

# Obstructive Sleep Apnea – Influence on the Cardiovascular System and Cognition



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**ABSTRACT**

Like obstructive sleep apnea, cardiovascular and cognitive disorders are frequently observed with a significant impairment of the quality of life and a high socio-economic relevance. The effects of an untreated obstructive sleep apnea (OSA) on the cardiovascular and cognitive disease risk and the therapy effect of OSA are scientifically proven for most cardiovascular and cognitive secondary disorders. For the clinical practice, there is a clear need for more interdisciplinarity. From a sleep-medical point of view, therapy indication should include the individual cardiovascular and cognitive risk, and cognitive diseases must be taken into account when considering therapy intolerance and residual symptoms. From the perspective of internal medicine, patients with poorly adjustable hypertension, atrial fibrillation, coronary artery disease, and stroke should be evaluated for OSA. In patients with mild cognitive impairment, Alzheimer’s disease, and depression, typical symptoms like fatigue, daytime sleepiness, and reduction in cognitive performance may overlap with OSA symptoms. The diagnosis of OSA should be integrated into the workup of these conditions, as treatment of OSA can reduce cognitive impairment and improve quality of life.

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## 1. Introduction

Obstructive sleep apnea (OSA) is by far the most common form of sleep-related breathing disorder. It is characterized by inspiratory flow limitations (hypopneas, apneas), snoring, and paradoxical respiratory movements of thorax and abdomen. Obstructive sleep apnea syndrome (OSAS) is the term used to describe OSA with the typical symptoms of daytime sleepiness and snoring. Often, both terms are used redundantly. The severity of OSA is classified according to the number of hypopneas and apneas occurring per hour (apnea-hypopnea index = AHI) into three severity levels: low-grade (syn. mild): AHI of 5–15/h, moderate: AHI of 15–30/h, and severe: AHI of > 30/h.

The following discussion refers to obstructive sleep apnea and its effects on the cardiovascular disease risk and cognitive performance in adults. Other rarer types of sleep-related breathing disorders (central sleep apnea, mixed forms) must be considered on a case-by-case basis depending on the cause and metabolic, neurologic, as well as cardiovascular comorbidities.

## 2. Obstructive sleep apnea and cardiovascular diseases

### 2.1. Pathophysiology

Obstructive sleep apnea is an independent risk factor for the development of various cardiovascular diseases. OSA leads to structural myocardial alterations and changes of the vascular microenvironment. The pathogenesis is multifactorial (► **Fig. 1**). The imbalance between airway opening (requiring muscle activity) and occlusion forces (due to anatomic constriction, airway resistance) results in pharyngeal obstruction, which leads to hypoxemia, hypercapnia, negative intrathoracic pressure, and an activation of the sympathetic nervous system with effects on hemodynamics and autonomic regulation. One of the most important factors for the development and prognosis of cardiovascular diseases in OSA is intermittent hypoxia. It is characterized by repeated short cycles of desaturation followed by rapid reoxygenation. Intermittent hypoxia triggers an increased oxidative stress as important factor for the development of vascular-endothelial dysfunctions (inflammation, decreased vascular tone) and arteriosclerosis [1–5].

These complex activations of neural, humoral, metabolic, and inflammatory mechanisms triggered by OSA lead to an increased risk of cardiovascular diseases such as arterial hypertension, cardiac arrhythmias, coronary heart disease and myocardial infarction, heart failure, and stroke.

Most trials on OSA and cardiovascular diseases are based on clinical observations and reveal a close correlation. The evidence and the proven therapy effects vary and are described for each condition.

There is a small number of studies on in vitro and animal models [6]. In vitro models mainly investigate the impact of intermittent hypoxia on oxidative stress and resulting cellular changes [7, 8]. Animal models are based on triggering intermittent obstructions (via tracheostoma, intratracheal balloons, nasal masks) or exposure to oxygen-reduced gas mixtures. This allows basic research on the OSA effects of hypoxia, hypercapnia, and sympathetic activation [9–14].

### 2.2. Arterial hypertension

Experimental and clinical data show that OSA acutely increases nocturnal blood pressure and can lead to a lack of nocturnal blood pressure drop. Physiologically, a decrease in blood pressure of at least 10% occurs during healthy sleep. This blood pressure reduction (syn. dipping) is due to a resetting of the control point of the baroreceptor reflex. OSA-related sympathetic activation with increased catecholamine release and stimulation of baroreceptors by intrathoracic pressure change may result in the development of chronic hypertension.

OSA is an independent risk factor for the development of arterial hypertension.

Approximately 50% of all patients with OSA suffer from arterial hypertension. About 30% of all patients with arterial hypertension have OSA. The risk of developing hypertension increases with the severity of OSA. In younger and middle-aged patients with moderate to severe OSA and daytime sleepiness, the relative risk of developing arterial hypertension increases to almost threefold. In refractory arterial hypertension and especially in nocturnal hypertension with failure to lower blood pressure (syn. non-dipping), OSA is present in up to 70% of the patients. Nocturnal hypertension and non-dipping are associated with high cardiovascular risk.

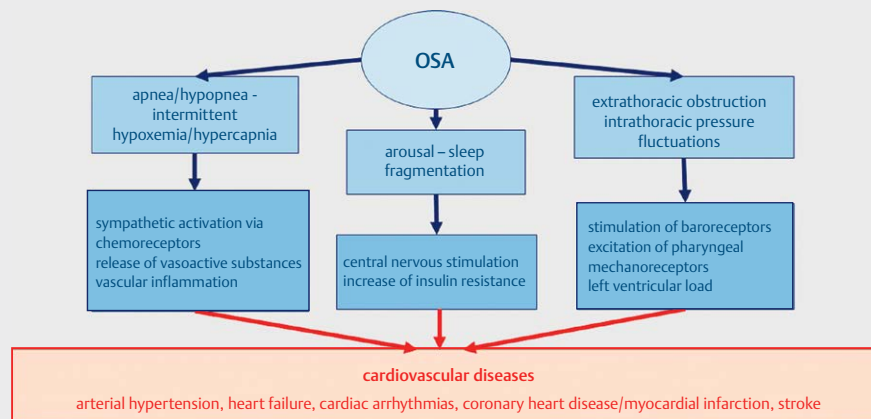
According to current recommendations [15, 16], polygraphic workup is recommended in cases of clinical suspicion of OSA, pathologic 24-h blood pressure profile, or refractory arterial hypertension.

The antihypertensive effect of OSA therapy depends on several factors. For positive airway pressure (PAP) therapy, the most important parameter is adequate duration of use (> 4 h per night). Usually, a combination of drug therapy and PAP therapy must be applied. Synergistic effects between PAP and drug therapy are observed with regard to blood pressure reduction, so that blood pressure medication should be adjusted regularly if patients adhere well to PAP therapy. PAP therapy lowers systolic and diastolic blood pressure more at night than during the day. The highest treatment effects are achieved in patients with refractory blood pressure, non-dipping, age < 60 years, and severe OSA with severe hypoxemia. The highest reduction (-10 mm Hg) was achieved in patients with severe OSA, arterial hypertension, and daytime sleepiness [17, 18]. Therapy with mandibular advancement splints also demonstrated a moderate reduction in mean arterial pressure [18].

### 2.3. Coronary artery disease and myocardial infarction

Pathophysiologically, OSA-related release of vasoactive substances, increased oxidative stress, and vascular inflammation result in arteriosclerotic damage to the coronary arteries with subsequent acute myocardial ischemia [15]. The incidence for coronary artery disease is two to three times higher in OSA patients [17, 19, 20]. In epidemiological studies and systematic reviews, moderate and severe untreated OSA showed a significantly higher incidence of fatal and nonfatal cardiovascular events [20–25]. Myocardial infarction occurs more frequently during nighttime in OSA patients with coronary heart disease [26].

The results of two larger randomized trials (SAVE, ISAAC) as well as meta-analyses of all randomized trials on incidence of cardiovascular events in OSA led to a controversial discussion, since these stu-



► **Fig. 1** Pathophysiological correlation between obstructive sleep apnea (OSA) and cardiovascular diseases.

dies could no longer clearly reveal the correlation between OSA and cardiovascular diseases [27–31]. In the current ISAAC trial (multi-center, randomized), patients with acute coronary syndrome were randomized 1:1 to a group with PAP therapy and to a group without PAP therapy, and followed-up for at least one year. A group with acute coronary syndrome but without OSA served as control group. There were no significant differences between the incidences of cardiovascular events in all three groups [30]. Interpretation of the results was critical because of the exclusion of symptomatic patients and the overall low utilization times of PAP therapy. Moreover, the main problem of all studies was the heterogeneity of the included patients with coronary artery disease [25, 32–34]. A post-hoc analysis of the ISAAC trial in 1701 patients yielded in the division into two phenotypes: patients without prior heart disease/previous acute coronary syndrome (81 %) versus patients with prior heart disease/previous acute coronary syndrome (19 %). For the phenotype without prior cardiovascular disease, the OSA group showed a significantly increased risk of cardiovascular events. In contrast, for the other phenotype, there was even a protective effect of OSA for cardiovascular events. These results support other findings and the hypothesis that the presence of obstructive sleep apnea may have a protective effect in persisting coronary stenosis by forming coronary collaterals through ischemic and hypoxemic conditioning [35–37]. Supporting this hypothesis, the protective effects in phenotype with previous cardiovascular disease were independent of age, sex, BMI, and location of the lesion, and notably occurred only in OSA and not in central sleep apnea.

In summary, there is an increased risk of cardiovascular events (myocardial infarction, acute coronary syndrome) in male patients with untreated moderate to high-grade OSA. According to current studies, the treatment effect of OSA is not as clearly demonstrable as for arterial hypertension.

## 2.4. Cardiac arrhythmias

OSA-related cardiac arrhythmias can occur as bradycardic and as tachycardic arrhythmias. The prognosis is critically dependent on the presence of other cardiac diseases and the type of arrhythmia [4].

Causes include intermittent hypoxemia/hypercapnia, increased sympathetic tone, and intrathoracic pressure fluctuations. Bradycardias can occur as higher-grade AV blocks to transient asystole and are a predictive marker for higher-grade OSA [4, 38]. In most cases, the cause is repetitive stimulation of the autonomic nervous system. Treatment of OSA often leads to a reduction in nocturnal bradycardic arrhythmias [4, 39].

Up to 70 % of all patients with atrial fibrillation have relevant sleep-disordered breathing. The prevalence of AF is increased five to six times in OSA and increases with age [4]. PAP therapy can lead to a significant reduction (up to 60 %) in the recurrence or progression of AF. The effectiveness of cardioversion or drug therapy is significantly lower in patients with untreated OSA [4]. Therefore, guidelines recommend sleep apnea screening and therapy for OSA in atrial fibrillation. To date, only observational studies with proven mechanisms and homogeneous data are available [40–42], and the results of randomized trials (SLEEP-AF, study of the PAP effect on atrial fibrillation burden) are currently pending. Drug therapy approaches are also currently under discussion for asymptomatic OSA and AF. In basic studies, changes in enzyme activity (calcium-calmodulin-dependent protein kinase II) as well as a disturbance in the synthesis of structural proteins (connexin 43) were found in the myocardial tissue of OSA patients. Drugs for both signaling pathways are in the state of pre-clinical development [2].

## 2.5. Heart failure

About 50 % of patients with stable heart failure suffer from moderate to severe OSA. The incidence is significantly higher in patients with acute decompensated heart failure [43]. As the severity of the heart failure increases, and especially in the presence of an impaired ejection fraction, the proportion of central apneas associated to impaired respiratory regulation (Cheyne-Stokes respiration) increases, so that the most common cause of central sleep apnea is more severe heart failure. In contrast, OSA is mostly observed in patients with heart failure with preserved ejection fraction [44].

In male patients, OSA is an independent risk factor for the development of heart failure [23]. Pathophysiologically, there is per-

sistent and progressive subclinical myocardial damage due to OSA-related increase in left ventricular afterload, sympathetic activation, and increased oxygen consumption with concomitant hypoxemia [4, 45].

The effects of PAP therapy are more easily detectable in heart failure patients than in healthy subjects [46]. There is no randomized controlled trial showing a clear survival (cardiovascular mortality) benefit with PAP therapy in heart failure. Single monocentric studies have shown a reduction in left ventricular afterload and an increase in left ventricular ejection fraction [47]. PAP therapy in heart failure patients is recommended in symptomatic OSA. In this case, there is an improvement in quality of life. In heart failure patients without daytime sleepiness, the indication for PAP therapy must be individualized [43, 48].

## 2.6. Stroke

Based on several mechanisms, OSA can be a trigger for an apoplectic insult. Oxidative stress leads to cerebral arteriosclerosis, which is the main cause of ischemic strokes. Acutely, increases in blood pressure or thromboembolic events as result of a cardiac arrhythmia can lead to a hemorrhagic insult. After stroke, secondary sleep-related breathing disorders occur in up to 70 % of the patients, which may lead to an increase in stroke damage and acute stroke mortality [49]. OSA is associated with stroke incidence independently of other risk factors [50, 51]. In cases of severe OSA, the incidence for stroke is increased 2–3-fold, independently of sex and age [50, 52].

The effect of PAP therapy on stroke incidence could not be revealed in a meta-analysis of 7 randomized trials [27]. Smaller randomized trials show that PAP therapy after stroke improves neurological recovery as well as sleepiness and depressive symptoms [50]. Therefore, PAP therapy is recommended as a therapeutic component in the context of multimodal management after stroke.

## 2.7. Determination of the individual cardiovascular risk

### 2.7.1. Arousal burden

The arousal burden is defined by the cumulative length of all waking reactions related to the sleep duration. The measurement is automated by analysis algorithms. The parameter describes sleep fragmentation significantly better than the apnea-hypopnea index (AHI) does, and is a potential predictor of long-term cardiovascular risk. In a systematic analysis of data from 8001 participants in three cohort studies, a high arousal burden was associated with increased cardiovascular mortality, especially in women [53].

### 2.7.2. Hypoxemia load

The hypoxemia load is calculated from the area under the desaturation curve during a respiratory event relative to the baseline saturation. This captures the hypoxemias that are specific to sleep apnea. Data analysis of two cohort studies (7534 participants) showed a significantly higher incidence of heart failure in men with a high hypoxemia load [54].

### 2.7.3. Biomarkers

In accordance with the pathophysiological basis, the search for biomarkers of cardiovascular risk was performed by analyzing markers

of oxidative stress and inflammation, adhesion molecules, and endothelial proteins [55]. A systematic review identified over 20 different biomarkers. Mostly studies with small numbers of participants and retrospective design are available. The cardiovascular conditions included are not redundant and range from studies of hypertension alone to inclusion of all cardiovascular events. Elevated levels of some biomarkers were associated with cardiovascular events in OSA: YKL-40 (glycoprotein)/low-density lipoprotein with coronary artery disease, high-sensitivity CRP/interleukin-1Ra/interleukin-8/TNF- $\alpha$  with acute cardiovascular events, intercellular adhesion molecule (ICAM 1) with acute coronary syndrome and cerebrovascular ischemia, and endoglin/fms-like tyrosine kinase 1 with arterial hypertension. Biomarkers for oxidative stress and catecholamine were not significantly increased in patients with OSA and cardiovascular disease in the few studies available on this topic [56].

### 2.7.4. Phenotyping

In recent years, attempts to identify OSA phenotypes have been made to incorporate new knowledge in OSA pathogenesis and its importance for a targeted, individualized treatment strategy [57]. Four pathophysiological phenomena are considered, which in individual cases have a different weighting on the development, the severity, and thus the treatment indication of OSA. Thus, in addition to the narrow/collapsed airway, ineffective upper airway dilator function during sleep, unstable respiratory control (high loop gain) and a low threshold for arousal responses are considered [58]. Depending on the expression of the four components and the resulting severity of OSA, first recommendations for a targeted therapy were developed, which – in addition to PAP therapy that is certainly the most frequently indicated one – include other therapy options such as weight reduction, positional therapy, mandibular advancement splint, surgical measures, and drug therapy also as first-line therapy or combination therapy.

A review on the cardiovascular risk summarized all studies with cluster analyses [59]. From the available data, four OSA subtypes (A-D) were clustered based on age, body mass index (BMI), sex, symptoms, and comorbidities as well as two OSA subtypes (E, F) based on polysomnography data and PAP adherence as major subtypes. Subtype A corresponds to the classic OSA patient (male, middle-aged, increased BMI, daytime sleepiness, few comorbidities). In this group, the parameter of excessive daytime sleepiness was most strongly associated with increased cardiovascular risk. Subtype B includes elderly, overweight patients, predominantly male, with mild to moderate symptoms, increased comorbidities, and severe OSA with a high hypoxemia burden. In this group, the prevalence of hypertension, diabetes, and cardiovascular disease is increased, but the risk of new onset myocardial infarction and stroke is not clearly higher. The above-mentioned preventive effect of OSA for cardiovascular events is discussed as the cause. Subtype C comprises predominantly middle-aged women with moderate obesity and insomnia symptoms (difficulty with initiating and maintaining sleep, non-restorative sleep) as well as moderate to severe OSA. The prevalence for cardiovascular diseases in this subtype is between subtype A and B. The risk for stroke is lower than in the other OSA subtypes. Subtype D includes younger male patients with upper airway resistance syndrome (snoring, sudden awakening with dyspnea) without significant daytime sleepiness

|                          | description   | brain areas involved   |   |
|--------------------------|---|--|---|
| reception of information | <b>attention</b><br>selection of internal and external stimuli to perform mental or motor actions |  |   |
|                          | ascending reticular activation system   | basic level of conscience, optimizes the processing of sensory stimuli | thalamus, limbic system, basal ganglia, frontal cortex                      |
|                          | posterior attention system  | orientation and localization of visual stimuli                         | posterior parietal cortex, thalamus, hippocampus, anterior cingulate cortex |
|                          | anterior attention system   | attention is drawn to an action, allows complex cognitive functions    | prefrontal cortex, thalamus   |
| processing               | <b>executive functions</b><br>control processes for action adaptation                             |  |   |
|                          | working memory  | phonological memory<br>visual-spatial memory<br>episodic buffer        | prefrontal cortex   |
|                          | inhibition  | suppression of interference factors, impulse control, error correction |   |
|                          | cognitive flexibility   | action planning, goal setting, prioritization, focusing                |   |
| storage                  | <b>memory</b><br>coding, storage, and retrieval of information                                    |  |   |
|                          | declarative (explicit) memory   | memories that can be consciously recalled                              | medial temporal lobe, diencephalon  |
|                          | non-declarative (implicit) memory   | unconscious memory and skills  | neocortex, amygdala, striatum   |

► **Table 1** Overview of cognitive functions.

and comorbidities. These patients have poor PAP adherence, and cardiovascular risk is unknown. The two subtypes of E and F differ with regard to hypoxemia. Subtype E groups patients with particularly severe OSA (AHI of 66–84/h) and marked hypoxemia parameters. This subtype has an increased risk of nonfatal or fatal cardiovascular event. Subtype F comprises patients with severe OSA (AHI of 34–68/h) and few hypoxemic events with lower PAP adherence and lower cardiovascular risk.

## 2.8. Summary

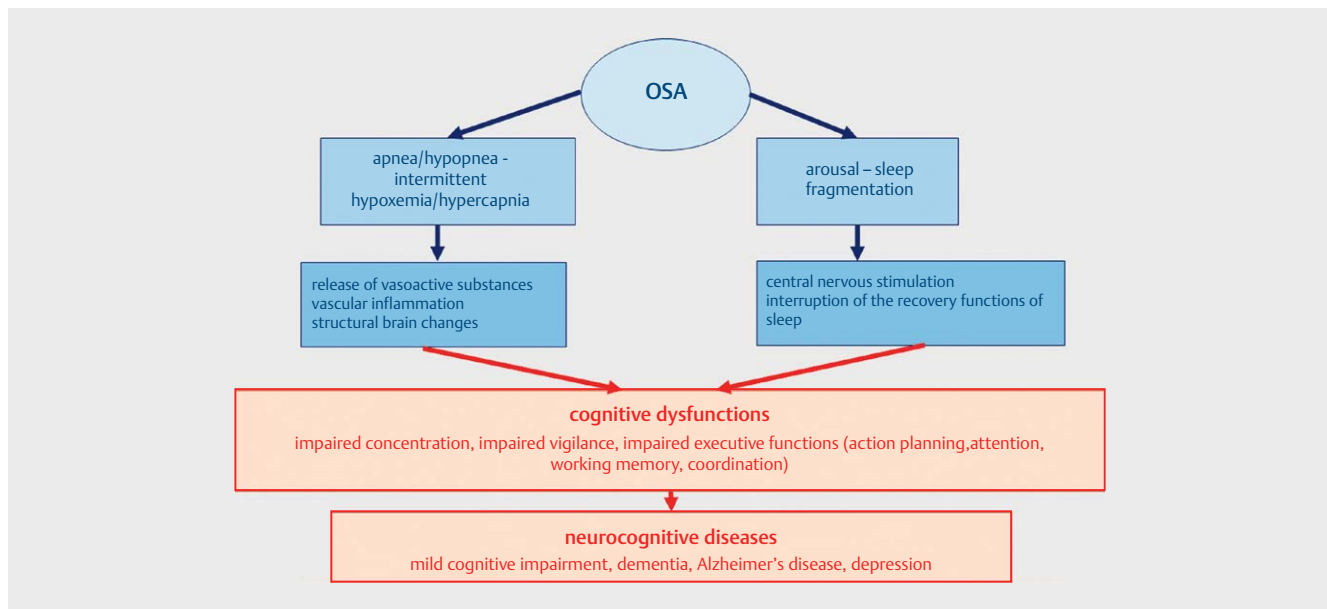
In summary, obstructive sleep apnea is a clear risk factor for cardiovascular disease. OSA is highly prevalent in cardiovascular disease patients with difficult-to-control arterial hypertension, coronary artery disease, arrhythmias, or heart failure and is associated with a poor prognosis. Therapy for OSA may usefully complement the treatment of cardiovascular disease because of its effects on arterial blood pressure and quality of life in selected patients. Therefore, integrative cardiology and sleep medical care for these patients is very important. The German Society of Cardiology has highlighted the significance of the comorbidity of sleep-related breathing disorders in cardiovascular disease in its position paper on sleep medicine in cardiology and with the initiation of a curriculum in

sleep medicine to obtain the additional qualification of cardiovascular sleep medicine.

The objective of current and future scientific development is the creation of individualized therapy concepts. The prerequisites for estimating the individual cardiovascular risk are constantly being approved through the use of artificial intelligence in the evaluation of large biological and measurement data volumes and their correlation. Thus, studies on effects of different therapies on cardiovascular risk in different patient groups with respect to age, sex, and comorbidities can be performed with greater evidence.

## 3 Obstructive sleep apnea syndrome and cognition

The term “cognition” (from the Latin word *cognitio*) is a collective term for processes and structures that relate to the reception, processing, and storage of information. The most important cognitive functions are attention, memory, and the executive functions (► **Table 1**) [60–63].



► **Fig. 2** Pathophysiological correlations between obstructive sleep apnea (OSA) and cognitive dysfunctions.

The term of cognitive disorders summarizes impairments of information processing in the brain. Cognitive impairment affects daily activities, occupational performance, and quality of life.

The association between OSA and cognitive impairments has been demonstrated in many studies with clear evidence [64–66]. The cognitive impairments are mainly manifest in areas of attention, executive functions, and memory compared with control groups. Cohort studies and meta-analyses also revealed an increased risk in OSA patients for the development of mild cognitive impairment, dementia, or Alzheimer's disease [64, 67–69]. 40% of dementias are due to modifiable risk factors, one of which is untreated OSA [70–72].

### 3.1. Pathophysiology

Decisive factors for cognitive and behavioral changes in obstructive sleep apnea are the apnea- and hypopnea-induced intermittent hypoxemias and sleep fragmentation (► **Fig. 2**). Mainly due to the intermittent hypoxemias, reversible and irreversible inflammatory changes of brain vessels, brain structures, and neurotransmitter systems occur [73–75]. Studies of brain metabolism and structures showed alterations in the integrity and structure of the white matter [76–79], hippocampus [80, 81], and a decrease in cortical thickness [82–84] in OSA patients. Most of the studies were performed using imaging techniques [85–88]. They show two partially opposite effects. Gray matter atrophy, higher white matter hyperintensity, lower fractional white matter anisotropy, and higher water diffusivities indicate cellular damage, some of which is irreversible. In contrast, gray matter hypertrophy and limited white matter diffusivity are more likely to reflect reversible consequences such as intracellular edema, reactive gliosis, or compensatory structural changes [89, 90].

Evidence of the morphologic disturbances primarily in the prefrontal cortex correlates with the executive function disorders most commonly seen in OSA patients [63].

Memory is subject to a broader range of influencing factors with activation of different brain regions so that the correlations cannot be clearly verified. Correlations are shown in sleep-related memory performance such as spatial memory and consolidation of memory content [64]. Language and psychomotor skills are unchanged in OSA patients compared to control groups [66, 91]. Sleep fragmentation has an additional reinforcing effect on hypoxemia-induced cognitive changes. The exact mechanisms are still unknown. A higher vulnerability to hypoxemic events due to changes in neurotransmitter homeostasis is discussed [60, 74, 92].

A correlation to OSA severity has been identified in attention and vigilance, but no correlation was found in executive functions, language, memory, and psychomotor functions [60, 65, 91, 93, 94]. Fine motor skills appear to be more sensitive to hypoxemic injury [73]. Executive function deficits correlate poorly with self-assessed or measured daytime sleepiness [94].

In meta-analyses and systematic reviews, correlations between OSA and single cognitive deficits could be better demonstrated in smaller sleep medicine-managed cohorts and controlled case studies than in large epidemiologic studies [71, 95, 96]. Large epidemiologic trials often capture only the history of OSA without assessing the severity or utilization efficiency of therapy. Smaller sleep medicine supervised studies show better diagnostic representation of OSA severity and controlled evidence of therapy utilization. Protective or vulnerable factors, which are less frequently assessed in epidemiological studies, also have a significant influence on the development of cognitive impairment.

Various influencing factors are discussed with regard to vulnerability and protection of the development of cognitive disorders. Important risk factors are age, sex, and menopause as well as con-

mitant diseases such as obesity, hypertension, and depression. Significant protective factors are cognitive reserve and physical activity.

## 3.2. Risk factors for cognitive deficits in cases of OSA

### 3.2.1. Age

OSA and advanced age (> 65 y) independently impair cognitive function. The combination of untreated OSA and advanced age has an additive effect with respect to cognitive impairment [97, 98]. In elderly patients with untreated OSA, conditions such as mild cognitive impairment and dementia are more likely to occur, and symptomatology is exacerbated in manifest cognitive disease [70, 99, 100]. Crucial factors are the number and extent of intermittent hypoxemia [101]. While low and moderate severity show less correlations, significant deteriorations in executive functions, memory, and attention are found in elderly patients and high severity OSA [68, 102, 103]. A systematic review of 68 studies showed that attention, executive functions, and memory were impaired in young and middle-aged patients (30–60 y), whereas this was not as evident in older patients (> 60 y) [68]. The cause is discussed to be the increasing influence of concomitant diseases such as cardiovascular disease, hypertension, and neurodegenerative diseases, which reduce the differences in cognitive impairment between patients with and without OSA in higher ages.

### 3.2.2. Sex

The prevalence of dementia is up to 29% higher in women than in men, up to 2/3 of Alzheimer patients are female. Discussed influencing factors are the longer life expectancy and hormonal differences (e. g. pharyngeal fat distribution, body trunk) in females. Differences are evident in symptomatology and in the development of sequelae. Men complain of OSA-typical symptoms such as snoring, breathing interruptions, or daytime sleepiness. In women, symptoms are more unspecific like headache, tiredness, depression, anxiety, and sleep disturbances [101]. Few studies show differences between OSA and cognition as a function of sex, as most studies on OSA are dominated by the male sex. Women with OSA were more likely to develop dementia than men [104]. Differences between men and women in symptomatology and effect on cognitive performance increasingly equalize after menopause and in higher ages [71, 99, 105].

## 3.3. Protective factors for cognitive deficits in cases of OSA

### 3.3.1. Cognitive reserve

Cognitive reserve defines the ability to optimize or maximize performance through differential recruitment of brain networks and the use of alternative cognitive strategies [106]. Morphologically, there are more synapses, a higher number of redundant neural networks, and more efficient processes with the same number of synapses. Educational level, intelligence level, and occupational activity are markers of cognitive reserve [107].

Studies revealed that highly intelligent OSA patients (IQ  $\leq$  90<sup>th</sup> percentile) show fewer attentional deficits than normally intelligent OSA patients, regardless of OSA severity and daytime sleepiness [64, 108]. The cause is thought to be the cognitive reserve of the highly intelligent patients who thus have a higher tolerance to neurodegenerative brain changes.

### 3.3.2. Physical activity

Physical activity is one of the clearest preventive factors for the development of Alzheimer's disease. Training programs lead to improved cognitive functions in inactive elderly patients by influencing neuroplasticity and reducing blood pressure, weight, and inflammatory parameters. In OSA patients, the negative effects add up through a cycle of daytime sleepiness, fatigue, and reduction in physical activity and weight gain [109].

The risk factors and protective factors need to be better investigated in future studies and taken into account in the interpretation especially of meta-analyses and epidemiological studies.

## 3.4. Therapy effects on cognitive disorders

Most studies are available on PAP therapy. Some few trials reveal therapy effects with mandibular advancement splints and surgical measures.

### 3.4.1. PAP therapy

Study results on the effect of PAP therapy are inconsistent due to the inhomogeneity of data, use of different test instruments, and frequent lack of recording of PAP use [110, 111].

A meta-analysis of 13 randomized trials (554 patients) revealed effects on attention [112]. In elderly patients, a meta-analysis (5 randomized trials, 680 patients) showed a slight improvement in cognitive function [113]. In both analyses, there was a significant improvement in daytime sleepiness with PAP therapy. One of the few studies of long-term effects investigated the PAP effect after 10 years (126 patients) in severe OSA and revealed improvements in memory function, attention, and executive functions [113]. Treatment effects are also seen in low-grade and moderate OSA, although they are less pronounced and more often result in lower treatment adherence or treatment discontinuation [114]. Crucial for the therapy effect is the duration of use and adherence [115, 116]. Therapy effects have been demonstrated after a minimum usage time of 3 months or more, and no positive effects were shown with a shorter usage time [64, 92, 117]. Some cognitive functions such as visual-constructive skills, executive functions, and memory respond poorly to PAP therapy compared to attention and vigilance [73, 102, 118–120].

The morphologically detectable changes are partially reversible by successful PAP therapy [66, 121–123]. The irreversible morphologic brain changes are associated with residual daytime sleepiness despite adequate therapy [64, 78, 124].

PAP therapy has a preventive effect on the occurrence and symptomatology of mild cognitive impairment, dementia, and Alzheimer's disease [65, 120, 125–127]. Meta-analyses of PAP therapy and depression revealed an overall improvement in depressive symptoms, but considerable heterogeneity was identified in study design and outcome [116, 128–130]. The greatest improvements were achieved when the initial burden of depression was significant at the time of study onset [129, 131].

### 3.4.2. Non-PAP therapy

There are few studies on cognition and other OSA therapies.

Therapy with mandibular advancement splints for six months improved attention, but showed no effect on working memory

[132]. An improvement in depressive symptoms was achieved during therapy with mandibular advancement splints [129].

A study with 32 participants showed a positive effect of uvulopalatopharyngoplasty on attention three to six months postoperatively [133].

### 3.5. OSA and neurocognitive diseases

#### 3.5.1. Mild cognitive impairment (MCI)

Mild cognitive impairment is defined as a level of thinking performance that is significantly below the one that can be expected according to the age and education of the person affected. In contrast to dementia, however, only minimal everyday impairments occur. MCI is considered as precursor to various forms of dementia. OSA is associated with mild cognitive impairment in up to a quarter of cases [64, 101, 120]. The manifestation of mild cognitive impairment occurred 10 years (72.6 versus 83.6) earlier in patients with untreated OSA than in patients with treated OSA in a long-term study [134].

#### 3.5.2. Alzheimer's diseases

Alzheimer's disease is the most common form of dementia, accounting for up to 80%. Studies on Alzheimer's disease suggest a reciprocal relationship between OSA and Alzheimer's disease [67]. Both diseases are common in the elderly population and frequently co-occur [97]. A meta-analysis found that OSA was five times more common in Alzheimer patients compared to age-matched controls [135]. The immediate adverse effects of OSA on cognition, particularly executive function and attention, may contribute to worsening the clinical picture and more rapid progression of Alzheimer's disease. Based on a combination of mechanisms (disordered sleep architecture, intermittent hypoxia and hemodynamic changes, effects of concomitant vascular disease), OSA represents a cumulative predisposing factor for the development of Alzheimer's disease. Unlike other predisposing factors such as genetic predisposition, age, and cerebral trauma, OSA can be diagnosed and treated. Treatment of OSA has a preventive effect on preclinical Alzheimer's disease as well as on slowing cognitive decline in clinical Alzheimer's disease [68, 70, 125, 127].

#### 3.5.3. Depression

OSA patients have twice the prevalence to acquire depression [136, 137]. Sleep fragmentation, in particular, leads to alteration in brain regions where emotional modulation occurs [93]. Depressive and OSA symptoms such as fatigue and loss of concentration overlap. Untreated OSA can lead to a worsening of depression, and depressive symptoms negatively affect treatment adherence and compliance in OSA [138, 139]. In general population and in study populations without OSA, prevalence of depression is lower in men than in women [140]. However, if OSA is present, this difference is no longer as clear [93]. In men with OSA, the severity of depressive symptoms correlated significantly with the severity of OSA. Women were at higher risk for clinically significant depressive symptoms only when the AHI was in the moderate range [141]. Treatment of OSA primarily improves overlapping symptoms such as fatigue and lack of motivation [129].

### 3.6. Determination of the individual cognitive risk

#### 3.6.1. Humoral biomarkers

Biomarkers of neurodegenerative diseases have been discussed as predictors of morphologic changes due to OSA and investigated in a few studies. These include phosphorylated tau protein (p-tau),  $\beta$ -amyloid, and neurofilament light chain (NFL). First trials show an association between OSA severity and p-tau [86, 142] and  $\beta$ -amyloid elevation in CSF [68, 86, 143] and plasma [144].

#### 3.6.2. Electrophysiological biomarkers

The event-related potential P300 in the EEG is a known predictor of cognitive processes. Changes in amplitude and latency of P300 are associated with memory and attentional changes. A study of 55 patients with severe OSA with a high hypoxemia load demonstrated a correlation with the amplitude of P300 potentials compared with normal subjects [145].

#### 3.6.3. Genetic predictors

Detection of the apolipoprotein E4 allele (syn. ApoE-4 allele) on chromosome 19 is a genetic risk factor for Alzheimer's disease. This genetic variant is found in 20–25% of all Alzheimer's patients and in up to 50% of Alzheimer's patients with a late disease onset. Animal studies in mice with ApoE-4 allele indicate increased vulnerability to cognitive deficits from intermittent hypoxemia and sleep interruptions [146]. The genetic variant of the ApoE-4 allele is discussed as a "vulnerability factor" for the development of cognitive deficits and sleep-related breathing disorders in elderly patients [98].

### 3.7. Summary

In summary, obstructive sleep apnea is a risk factor for cognitive deficits and associated diseases. OSA is common in patients with mild cognitive impairment, Alzheimer's disease, and depression and is associated with a worse prognosis. Therapy for OSA can reduce cognitive impairment. In neurocognitive disorders, OSA therapy is an additive treatment option to improve symptomatology and quality of life in selected patients.

To improve the evidence regarding the cognitive effects of OSA and development of individualized therapy recommendations, long-term studies are particularly needed taking into account age, sex, educational level, physical activity, duration of untreated OSA combined with standardized examination methods of cognitive functions and OSA as well as accurate recording of adherence to OSA therapy measures.

#### Conflict of Interest

The authors declare that they have no conflict of interest.

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