Obstructive Sleep Apnea and selected comorbidities- literature review of cohort studies

Keywords
sleep- disordered breathing, intermittent hypoxia, AHI, multimorbidity, prevalence

Abstract
This abstract was sent without corrections marked in red— the abstract with these corrections has been attached as a file in the “Explanation letter” section.

Obstructive sleep apnea (OSA) is the most common type of sleep-related breathing disorder, characterized by repeated episodes of upper airway collapse and resulting hypoxia during sleep. Intermittent hypoxemia may exert a multisystemic impact and modulate the course of comorbidities. Pathophysiological mechanisms such as oxidative stress, inflammation, and endothelial dysfunction contribute to adverse health outcomes, including cardiovascular disease, cerebrovascular complications, metabolic disorders, cancer, neurodegenerative conditions, or behavioral abnormalities. Treatment of OSA may mitigate the progression of comorbidities and reduce the associated social and economic burden. This literature review aims to explore the relationships between OSA and selected co-morbid diseases, including COPD , stroke, diabetes, cancer and hypertension, utilizing the cohort studies in the literature.

Introduction

Obstructive sleep apnea (OSA) is the most common type of sleep-related breathing disorder, characterized by repeated episodes of upper airway collapse. The respiratory events, including ~~such as~~ hypopnea and apnea result in ~~cause~~ intermittent hypoxemia and~~,~~ hypercapnia, thereby ~~and~~ contributinge to sleep fragmentation. [1, 2, 3, 4, 5, 6] Due to pressure fluctuations inside the thorax, the organs located there are particularly prone to dysfunction. [2] From a pathophysiological standpoint ~~physiopathological perspective~~, the hallmark ~~main~~ features of OSA include oxidative stress, low-grade inflammation and endothelial dysfunction. [5, 7] Clinically, patients often present with loud snoring, recurrent awakenings during sleep, morning headaches, excessive daytime sleepiness and cognitive impairment. [3, 4, 8] Daytime sleepiness leads to reduced quality of life, increased risk of motor vehicle accidents, workplace accidents. [1, 3, 4, 9] The gold standard in OSA diagnostics is polysomnography (PSG); however, due to the limited availability, cost, or patients preference, often pneumograms or home sleep studies are utilized. [10] The severity of OSA is determined by the apnea-hypopnea index (AHI), which indicates the number of apneas and hypopneas per hour of sleep. OSA is defined as mild with an AHI of 5 to <15, moderate with values of 15 to <30, and AHI of 30 or more indicates severe disease. Treatment for OSA includes lifestyle modifications, positive airway pressure (PAP) therapy, oral appliances, and surgical interventions in selected patients. Surgical management options ~~interventions~~ include ablative and functional procedures targeting the upper airway or stimulation of the hypoglossal nerve ~~surgeries in the upper airway or hypoglossal nerve stimulation~~. [11] The chronic effects of untreated OSA exert a multisystemic impact, ~~affect virtually every organ,~~ being particularly associated with cardiovascular disease (CVD), cerebrovascular complications ~~sequelae~~, metabolic disorders, cancer, neurodegenerative conditions ~~diseases~~ or behavioral abnormalities. [2, 3, 4, 5, 8]

Chronic Obstructive Pulmonary Disease ~~(COPD)~~

Research on lung disease and OSA raises the topic of overlap syndrome (OS). This condition, first ~~It is a condition~~ described by David Fenley in 1985, refers to the coexistence of ~~where~~ chronic obstructive pulmonary disease (COPD) and OSA within the same individual ~~occur at the same time~~. [12, 13] Both diseases are ~~quite~~ common respiratory disorders ~~of the respiratory system~~, where in COPD airflow limitation occurs ~~we deal with limited airflow in~~ the lower respiratory tract, while in OSA, obstruction arises in the upper respiratory tract. [7,12, 14] In COPD, the reduction in airflow is permanent, and is primarily caused by smoking or exposure to environmental pollutants~~tion~~. [13] The disease represents a ~~is~~ progressive ~~and~~ inflammatory disorder that manifests ~~presenting~~ clinically with dyspnea, chronic cough, and sputum production ~~expectoration~~. [7, 13] It is important to note that patients with COPD often have other chronic diseases, which are ~~is~~ associated with increased mortality. [12, 14] The EpiChron study showed that multimorbidity is more prevalent in patients with chronic obstructive airway diseases compared to ~~than in~~ the general population. [12] The co-existence~~occurrence~~ of COPD and OSA worsens patients prognosis, reduces the quality of life and increases the mortality rate ~~probability of death~~. [7, 15, 16] Furthermore, ~~Overlap syndrome~~ OS is associated with a higher incidence of cardiovascular and metabolic diseases, as well as a~~n~~ greater frequency of ~~increased~~ COPD exacerbations, increased ~~more frequent~~ hospitalizations and elevated ~~higher~~ healthcare costs. [14, 17] Although ~~It is known that~~ both conditions share overlapping pathophysiological mechanisms, it remains unclear ~~may influence each other based on pathophysiology, but it is not entirely clear~~ whether COPD predisposes individuals to ~~the more frequent occurrence of~~ OSA or ~~and~~ vice versa. [7] However, it is increasingly believed that COPD may predispose to OSA. [13]

The “Obstructive Lung Disease and Obstructive Sleep Apnea” study, with the cohort consisted mainly of men (military veteran population) reported ~~found~~ ~~an overlap syndrome~~ OS incidence of 5%. The co-existence~~occurrence~~ of OSA with asthma or COPD, was identified ~~found~~ in 8% of patients in the cohort. The term “alternative overlap syndrome” is used in the literature to define the coexistence of asthma and OSA. [15] ~~The prevalence of OSA increased with increasing severity of COPD.~~ The prevalence of OSA among COPD patients was similar in studies by Tianfeng Peng et al. and Jose M. Marin et al., who used polygraphy as a diagnostic tool for OSA, reporting rates of 29.1% and 32%, respectively. [17, 18] According to studies utilizing PSG, revealed even higher prevalence rates- 44.19% (Khaled Alkhayat et al.) and 50% (Osama Ibrahim Mohammad et al.) (Table I). [16, 19] The prevalence of OSA increased with increasing severity of COPD. It should be highlighted ~~noted~~ that the administration of inhaled corticosteroids may contribute to the development of OSA due to steroid- induced upper airway ~~the onset of upper respiratory tract~~ myopathy or extrapulmonary inflammation. [16]

Studies have demonstrated ~~It is known from studies~~ that the incidence of ~~overlap syndrome~~ OS increases with age. [20] Identification of patients with OSA remains ~~appears to be~~ a barrier to ~~making a~~ diagnosings ~~of overlap syndrome~~ OS, primarily due to the overnight and expensive ~~PGS~~ PSG testing. [7] In 2023, Tianfeng Peng et al. ~~Tianfeng Peng et al. in a 2023~~ developed a nomogram that enables rapid OSA diagnosis among ~~in~~ COPD patients in outpatient settings, incorporating independent risk factors, like age, neck circumference (NC), ~~type 2 diabetes~~ type 2 diabetes mellitus (T2DM), the modified Medical Research Council~~'s modified~~ questionnaire (mMRC), the Sleep Apnea Clinical Score Questionnaire (SACS) and C-reactive protein (CRP). [17]

Patients with overlap syndrome have higher body mass index (BMI) compared to those with COPD or OSA alone. [14, 17, 19] Bianca Stepan el al. indicated that ~~overlap syndrome~~ OS patients are older ~~patients are older~~, more obese, have ~~a~~ higher NC and waist-to-hip ratio

(WHR) compared to isolated OSA ones. Considering nocturnal oxygen saturation, worse indices ~~rates~~ are observed in ~~overlap syndrome~~ OS than in COPD or OSA alone. [14, 19] ~~Alkhayat et al.~~ Khaled Alkhayat et al. observed ~~noted~~ that ~~overlap syndrome~~ OS patients exhibit higher mean PaCO2 levels resulting from ~~due to~~ hypoventilation during sleep, ~~which may~~ contributeing to chronic hypercapnia in COPD. Polysomnographic parameters such as AHI, respiratory disturbance index ~~(RDI)~~ and oxygen desaturation index ~~(ODI)~~ were significantly higher in the ~~overlap syndrome~~ OS group than in the COPD group. Additionally, ~~in the overlap syndrome~~ OS group showed higher scored on the Epworth Sleepiness Scale ~~(ESS)~~ and Pittsburgh Sleep Quality Questionnaire ~~(PSQI)~~ ~~scores were observed~~. [19] The results forming the basis for ~~of the studies based on which~~ the nomogram for rapid ~~diagnosis of~~ OSA diagnosis in COPD ~~was constructed~~ indicate that, compared to COPD- only patients, those with ~~overlap syndrome~~ OS exhibit ~~versus COPD patients have~~ higher BMI, NC~~,~~ and SACS scores, poorer ~~worse~~ sleep quality and a greater burden of comorbidities ~~more underlying diseases~~. In addition, they have fewer COPD exacerbations in the previous year, lower CRP, mMRC and have better airway obstruction. [17]

Kimberly L. Sterling et al. showed~~,~~ that PAP therapy was associated with reduced hospitalizations, emergency room visits, and lower healthcare costs in patients with OS. The results of the study also indicated that PAP treatment reduced severe exacerbations in COPD, underscoring its therapeutic relevance for this patient group ~~which is an important component of treatment for this condition.~~ [21] In the 10-year survival analysis, a significant association was confirmed between lower mortality and initiation ~~of treatment~~ or better adherence to PAP therapy. In this study, the highest mortality was noted in the coexistence of asthma, COPD and OSA. [15]

Stroke

OSA is a risk factor for ischemic stroke. [22] Among ~~In~~ patients who have experienced ~~undergone~~ a stroke, this breathing disorder is relatively prevalent yet frequently underdiagnosed ~~quite common but not sufficiently recognized~~. [23] OSA is known to be associated with recurrent ischemic stroke. [23, 24] The risk of stroke increases proportionally with the severity of OSA. [25, 26] In the study by Tuuli-Maria Haula et al., the prevalence of mild OSA in the ischemic ~~group of~~ patients ~~with ischemic stroke~~ was 20%, while ~~and~~ moderate to severe OSA was 39%. [27] Another study by the same author showed that the number of ~~cases of~~ moderate to severe OSA cases was higher in patients who survived a wake-up stroke ~~(WUS)~~ compared to those who did not. [22] A study ~~of the~~ assessing OSA prevalence ~~of OSA~~ in patients with acute ischemic stroke in a Taiwanese population showed that the disease was mild in 21.4%, moderate in 25.2%, and severe in 44.7% of patients. Overall, 91.2% of study participants were diagnosed with OSA during the acute phase of ischemic stroke. Based on these ~~the~~ results, it was suggested that elderly people, especially those over 65 years of age, show a significantly higher probability of developing moderate to severe OSA compared to younger people after stroke. This observation may be explained by the increased collapsibility of the upper airway in older populations. ~~The pathophysiological explanation for this is increased airway collapsibility in older people.~~ [25] Sex- based differences in clinical characteristics among stroke patients with comorbid OSA have also been documented. ~~Differences between gender and clinical characteristics for stroke and comorbid OSA have been documented.~~ In a retrospective study ~~conducted by Camron Edrissi et al.~~of patients with OSA and acute ischemic stroke ~~(AIS)~~, conducted by Camron Edrissi et al., it was observed that women were more likely to have peripheral vascular disease ~~(PVD)~~, depression and to have higher high- density lipoprotein ~~HDL~~-cholesterol levels and BMI than men. [26]

It has been shown that the presence of OSA in post-stroke patients is associated with a numerous adverse health outcomes ~~number of negative health consequences~~. The presence of moderate and severe OSA in stroke survivors can exacerbate neurological ~~their~~ disability through ~~due to~~ recurrent hypoxemia, fluctuations in blood pressure, increased cardiac arrhythmias and cerebral ~~brain~~ hypoperfusion. Such patients are at risk of prolonged rehabilitation associated with the adverse ~~negative~~ effects of sleep-disordered breathing (SDB) including sleep-wake rhythm disturbances as well as cognitive and mood impairment~~.~~ which collectively contributes to extended hospitalization ~~This contributes to prolonged hospitalization~~. [22, 27] Therefore, timely OSA diagnosis in post- stroke patients is emphasized to facilitate effective treatment and improve recovery outcomes. ~~The need for OSA diagnosis in the group of post-stroke patients is emphasized to enable effective treatment and prevent a worse course of convalescence.~~ [27] The clinical phenotype of OSA in stroke patients is heterogeneous, warranting an individualized therapeutic approach ~~diverse and therefore an individual approach to these patients is suggested~~. [23] The American Heart Association/American Stroke Association provides a class 2a recommendations ~~that~~ stating: "In patients with an ischemic stroke or transient ischemic attack (TIA) and OSA, treatment with positive airway pressure (e.g. CPAP) can be beneficial for improved sleep apnea, BP, sleepiness, and other apnea-related outcomes." In addition, the guidelines underscore the potential value of OSA diagnostic evaluation in patients with ischemic stroke or TIA ~~include information on the possibility of using diagnostics for OSA in patients with ischemic stroke or TIA~~. [28]

Diabetes

Sleep-disordered breathing ~~(SDB)~~ is associated with glucose intolerance (GIT) and insulin resistance (IR). [29, 30] Glucose metabolism disorders are known to be common in patients with OSA. [31] These chronic diseases, ~~which are~~ OSA and ~~type 2 diabetes mellitus~~ T2DM,

share common risk factors including age, male gender, high BMI and genetic predisposition. [30,31] Both conditions synergistically increase the likelihood of cardiovascular complications. [30] The development of complications is caused by long-term hyperglycemia, systemic inflammation and oxidative stress, which contribute to accelerated atherosclerosis and endothelial dysfunction. [30,32–34] Key pathophysiological mechanisms linking OSA to ~~related to~~ glucose metabolism disorders ~~in OSA~~ are hypoxemia and sleep fragmentation [35], which result in increased levels of proinflammatory cytokines e.g. interleukin-6 (IL- 6) and tumor necrosis factor ~~(TNF)~~, activation of the sympathetic nervous system and alteration of the hypothalamic-pituitary axis. Sympathetic overactivity promotes ~~increases~~ hepatic glycogenolysis and gluconeogenesis. While leptin secretion ~~There~~ is decreased ~~secretion~~ or resistance ~~to leptin~~, and inflammatory adipocytokines are released. The degree of nocturnal hypoxia has been shown to correlate ~~be associated~~ with the severity of ~~glucose intolerance (GIT)~~ GIT and ~~insulin resistance~~ IR. Changes in glucose homeostasis during intermittent hypoxia have been demonstrated ~~documented~~ in animal models and human studies. [30,31,36,37] T2DM, by promoting peripheral neuropathy and impaired neural control of ventilation and the upper respiratory tract, potentially contributes to the occurrence of OSA or to its aggravation. [33] Conversly ~~On the other hand~~, sleep structure disturbances ~~disorders~~ in OSA may predispose to ~~insulin resistance~~ IR (Figure 1). It has been shown that inhibition of slow-wave sleep leads to reduce ~~insulin resistance~~ IR. [31]

Obesity may occur in both OSA and diabetes. [32] OSA risk factors such as neck fat accumulation and high CRP and IL-6 levels are associated with visceral obesity, which is strongly linked to ~~known to affect~~ ~~insulin resistance~~ IR. [31] Although obesity is a common factor in both OSA and T2DM, ~~insulin resistance~~ IR or GIT may also ~~can~~ develop in non-obese OSA patients ~~patients with OSA even in the absence of obesity~~. [31,34] Metrics such as weight, BMI, hip circumference and waist circumference have been shown ~~were observed~~ to

increase with increasing AHI. [30] It has been suggested that ~~the waist-to-hip ratio~~ WHR may more accurately represent the impact of obesity on SDB than BMI ~~better than BMI represents the effect of obesity on breathing disorders during sleep~~. [37] Studies indicate ~~It has been reported~~ that overweight and obese women over 70 years with mild OSA and T2DM are at significantly increased ~~face a significant~~ risk of major adverse cardiovascular events. [33]

A study by Marie Bruyneel et al. found that 66% of overweight and obese patients with moderate to severe OSA had diabetes or ~~glucose intolerance~~ GIT, with 28% being newly diagnosed. The authors ~~This study~~ concluded that ~~insulin resistance~~ IR is positively correlated ~~associated~~ with the severity of OSA, however, this relationship was not confirmed for overt diabetes or GIT~~. Such a relationship has not been confirmed in relation to diabetes and glucose intolerance.~~ To determine ~~insulin resistance~~ IR, the homeostatic model assessment index was used, with higher values ~~of which were~~ observed in patients with more severe OSA. [31] More frequent ~~insulin resistance~~ IR with AHI> 30 was confirmed in the PROOF study. It showed an association between triglyceride concentrations and fasting glucose levels ~~glycemia~~, and OSA severity. Patients with severe OSA exhibited both higher IR and greater metabolic derangements than those without apnea ~~which were significantly higher in patients with severe OSA than in those without apnea, and a higher insulin resistance rate~~. After 7 years of follow-up, a low incidence of T2DM was found in patients with severe, asymptomatic and untreated OSA. Studies have further shown that newly diagnosed asymptomatic OSA constitutes ~~is~~ a risk factor for ~~insulin resistance~~ IR, which ~~was~~ increased by 36% in ~~with~~ moderate OSA, ~~while severe OSA increased the risk of insulin resistance IR~~ and by 2.2 – fold ~~times~~ in severe OSA after 7 years. [30]

An analysis of the Determining Risk of Vascular Events by Apnea Monitoring study, which attempted to identify polysomnographic predictors associated with diabetes and prediabetes, did not reveal ~~find~~ a significant correlation ~~association~~ between these conditions

and AHI. However, it was ~~has been~~ suggested that hypoxia may better reflect the state of carbohydrate metabolism in patients with OSA than AHI. [37] Based on the SantOSA cohort study, hypoxemia was considered a superior prognostic marker for mortality in OSA compared to AHI ~~better marker than AHI considering mortality in patients with OSA~~. [38] In the Determining Risk of Vascular Events by Apnea Monitoring study, a 9% increase in the risk of diabetes was observed for each 10% increase in total sleep time spent with ~~at~~ oxygen saturation < 90%. The same risk was noted for every 10 additional respiratory arousals ~~events of increase in the number of respiratory awakenings~~ per hour. Conversely, ~~H~~higher mean nocturnal oxygen saturation resulted in a lower incidence of diabetes and prediabetes. [37] Polysomnographic phenotypes characterized by periodic limb movements, hypopnea and hypoxia have been linked to an elevated risk of T2DM relative to non-OSA individuals ~~Based on polysomnography, phenotypes with periodic limb movements during sleep as well as hypopnea and hypoxia were indicated, which show an increased risk of T2DM compared to people without OSA~~. [35]

Ethnic variations in OSA phenotypes have also been described ~~Differences in OSA phenotypes have been investigated in relation to ethnicity~~. For example, Chinese patients are more likely to experience snoring, while African and Hispanic patients are more likely to experience excessive daytime sleepiness. In a comparison of Caucasians and Africans with OSA, it was found that diabetes is more common in the African race. At the same time, African patients were characterized by a healthier lifestyle, lower BMI, fewer comorbidities and less dyslipidemia. Sleep studies showed ~~that they had~~ a higher AHI in rapid eye movement sleep and a lower periodic leg movements index compared to Caucasians. In the clinical picture of the African population, nighttime choking, which may be related to the features of facial anatomy and cognitive impairment were more common. [29]

The quality of life of diabetic patients ~~with diabetes~~ is reduced mainly due to microvascular complications and ~~cardiovascular disease~~ CVD. Patients with diabetes who develop OSA constitute a high-risk group. A population-based cohort study showed that patients with T2DM who developed OSA had a more than a ~~>~~50% increase in the risk of combined cardiovascular disease (CVD), ischemic heart disease ~~(IHD)~~, heart failure (HF) and stroke/TIA and a 53% higher risk of developing atrial fibrillation ~~(AF)~~ compared to T2DM without OSA. Additionally~~, In addition~~, the increased risks were noted ~~: 32%~~ for peripheral neuropathy ~~(PN)~~ (32%), ~~42% for~~ diabetes-related foot disease ~~(DFD)~~ (42%), and ~~18% for~~ chronic kidney disease ~~(CKD)~~ in stages 3 to 5 (18%). All- cause mortality ~~Mortality (from all causes)~~ was 24% higher among participants with both T2DM and OSA compared to those with diabetes alone ~~in the group of participants with T2DM and OSA showed a 24% increase relative to participants with T2DM without OSA~~. [34] A study by Qian Zhang et. al. confirmed that depending on the presence of diabetes, the association between OSA and mortality differed. [32] In the study by Gonzalo Labarca et al., after 5 years of follow-up, an independent risk of cardiovascular mortality was found in the co-occurrence of OSA and DM compared to the presence of both diseases alone. [38]

To improve ~~facilitate~~ the diagnosis of OSA in diabetic patients, a nomogram was developed incorporating ~~created that took into account~~ WHR, smoking status, BMI, serum uric acid ~~(UA)~~, homeostasis model assessment insulin resistance index ~~HOMA2-IR~~ and history of fatty liver. It allows ~~for~~ the early ~~initial~~ identification of OSA high- risk patients ~~at risk of OSA~~ before deciding which ones should be referred for ~~PGS~~ PSG- testing, which remains resource- limited ~~study with limited access~~. [36] According to a small-scale study on ~~a small sample of~~ patients with moderate to severe OSA, only short-term CPAP treatment ~~was only able to~~ improved insulin sensitivity in patients without obesity. [32]

Cancer

Cancer is the second leading cause of death in the United States. [39] Global statistics for 2022 documented 20 million new cancer cases and 9.7 million cancer-related deaths. The most frequently diagnosed cancer was lung cancer (12.4% of all cases), followed by breast cancer in women (11.6%), colon cancer (9.6%), prostate cancer (7.3%) and stomach cancer (4.9%). The leading cause of death was also lung cancer (18.7% of all cancer deaths), followed by colon cancer (9.3%), liver cancer (7.8%), breast cancer in women (6.9%) and stomach cancer (6.8%). [40] Overall, global cancer mortality was decreasing until 2021 due ~~thanks~~ to a reduction in smoking, improved early diagnostics capabilities, and advancements in therapeutic modalities ~~of certain cancers that allow them to be detected at an earlier stage, and the development of therapeutic options~~. [39,41] Nevertheless, an increase in the incidence of 6 out of 10 most commonly diagnosed cancers was reported. [39] Additionally, the COVID-19 ~~coronavirus~~ pandemic exacerbated difficulties in access to health care facilities, which resulted in the ~~a~~ delay of ~~in the~~ diagnosis and treatment of cancer patients [39]

Tissue- level hypoxia in OSA patients ~~with OSA~~ creates conditions of susceptibility to the development of malignancies. [42] Studies on melanoma in mice have provided information that intermittent hypoxia can influence cancer growth in vitro and promote metastasis. [43,44] Oncogenic processes in OSA are associated with oxidative stress, inflammatory reactions, angiogenesis, as well as increased sympathetic activity and impaired immune response. [44–50] Among the key molecular mediators of these processes, hypoxia-inducible factor-1 plays a central role in orchestrating cellular responses to hypoxic stress ~~When considering the pathophysiological mechanisms that may promote cancer growth in OSA, attention is drawn to hypoxia-inducible factor-1 (HIF-1), which plays an important role in hypoxia-related reactions~~. [42–44] Exposure to intermittent hypoxia and/or sleep fragmentation may differentially affect cancer cells ~~differently~~, depending on the type of malignancy. [45] Therefore, OSA may

have a prognostic impact or cause an increased risk of developing only certain types of cancer. [42]

Ross J. Marriott et al. were the first to report an independent association between nocturnal hypoxemia and cancer prevalence. In this large-sample study (>241,439 patient-years) using PSG data, nocturnal hypoxemia~~,~~ rather than ~~not~~ AHI~~,~~ was ~~found to be~~ independently positively correlated ~~associated~~ with cancer prevalence. The observed associations between OSA severity (based on AHI and nocturnal hypoxemia) and cancer incidence were explained by the influence of cancer development factors such as older age, gender, smoking and BMI. However, after ~~an~~ 11.2- year follow-up period, there was no independent association between OSA severity and cancer incidence. [43] In contrast, Tetyana Kendzerska et al. demonstrated that both OSA severity and nocturnal hypoxemia were independently associated with cancer incidence. Patients with severe OSA had a 15% higher ~~increased~~ risk of cancer incidence compared to those without OSA, while severe hypoxemia [defined as >30% of sleep spent with oxygen saturation <90% (T90)] was associated with a 30% increased risk. [45] Similar findings were reported by Hailin Xiong et al., who observed ~~also noted~~ a positive correlation between higher AHI values and cancer risk ~~higher risk of cancer with increasing AHI~~, particularly among patients with OSA under 65 years old. [44] In the study by Grégoire Justeau et al., nocturnal hypoxemia measured by T90 was associated with the occurrence of lung and breast cancer. [48] Tetyana Kendzerska et al. reported the association of periodic limb movements during sleep with cancer. Furthermore, ~~This study also showed that~~ reduced sleep quality measured by a.o. reduced rapid eye movement sleep and increased wakefulness after sleep onset ~~(WASO)~~ were associated with an increased risk of malignant tumors. [51]

A multicenter retrospective cohort study identified nocturnal hypoxemia and sleep fragmentation as markers of OSA severity significantly associated with cancer-related

mortality. To determine hypoxemia and sleep fragmentation, the percentage of T90, mean oxygen saturation ~~SaO2~~ and percentage of stage 1 sleep were measured. However, AHI was not linked to cancer mortality, which is consistent with other studies (Hailin Xiong et.al.). [44,46] According to this study, T90 was also not significantly associated with cancer mortality, while OSA increased all-cause mortality. [44]

Not all cohort studies have confirmed that OSA increases cancer incidence or mortality. [50] Nevertheless, mounting evidence supports an OSA- related risk in specific malignancies, particularly lung and colorectal cancer (CRC)- both characterized by high mortality rates ~~The literature does, however, provide evidence of OSA association with specific types of cancer, including lung cancer and colorectal cancer (CRC), both of which have high mortality rates~~. [45] A study on the Korean population identified OSA as an independent risk factor for lung cancer across both sexes and age groups, with association being most pronounced in women and older adults ~~proved an independent association between OSA and increased risk of lung cancer. It was present in both genders, across age groups and was more pronounced in women and the elderly~~. [47] Similarly, a ~~A~~ retrospective cohort study found an increased risk of CRC associated with OSA. [42]

Regarding CPAP adherence in patients with OSA, studies found no clear evidence linking good adherence (defined as ⩾4 h per night) to reduced incidence of cancer. For lung cancer, a near- significant trend toward risk reduction was observed, though not statistically conclusive ~~association was near statistical significance but not conclusive~~. [49]

Hypertension

The physiological changes induced by OSA predispose individuals to the development of CVD, including hypertension, stroke, arrhythmia, coronary artery disease (CAD), and HF. [52] OSA is considered as a cause of secondary hypertension in 30% to 50% of patients with

hypertension. [53,54] Additionally, OSA is prevalent in a significant proportion of patients with resistant hypertension. [55,56] In ~~case of~~ OSA-related hypertension, masked hypertension and elevated nocturnal blood pressure are frequently observed ~~common~~. [56] The major ~~main~~ risk factors for OSA, such as age, male gender and higher BMI are also strongly associated with hypertension. [55] When OSA and hypertension coexist, the risk of cardiovascular events increases. [53] Moreover ~~Furthermore~~, short sleep duration (<6 hours) alone has been shown to heighten the risk of developing hypertension and CVD. [56]

The UROSAH study demonstrated that in patients with hypertension and OSA, a higher BMI is a risk factor for cardiovascular events. A more pronounced ~~stronger~~ positive association between obesity and cardiovascular events has been observed in younger individuals. [53] An additional publication based on the UROSAH cohort established a significant relationship ~~association~~ between the cardiometabolic index and the risk of CVD. The cardiometabolic index, developed in 2015, is a marker used to assess the risk of metabolic diseases such as diabetes, hypertension, left ventricular hypertrophy or stroke. It is calculated using the waist-to-height ratio and triglyceride/high-density lipoprotein cholesterol ~~(TG/HDL-C)~~ ratio. The "obesity paradox" proposed in the literature, suggest that BMI alone may inadequately reflect metabolic risk, as visceral adipose tissue (VAT) is more pathophysiologically relevant indicator ~~which diminishes the significance of, e.g. BMI as a real indicator of metabolic state, visceral adipose tissue (VAT) seems to better show the disorders occurring in obesity~~. VAT is a metabolically active tissue, it exhibits ~~that shows a~~ high lipolytic effect~~,~~ contributing to endothelial dysfunction, local inflammation and prothrombotic states ~~which brings with it several consequences in the form of, a.o., endothelial dysfunction or induction of local inflammation~~. It is responsible for atherosclerotic complications, contributes to thrombosis and increases risk of ~~insulin resistance~~ IR and hyperglycemia. VAT-related disorders create conditions favorable for the

development of T2DM, metabolic syndrome, dyslipidemia and hypertension. It is suggested that cardiometabolic index reflects the distribution of VAT, the measurement of which requires the use of diagnostic imaging techniques. Thus, cardiometabolic index may become a screening tool as a predictor of CVD. [57]

A multicenter study in China identified age, AHI, and hemoglobin (Hb) as independent risk factors for hypertension in the elderly. ~~Glucose concentration appeared to be a risk factor in men.~~ Higher AHI or Hb levels correlated with higher ~~greater~~ hypertension severity. Intermittent nocturnal hypoxemia, detected by carotid artery chemoreceptors, triggers sympathetic nervous system activation during wakefulness, leading to sustained elevations in blood pressure ~~Due to intermittent nocturnal hypoxemia, which is detected by carotid artery chemoreceptors, the sympathetic nervous system is activated during the day, leading to an increase in blood pressure~~. Another potential mechanism contributing to hypertension in OSA might be an elevated circulating red blood cell count and hemoglobin level, as a result of erythropoietin stimulation by hypoxia, which contributes to increased peripheral vascular resistance ~~Another mechanism resulting in hypertension in OSA may be increased circulating red blood cell (RBC) count and Hb levels due to erythropoietin stimulated by hypoxia, which contributes to increased peripheral vascular resistance~~ (Figure 2). [54]

Depending on the polysomnographic phenotype of OSA, hypertension occurs with different frequency. The Sunmin Park et al. study distinguished three subtypes: ~~between groups with~~ predominant apnea, predominant hypopnea, and predominant respiratory effort-related arousal ~~(RERA)~~. A higher prevalence of hypertension was noted in the groups with predominant apnea and predominant hyponea. Those ~~Patients~~ with predominant hypopnea also had significantly higher rates of hyperlipidemia, CAD and HF compared to the other groups. [58] Additionally, respiratory events during rapid eye movement sleep are positively

correlated ~~significantly associated~~ with morning hypertension. In this phase of sleep, an increased severity of OSA can be explained by the reduced activity of the genioglossus muscle, promoting increased collapsibility of the upper respiratory tract. Respiratory events in the rapid eye movement phase predispose to a higher risk of CVD than those occurring in the non-rapid eye movement phase. A study conducted by Catherine Falla et al. revealed a significant association between respiratory events during rapid eye movement sleep and morning hypertensive blood pressure values. [52]

~~Positive airway pressure~~ PAP therapy, the gold standard treatment for OSA, has demonstrated efficacy ~~may be useful~~ in normalizing blood pressure, particularly ~~especially~~ in the patients with ~~case of~~ resistant hypertension. [59] In this group of patients ~~with resistant hypertension~~, the blood pressure- lowering effect of CPAP therapy was observed to be twice as strong at night as during the day. [56] The beneficial impact of PAP treatment is associated with a reductions in inflammatory mediators such as CRP and IL-6 and oxidative stress markers including nicotinamide adenine dinucleotide phosphate oxidase, malonaldehyde. [60]

PAP therapy appears to have a stronger effect on reducing diastolic blood pressure. A prospective ~~study with a~~ 5-year follow-up study demonstrated that long-term PAP therapy in patients with OSA ~~led to~~ improved blood pressure control. The rate of adherence to PAP therapy was 39.58%. The main barriers to adherence included economic burden and technical difficulties related to device usage, such as mask leakage ~~The primary barriers to adherence included therapy costs and challenges with device usage, such as mask leakage~~. [59] According to the study by Yi-Chih Lin et al., in ~~the~~ case of poor CPAP adherence in OSA patients ~~patients with OSA~~, uvulopalatopharyngoplasty (UPPP) may serve ~~be~~ a beneficial alternative, however, surgical intervention ~~but the surgery~~ was less effective in preventing hypertension onset ~~the development of hypertension~~. Nevertheless ~~However~~, ~~it should be emphasized, that~~ UPPP has been shown to reduce ~~the occurrence of~~ hypertension occurrence in ~~the group of~~

~~patients affected by~~ OSA~~-~~ affected individuals. [55] ~~In the group of patients with resistant hypertension, the blood pressure- lowering effect of CPAP therapy was observed to be twice as strong at night as during the day. [56] -~~

Conclusions

The described associations between ~~of~~ OSA and ~~with~~ selected comorbidities ~~diseases~~ indicate that OSA should not be regarded as an isolated disorder ~~is not a separate condition,~~ but rather due to its shared pathophysiological mechanisms it ~~connections~~ coexists with and modulates ~~affect~~ the course of diseases such as COPD, stroke, diabetes, cancer and hypertension. This underscores the importance of an interdisciplinary approach to managing OSA, which clinicians should prioritize. In many clinical contexts ~~cases~~, the effective treatment of OSA may ~~can~~ complement the management of underlying chronic conditions ~~diseases~~, thereby mitigating their progression and reducing ~~helping to alleviate their impact while reducing~~ the associated social and economic burden.

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Obstructive sleep apnea

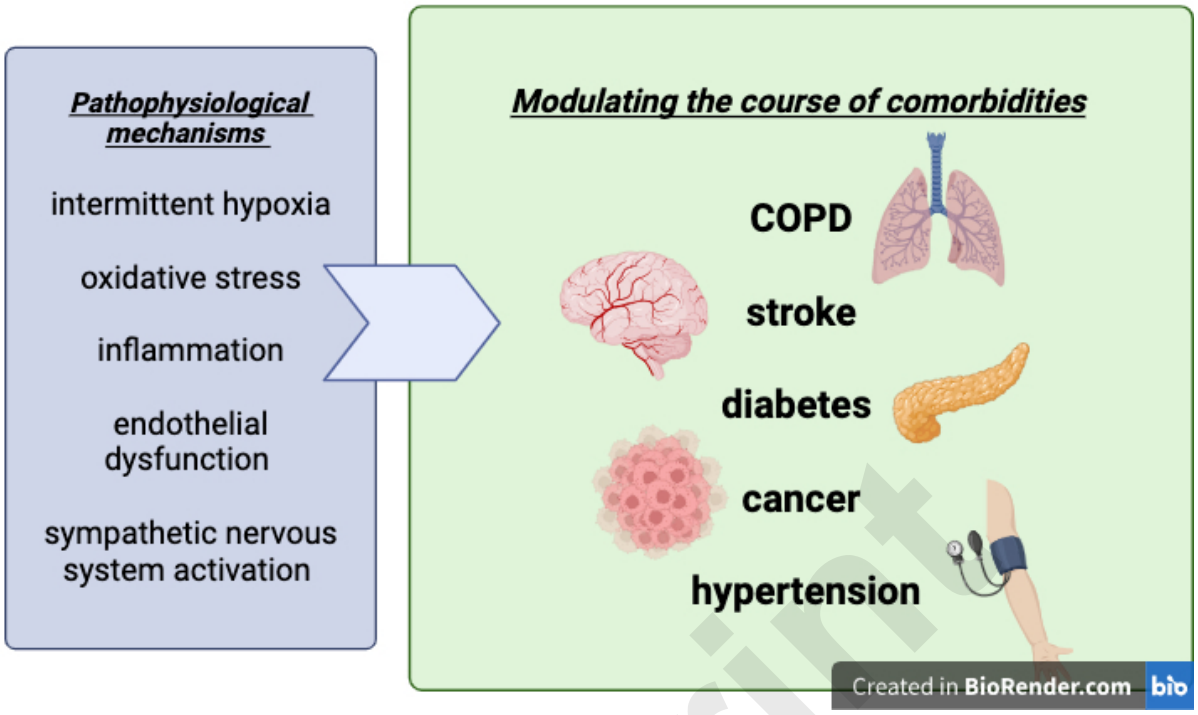
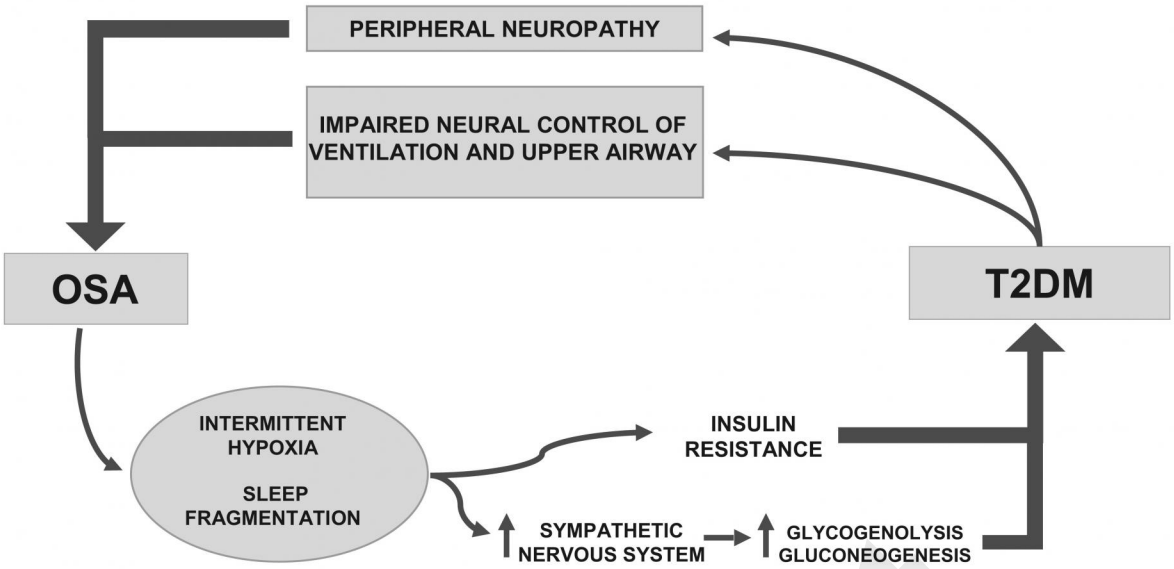


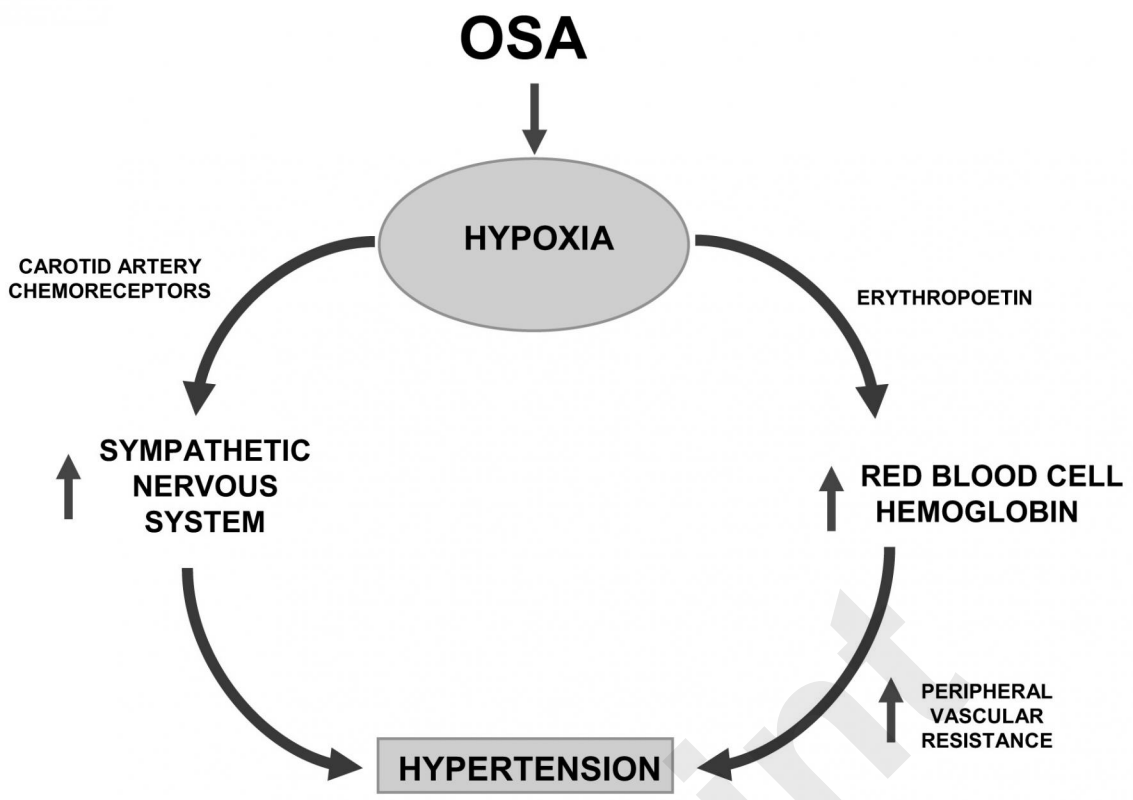
Table I. Prevalence of OS

Authors, year of publication	Population description	Sample size	Type of study	Sleep study	Findings
Ioachimescu et al 2020	veterans (Atlanta Veterans Affairs) with an acute hospitalization and in whom asthma, COPD, OSA, overlapping conditions, or none of these disorders at baseline had been diagnosed	4980	longitudinal, point-of-care	PSG	5%- patients with COPD and OSA (no asthma), 8%- patients with OSA plus either asthma or COPD
Mohammad et al 2021	patients with stable COPD	100	prospective study	PSG	50% patients with COPD had OSA
Alkhayat et al 2021	patients with COPD free from exacerbation for at least 4 weeks before the study	86	prospective study	PSG	44.19% patients with COPD had OSA
Peng et al 2023	patients with COPD with a recent deterioration of cough, expectoration of phlegm, and shortness of breath	330	retrospective study	PG	29.1% patients with COPD had OSA
Marin et al 2025	patients with COPD clinically stable patients with COPD receiving therapy according to international guidelines at enrollment	428	multicenter, prospective study	PG	32% patients with COPD had OSA

COPD- chronic obstructive pulmonary disease, OSA- obstructive sleep apnea, OS- overlap syndrome, PG- polygraphy, PSG- polysomnography



Associations between OSA and T2DM



Mechanisms of hypertension development in OSA