blood-based biomarkers of AD neuropathology in dementia

Some studies found lower blood $A\beta_{42}$ levels in patients with AD or MCI, but also in cognitively normal and MCI adults who will later develop dementia (see [66] for a review). However, others have failed to replicate these results and even reported higher blood $A\beta_{42}$ levels in cognitively normal adults

in their preclinical stage of AD [66]. A meta-analysis of 7 studies showed that higher blood $A\beta_{42}$ levels were present in subjects with preclinical AD [67]. Blood $A\beta_{42}$ levels may depend on the stage of the disease: enhanced levels might be present in earlier stages of the disease, and then levels decrease as the cognitive decline progresses [66, 67]. This pattern could represent increased $A\beta$ production and reduced clearance at first, with aggregation into plaques later on. Results seem less promising for blood $A\beta_{40}$ levels, as both increased and decreased levels were reported in AD patients [66]. A meta-analysis indicated high blood $A\beta_{40}$ levels in the preclinical stage of AD [67], whereas unchanged levels in these early stages were also reported [66]. Overall, mixed results were obtained on blood $A\beta_{40}$ levels at all stages of the disease. On the other hand, the blood $A\beta_{42/40}$ ratio yields more promising results. A meta-analysis including over 10 000 subjects concluded that a low blood $A\beta_{42/40}$ ratio was associated with a high risk of developing all-cause dementia [68]. A low blood $A\beta_{42/40}$ ratio was indeed reported in subjects with AD, MCI and with preclinical AD [66].

A higher blood tau level is a new marker measured with high-sensitivity techniques that has been associated with the presence of AD and MCI [66]. A recent study with a three-year follow-up found that high tau protein levels were associated with the progression from cognitively normal to MCI, but not from MCI to all-cause dementia [69]. This could be due to the short follow-up period and to the low number of dementia cases observed and thus, other studies are needed to confirm blood tau protein level as a biomarker for dementia and whether they are associated with neurofibrillary tangles in the brain.

4.2. Blood-based biomarkers of AD neuropathology in OSA

In young adults, whereas OSA was not associated with blood $A\beta_{42}$ and $A\beta_{40}$ levels, moderate-severe OSA was associated with increased blood total tau levels compared to both mild OSA and controls [70]. In another study, middle-aged OSA subjects had significantly higher blood $A\beta_{40}$ and $A\beta_{42}$ levels as well as phosphorylated tau levels compared to controls, although unchanged total tau

levels were observed [71]. Overall, these first reports suggest that OSA may lead to increased blood tau and Aβ levels.

5. Blood-based proteomic biomarkers of inflammation

5.1. Blood-based inflammatory biomarkers of dementia

Inflammation is hypothesized to play a major role in VaD and AD [30, 31, 72]. In fact, there may be a bidirectional relationship between inflammation and neurodegeneration: inflammation is caused by Aβ deposition, oxidative stress, and cellular damage; and inflammation is followed by Aβ generation, blood-brain barrier (BBB) pathology, and further oxidative stress. A recent meta-analysis investigating 51 biomarkers in 171 studies concluded that inflammatory biomarkers are increased in AD [73], including IL-1β, IL-2, IL-6, IL-18, chemokine ligand-10, TNF-α converting enzyme and TNF receptors, and interferon gamma (IFN-γ). All of them are cytokines or chemokines involved in the immune response and glial activation [73]. Other elevated blood inflammatory biomarkers in AD patients included α1-antichymotrypsin (ACT) and high-sensitivity c-reactive protein (hsCRP), two acute-phase proteins involved in coagulation and lysis, and vascular cell adhesion molecule-1 (VCAM-1), an adhesion molecule which assists other markers to reach the inflammation site [73]. Most significant results were observed for IL-1β, IL-6, ACT, hsCRP and TNF receptors. However, a few studies showed either unchanged or reduced levels in AD patients [73]. As for VaD patients, they also show elevated cytokines compared to controls, including IL-1β, IL-4, IL-5, TNF-α, and IFN-γ [74].

In MCI subjects, despite the fact that most blood inflammatory biomarkers are unchanged, some studies have reported that a few cytokines are upregulated, including IL-1β, TNF-α, intercellular adhesion molecule 1 (ICAM-1), and IFN-α [75]. In six large cohort studies, higher blood levels of hsCRP, ACT and IL-6 were all associated with either a higher risk of cognitive decline or all-cause

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dementia, AD and vascular dementia (see [76] for a review), even though there are inconsistencies regarding which specific biomarkers were elevated.

5.2. Blood-based inflammatory biomarkers investigated in OSA

It is well known that OSA may lead to an inflammatory response [29, 77]. In a first meta-analysis of 15 studies, it was reported that blood hsCRP levels are higher in OSA patients compared to controls and that these levels are modulated by obesity and OSA severity [78]. The second meta-analysis of 47 articles found that blood TNF-α levels are also elevated in OSA subjects [79]. Finally, the third meta-analysis of 51 studies showed that blood levels of CRP, TNF-α, IL-6, IL-8 and adhesion molecules (ICAM-1, Selectins and VCAM-1) are increased in OSA subjects [80]. In these meta-analyses, the large majority of studies showed elevated blood inflammatory biomarkers in OSA.

6. Blood-based proteomic and metabolomic biomarkers of oxidative stress

6.1. Blood-based biomarkers of oxidative stress in dementia

Oxidative stress is the production of highly reactive free radicals that damage nucleic acids, proteins and lipids [81]. In dementia, oxidative stress is hypothesized to be an important mechanism leading to tissue damage (see [81] for a review). It occurs following inflammation and Aβ deposition [31], suggesting that oxidative stress may be an effector between dementia pathology and neuronal death. Moreover, oxidative stress leads to atherosclerosis and is involved in VaD pathogenesis [82].

Homocysteine is an amino acid with proprieties that makes it one of the most promising blood biomarkers for all-cause dementia. Indirectly, hyperhomocysteinemia is a marker of B12 deficiency, which can cause cognitive decline [83]. Directly, high levels of homocysteine cause oxidative stress, and thus, it is involved in BBB dysfunction, cardiovascular and cerebrovascular diseases, neuronal death, enhanced Aβ toxicity, Aβ generation and deposition as well as tau protein phosphorylation [83]. In 2002, homocysteine was already shown to be associated with dementia [84], and a meta-analysis of

10 studies concluded that homocysteine blood levels are elevated in AD patients [73]. This result was replicated in both AD and VaD patients in another meta-analysis of 13 studies [85], with higher levels in VaD than in AD [85]. Overall, many cohort studies showed that elevated blood levels of homocysteine are associated with the incidence of all-cause dementia up to 35 years later [83].

Reduced blood levels of antioxidants were reported in AD and MCI, including superoxide dismutase (SOD), selenium, vitamin E, and total antioxidant capacity [81]. In VaD, blood levels of many antioxidants are also reduced, including vitamins E, C and A as well as SOD [82]. Interestingly, supplements of vitamins C and E in the elderly may protect against the development of VaD, as well as mixed dementia [86], but more studies are needed to set the appropriate intake levels for these vitamins.

Biomarkers of free radicals, damaged proteins, lipid peroxidation and nucleic acid oxidation are increased in both AD and MCI patients compared to controls: hemo-oxygenase-1, protein carbonyls, oxidized protein products, malondialdehyde (MDA), hydroperoxides, 8,12-isoiPF(2alpha)-VI, 8-hydroxy-2-desoxyguanosine (8-OHdg) and 8-oxoguanine [81]. Overall, patients with dementia or at risk show reduced antioxidant capacity combined with increased oxidative stress production and damage.

6.2. Blood-based biomarkers of oxidative stress in OSA

OSA produces oxidative stress directly via intermittent hypoxia and mitochondrial dysfunction, as well as indirectly through associated comorbidities, such as obesity and hypertension [87]. Oxidative stress may be an important mechanism by which OSA is associated with neurodegeneration [29]. Two meta-analyses of ten studies concluded that homocysteine levels are elevated in OSA, especially in subjects with severe OSA and in subjects under 50 years of age [88, 89]. In fact, all included studies indicated higher homocysteine levels in severe OSA subjects. In another meta-analysis of 6 studies, blood homocysteine levels were significantly reduced after three months of CPAP [90].

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A recent review has comprehensively discussed oxidative stress in OSA in relation with altered neurocognitive functioning [87]. Lower antioxidant blood levels were reported in OSA subjects, including SOD and vitamin E [87]. Moreover, OSA subjects exhibited increased blood levels of proteins and metabolites associated with oxidative stress and damage, including oxidized protein products, MDA and 8-OHdg [87]. All of these were correlated with impaired cognition in various cognitive domains, such as attention, memory, language, and executive function [87]. Moreover, higher levels of MDA and oxidized proteins products were found in subjects with both MCI and OSA compared to OSA subjects without MCI [91]. These studies strongly suggest that oxidative stress in OSA is a mechanism underlying cognitive impairment.

7. Blood-based proteomic and metabolomic biomarkers of lipid metabolism

7.1. Blood lipoproteins and lipids as biomarkers of dementia

Clusterin (also named APOJ) is one of the most promising biomarkers of dementia and is involved in cholesterol homeostasis and transport in the brain in partnership with APOE [34]. Moreover, clusterin interacts with Aβ, which gives it both neuroprotective and neurotoxic roles. At relatively low Aβ concentration, clusterin can play a neuroprotective role by binding Aβ and thus, facilitating its clearance and inhibiting its aggregation [92]. On the other hand, it can also play a neurotoxic role by contributing to the formation of Aβ oligomers and by mediating Aβ toxicity through the activation of cytotoxic pathways [92]. Blood clusterin levels are increased in both AD and MCI subjects as compared to controls [93, 94], and are associated with the risk of developing AD [95] even though these results were not supported by all groups (see [93] for a review). Moreover, higher clusterin levels predict faster progression of cognitive decline in MCI and AD subjects [94, 95]. The relation between blood clusterin levels and cognitive decline seems, however, not linear: higher clusterin levels were associated with a higher risk of all-cause dementia in subjects over 80 years, but with a lower risk of

all-cause dementia and stroke in subjects younger than 80 years [96]. This finding supports the neuroprotective/neurotoxic duality of clusterin that appears to be moderated by age.

Because both APOE and high-density lipoprotein cholesterol (HDL-C) have protective functions (i.e., Aβ clearance, metabolite exchanges between neurons and glia, transport of cholesterol to be eliminated and reduction of atherosclerosis), their reduced blood levels in association with dementia may represent reduced neuroprotection [97]. Lower blood APOE levels are generally observed in prodromal AD and AD patients, particularly in *APOE4* carriers [98], and are associated with increased risk of developing dementia (see [93] for a review). However, other studies showed surprisingly unchanged blood APOE levels in AD patients [93]. Although many studies were performed on HDL-C, only about half found lower HDL-C levels in AD patients or in non-demented adults who will develop AD [93].

7.2. Blood lipoproteins and lipids investigated in OSA

To our knowledge, only one study investigated clusterin blood levels in OSA and found that clusterin levels were elevated and associated with a worse memory performance [99]. Blood APOE levels were also shown to be slightly elevated in middle-aged OSA subjects compared to controls [100]. This could represent compensatory mechanisms in order to protect against atherosclerosis processes. A large meta-analysis including 64 studies that include over 18 000 subjects showed that OSA is associated with abnormal lipid profiles, which include low blood HDL-C levels [101]. The authors hypothesized that oxidative stress and inflammation in OSA might cause dyslipidemia, which could be followed by atherosclerosis. A meta-analysis of six studies reported that CPAP treatment reduces total cholesterol but does not affect HDL-C levels [102].

8. Proposed research agenda to investigate promising fluid biomarkers of dementia in OSA

8.1. Summary of promising fluid biomarkers of dementia that could be used in OSA

OSA is increasingly recognized as a prevalent risk factor for dementia. What makes OSA particularly appealing in the context of preventive dementia strategies is that it can be treated efficiently with CPAP or other interventions. Whether screening and treating OSA could have an impact on the incidence of dementia remains to be investigated. To achieve this goal, epidemiological and mechanistic evidence needs to be drawn from intensive research efforts to properly establish OSA as a modifiable risk factor. Establishing a panel of promising biomarkers linking OSA to dementia has the potential to significantly advance our understanding of the pathophysiological mechanisms involved in neurodegeneration. Moreover, studying large cohorts of older adults with OSA using those biomarkers could also help developing protocols to identify OSA individuals who are at risk of dementia.

While OSA and dementia show different profile in terms of genetic susceptibility, there is important overlap between these two conditions with regards to associated fluid biomarkers, suggesting common pathophysiological mechanisms such as AD neuropathology, inflammation, oxidative stress, and metabolic dysfunctions. In Table 1, we summarized the strongest biomarkers identified in dementia research that are concordant or share similar profiles with OSA. CSF and blood biomarkers of AD neuropathology are only partially concordant in the early stages of dementia and in OSA, but very few studies were performed in OSA. The strongest similarities are for biomarkers of inflammation and oxidative stress, which show a very similar pattern in OSA and both AD and VaD. However, because there are many biomarkers representing inflammation and oxidative stress, it is unclear whether a single one is especially useful compared to the others. However, homocysteine emerged as an

important biomarker for both dementia and OSA. Finally, lipoproteins such as APOE and HDL-C are interesting but not consistent in dementia research, and do not seem to be affected by CPAP.

Because of this important overlap regarding biomarkers findings in dementia and OSA research, we hypothesize that OSA may lead to pathophysiological processes involved in neurodegeneration pathogenesis (see Figure 1). However, this hypothesis is made on the basis that these mechanisms play a causal role in neurodegeneration, and are not solely markers of its presence. Because dementia is a complex disease that involves several pathological pathways, biomarkers probably represent both cause and effect of neurodegeneration, and thus, longitudinal cohort studies are needed to understand which biomarkers represent pathological mechanisms in OSA and dementia.

Of note, the weight of the evidence presented in the current review is different for biomarkers in dementia and OSA research. Indeed, we constructed this review with the strongest biomarkers in dementia research, and then reviewed whether these specific biomarkers were also investigated in individuals with OSA. Therefore, more studies are needed to assess biomarkers levels in OSA, including $A\beta$ and tau levels in CSF and blood, CSF lactate levels, and clusterin. On the other hand, some biomarkers found in relation to dementia were studied repeatedly in OSA, including inflammatory cytokines and acute-phase proteins, homocysteine, oxidative stress markers and HDL-C. It is, however, important to note that, despite the fact that many dementia biomarkers were evaluated in OSA individuals compared to a control group, they were not yet investigated in OSA in relation to the risk of dementia.

In addition to candidate biomarkers that were selected based on the current literature, longitudinal discovery studies investigating hundreds of biomarkers are necessary to identify a specific panel of biomarkers and mechanisms for both OSA and dementia. Combining multiple biomarkers would be a promising approach in OSA-related dementia, since there is little overlap between studies for any single biomarker [103]. For example, the combination of CSF $A\beta_{42}$ and tau proteins are more reliable

than any of them individually to identify MCI individuals who will progress to AD [53]. With the expectation that a biomarker panel is identified and replicated, individuals at higher risk of incident dementia could be regularly screened with this panel combined with the evaluation of their genetic susceptibility measured with a PS.

8.2. Limitations of fluid biomarkers

However, fluid biomarkers have their own limitations, which should be considered when designing a cohort study or a clinical protocol. CSF collection is more invasive than blood collection and requires medical expertise, which may be more challenging in some clinical settings, large cohort studies, and longitudinal studies with multiple testing. Thus, blood-based biomarkers are the easiest to perform, but they are limited by the BBB, which restricts the accessibility of neurodegeneration biomarkers via the blood. Nevertheless, brain biomarkers can be cleared from the cerebral extracellular fluid into the blood by multiple normal and pathological mechanisms [104], giving partial access to neurodegenerative biomarkers through blood. Importantly, the BBB starts to break down relatively early in aging and with the progression of dementia [72]. This phenomenon can also be observed in OSA [77]. This suggests that the presence of OSA may allow detecting blood-based biomarkers of dementia even sooner because of the double insult on the BBB.

Another important limitation for blood biomarkers is their non-specificity: many organs other than the brain produce them. For example, Aβ peptides are not exclusive to the brain and can be produced by other peripheral cells such as platelets or muscle cells [105]. Another example is inflammation: many comorbid diseases occurring in the elderly are characterized by organ inflammation that may influence blood biomarkers [106]. The non-specificity of peripheral biomarkers is a limitation when we seek to measure cerebral rather than systemic processes. However, some argue that dementia is a systemic disease: pathological processes in the brain are also present in peripheral cells, such as Aβ production or systemic inflammation, and could also contribute to further neurodegeneration [107,

108]. Thus, understanding the potentially bidirectional relationship between peripheral and central pathophysiological mechanisms involved in dementia would clarify how and when blood biomarkers are the most useful in OSA research.

8.3. Identifying OSA subjects at risk of dementia with the use of fluid biomarkers

Because all OSA patients probably do not face the same risk of developing dementia, stratified analyses of OSA subjects as a function of incident dementia could help identify which characteristics and their associated biomarker profile best predict dementia. Factors that may modulate the association between OSA and biomarkers of dementia include demographic factors (age, sex, race), lifestyle (cognitive reserve, physical activity), OSA severity (mild, moderate and severe OSA, hypoxemia, sleep fragmentation, daytime sleepiness), genetic polymorphisms and comorbidities (obesity, cardiovascular risk factors and diseases, depression).

We also need to evaluate whether fluid biomarkers are associated with neuroimaging anomalies and neuropsychological deficits in OSA. This would help clarify how fluid biomarkers predict brain changes in terms of structure and function, and thus, further our understanding of underlying mechanisms. The temporal relationship between dementia biomarkers should also be validated within the OSA population to increase our ability to predict the progression to dementia. Aβ deposition occurs first, followed by tau dysfunction, brain atrophy, cognitive decline and finally, clinical presentation [6]. This theoretical model was challenged by data-driven modelling using artificial intelligence where vascular deregulation and inflammation changes significantly precede Aβ and tau alterations in subjects at risk of conversion to dementia [109]. Moreover, assessing whether neurodegenerative processes and OSA effects have an additive or interaction effect on fluid biomarkers would help predict cognitive decline and clinical progression.

8.4. Effects of OSA treatment on fluid biomarkers levels

One of the most important questions is whether an effective treatment for OSA positively impacts the levels of fluid biomarkers and slows or even prevents incident dementia. These results could become strong incentives for patients to comply with OSA treatment, and for clinical care professionals and public health policy makers to promote OSA treatment if other studies confirmed them. Indeed, CPAP may delay the age at which clinical manifestations appear [13]. Moreover, a few studies reviewed here suggest that abnormal levels of some fluid biomarkers in OSA subjects are reversible with CPAP [63, 64, 90]. The incidence of dementia should be assessed in treated OSA subjects compared to those who refused treatment, and the effectiveness of the CPAP treatment could be documented with fluid biomarkers.

In patients with dementia, an effective CPAP treatment in those with OSA improved neuropsychological functions or slowed the rate of cognitive decline [17, 18]. These results suggest that treating OSA in demented patients is beneficial, possibly because the OSA-related mechanisms contributing to neurodegeneration are withdrawn. Treatment effects on fluid biomarker levels in demented OSA patients may explain how OSA contributes to clinical neurodegeneration, but also document short and long-term effects of OSA treatment on brain health. Moreover, combining the evaluation of fluid biomarkers with a CPAP treatment could be applied in subjects at earlier stages of neurodegeneration, including MCI subjects, *APOE4* carriers, or those with a high genetic susceptibility measured with a PS.

8.5. *Necessity of large cohort studies to investigate fluid biomarkers of dementia in OSA*

In order to establish a specific biomarker panel and underlying mechanisms in OSA that are associated with neurodegeneration, large longitudinal cohort studies are needed. A long follow-up period as well as a large sample size would allow sufficient dementia cases to emerge for a reliable assessment of the relationships. In addition, large sample sizes are necessary to stratify the population according to demographic characteristics and comorbidities to establish a clinical portrait of OSA

individuals at risk of developing dementia. In OSA treatment studies, long follow-up periods are also

necessary to determine the optimal minimum treatment duration for an effect on fluid biomarkers levels

and incident dementia. Because techniques for studying fluid biomarkers are fairly inexpensive,

investigation of biomarkers in OSA in association with dementia could be implemented in various large

cohort studies. Cohort studies on aging, dementia, and cardiovascular risk factors would necessarily

have a significant proportion of individuals presenting OSA given its high prevalence in this portion of

the population. Moreover, international collaborations and networks are a promising solution in order

to profit from large samples and produce clearer and stronger results. Therefore, we propose that OSA

assessment should be included in large cohort studies investigating preclinical dementia using

ambulatory devices or polysomnography.

Practice points

- Obstructive sleep apnea is increasingly recognized as a risk factor for dementia and is
  associated with potential mechanisms that might lead to neurodegeneration;

- There is a large overlap in biomarkers that were evaluated independently in dementia and in
  obstructive sleep apnea. For most of them, the nature and direction of the changes are strikingly
  similar;

- Amyloid-β, tau proteins, cytokines, acute-phase proteins, homocysteine, oxidative stress
  markers, and clusterin seem to be key candidate fluid biomarkers to predict and understand the
  development of neurodegeneration in patients with obstructive sleep apnea.

Proposed research agenda

With large cohort studies and a network approach, the following questions should be investigated:

- Which specific fluid biomarker panel is associated with incident dementia in individuals with obstructive sleep apnea?

- Which specific biomarker panel is more informative about the mechanisms underlying the link between obstructive sleep apnea and dementia?

- What demographic and biomarker pattern characterizes the adults with obstructive sleep apnea who are at higher risk of developing dementia?

- Does treatment with continuous positive airway pressure normalize fluid biomarker levels in individuals with obstructive sleep apnea and, if so, does it protect from or delay the incidence of dementia?

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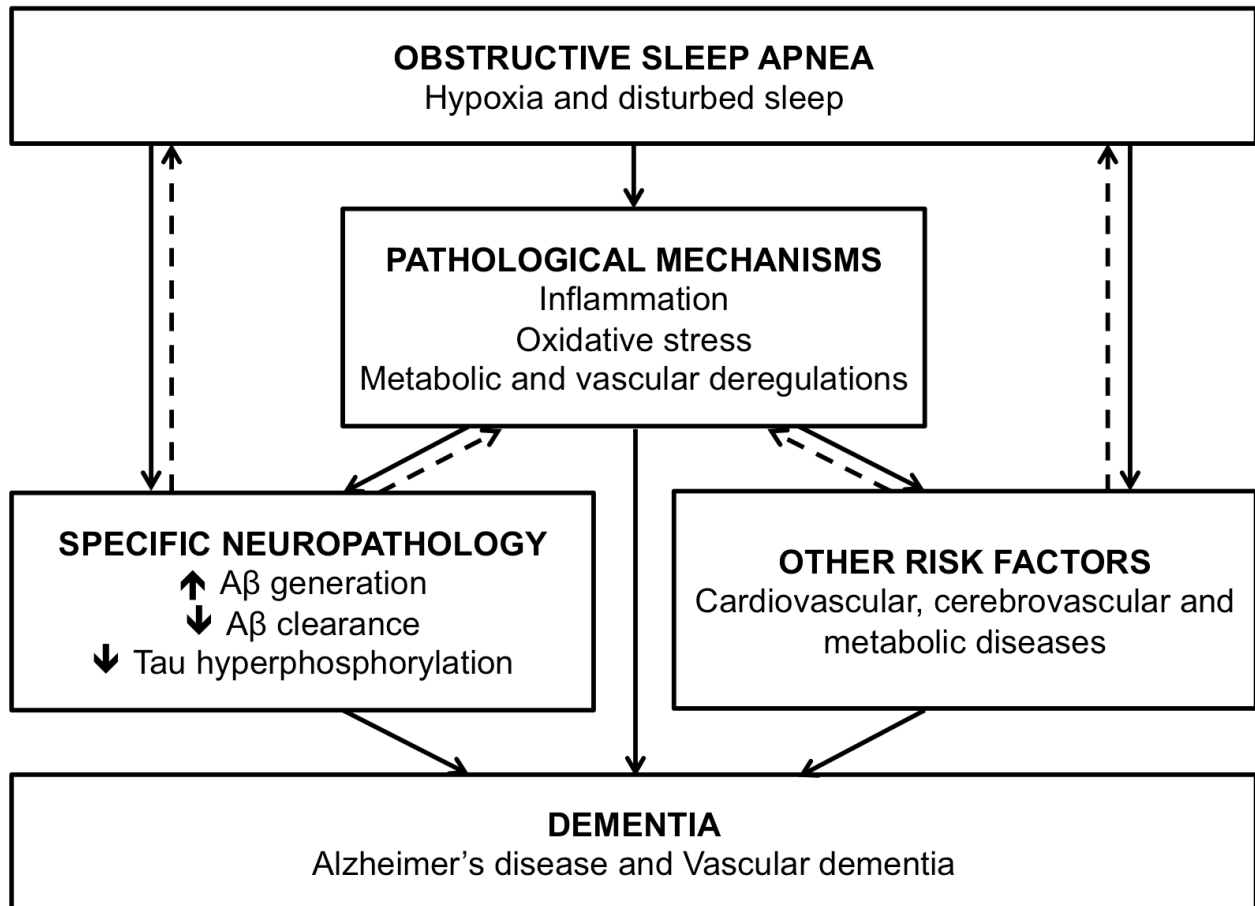
Figure and Table

Figure 1. Potential mechanisms linking obstructive sleep apnea (OSA) to the development of dementia. Recent evidence suggests that the hallmarks of OSA, i.e., hypoxia and disturbed sleep, may directly contribute to the development of the neuropathology of Alzheimer's disease (AD) in the brain. Secondly, OSA may indirectly be involved in the incidence of dementia via its role in the development of other risk factors. Of note, OSA is a risk factor for stroke and cerebrovascular events, which in turn are a core pathophysiological component of vascular dementia. Moreover, OSA may also indirectly contribute to the development of dementia via secondary pathological mechanisms involved in neurodegeneration, such as oxidative stress. These mechanisms may also interact with concomitant AD neuropathology or other risk factors. Dotted arrows represent potential bidirectional relationships. The

presence of amyloid-β (Aβ) deposition in the brain has been associated with sleep impairments as well as pathological mechanisms such as inflammation. Other risk factors, such as obesity, are associated with the development of OSA and other pathological mechanisms, such as inflammation.

Table 1. Most promising fluid biomarkers of dementia investigated in OSA

Biomarkers	Stages of neurodegeneration		
	Dementia (all-cause dementia, AD or VaD)	**Early stages** (MCI, preclinical or prodromal dementia)	**OSA**
CSF			
Aβ$_{42}$	↓ [52-54]	↓ [53]	↓ [62-65]
Tau proteins	↑ [52, 53]	↑; unchanged [52, 53]	unchanged [62, 63]
Blood			
Proteomics – AD neuropathology			
Aβ$_{42}$	mostly ↓ [66]	↑; unchanged; ↓ [66, 67]	↑; unchanged [70, 71]
Aβ$_{42/40}$ ratio	↓ [66]	mostly ↓ [66, 68]	-
Tau proteins	↑ [66]	↑ [66, 69]	↑ [70, 71]
Proteomics – Inflammation			
Cytokines (IL-6, IL-1β, TNF-α)	mostly ↑ [73, 74]	↑; unchanged [75, 76]	↑ [79, 80]
Acute-phase proteins (hsCRP, ACT)	mostly ↑ [73]	mostly ↑ [76]	↑ [78, 80]
Proteomics and metabolomics – Oxidative stress			
Homocysteine	↑ [73, 83, 85]	↑ [83, 84]	↑ [88, 89]
Superoxide dismutase	mostly ↓ [81, 82]	mostly ↓ [81]	↓ [87]
Vitamin E	↓ [81, 82]	↓ [81]	↓ [87]
MDA/8-OHdg	mostly ↑ [81]	mostly ↑ [81]	↑ [87, 91]
Proteomics and metabolomics – Lipid metabolism			
Clusterin	↑; unchanged [93, 94]	↑; unchanged; ↓ [93-96]	↑ [99]

AD, Alzheimer's disease; VaD, vascular dementia; MCI, mild cognitive impairment; OSA, obstructive sleep apnea; CSF, cerebrospinal fluid; Aβ, amyloid-β; IL-6, interleukin-6; IL-1β, interleukin-1β; TNF-α, tumor

necrosis factor-α; hsCRP, high-sensitivity c-reactive protein; ACT, α1-antichymotrypsin; MDA,

malondialdehyde; 8-OHdg, 8-hydroxy-2-desoxyguanosine.