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# Obstructive Sleep Apnea: Association to Neurocognitive Impairment. Therapeutic Strategies and Priorities

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## Abstract

***Introduction:*** *Obstructive sleep apnea (OSA) refers to a fairly common, multisystem chronic disorder which results due to reoccurring partial as well as total pharyngeal obstruction in the course of sleeping. OSA presents with typical symptoms such as excess sleepiness, involvement in vehicle accidents due to falling asleep at the wheel and some degree of systemic hypertension. There has been indication of an indirect connection between excess daytime sleepiness and the future incidents of cognitive decline and dementia.*

***Aim:*** *The main aim of this review is provision of a current summary of the knowledge and practice on diagnosing and treating patients with OSA and associated neuro-cognitive deficit disorders.*

***Methodology:*** *The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology was used for doing a review of relevant published literature.*

***Results:*** *This review shows that there is a definite association between OSA and associated neuro-cognitive deficit disorders due to the pathophysiological changes caused by OSA.*

***Conclusion:*** *The evidence from this review underlines the importance of early identification of cognitive decline (using neur0-imaging and other tests), definite diagnosis and subsequent proper choice of treatment and management options (in accordance with the associated comorbidities presented by the patient) so as to lower morbidity and mortality rates.*

## Methodology

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology, a search for relevant published literature was done using PubMed [1]. The key words and phrases used together with Boolean operators included: ("Obstructive sleep apnea," OSA related syndromes" [Mesh] AND OR "OSA and associated neuro-cognitive deficit disorders, [Mesh] OR "OSA associated neuro-cognitive disorders and dementias" [Mesh]). Other relevant studies were found by a review of the primary studies obtained in the search as well as reference tracing of selected articles. The inclusion and exclusion criteria were:

- Any articles that reported the incidence, prevalence, epidemiology, management and association of OSA with other neuro-cognitive disorders.
- Only peer-reviewed research studies which were published in English language from 2007-2017 were included in this review.
- Specific case studies, case letters and grey literature as well as studies not published in English were excluded.

The above outlined search strategy allowed for the retrieval a total of 312 articles following the removal of duplicates from various sources. The identified results were then reviewed by a single independent researcher. From the 312 articles obtained, only 24 studies were relevant to the topic of review. Article relevance was found after looking at the title of the article and reading their abstracts. After a full text review, 15 of the 24 relevant articles were found have direct association with the main aims of this review and accordingly, these 09 articles were used to extract qualitative data and summarize the findings from this literature review.

## Introduction and Background

Obstructive sleep apnea (OSA) refers to a fairly common, multisystem chronic disorder which results due to reoccurring partial as well as total pharyngeal obstruction in the course of sleeping [2, 3]. People having OSA suffer from constant upper airway when sleeping and this result in oxygen de saturating together with disruptions of the sleep cycle. The most common symptoms of OSA are snoring, witnessed apneas and feeling sleepy during the day. The pathogenesis of OSA shows variations but the underlying factors include smaller upper airway lumen,

lack of stability in respiratory control, lowered arousal threshold, decreased lung volume as well as malfunctions of the upper airway dilatory musculature. The underlying determinants as well as risk factors for OSA are overweight, being obese, being from the male sex, age-related issues, menopause, abnormal fluid retention, adeno-tonsillar hypertrophy as well as chronic smoking. OSA presents with typical symptoms such as excess sleepiness, involvement in vehicle accidents due to falling asleep at the wheel and some degree of systemic hypertension. This disorder is also associated with incidents of myocardial infarction, congestive heart failure, strokes as well as diabetes mellitus (this needs further research for validation). At present, the therapy option that is conventionally used is continuous positive airway pressure which has been found to show an adherence rate of 60 to 75%. Some patients are not able to tolerate this therapy and for them, bi-level positive airway pressure and adaptive servo-ventilating techniques serve as the therapy of choice. Some other therapeutic measures used for OSA include dental devices, surgical interventions and weight reduction [2].

OSA patients also show nocturnal apneas with hypopneas, occasional hypoxia, incidents of re oxygenation or hyper-/hypocapni combined with fragmented sleep patterns and alterations in their cerebral blood flow [4-6]. The prevalence of this disorder has been significant within the general population with figures suggesting that the prevalence rates fall between 3 to 7% [7]. However a more recent review on prevalence of OSA in adults showed different results. This study showed that with a ≥ 5 events/h apnea-hypopnea index (AHI), the total prevalence within the general population was somewhere from 9% to 38% with higher rates in males. The prevalence rates became higher with increasing age and, certain vulnerable population sets like the elderly; they were around 90% in males and 78% in females. With a ≥ 15 events/h AHI, the prevalence rates within the general adult population fell between 6-17%, and went as high as 49% in the elderly populations. OSA was found to be more prevalent in obese males and females. This recent review has documented that overall, with increasing age, in the male gender, and in people having a bigger body-mass index (BMI) ratio, there is higher OSA prevalence [8]. OSA was also prevalent in people suffering from cardiovascular and metabolic diseases [5, 6, 9]. In terms of global prevalence of OSA, the World Health Organization (WHO) has published global statistics on it (see in Table 1 below) [10].

**Table 1:** Global surveillance, prevention and control of chronic respiratory diseases. A comprehensive approach

| Country and reference | Population subjects | Age (years) | Criteria | Prevalence (%) |
|---|---|---|---|---|
| USA *(225)* | 352 men<br>250 women | 30–60<br>30–60 | Hypersomnia and RDI>5 | 4.0 (M)<br>2.0 (F) |
| Spain *(226)* | 2148<br>1050 men<br>1098 women | 30–70 | AHI >5 plus symptoms | 6.5 (M)<br>3 (F) |
| USA *(227)* | 4364 men<br>Subsample: 741 | 20–100 | AHI>10 plus daytime symptoms | 3.3<br>45–64 years: 4.7 |
| United Kingdom *(228)* | 893 men | 35–65 | $ODI_4$ >20, symptomatic<br>$ODI_4$>10<br>$ODI_4$>5 | 0.3<br>1.0<br>4.6 |
| Australia *(229)* | 294 men | 40–65 | RDI>10<br>Subjective EDS and RDI>5 | 10.0<br>3.0 |

RDI, respiratory disturbance index; AHI, apnea/hypopnea index; $ODI_4$, oxygen desaturation > 4%; EDS, excessive daytime sleepiness; M, males; F, females.

**Adapted Source:** World Health Organization; Global surveillance, prevention and control of chronic respiratory diseases, A comprehensive approach [10].

Many new studies have underlined the fact that OSA results in emotional as well as cognitive deterioration and is now being thought of as one of the unusual but treatable risk factors responsible for neurodegenerative dementia [11, 12]. The association between OSA and cognitive impairment is still under debate since evidence collected so far shows conflicting results. Some studies however have been able to indicate an indirect connection between excess daytime sleepiness and the future incidents of cognitive decline and dementia [13-15]. OSA is a contributing factor for the development of systemic hypertension which in turn is used to examine the degree of progression of associated white matter change. It has been stipulated that OSA mediates white matter change in the brain. This is possible due to the fact that there is a high prevalence rate of OSA coexisting with white matter change that comes prior to stroke incidents with corresponding cognitive impairment. This suggests a strong association of progressing white matter change mediating the stroke and dementia incidence in patients suffering from OSA [16, 17]. OSA has been connected with the development of Alzheimer's disease, Huntington's disease or other dementias, Parkinson's disease, restless legs syndrome and cerebrovascular involvement including stroke [18-20].

The main aim of this review is provision of a current summary of the knowledge and practice on diagnosing and treating patients with OSA and associated neuro-cognitive deficit disorders.

## Neuro-cognitive impairment due to OSA & evidence of neuro-cognitive deficit because of OSA

The studies were reviewed in order to explore how OSA causes neuro-cognitive impairment and to identify the evidence or data which supports such a premise. The findings from the review are shown in Table 1 below (evidence table for this review).

OSA has been found to cause a serious impact on the patient's physical as well as mental health, mainly because of the associated neuro-cognitive impairments and comorbidities like various types of dementias (these include lesions resulting from cerebral white matter changes, Alzheimer's disease, Huntington's disease, Parkinson's disease presenting with restless legs syndrome and/or cerebrovascular alterations) [21]. OSA promotes neuro-degeneration causing alterations mainly due to the two intrinsic processes involved with it namely intermittent hypoxia and sleep fragmentation. Due to the pathophysiological effect of hypoxia with relation to resulting hypertension, hypo-perfusion, and malfunctions of glucose metabolizing processes as well as the undesirable effects on cardiovascular, neuro-circulatory and cellular metabolic pathways, amyloid β generation and tau phosphorylation become up regulated. This in turn causes memory related cognitive loss and eventually this may progress to future presentation of Alzheimer's disease [15, 22].

Daulatzai formulated different kinds of malfunctions related and linked to OSA which is thought to contribute in progression of cognitive impairment [21]. Chronic incidents of hypoxia or re oxygenation coupled with sleep fragmentation are connected to transient stopping of breathing in OSA and they have a bad effect on a multitude of physiological functionalities, while also initiating

the up regulation of Ab and tau hyper phosphorylation. These two events in turn cause a damaging effect on cortical & hippocampal neurons, resulting in progression of their degenerative process and even cell death also known as apoptosis. Due to this neuro-degenerative impact, there results gray matter atrophy leading to impaired memory together with cognitive decline, these are the main symptoms seen in Alzheimer's diseases. It is worthy of note that caspases are actually cysteine proteases. Caspases 8 & 10 take part in the extrinsic apoptosis pathway which starts after binding & activation of cell surface death receptors happens. Caspase 9 is connected to the intrinsic apoptosis pathway which happens due to the releasing of cytochrome C from the mitochondria [21].

In addition, OSA-associated inflammatory as well as oxidative stress results in the impairment of synaptic functionality and issues in neural circuitry. This is the main underlying cause of neuro-cognitive impairment and associated disorders in OSA patients. Gradually this results in a progressive decline in neuronal function within the main sections of the brain, changes in the white matter and eventually results in full-scale cognitive decline. In the case of Alzheimer's disease-related neuro-cognitive dysfunction and similar issues in other dementias, it has been observed that OSA caused cognitive impairments occurs together with impact on many cognitive domains [23, 21].

**Table 2:** OSA and its association with neuro-cognitive disorders

| # | Study Authors | Year of Publcation | Study Design | Level of evidence | Population Studied | Outcome |
|---|---|---|---|---|---|---|
| **First group of studies: OSA is associated with neuro-cognitive impairment and deficit** | | | | | | |
| 1 | Daulatzai | 2015 | Retrospective review study | 4 | OSA patients with various associated disorders selected in different reviewed studies | |
| 2 | Canessa et al | 2011 | Cohort Observational study with controls | 3 | Seventeen male patients with severe, never treated OSA in the age range, of 30-55 together with 15 healthy male control subjects that matched the test cohort in age & education were examined. Inclusion criteria for OSA were patients with an AHI of more than 30 while the inclusion criteria for control cohort was an AHI of below 5 and not receiving any kind of psychiatric therapy and free of any medical disorders (Canessa et al., 2011) | Neuro-psychologic finding in the pretreatment OSA presented with impairments in several cognitive areas as well as in mood swings & levels of sleepiness. The observed impairments were related to focal decrease of gray-matter volume within the left hippocampus (entorhinal cortex), left posterior parietal cortex as well as within the right superior frontal gyrus. Following treatment, significant enhancement was seen in terms of memory, attentiveness & executive functioning which paralleled gray-matter volume increases within the hippocampal & frontal sections (Canessa et al., 2011) |
| 3 | Torelli et al | 2011 | Observational study with controls | 3 | The study participant cohort was made up of thirty patients, sixteen of which were recently diagnosed as being right-handed patients suffering from moderate to serious levels of OSA while the remaining fourteen severed as the normal controls. The OSA group of sixteen had all not received any form of treatment for OSA. | The results of this study show that most of the significant type of cognitive impairment observed within the OSA patients is related to brain tissue damage inside areas connected to many kinds of cognitive tasks. The researchers concluded that OSA was responsible for increasing their brain's vulnerability of the impacts of aging as well as other clinical and pathology-based alterations. |
| 4 | Jaussent et al | 2012 | An 8 year long longitudinal study. | 1 | 4,894 patients that did not have dementia were recruited from three French cities and at baseline they had a Mini-Mental Status Examination (MMSE) score $\geq$ 24 points | The findings show that the number of insomnia complaints & DMS were negatively related to MMSE cognitive decline, while the remaining three parts of insomnia (SQ, DIS, EMA) were not significantly related to MMSE cognitive decline (Jaussent et al., 2012) |
| 5 | Kim et al | 2013 | Cross-sectioal, population based prospective study | 2 | 503 patients with mean ± SD, age 59.63 ± 7.48 who had not in the past been diagnosed of any cardiovascular & neurological diseases | Multivariate logistic regression analyses show that moderate to severe OSA was significantly connected to the occurrence of white matter changes in patients as compared with no those that did not have OSA. Moderate to severe OSA can be used as an independent risk factor for white matter changes in middle-aged and elderly populations (Kim et al., 2013) |
| 6 | Guarnieri and Sorbi | 2015 | Literature review study | 4 | Elderly patients with mild cognitive impairment and several types of dementias | The findings of this review show that sleep disorders are highly underestimated & do not get the appropriate medical attention in the global management of dementia patients. Sleep disturbances do have a huge effect on cognitive as well as the physical functions in individuals that already show cognitive decline and might also be linked to important psychological distress with accompanying depression. They are also linked with the severity of behavioral issues & cognitive impairment (Guarnieri & Sorbi, 2015) |
| **Second group of studies: OSA and its association with particular neuro-cognitive disorders** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | Osorio et al | 2015 | Retrospective cohort study | 3 | Patients were participants from the Alzheimer's Disease Neuro imaging Initiative (ADNI) cohort. | The findings from this study show that the presence of OSA related breathing problems were related to an earlier age at cognitive impairment. The results also indicate that patients treated with CPAP show delayed progression of neuro-cognitive impairment (Osorio et al., 2015) |
| 8 | Kaminska, Lafontaine and Kimoff | 2015 | Literature review study | 4 | Patients with Parkinson's disease and OSA involvement in the non-motor symptoms (NMS) of this disease | The study results demonstrate that many several questions need to be examined in future research on the association between Parkinson's disease and OSA. The finding indicate that this association may be bidirectional and OSA could be a potential manifestation of Parkinson's diseases and also a factor that contributes to its symptoms as well as progression (Kaminska, Lafontaine, & Kimoff, 2015) |
| 9 | Ravesloot et al | 2017 | A systematic review and meta-analysis | 4 | Patients with OSA or those with position-dependent OSA known as POSA. | The review examined 3 prospective cohort studies as well as 4 randomized controlled trials. The findings from the data collected thus there is strong evidence which indicates that that the new generation of devices for positional therapy are efficient in decreasing the apnea-hypopnea index for the duration of short-term follow-up. These devices are also easy to use for patients as well as doctors and can be reversible. It was seen that under study conditions with short-term follow-up, compliance is good but in the long term compliance is not possible to measure due to inability to collect needed data. Additional long-term (Ravesloot et al, 2017) |

## Clinical Diagnosis

The diagnosis of OSA usually entails taking patient history, carrying out a physical examination and then conclusive diagnostic testing. The American College of Physicians (ACP) developed a validated clinical diagnosis guideline for presenting the evidence and provided clinical recommendations on how to carry out diagnosis of OSA in adults in 2014. Their recommendations are as follows:

**Recommendation 1:** The ACP recommended that a monitored sleep study should be done for patients that show symptoms of unexplained and excessive daytime sleepiness. This however will only provide only low-quality evidence and further tests are needed for definitive diagnosis [24].

**Recommendation 2:** The ACP recommended use of polysomnography for diagnostic testing in patients suspected of having OSA after physical examination. The ACP recommended use of portable sleep monitors in patients that do not suffer from serious comorbidities as an option to use of polysomnography or in places where polysomnography is not viable. This has been deemed as providing moderate-quality evidence for diagnosing OSA. It is still being debated on the kind as well as level of respiratory abnormalities, the presence or kind of symptoms and the most suitable sleep monitoring device in diagnosis of OSA (25, 24). Questionnaires utilized in prescreening patients for more testing are used and the validated one used is the Epworth Sleepiness Scale (26). The various kinds of monitor devices are shown in Table 3 below.

**Table 3:** Various monitoring devices used in diagnosing OSA

| Accuracy of Portable Monitors and Questionnaries for Diagnosis of Obstructive Sleep Apnea | | | | |
|---|---|---|---|---|
| **Tool** | **Over all Quality of Evidence** | **AHI Cutoff; events/h** | **Sensitivity, %** | **Specificity, %** |
| Type II monitor | Moderate | 5<br>10<br>30 | 89-94<br>79-100<br>61-77 | 36-77<br>71-100<br>96-98 |
| Type III monitor | Moderate | 5<br>15<br>30 | 83-97<br>64-100<br>70-96 | 48-100<br>41-100<br>79-100 |
| Type IV Monitor<br>≥ 2 channels<br><br>1 channel/oximetry | Moderate<br><br><br>Moderate | 5<br>15<br>30<br>5<br>15<br>30 | 75-100<br>67-98<br>80-100<br>27-100<br>39-100<br>18-100 | 43-100<br>50-100<br>74-98<br>67-100<br>32-100<br>29-100 |
| Berlin Questionnarie | Low | 5<br>15<br>30 | 37-93<br>40-83<br>17-87 | 17-95<br>20-97<br>37-77 |
| Epworth Sleepiness scale | Low | 5<br>15<br>30 | 24-96<br>21-50<br>36-50 | 29-89<br>43-83<br>70-79 |

| | | | | |
|---|---|---|---|---|
| Multivaria Apnea Predition Index | Low | 5<br>15<br>30 | 84<br>86<br>90 | 46<br>31<br>66 |
| Pittsburgh Sleep Quality index | Low | 5<br>15<br>30 | 72<br>14<br>No Data | 0<br>86<br>No data |
| STOP-BANG Questionnarie | Low | 5<br>15<br>30 | 36-97<br>44-99<br>56-100 | 18-89<br>11-77<br>11-74 |

**Adapted Source:** Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. Annals of internal medicine 161: 210-220. [24]

A summary of the diagnostic recommendations of the ACP is shown in Figure 2 below and can be used in the clinical diagnosis of OSA in adults.

**Table 4:** Summary of the ACP 2014 guidelines for diagnosing OSA

SUMMARY OF THE AMERICAN COLLEGE OF PHYSICIAN GUIDELINE ON DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA IN ADULTS

| | |
|---|---|
| Disease/Condition | OSA |
| Target Audience | Internists, family physicians, and other clinicians |
| Target Patient Population | Adults with suspected OSA |
| Screening and Diagnostic Tests | PSG<br>Type II, III, and IV portable monitors<br>Questionnaires |
| Interventions | Strategies to manage OSA |
| Outcomes | All-cause mortality, cardiovascular mortality, nonfatal cardiovascular disease, stroke, hypertension, type 2 diabetes, postsurgical outcomes, and quality of life |
| Recommendations | *Recommendation 1: ACP recommends a sleep study for patients with unexplained daytime sleepiness. (weak recommendation, low-quality evidence)*<br>*Recommendation 2: ACP recommends polysomnography for diagnostic testing in patients suspected of obstructive sleep apnea. ACP recommends portable sleep monitors in patients without serious comorbidities as an alternative to polysomnography when polysomnography is not available for diagnostic testing. (weak recommendation, moderate-quality evidence)* |
| High-Value Care | Clinicians should target their assessment of OSA to individuals with unexplained daytime sleepiness. |
| Clinical Considerations | The utility of portable monitors for diagnosing OSA in patients with comorbid conditions, such as chronic lung disease, congestive heart failure, or neurologic disorders, is unknown.<br>Although portable monitors may be used to diagnose OSA, AHI measurements from these devices may differ significantly from those taken with PSG.<br>CPAP treatment does not reduce CHD events and mortality in patients with OSA who do not have daytime sleepiness. |

**Adapted Source:** Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. Annals of internal medicine 161: 210-220. [24]

## Management of OSA for prevention of cognitive decline and behavioral problems

Pharmacological drugs do not play any part in the treatment of OSA but are used in patients suffering from central sleep apnea (CSA) as well as heart failure. Therapy using oral devices is common in the management of patients having mild or moderate OSA. Use of positive airway pressure (PAP) is still the main form of therapy for OSA patients having moderate to severe OSA. Use of bi-level PAP is suggested as a treatment option for those with respiratory failure (particularly alveolar hypoventilation with hypercapnia). Adaptive servo-ventilation is being utilized as a treatment option for cardiac patients presenting with Cheyne-Stokes respiration. Surgical interventions for the upper airways or of the maxillo-mandibular skeleton are done in some OSA cases. Bariatric surgery is an optional treatment used in very obese patients having OSA and is not able to have weight lose using conventional measures like diet and physical training [27]. The CPAP device remains the gold standard for the treatment and management of OSA. IT utilizes pressure in providing a pneumatic splint for maintaining airway patency. Issues of patients not compiling resulted in the development of several advanced CPAP-related devices as well as treatment modalities. Even though CPAP use lowers morbidity and mortality rates there is need for proper follow-up so as to make sure that compliance in the management of OSA and other comorbidities is present [28]. Some different and new methods for management of OSA are also present examined the relation between reported sleep issues at baseline (this includes insomnia problems as well as too much of daytime sleepiness and medicines and cognitive impairment within a community-living elderly cohort [14]. The study was a substantive eight year longitudinal research set in three French cities. The findings from this study indicate that excess daytime sleepiness might have an independent relation with the risk of cognitive decline in elderly people. These findings give major public health implications since excess daytime sleepiness could serve as for possibly treatable risk factors like cognitive decline and the start of dementia [14]. The study by also provides evidence for a concrete relationship between OSA and white matter changes in the brain leading to cognitive decline [14]. The main findings from this study show that moderate to severe cases of OSA, but not mild ones show positive independent association with the a higher prevalence of white matter changes. This increased prevalence of moderate to severe OSA with white matter changes indicates that the progression of this disease has an impact on the outcome of structural alterations of the brain. An increased risk of white matter changes might result due to several pathophysiological mechanisms that are impacted by direct hemodynamic alterations as well as intermittent hypoxemia leading to subsequent vascular changes resulting in presentation of symptomatic cerebrovascular diseases. Therefore, it has been indicated that early identification and timely treatment of OSA might decrease the risk of stroke as well as vascular dementia. Use of developed brain imaging methods like diffusion-tensor imaging might be helpful in examining white matter changes within what seems to be a normal brain and help not only in understanding the connection of OSA to white matter changes but also be useful in management that can prevent cognitive decline [17].

In around 50 to 75% of patients suffering from OSA, the frequency as well as the length of apneas is affected by the position of the body. This is known or called position-dependent OSA or POSA. Patients suffering from POSA can receive treatment using a tiny device that is attached to their neck or chest area. Such devices are a newly developed generation of devices that are utilized in positional therapy. They give a very subtle vibration based stimulus which does the job of preventing the patients from making use of the supine position during sleep. A recent study done just this year has tried to determine whether positional therapy is efficient as a management option in the enhancement of sleep and reducing daytime sleepiness. This study also assessed compliance levels of patients. Although the findings show that these devises are good at decreasing AHI in short term follow up, it was impossible to determine their effectiveness in the long term due to lack of long

term follow up data. In the future, new research studies are required for confirming what part positional therapy can have when used as the only or one of the many therapies or combined treatment modality for OSA patients and also ascertain patient long term compliance issues [29].

## Discussion

The diagnosis as well as treatment of OSA has undergone continuous improvement with ongoing development in detection of cognitive decline, white matter changes and neuro-generative aspects of OSA that make it the onset for other comorbidities. There is need to understand that OSA has an independent impact on the progression as well as related morbidity and mortality rates of such comorbidities. Thus, primary care doctors need to make sure that all suspected cases of OSA are correctly properly diagnosed, cognitive decline is detected through neuro-imaging and timely treatment as well as management is done. At the global level the rate of OSA is increasing and this will continue to raise the numbers of patients suffering from this disorder and related comorbidities linked to cognitive impairment will also rise proportionately (all this is because of the world having an increasing elderly population with a high prevalence of OSA) [21, 8]. A lot of evidence-based findings from the studies reviewed in this review show the relationship between aging, obesity and OSA with clear connections to OSA being involved in their patho-physiology based mechanisms as well as changes in cellular pathways together with cognitive decline and neuro-degenerative damage (See Figure-1) [15, 21, 30]. It has been demonstrated that if a patient has a history of hypertension resulting from OSA this may be the start of vascular dementia, especially if there is any incident of cardiovascular complications, heart disease and/or diabetes [18, 28].

Chronic intermittent hypoxia as seen in OSA results in initiation of several pathology-related mechanisms with cognitive changes (see Figure 1 shown previously). These mechanisms cause cognitive impairment in untreated OSA patients. OSA has a wide range of effects on cognitive functions and impairs things like sustained attention, working memory, visuospatial learning, motor performance as well as executive functionality [13, 21, 31]. The range of evidence discussed in this review underline the relationship between OSA-associated pathological change and the start of memory as well as other cognitive dysfunction progressing to other comorbidities. The present insights on the relation of OSA, the pathophysiology of cognitive decline and other diseases indicates need for early diagnosis with suitable methods and subsequent use of a combination of treatment options [32].

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