

Obstructive Sleep Apnea's Role with Cognition, Multimorbidity, and Mental Health

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### Abstract

Obstructive Sleep Apnea is a sleep disorder characterized by an obstruction in the throat which halts breathing. Consequently, the person's sleep is disrupted many times every hour, and affected individuals are at a heightened risk of death when they go to sleep. The purpose of this literature review is to examine the chronic effects from hypoxia. Cognitive impairments, associations with multimorbidity and a correlation with damaged mental health are all studied effects of untreated obstructive sleep apnea. Studies were chosen that analyzed the damage resulting from hypoxia. The results show that there appears to be a correlation with untreated obstructive sleep apnea and cognitive impairment ranging from memory loss, decreased psychomotor speed, and problems with recall. A reduction in grey matter volume in the brain was also observed. Improvement in cognitive ability and an increase in grey matter volume was found after repetitive treatment in most studies. Heightened instances of multimorbidity were observed in those with severe OSA. Correlations with problems of mental health were unclear and appeared to have no true causation but had shared independent symptoms found in both mental illness and OSA. This literature review illustrates a need for more research for sleep disorders like obstructive sleep apnea because of correlations with chronic impairment that affect the quality of daily life. There is high demand to understand the complete mechanism from hypoxia that leads to these impairments and also a need to make this underdiagnosed disorder a more common concern in primary care environments.

## Introduction

Obstructive Sleep Apnea (OSA) is a consequential disease that often goes unnoticed because of its characteristics. This disorder occurs during sleep, and unless the affected has an observant and medically knowledgeable partner sleeping next to them, the person can experience long-term effects from sleep apnea that will not only affect the quality of their daily lives but put him or her at risk of death every time they sleep. Obstructive sleep apnea is underrepresented in prevalence statistics because of the individual's lack of consciousness while serious symptoms are present. Obvious short-term effects will stem from hypoxia, but there are possible chronic consequences that affect cognition and attention. These long-term cognitive effects are important in research, because primary care physicians need to further educate their patients on the effects of low oxygen. Hypoxia, as a result of obstructive sleep apnea, causes a wide array of cognitive impairment ranging from grey matter volume loss, problems with memory consolidation, and poor learning outcomes.

Obstructive sleep apnea is characterized by the collapsing of the throat while asleep. This obstruction can occur at any stage of the sleep cycle; it is caused by excess fat deposits weighing down the neck rather than a byproduct of disrupted sleep architecture. The throat collapse obstructs oxygen flow to the brain; consequently, O<sub>2</sub> levels in the blood dip while CO<sub>2</sub> levels rise. As severity worsens and apneic events become more prevalent throughout repeated nights, risk of death becomes more prominent. Throughout the night, the number of involuntary breathing pauses or "apneic events" may occur 20 or 30 times per hour in severe cases, (National Institute of Health, 1995). This lack of oxygen caused by the collapse will increase CO<sub>2</sub> levels in the blood. The CO<sub>2</sub> levels will result in a neuronal arousal, which directs the brain to open the

throat up to allow oxygen to flow into the lungs, (National Institute of Health, 1995). The nerve impulse directing the opening of the throat will cause a loud snore or gasp while the person is sleeping. Excessive snoring is a result of OSA, but it does not imply everyone who snores experiences a complete obstruction. Snoring is a result of a narrowed airway or partial blockage, and the sound is air pushing through the throat. However, apneic events are the differentiating factor between snoring and OSA. An apneic event is characterized by a complete blockage of the throat which causes the person to quit breathing completely for around 10 seconds. The obstruction will result in a period of silence, due to lack of breathing, followed by a loud gasp; this is a strong indicator of obstructive sleep apnea.

Obstructive sleep apnea can be due to excessive weight gain, abnormalities in the throat region, or a genetic predisposal. The genetics behind OSA are not completely understood but may be attributed to genes involved in the following processes: tissue development in the face and neck, inflammatory response, nerve cell communication and breathing regulation, (National Institute of Health, 2018). The obstruction tends to happen when the throat muscles and tongue relax during sleep and partially block the opening of the airway, (National Institute of Health, 1995). Excess tissue in the throat is observed in obese people due to the higher amount of fat in the throat region. Around 4% of middle-aged men and 2% of middle-aged women are diagnosed with sleep apnea, and it is estimated that around 18 million Americans have this disorder, (National Institute of Health, 1995). Although people who are diagnosed follow the treatment plan, many who have this disorder leave it untreated. Avoidance of treatment can be attributed to the uncomfortableness of wearing a mask while sleeping, along with the inconvenience it may bring. It is predicted that up to half of the diagnosed do not actively use continuous positive airway treatment (CPAP) to eliminate symptoms. The CPAP opens up the throat during sleep to

maintain appropriate air pressure and prevents the throat from collapsing, thereby maintaining a steady airflow to the lungs. The long-term effects result from exposure to low O<sub>2</sub> and high CO<sub>2</sub> levels without intervention, and these effects may lead to a premature death.

### Literature Review

#### Cognitive Impairments

Untreated obstructive sleep apnea induces cognitive impairments. Canessa et al. focused on specific aspects of cognition to identify the true risk and implications that can arise from hypoxia. Seventeen severe obstructive sleep apnea patients underwent a polysomnography test before and after treatment. A polysomnography test measures muscle movement, brain waves (EEG reading), and O<sub>2</sub> and CO<sub>2</sub> levels while the patient sleeps. Polysomnography tests can be used to diagnosis obstructive sleep apnea, because all of the physiological aspects common to OSA are measured. The severity is recorded based on O<sub>2</sub> saturation drops; to be considered an apneic event, the polysomnography has to show a cessation of oxygen resulting in an 80-100% decrease in airflow for around 10 seconds. This will be followed by an arousal on the graph, usually marked by obvious oxygen desaturation.

Using polysomnography, Canessa measured apnea and hypopnea events to determine severity. Apnea events were characterized by 80% drops in respiratory amplitude for more than 10 seconds; hypopneas were characterized by 30% drops in amplitude for more than 10 seconds, (Canessa et al., 2011). Additionally, all of the subjects participated in different types of recall, long-term and short-term memory tests before and after 3 months of treatment with a CPAP. The scores were evaluated and compared. Along with the polysomnography and cognitive testing, the individuals also self-evaluated their level of drowsiness and depression in two separate questionnaires before and after the 3 months of treatment.

The results demonstrate that cognitive impairments are more common in those with untreated OSA. The study explained the cognitive deficit by a structural change in the brain. A significant reduction of grey matter volume in pretreatment patients, compared with control subjects, was observed in the left posterior parietal cortex and right superior frontal gyrus (Canessa et al., 2011). After CPAP use, however, a significant increase of overall GM volume was observed in patients with OSA ( $P < 0.05$ ) despite no significant increase of total intracranial volume, (Canessa et al., 2011). Grey matter is specifically important for knowledge and memory. It contains many neuronal cell bodies, and once grey matter begins to atrophy, these functions are affected. A loss of grey matter is, therefore, associated with a loss of cognitive function. Grey matter loss is presumed to be correlated with hypoxia, because once hypoxia was not occurring, grey matter increased. Along with an increase in grey matter, the subjects also experienced statistically significant improvement in cognitive tests, like the Stroop test. The Stroop test evaluates cognition by writing the name of a color in a different color of ink. The individual must say the color instead of the word, and the number of words correctly spoken are recorded in an allotted time. After the 3 months of treatment, the scores from the Stroop test, along with the other scores that evaluated memory and recall, improved.

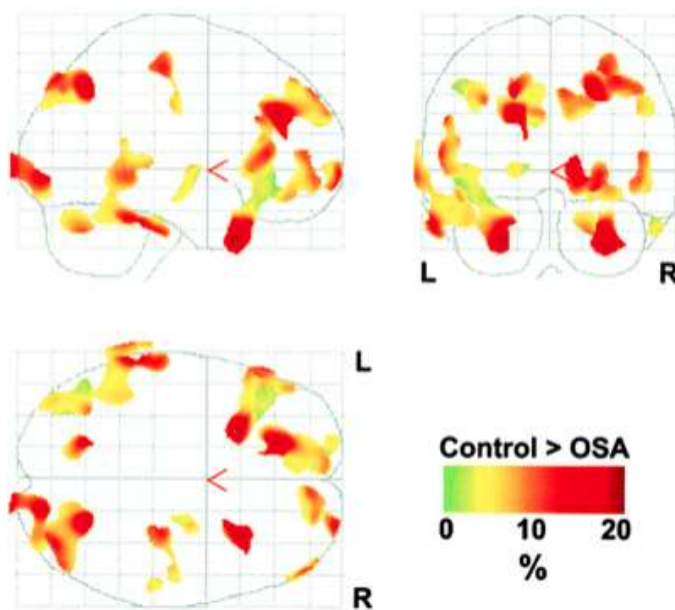
Overall, the study by Canessa et al. identifies statistically significant improvement resulting from repetitive CPAP use. Neuropsychologic results demonstrated impairments in memory, attention, executive functions, and constructional abilities and also resulted in higher daytime sleepiness and likelihood of depression for patients with untreated OSA, (Canessa et al., 2011). All of these impairments are thought to be associated with loss of grey matter volume in the left hippocampal entorhinal cortex, the left posterior parietal cortex, and the right superior frontal gyrus, (Canessa et al., 2011). The hippocampal entorhinal cortex is important for forming

long term memory, the posterior parietal cortex is important in receiving higher order sensory signals that deal with attention, and the superior frontal gyrus is part of the frontal lobe and helps with impulse control. The first two brain structures make sense in their role with cognition, however, it is not clear how impulse control can cause a decline in cognition. It is possible that while doing these tests high impulsivity will cause the individual to quickly solve problems without as much thought.

A significant improvement in cognitive function was seen after 3 months of treatment with proper and nightly use of a CPAP; the individuals scores were not only statistically higher in the memory and recall tests, but their self-reported questionnaires for drowsiness and depression also improved after the 3 months of abiding to a treatment plan. This declination in function is attributed to grey matter loss from hypoxia, because there is a positive relationship between grey matter, oxygen, and cognitive function. As grey matter increases, cognitive function increases as a result of sufficient oxygen during sleep.

More evidence for grey matter loss was analyzed in a study by Macey et al. This study measured grey matter, white matter, and cerebral spinal fluid (CSF) in control subjects and subjects with OSA. The control group contained 21 men, and they were compared with 21 men who had been diagnosed with OSA. The study found that in control subjects, grey matter decreased with age, while white matter did not change, and CSF increased. The increase in CSF may be attributed to enlarged ventricles, which is associated with aging. White matter and CSF were not significant aspects of brain structure in the comparison for OSA and the controls, however. Even more substantial reduction of grey matter was found in the subjects diagnosed with OSA; the amount of reduction depended on the severity. As severity increased, grey matter reduction also increased; the areas of the brain with grey matter loss contained up to 20% less

volume than the control subjects, (Macey et al., 2002). Overall, the effects of OSA were less than aging effects. Significant regional differences in gray matter between groups ranged from 2 to 18% which is shown in the figure below, (Macey et al., 2002). Although the amount of grey matter lost was not overwhelming, it still was significant. This study mirrors the results found in the study by Canessa et al. and suggests that grey matter is a culprit of cognitive declination for those diagnosed with obstructive sleep apnea.



*Figure 1.* These glass brains highlight the specific areas of the brain that were statistically less in grey matter volume for those diagnosed with obstructive sleep apnea. The color shown demonstrates the reduced percentage of lost grey matter in each region.

The study continued to examine possible causes of grey matter loss. A portion of the anatomic differences is likely to result from hypoxic, hypercapnia, heightened blood pressure, and obstructed breathing, (Macey et al., 2002). Repetitive, hypoxic events are correlated with grey matter damage and reduced cerebral blood flow. When oxygen is not flowing into the lungs, blood flow is significantly reduced to the brain. Consequently, brain structure is affected. Macey et al. suggests that reduced grey matter volume in the brain is due to ischemia, however, there can be more factors that attribute to the loss. Volume changes may have been present before the onset of OSA and may have contributed to characteristics of this syndrome, (Macey et al., 2002).



If this study were to incorporate a CPAP treatment for the individuals, the grey matter volume could be measured again in a few months after continuous treatment to conclude whether sufficient oxygen to the brain would reverse this loss.

Another study did not identify statistically significant evidence that those with OSA were more cognitively impaired than those without, but they did identify the importance of wearing the CPAP and adhering to the treatment directions. The researchers instructed the subjects to participate in the Montreal Cognitive Assessment (MoCA) tests before and after treatment. MoCA examines recall, memory, concentration, and other cognitive functions through short tests; it only takes around 10 minutes. Patients who used a CPAP for longer than 4 hours per night had a faster psychomotor speed in a subsequent MoCA test than those who did not adhere to treatment. No other significant effects of CPAP use were found in this study, (Dostálová, Kolečárová, Kuška, Pretl & Bezdicek, 2018). Although the data did not show concrete evidence for cognitive improvement, CPAP use still proved to be beneficial, once again highlighting the importance of adhering to treatment directions.

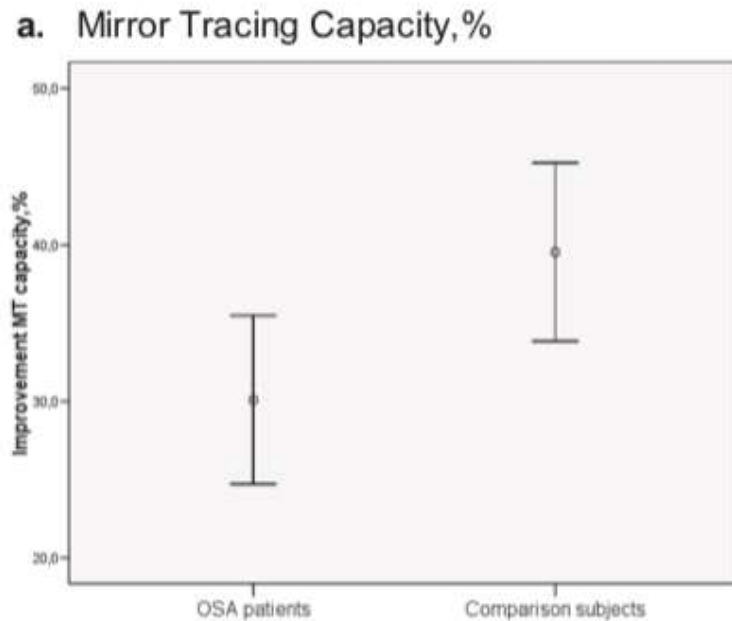
Additionally, the researchers found a correlation between time of diagnosis and severity of symptoms. Further studies should be more longitudinal of non-adherent individuals with sleep apnea because of this association. There was also a small sample size in this study, which could also prompt further studies to evaluate more individuals placed in groups based on their severity to account for a larger population. With a small sample study, comparing patients who have just started presenting symptoms with those who have had untreated apneic symptoms for many years will not yield acceptable results. It is important not only to obtain a large sample size, but also to separate experimental groups by severity and time since diagnosis. In future studies, more longitudinal and larger sample sizes will provide more accurate results.

Declarative and procedural memory are also affected by obstructive sleep apnea. In a study by Kloefer et al., many aspects of memory were affected from the lack of oxygen while sleeping and additionally from daytime sleepiness. Deficits in learning were demonstrated for both declarative memory (explicit, hippocampus-dependent memory) and procedural memory (implicit, hippocampus-independent memory). Memory deficits might be due to functional or structural alterations in the brain critical for memory or from chronic fatigue resulting from fragmented sleeping patterns, (Kloefer et al., 2009). The study continues to investigate these claims that have been supported in the past. The researchers attempt to identify the mechanism that causes a difference in memory consolidation after a period of sleep.

In the study by Kloefer et al., fifteen patients with moderate OSA and twenty healthy subjects were assessed. The subjects spent the night in the laboratory and a polysomnography machine analyzed the degree of severity. Declarative and procedural memories were also evaluated at a period before sleep (19:00 to 23:00), and then again once the patients were awake (7:00 to 8:30). During the evaluation period before the subjects went to sleep, it was a learning session; once they woke up, it was a recall session on what they had learned the night before, (Kloefer et al., 2009).

Their procedure learning task consisted of tracing different images with an electric stylus as quickly as possible. Draw time and error count were measured; for training, they traced the image of a star until less than 15 errors were made. After training was complete, the subject was directed to trace 6 different, new images. The next morning, to keep conditions controlled the subjects traced the initial star again. Then, the six images from the night before were placed in a random order and they were directed to trace them. Overnight memory formation was analyzed by the percentage of improvement in draw time, errors made, and error capacity, (Kloefer et al.,

2009). No statistical difference in the errors made in the tests prior to sleep was found. However, the results from the procedural tests in the recall phase the morning after provided insight to memory formation. Regarding procedural memory, the analysis comparing averaged evening and morning scores demonstrated a significantly lower improvement capacity in OSA patients (30.1% +/-9.7%) than healthy subjects (39.5% +/-12.2%), (Kloepfer et al., 2009). The number of errors were statistically significant OSA patients, but no difference in error time was found, (Kloepfer et al., 2009).

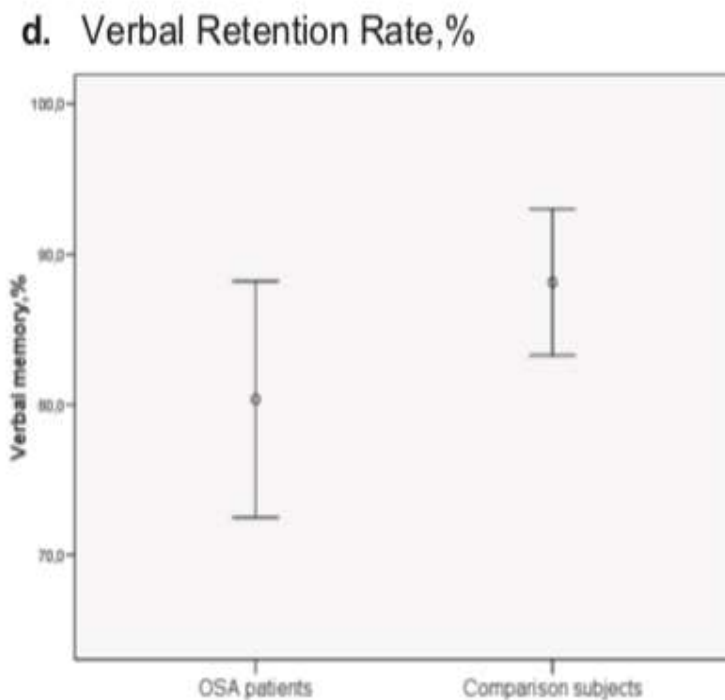


*Figure 2.* The difference in improvement for mirror tracing for procedural memory in OSA patients and control subjects was significant. The improvement for the control subjects was around 10% higher than subjects with

OSA. This data demonstrates the greater capacity for procedural memory in those without OSA, specifically after sleeping.

For declarative memories, the subjects were required to memorize a line-drawn path on a map. Along with the visual task, they were assigned to a verbal test. In the verbal test, subjects were provided information about the construction of a building; this includes names, proportional content and more, (Kloepfer et al., 2009). Visual and verbal recall were assessed

immediately after, and once again once the subjects woke up. The results show a similar course of impairment. Regarding declarative memory, OSA patients showed a significantly reduced verbal retention rate after sleep (80.4% +/-13.6%) when compared to healthy subjects (88.2% +/-10.4%). Patients with OSA also tended to show a lower retention rate of declarative visual memory, but this was not statistically significant, (Kloepfer et al, 2009).



*Figure 3.* This figure illustrates the difference of improvement in declarative memory and verbal retention rate. The control subjects scored about 8% higher than those with OSA, which is statistically significant. The subjects did not only score lower, but they also demonstrated a

slower retention rate when regurgitating the information from the night before.

Etiological factors were explored that may have led to problems in developing declarative and procedural memories; possible further studies could be executed more efficiently to uncover the actual mechanism leading to cognitive impairments. This study does not come to a conclusion on how hypoxia causes impairment. In the future, more developed data could be acquired if this study was repeated with a treatment period added. The declarative and procedural

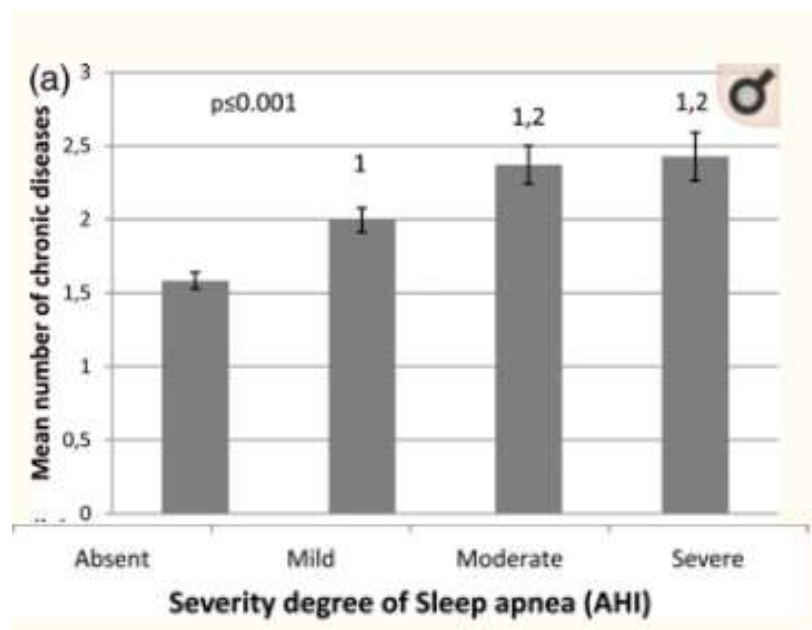
memory tests would be repeated after the treatment with a CPAP or similar device to track improvement. This method was performed by Canessa et al., and the individuals did show statistically significant improvement after adhering to a treatment plan.

### Multimorbidity

Cognitive deficits from untreated obstructive sleep apnea are not the only concern from prolonged hypoxia; affected individuals are also at risk for multimorbidity, the presence of more than one chronic disorder. However, since obstructive sleep apnea is so underrepresented and diagnosed in present day, it is difficult to pinpoint the true etiology for multimorbidity. Recent estimates suggest approximately 75-80% of OSA cases may be undiagnosed, so the true association between OSA and chronic disease is unclear, (Ruel et. al, 2018). However, even though there is a misrepresentation of numbers for OSA individuals, a strong correlation between chronic disorders and obstructive sleep apnea is present. This study done by Ruel et. al focused primarily on middle age men. Of a random sample obtained through the Electronic White Pages and computer-assisted telephone interviews, 2038 35-year old male participants were gathered in South Australia. 1445 of these participants that had never been diagnosed with OSA agreed to a sleep test. By the end of the research period, 837 successfully completed the polysomnography test, (Ruel et. al, 2018).

Multi-morbidity for these men was defined as two or more of the following conditions: asthma, heart disease, diabetes, depression, hyperlipidemia, hypertension, obesity, osteoarthritis and rheumatoid arthritis, (Ruel et. al, 2018). Once the sleep study results were analyzed, the men were split into four groups: absent, mild, moderate, and severe OSA. Overall, men in the severe group had 0.78 more chronic diseases (CDs) than those without an OSA diagnosis, (Ruel et. al, 2018). Additionally, the results were compared to show the instance of multimorbidity in those

with and without OSA. Among the 743 men included, 58% of the population had multi-morbidity. The proportion of those with multi-morbidity was higher in those with OSA than those without (67% v. 48%,  $p < 0.001$ ). There was no difference in multimorbidity proportion between the mild, moderate, and severe groups, but the mean number of CDs was significantly higher in the moderate and severe groups, (Ruel et. al, 2018). When only looking at whether the individual had a chronic disease, there was no difference between categories (no, mild, moderate, severe) because it did not account for the number of chronic diseases. When analyzing the number of CDs present, however, as the severity of OSA increased the number of CDs did as well. This supports the idea that OSA is correlated to a higher chance of multimorbidity.



*Figure 4.* This figure demonstrates the correlation of the number of chronic diseases with increasing severity of obstructive sleep apnea. This figure demonstrates that those without OSA have a smaller probability of being diagnosed with more than one disorder.

As the severity increases, the mean number of chronic diseases does as well.

Another interesting piece of evidence was centered on the prevalence of obesity. Obesity is a predominant cause of OSA, so it is expected that this would be one of the most common conditions for those with multimorbidity. Obesity was the only chronic disease for which there was a significant difference between the mild and the moderate/severe group (+20%,  $p < 0.05$ ),

(Ruel et. al, 2018). This demonstrates the possibility of a positive linear relationship between obesity and OSA. As the severity of OSA increases, so does the BMI (body mass index) of the individual.

A study by Robichaud-Hallé et al. also focused on the prevalence of chronic diseases with OSA-- specifically hypertension and heart disease. Fletcher reported that 70 to 90% of patients with OSA are also diagnosed with hypertension. Associations between OSA and heart failure, OSA and arrhythmias, OSA and diabetes, OSA and insulin resistance, and OSA and metabolic syndrome were also reported, (Robichaud-Hallé et. al, 2012). Not only does this study stress the strong correlation with serious, chronic diseases, but it urges the primary healthcare system to become more aware of sleep disorders, like obstructive sleep apnea, during annual check-ups. Evidence of an association between OSA and multimorbidity could be an important incentive to screen more frequently for OSA in primary care settings, (Robichaud-Hallé et. al, 2012). Because OSA is highly underdiagnosed, it is important to evaluate the possibility of obstructive sleep apnea, especially when patients presenting these other chronic diseases come in for a check-up. If the patient is overweight and reports excessive daytime sleepiness or problems with cognition, a sleep test should be ordered instead of overlooked or forgotten.

In this study, patients were categorized by the severity of their sleep apnea based on a polysomnography test. After the test, patients were instructed to provide information about multimorbidity and socio-demographic variables. In the questionnaire the patients assessed how each condition (if applicable) limited their daily activities on a scale of 1 to 5, with 5 being most limiting. The questionnaires were mailed, and the goal was to receive at least 30 replies from each group (absent, mild, moderate and severe OSA). In total, exactly 120 completed the self-

evaluation, and the average age was 55.5 years, with the majority being male, (Robichaud-Hallé et al., 2012).

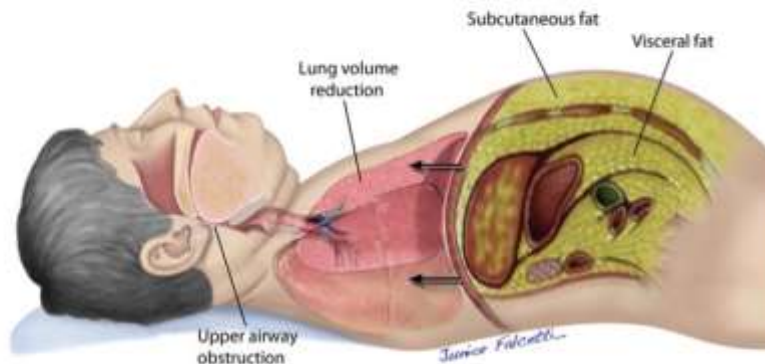
Although the number of diseases did not increase with the accordance with severity of OSA, a correlation was still found between the two. In this study there was a link between severe obstructive sleep apnea and the severity of the other chronic disorders they were diagnosed with. These results are the first documentation of an increased severity in chronic disorders if the patient has a comorbid diagnosis with OSA. The study also showed an association between OSA and multimorbidity sub-scores (cardiac, vascular, metabolic syndrome), (Robichaud-Hallé et al., 2012). Although the number of diseases did not increase along with severity, it still is presented in the data the seriousness of specific aspects of the diseases were more dangerous with worsening severity of OSA. Further studies need to be done to evaluate this relationship and how hypoxia is causing subsequent disorders to be more life threatening. Once again, this study demonstrates the importance of primary care physician's role in bringing more awareness and understanding for the underdiagnosed disorder of OSA.

Obstructive sleep apnea has a reported a correlation with multimorbidity. Obesity, metabolic syndrome, hypertension, and heart disease are the major chronic diseases seen in conjunction. It is estimated that 50% to 60% of people who are obese and diagnosed with metabolic syndrome have OSA. The prevalence of OSA is even higher in obese patients with diabetes mellitus and morbid obesity, (Drager et. al, 2013). This study specifically focuses on the evidence of this association. It is clear that these disorders are strongly linked, but the reason is still unclear. Obesity has already been marked as a predominant etiological factor. Obesity is a risk factor for OSA because it promotes enlargement of the soft tissue structures within and surrounding the airway; this contributes significantly to the obstruction. An excess of fat deposits



around the throat has also been observed under the mandible and tongue, in the uvula and in the soft palate, (Drager et. al, 2013). Because obesity is the strongest cause of OSA, are other chronic disease present because of obesity or because of the long-term effects resulting from hypoxia? Once again, more longitudinal studies would be helpful here because at this point, only correlations are found rather than causation.

**Figure 1**



**Obesity Predisposes to Obstructive Sleep Apnea**

Anatomic factors that predispose obese patients to obstructive sleep apnea.

*Figure 5.* This figure

depicts the presentation of obstructive sleep apnea. The subjects high subcutaneous and visceral fat is high in volume and

push on the lungs upwards while in supine position. With reduced lung volume from the subcutaneous and visceral fat, the upper airway is easily obstructed, and airflow is limited or ceased. This depiction not only emphasizes the excess tissue in the throat as being causal to OSA but body fat, as well.

Additionally, intermittent hypoxia and fluctuations in oxygen levels may have an effect. A study involving mice viewed the effects of intermittent hypoxia, which occurs in OSA, and found that it caused large-amplitude oxygen swings in the liver, mirroring swings of SpO<sub>2</sub>, (Drager et. al, 2013). The article continues that this lack of oxygen and the effect on adipose tissue may be an indicator of the cardiometabolic dysfunction. The amplification of hypoxia in the adipose tissue may represent an important mechanism of cardiometabolic dysfunction in

OSA because it caused lipolysis, chronic inflammation, macrophage infiltration, reduction of adiponectin level, elevation of leptin level, adipocyte death, endoplasmic reticulum stress, and mitochondrial dysfunction, (Drager et al., 2013). These effects are usually only labeled as a result of obesity, metabolic syndrome and other associated disorders. OSA is often pushed aside and labeled in the category of “other fields of medicine” rather than as an explanation for cell death, stress, and dysfunction that the body presents. This is the first study that views the intermittent hypoxia as a major cause instead of as a correlation.

Not only do issues with metabolic syndrome present in mice, but humans have also participated in similar tests. Healthy volunteers were exposed to 6 hours of intermittent hypoxia. They developed insulin resistance and also had impaired beta cell function. This chronic intermittent hypoxia also impaired clearance of triglyceride-rich lipoproteins and inactivated adipose lipoprotein lipase, (Drager et. al, 2013). Continuous studies have been shown to produce affects that mirror problems found. Even with this evidence, however, there are no consistent data labeling OSA as a risk factor for dyslipidemia, (Drager et. al, 2013). Researchers tend to ignore clear correlations between OSA and other serious, chronic conditions. More studies need to be funded to further explain the relationship between OSA and chronic conditions that arise from intermittent hypoxia. In depth research on intermittent hypoxia is essential to provide evidence that will reach primary care providers and consequently affect those that suffer from multimorbidity. Hypoxia has an effect on the body, but with so many different chronic diseases affecting physiological function at the same time, it is not clear what exact effect this is to differentiate it from the next possible etiological cause.

### Mood Disturbance and Mental Illness

Multimorbidity and obstructive sleep apnea usually highlight correlations between diabetes, metabolic syndrome, and obesity. However, along with physical disorders, there appears to be an association with mental disorders that result from the continuously low O<sub>2</sub> levels. The prevalence of anxiety and depression have been examined most frequently out of the psychological disorders. After discussing the etiology of cognitive impairment stemming from hypoxia, it comes as no surprise that other brain functions would be altered, too. Affects in cognition rooted in memory, recall and learning are obvious effects; however, the brain is much more active than this. Emotional stress from hypoxia may be caused by a similar mechanism, but there is not as much evidence for mental effects as cognitive ones.

Harris et al. attempted to uncover the truth behind the correlation between OSA and depression. The combination of these diagnoses may be misguided; it is important to note that both disorders can present with similar symptoms. Individuals suffering from OSA clearly will have excessive daytime sleepiness because of the low levels of O<sub>2</sub> throughout the night and because of the brief periods they are awoken due to apneic events. Depression is also characterized with excessive daytime sleepiness but for a different reason. Depression is usually marked with repeated nights of insomnia; the individual has trouble falling asleep and staying asleep, and insomnia explains why the person is so fatigued during the day. Because of this, evaluation has to be more focused on cognitive symptoms of depression that are listed in the DSM-V. There must be an attempt to overcome the difficulty of measuring depressive symptoms because OSA is likely to produce similar symptoms; only cognitive features of depression, such as feelings of guilt or worthlessness, self-blame, and ruminative thoughts and crying should be used in characterizing depressive symptoms for those with OSA, (Harris et al., 2009). It is

extremely important to choose a suitable evaluation method in studies that focus on this correlation. The article goes on to discuss the Beck Depression Inventory test. This test is a self-evaluation of depression. However, when those with OSA take this test and they list out symptoms that are present in both disorders; it is possible they are receiving a depression diagnosis that is not correct. The Beck Depression Inventory was one of the tests used in a study discussed earlier performed by Canessa et al. This study reported lower amounts of depressive symptoms after 3 months of adhering to CPAP directions; however, Harris et al. challenges this claim and promotes the importance of further identifying symptoms rooted solely in cognitive analysis rather than self-evaluation.

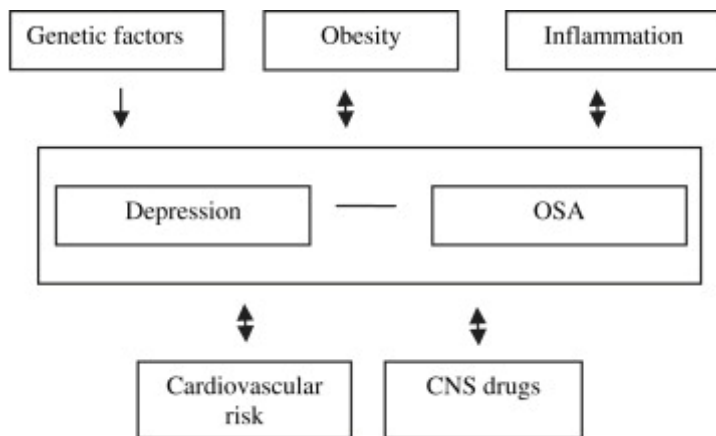


Figure 6. This flow chart shows the interaction between depressive and sleep apnea symptoms that can coincide based on different causes. The root of shared symptoms can be brought on by many different elements ranging from genetics,

inflammation and obesity. The association between OSA and depression is not clear cut, and correlations should be evaluated on a case by case basis.

Harris et. al continues to discuss correlational and prevalence studies that have found mixed results regarding the correlation between the two disorders. Rates of depression have also been extracted from 24 reports of studies in OSA and they give a range of 7-63%, (Harris et. al, 2009). Clearly, this range is very vast, and more longitudinal and focused studies may give more understanding about the true prevalence of depression. One large-scale cohort study has shown

an increased risk of developing depression as OSA develops or worsens, and it discusses a “dose-response relationship” between how severe the OSA is and the likelihood of showing signs of depression, (Harries et al., 2009). Harris highlights the importance of evaluating depression rates and OSA dependent on the severity of OSA. Those with mild OSA are thought to experience less cognitive symptoms from depression, while those with heightened severity will have a higher chance of being diagnosed with depression. Moving from one OSA severity level to a higher one in the time of 4 years was associated with a 1.8 odds ratio of developing depression during that same period, (Harris et al., 2009). It is possible that depression rates may not be understood because researchers are grouping together all types of OSA, rather than using longitudinal studies to evaluate depressive symptoms as the disorder worsens. Onset of depression may be more progressive; after a certain amount of time with hypoxia during sleep, the possibility of depression increases because of the long-term effects low oxygen has on the body, so this correlation will not be seen in early stages without treatment.

The article by Sanchez et al. also focuses on mood disturbance in those with sleep disorders. This article cites many different studies to understand the correlation of mood disturbance and OSA. One study cited was performed by Barnes et al. Barnes et al. compared use of a CPAP and an oral placebo in patients with mild OSA. They did not find any significant difference between the two groups regarding their quality of life, nor in mood, (Sanchez et al. 2009). This finding carries over from Harris' review of studies. There seems to be no association with true mood disturbance unless evaluated on the basis of physical symptoms. Here, with a placebo present, it was expected that the control subject's quality of life would not increase while the individual wearing the CPAP would. However, there was no difference between the two, and this is another source of evidence that mood and depression are not byproducts of hypoxia, but

something else. Another aspect to consider is the duration of therapy (8 weeks maximum in the Barnes et al. study); the efficacy of the CPAP on mood disturbance should be studied over a longer period of time, (Sanchez et. al, 2009). Many problems with clinical trials for OSA are a result of poor research set up. It is possible that longitudinal studies would be more useful to examine the long-term effects stemming from OSA, however, funding may not be suitable for this type of research. Once again, that could fall on the problem of OSA being underdiagnosed and overlooked in healthcare settings.

Sanchez goes on to review Barnes et al. study. Although Barnes et al. was not able to find a significant correlation between mood disturbance and OSA, differences between the placebo control group and CPAP group was still significant. The comparison of placebo and CPAP conducted by Barnes et al. found a significant improvement after CPAP in verbal fluency and vigilance. Out of both of these, however, the effect of the CPAP was significantly different than the oral placebo only for verbal fluency, (Sanchez et al., 2009). Cognitive function has continuously shown to be improved after CPAP use; however, cognition effects may only include those associated with memory, recall and language rather than emotion.

A study by McCall, Harding, and O'Donovan also attempted to uncover the link between depression and obstructive sleep apnea. Because of the link OSA has with a depression diagnosis, McCall et al. evaluated men and women with moderate to severe OSA to differentiate if the cause was based on the hypoxic nature of this disorder. This study found a difference in gender in evaluation. Higher depressive symptoms were reported in women than in men, (McCall, Harding & O'Donovan, 2007). This is not surprising; in regular rates of depression, women are diagnosed with depression much more frequently than men are. This pattern is seen in OSA, as well, based on this study. McCall et al. also found more of a correlation of sleep

apnea and depression than the past studies discussed. While looking at both men and women, 44.6% had at least mild depressive symptoms. When splitting up the prevalence based on gender, 62% of women exhibited symptoms while only 39% of men did. In the entire sample, 11.6% had at least moderate depressive symptoms, including 28% of women versus 6% of men, (McCall et al., 2007). A significant amount of the subjects studied presented with symptoms; this test also accounted for sleepiness of the patient based on the excessive daytime sleepiness scale (EDS), so it is possible the symptoms the men and women were reporting did not just mirror some of the symptoms coinciding with OSA, but the individuals were also experiencing depressive symptoms rooted in cognition.

Although this study found supportive evidence of a correlation between depression and OSA, there are still limitations and further questions that must be answered with future studies. The findings suggest that depressive symptoms in women with OSA could originate from different factors rather than just OSA severity, and that depressive symptoms need further examination specifically in women with OSA, (McCall et al., 2007). Because women self-report depression much more frequently than men, it may be possible that their evaluation indicating depression is not reliant on symptoms resulting from OSA but rather a predisposition to depression or even a higher willingness of honesty when filling out the questionnaire. A study specifically focused on women diagnosed with OSA and their likelihood of depression should be done in the future to either support or deny the findings of this study. McCall et al. also examines a factor that no previous study has focused on—disruption of sleep architecture. It is possible that hypoxia is not the correlation between depressive symptoms and OSA but instead the disruption of the stages of sleep throughout the night. This breakdown of sleep architecture seems to not only directly affect EDS but also mood disturbance. The study has several

limitations. The sleep-stage information was unavailable for this specific sample, and it is possible that interruption of normal sleep architecture may be another etiological factor in the expression of depressive symptoms, (McCall et al., 2007). Instead of focusing on physiological aspects of polysomnography tests, it may be beneficial to specifically analyze sleep-stage information. If the subjects are losing out of large quantities of deep sleep, light sleep, or REM sleep, the disruption of their normal sleeping pattern could explain mood disturbance throughout subsequent days.

Overall, this study does not have enough evidence to provide a conclusion, but they are able to distinguish the presence of a correlation. Similar to past studies, the etiological cause of this correlation is not certain; McCall, Harding, and Donovan suspect the symptoms may be due to the insomnia and sleep disturbance that present during OSA and not hypoxia. However, more studies need to be evaluated, specifically regarding the association of depressive symptoms and women, to come to a logical conclusion on the possibility of OSA extending into mental health issues.

Macey, Woo, Kumar, Cross and Harper discovered a similar link between depressive symptoms and OSA; they also attributed their findings to other symptoms from OSA rather than hypoxia. A strong link between the Apnea/Hyponea Index (AHI) and accompanying depressive symptoms were not present in newly-diagnosed patients who were not undergoing treatment and who also did not present with another chronic disorder. However, simply the presence of OSA rather than the AHI was associated with abnormally high levels of depressive and anxious symptoms, daytime sleepiness, and poor sleep quality, (Macey, Woo, Kumar, Cross & Harper, 2010). This results once again attributed the symptoms to other factors rather than apneic and



hyponeic events during sleep. The disruption in sleep architecture may be a factor here which also explains the daytime sleepiness that the subjects experienced.

Along with the changes in sleeping patterns, Macey et al. performed neuroimaging of the brain to detect if a structural change was behind the increase of depressive symptoms. The variations in affective and mood symptoms in particular are likely to be associated with variations in a number of symptoms related to neural functioning. In subsets of the present 49 OSA patients, depressive symptoms were correlated with brain structural changes. This was similar for symptoms of anxiety, (Macey et al., 2010). This association aligns with ideas presented to explain the declination of cognitive function. It is suspected that in cognitive impairments resulting from untreated obstructive sleep apnea can also be attributed to structural brain changes. Grey matter is specifically what decreases as a result of untreated OSA. In further studies, it is important to investigate whether a decrease of grey matter can also be attributed to the increase of depressive and anxiety symptoms since grey matter appeared to play such a role in the declination of cognitive symptoms.

Another result from neuroimaging indicated that structural changes are not only due to severity of OSA but other factors as well. Neuroimaging findings show differential effects on brain structure because of diabetes, the sleep state in which apneas occur, and the person's sex, (Macey et al., 2010). Macey et al. did not have data to extend on these findings, so further research is necessary to understand the limiting factors that cause a structural change based on these differences. The structural change that is seen based on sex is especially interesting because of women's likelihood of developing both anxiety and depression over men. This structural change may show the true etiological cause that results in this differentiation; women

may have higher levels of depression not only because they report symptoms more often, but because they are actually predisposed to a change in brain chemistry.

This study concludes in the same fashion that other articles did while focusing on the relationship between OSA and mental illness. Determining the causation of the association of OSA and mental illness is not clear, since several mental illnesses, including depression, are classified by symptoms that include sleep disturbances, (Macey et al., 2010). The true cause of association between the two will need to be evaluated in further studies. It is possible that structural changes of the brain, sleep disturbance, or misunderstanding of symptoms are attributions that have led to the ideas of mental illness' relationship with obstructive sleep apnea.

#### Conclusion and Future Study

Overall, there are many suspected impairments that can arise from untreated obstructive sleep apnea. Declining cognitive abilities, high levels of multimorbidity, and correlations with depressive and other mental illness symptoms are dangers that can occur if treatment recommendations are not meant. All of these effects can likely be attributed to brain structural changes resulting from continuous hypoxia or from the disturbance of sleep architecture. More longitudinal studies and narrowed topics of interests could lead to more accurate results that would impact the way OSA is viewed in today's healthcare setting.

Future study of OSA and the impacts from leaving it untreated are important to cease the major issue of underdiagnosed cases. Quality of life and daytime sleepiness will drastically improve as a result of treatment. Specifically, for declination of cognitive ability, future study should be more longitudinal and organized in two trials; one before treatment and one after continuous treatment. The issue of grey matter loss is extremely consequential, and it is possible that other issues are arising from this brain structural change that are unnoticed today. If this

disorder is truly changing the chemistry of the brain, there are surely more downstream effects that will arise and cause more problems later on for the affected person.

Problems with cognition are also important to study in those with untreated OSA because of the impact on one's quality of life if they begin to experience issues with memory consolidation. There is little to no information on the extent that untreated OSA can have on the brain and memory formation after a lifetime of no treatment. It may start out with minor declines in recall, long-term, and short-term memory, however there are studies being published today that focus on the higher risk those with OSA have in developing dementia or Alzheimer's disease. Both of these would only lead to a worse prognosis for the subject. Issues in memory consolidation are not limited to minor forgetfulness in daily life; these problems can lead to lifelong impairment that result in premature death.

Multimorbidity is another reason to stress the importance of future study of OSA. Obesity is an epidemic in this country; if there is more recognition of problems that are generated from obesity, health may finally become more of a priority for Americans. Those who are diagnosed with OSA as well as other serious disorders are dramatically lessening their quality of life. If this correlation is as strong as research has presented it, then our healthcare system needs to take steps to eliminate symptoms stemming from OSA. Not only should treatment be monitored and encouraged, but diagnoses of OSA should be taken more seriously and screened for more frequently.

Lastly, OSA recognition and study is essential because of obstructive sleep apnea's possible relation to mental illness. Although this may not directly be a result of hypoxia, there still is a correlation that must be studied to understand the effect it is having on people's mental health. If this correlation is as prevalent as many studies have reported it, then not only is the

physical health of these patients at stake, but their mental stability is as well. Mental health is often overlooked in our culture today; maybe if its prevalence is brought to light and studied more, our culture can understand and move forward and diminish suffering.

Overall, obstructive sleep apnea seems to present with many other debilitating factors that are not mechanistically understood. Correlations are shown, but they are often lacking true etiology. It is essential that obstructive sleep apnea becomes more prevalent and tested for; those who are not medically knowledgeable will usually not understand the cause of their daytime sleepiness or irritability, so future study, education, and recognition are critical. Cognitive deficits rooted in attention, long-term and short-term memory, predisposition to multiple chronic disorder, and increased risks of developing mental illness are all observed effects of prolonged hypoxia throughout sleep. With more public education and a push for treatment, it is possible that those suffering with obstructive sleep apnea will be able to improve, and even possibly eliminate these symptoms that plague their daily lives.

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