

# Sleep Apnea

Subjects: Respiratory System

Contributor: Stavroula A. Paschou, Evanthia Bletsas, Katerina Saltiki, Paraskevi Kazakou, Kanella Kantreva, Paraskevi Katsaounou, Nikolettta Rovina, Georgia Trakada, Petros Bakakos, Charalambos V. Vlachopoulos, Theodora Psaltopoulou

Obstructive sleep apnea (OSA) is a common but largely undiagnosed clinical condition, which is turning into a serious public health issue. Of note is that its prevalence is gradually increasing in parallel with the obesity and type 2 diabetes mellitus (T2DM) epidemics.

Keywords: obstructive sleep apnea ; prediabetes ; diabetes ; cardiovascular disease

---

## 1. OSA: Prevalence, Diagnosis, Pathophysiology, and Treatment

Obstructive sleep apnea (OSA) is a common but largely undiagnosed clinical condition, which is turning into a serious public health issue. It affects almost 1 billion people worldwide, and more than 30 million people are underdiagnosed in Europe <sup>[1][2]</sup>. Of note is that its prevalence is gradually increasing in parallel with the obesity and diabetes epidemics <sup>[3]</sup>. OSA is characterized by autonomous nervous system disturbances and the recurrent complete or partial collapse of upper airways (apneas or hyponeas) during sleep, leading to intrathoracic pressure changes, periodic reduction, or cessations in airflow; as a result, hypoxia, hypercapnia and frequent arousals from sleep occur <sup>[3][4]</sup>.

Mechanisms involved in pharyngeal collapses are quite complicated and multifactorial, and are highly associated with instability of the upper airway. Typical symptoms include gasping, witnessed apneas, nocturia, headache, intense daytime sleepiness, depression, anxiety or irritation, and deficits in memory and attention, with the subsequent risk of road accident by day <sup>[5][6][7][8][9]</sup>. This clinical condition of altered sleep architecture leads to impaired performance and seriously affected quality of life, thus negatively impacting both physical and mental health <sup>[10]</sup>. Obesity seems to be the most prevalent risk factor for OSA, with more than 40% of patients with body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> suffering from OSA <sup>[4]</sup>. Notably, OSA is much more widespread among patients with cardiovascular risk factors such as type 2 diabetes mellitus (T2DM), hypertension, or established cardiovascular disease (CVD) <sup>[11]</sup>, with its prevalence ranging from 30% to 60% among these patients <sup>[12]</sup>.

Nocturnal polysomnography is the gold standard for diagnosing OSA <sup>[13]</sup>. Apnea hypopnea index (AHI) seems to be a strong indicator of OSA severity, as well as a valuable clinical marker of whether or not to treat OSA. According to the American Academy of Sleep Medicine (AASM), OSA can be classified according to the AHI, which defines mild OSA as 10–15 events/h, moderate OSA as 15–30 events/h, and severe OSA as  $\geq 30$  events/h <sup>[14]</sup>. However, this diagnostic procedure cannot be applied in all patients at risk for sleep apnea, considering that it is quite expensive, time-demanding and inconvenient for some patients. Thus, AASM recommendations for the diagnosis of OSA also include questionnaires and other prediction algorithms, along with home sleep apnea testing by respiratory polygraphy <sup>[14]</sup>. So far, there are no pharmacological therapies approved for the management of OSA <sup>[4]</sup>. Nevertheless, AD109, a combination of the selective norepinephrine reuptake inhibitor, atomoxetine, with the selective antimuscarinic, roxybutynin, which has completed the Phase II clinical trials, activates the upper airway dilator muscles, maintains an open airway during sleep, and thus seems to be a promising and effective novel oral medication for OSA <sup>[15]</sup>. Although continuous positive airway pressure (CPAP) seems to be quite a beneficial therapy for the management of OSA, a large meta-analysis indicated unexpectedly that CPAP does not improve cardiovascular outcomes among patients with OSA <sup>[16]</sup>, possibly due to lack of adherence among these populations <sup>[17]</sup>. Nevertheless, other available conservative strategies include lifestyle intervention programs, such as weight loss, treating the underlying metabolic disorder, and CVD seem to be quite effective, offering successful management of OSA in more than 50% of the patients <sup>[18][19]</sup>.

## 2. The Relationship between Sleep Apnea and CVD

OSA is a quite a prevalent comorbidity among patients with CVD, considering that 38 to 65% of patients with coronary artery disease (CAD) and 12 to 55% of patients with heart failure (HF) may have co-existing OSA across various ethnicities <sup>[20]</sup>. Moreover, high rates of sudden cardiac death during sleep have been reported among patients with OSA

[21]. Several studies highlight that OSA may act as a protentional risk factor for the occurrence and development of CVD, such as hypertension [22][23], CAD [24], HF [25][26], pulmonary hypertension [21][27], atrial fibrillation (AF) and other cardiac arrhythmias [28][29], as well as stroke [30][31].

OSA and hypertension frequently co-exist. Notably, the prevalence of OSA ranges from 30% to 50% among hypertensive patients [32]. Patients with OSA are at higher risk of developing hypertension within 4 years of OSA diagnosis, independently of known co-existing risk factors [33]. Notably, patients with hypertension and OSA display specific hypertension-associated clinical patterns, such as resistant hypertension, masked hypertension, nondipping nocturnal blood pressure [34]. Indeed, some patients may have increased blood pressure during sleep only, or during sleep and wakefulness, thus a 24-h monitoring of blood pressure is highly advised among these patients [35].

Notably, individuals with sleep-disordered breathing, especially severe OSA, have a two- to fourfold higher risk of complex arrhythmias than those without sleep-disordered breathing [36]. Moreover, higher rates of major adverse cardiac events (MACEs) have been reported among patients with moderate-severe OSA and AF [37]. Furthermore, patients with OSA and AF are more likely to fail antiarrhythmic therapy [38]. These data imply that there is a strong relationship between the presence of AF, the severity of OSA, and the risk of cardiovascular events.

Considering that OSA has been linked to AF, it seems to be an independent risk factor for ischemic stroke, as well as stroke reoccurrence [39]. Severity of OSA is also positively correlated with the incidence of stroke [40]. Notably, it has been reported that patients with severe OSA have a two-fold higher risk of stroke within 6 years of diagnosis when compared to those without [41]. Moreover, patients with stroke and OSA are more likely to experience adverse neurocognitive outcomes, such as delayed functional recovery and motor recovery, daytime somnolence, depression, and longer periods of hospitalization in the neurorehabilitation units when compared to those without OSA [42].

The risk of fatal and non-fatal CV events among patients with OSA is up to 3 times higher when compared to the controls [43]. According to a meta-analysis, OSA is a significant predictor of serious adverse outcomes among patients with CVD or cerebrovascular disease [44]. More specifically, OSA was significantly associated with increased risk of stroke (RR 1.94, 95% CI 1.29–2.92), CVD (RR 1.83, 95% CI 1.15–2.93), and all-cause mortality (RR 1.59, 95% CI 1.33–1.89) after stroke or CVD. Moreover, Salari et al. reported also OSA as a significant CV risk factor; moreover, there is a significant relationship between the severity of OSA and the risk of CVD, heart attack and CV death, according to their recent meta-analysis [45]. According to current literature, OSA is an independent predictor of MACEs and cerebrovascular events, as well as CV mortality among patients undergoing post-percutaneous coronary intervention (PCI), with an adjusted hazard ratio of 1.57 (95% CI 1.10–2.24) [46]. Furthermore, it has been indicated that patients hospitalized with non-ST elevation acute coronary syndrome (ACS) with an history of OSA have a greater risk of composite of MACEs, such as death, non-fatal MI and refractory angina during hospitalization, which significantly aggravates their CV prognosis [47].

OSA seems to act as a risk factor for the development of both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) [48]. The prevalence of OSA is around 10–35% among patients with HF [25]. Of note is that observational studies demonstrate that survival rates are generally lower among patients with HF and OSA compared to those without OSA [25].

According to a recent meta-analysis, OSA has been also associated with an overall significant increase in risk of aortic dissection by 60%, possibly due to the mechanisms of sympathetic vaso-activity and inflammation, induced by intermittent hypoxia [49]. Additionally, it was also reported that patients with moderate or severe OSA have a greater risk of aortic dissection by up to 443%, suggesting that the severity of OSA has a positive correlation with the risk of aortic dissection [49].

OSA triggers respiratory, nervous, metabolic, and immune system activation, thus raising the risk of CVD. OSA-induced intermittent hypoxia and sleep disruption promote autonomic nervous system dysfunction, increased nocturnal sympathetic activity and catecholamine secretion, activation of the renin-angiotensin-aldosterone system, oxidative stress, and low-grade chronic inflammation [50][51][52]. The hemodynamic consequences of OSA also include severe vascular dysfunction and remodeling, such as endothelial dysfunction and arterial stiffness, vascular inflammation, thrombosis and platelet reactivity, leading to accelerated atherosclerosis [53][54][55]. Notably, endothelial dysfunction and arterial stiffness, strong markers of atherosclerosis [56][57][58], are strongly associated with OSA, mediated by hypoxia, hypercapnia, and oxidative stress, thus increasing CV risk [59]. Impaired endothelium-dependent vasodilation along with suppressed production of endothelium-dependent vasodilator substances, such as nitric oxide (NO), and elevated levels of endothelin-1 and other growth factors, have been described in OSA [60][61]. Moreover, OSA has been associated with

hypercoagulability and platelet reactivity, since elevated levels of fibrinogen and other prothrombotic factors have been reported among patients with OSA [62].

Notably, OSA-induced intermittent hypoxemia stimulates ventilation, thus leading to increased negative pressure in the chest, increased resistance, heart rate, and blood pressure. As a result, preload and afterload are significantly elevated, particularly among patients with established CVD, leading to left ventricular hypertrophy, and atrial stretch and enlargement, as well as myocardial remodeling and fibrosis [63], which act as a good substrate for the occurrence of AF [64]. Moreover, a greater left ventricular afterload may provoke myocardial ischemia, QTc prolongation, and ventricular arrhythmias [65]. Moreover, repetitive episodes of apnea during sleep activate the sympathoadrenal system, resulting in a sustained elevation of sympathetic activity and increased concentrations of catecholamines while awake, which are a good substrate for ventricular repolarization and the occurrence of arrhythmogenic events [66][67].

Based on the previous findings, patients with OSA are more likely to develop coronary atherosclerosis, myocardial injury, left ventricular remodeling, and vascular dysfunction. According to a large meta-analysis, patients with OSA have significantly higher levels of carotid-intima media thickness (CIMT), which is a strong marker of atherosclerotic process [68]. OSA has also been associated with coronary artery calcification, plaque instability and vulnerability [24][69].

Notably, common echocardiographic findings among patients with OSA are the following: elevated right-side pressures, pulmonary hypertension, tricuspid and mitral regurgitation, diastolic dysfunction, left atrial enlargements, and left ventricular hypertrophy [70]. According to a recent meta-analysis of imaging studies, including 3082 patients with OSA and 1774 matched controls, higher left atrial diameter, higher left atrium volume index, wider left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and left ventricular mass, higher left ventricular mass index, interventricular septum diameter and posterior wall diameter, as well as higher left ventricular myocardial performance index were observed among patients with OSA [71]. In addition, left ventricular ejection fraction was significantly decreased in OSA patients, while increased right ventricular diameter and right ventricular myocardial performance index along with decreased tricuspid annular plane systolic excursion and right ventricular fractional area change were displayed among patients with OSA [71].

---

## References

1. Kapur, V.; Strohl, K.P.; Redline, S.; Iber, C.; O'Connor, G.; Nieto, J. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep Breath.* 2002, 6, 49–54.
2. Benjafield, A.V.; Ayas, N.T.; Eastwood, P.R.; Heinzer, R.; Ip, M.S.M.; Morrell, M.J.; Nunez, C.M.; Patel, S.R.; Penzel, T.; Pépin, J.-L.; et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: A literature-based analysis. *Lancet Respir. Med.* 2019, 7, 687–698.
3. Lévy, P.; Kohler, M.; McNicholas, W.T.; Barbé, F.; McEvoy, R.D.; Somers, V.K.; Lavie, L.; Pépin, J.L. Obstructive sleep apnoea syndrome. *Nat. Rev. Dis. Primers* 2015, 1, 15015.
4. Veasey, S.C.; Rosen, I.M. Obstructive Sleep Apnea in Adults. *N. Engl. J. Med.* 2019, 380, 1442–1449.
5. Tuleta, I.; Pabst, S.; Juergens, U.R.; Nickenig, G.; Skowasch, D. Obstructive sleep apnoea as a risk factor for atherosclerosis—Implication for preventive and personalised treatment. *EPMA J.* 2011, 2, 39–47.
6. Vinnikov, D.; Blanc, P.D.; Alilin, A.; Zutler, M.; Holty, J.-E.C. Fatigue and sleepiness determine respiratory quality of life among veterans evaluated for sleep apnea. *Health Qual. Life Outcomes* 2017, 15, 48.
7. Tregear, S.; Reston, J.; Schoelles, K.; Phillips, B. Obstructive sleep apnea and risk of motor vehicle crash: Systematic review and meta-analysis. *J. Clin. Sleep Med.* 2009, 5, 573–581.
8. Marin, J.M.; Carrizo, S.J.; Vicente, E.; Agustí, A.G.N. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. *Lancet* 2005, 365, 1046–1053.
9. Kerner, N.A.; Roose, S.P. Obstructive Sleep Apnea is Linked to Depression and Cognitive Impairment: Evidence and Potential Mechanisms. *Am. J. Geriatr. Psychiatry* 2016, 24, 496–508.
10. Lee, J.J.; Sundar, K.M. Evaluation and Management of Adults with Obstructive Sleep Apnea Syndrome. *Lung* 2021, 199, 87–101.
11. Mehra, R. Sleep apnea and the heart. *Cleve. Clin. J. Med.* 2019, 86, 10–18.
12. Cepeda-Valery, B.; Acharjee, S.; Romero-Corral, A.; Pressman, G.S.; Gami, A.S. Obstructive sleep apnea and acute coronary syndromes: Etiology, risk, and management. *Curr. Cardiol. Rep.* 2014, 16, 535.

13. Bailly, S.; Destors, M.; Grillet, Y.; Richard, P.; Stach, B.; Vivodtzev, I.; Timsit, J.-F.; Lévy, P.; Tamisier, R.; Pépin, J.-L.; et al. Obstructive Sleep Apnea: A Cluster Analysis at Time of Diagnosis. *PLoS ONE* 2016, 11, e0157318.
14. Kapur, V.K.; Auckley, D.H.; Chowdhuri, S.; Kuhlmann, D.C.; Mehra, R.; Ramar, K.; Harrod, C.G. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J. Clin. Sleep Med.* 2017, 13, 479–504.
15. Rosenberg, R.; Abaluck, B.; Thein, S. Combination of atomoxetine with the novel antimuscarinic aroxybutynin improves mild to moderate OSA. *J. Clin. Sleep Med.* 2022.
16. Yu, J.; Zhou, Z.; McEvoy, D.; Anderson, C.; Rodgers, A.; Perkovic, V.; Neal, B. Association of Positive Airway Pressure with Cardiovascular Events and Death in Adults with Sleep Apnea: A Systematic Review and Meta-analysis. *JAMA* 2017, 318, 156–166.
17. Bakker, J.P.; Weaver, T.E.; Parthasarathy, S.; Aloia, M.S. Adherence to CPAP: What Should We Be Aiming For, and How Can We Get There? *Chest* 2019, 155, 1272–1287.
18. Hudgel, D.W. Critical review: CPAP and weight management of obstructive sleep apnea cardiovascular co-morbidities. *Sleep Med. Rev.* 2018, 37, 14–23.
19. Hudgel, D.W.; Patel, S.R.; Ahasic, A.M.; Bartlett, S.J.; Bessesen, D.H.; Coaker, M.A.; Fiander, P.M.; Grunstein, R.R.; Gurubhagavatula, I.; Kapur, V.K.; et al. The Role of Weight Management in the Treatment of Adult Obstructive Sleep Apnea. An Official American Thoracic Society Clinical Practice Guideline. *Am. J. Respir. Crit. Care Med.* 2018, 198, e70–e87.
20. Javaheri, S.; Barbe, F.; Campos-Rodriguez, F.; Dempsey, J.A.; Khayat, R.; Javaheri, S.; Malhotra, A.; Martinez-Garcia, M.A.; Mehra, R.; Pack, A.I.; et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. *J. Am. Coll. Cardiol.* 2017, 69, 841–858.
21. Gami, A.S.; Olson, E.J.; Shen, W.K.; Wright, R.S.; Ballman, K.V.; Hodge, D.O.; Herges, R.M.; Howard, D.E.; Somers, V.K. Obstructive sleep apnea and the risk of sudden cardiac death: A longitudinal study of 10,701 adults. *J. Am. Coll. Cardiol.* 2013, 62, 610–616.
22. Hla, K.M.; Young, T.B.; Bidwell, T.; Palta, M.; Skatrud, J.B.; Dempsey, J. Sleep apnea and hypertension. A population-based study. *Ann. Intern. Med.* 1994, 120, 382–388.
23. Young, T.; Peppard, P.; Palta, M.; Hla, K.M.; Finn, L.; Morgan, B.; Skatrud, J. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch. Intern. Med.* 1997, 157, 1746–1752.
24. Shah, N.A.; Yaggi, H.K.; Concato, J.; Mohsenin, V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep Breath.* 2010, 14, 131–136.
25. Wang, H.; Parker, J.; Newton, G.E.; Floras, J.S.; Mak, S.; Chiu, K.-L.; Ruttanaumpawan, P.; Tomlinson, G.; Bradley, T.D. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J. Am. Coll. Cardiol.* 2007, 49, 1625–1631.
26. Gottlieb, D.J.; Yenokyan, G.; Newman, A.B.; O'Connor, G.; Punjabi, N.M.; Quan, S.F.; Redline, S.; Resnick, H.E.; Tong, E.K.; Diener-West, M.; et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The sleep heart health study. *Circulation* 2010, 122, 352–360.
27. Somers, V.K.; White, D.P.; Amin, R.; Abraham, W.T.; Costa, F.; Culebras, A.; Daniels, S.; Floras, J.S.; Hunt, C.E.; Olson, L.J.; et al. Sleep apnea and cardiovascular disease: An American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J. Am. Coll. Cardiol.* 2008, 52, 686–717.
28. Bitter, T.; Westerheide, N.; Prinz, C.; Hossain, M.S.; Vogt, J.; Langer, C.; Horstkotte, D.; Oldenburg, O. Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. *Eur. Heart J.* 2011, 32, 61–74.
29. Drager, L.F.; McEvoy, R.D.; Barbe, F.; Lorenzi-Filho, G.; Redline, S.; INCOSACT Initiative (International Collaboration of Sleep Apnea Cardiovascular Trialists). Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science. *Circulation* 2017, 136, 1840–1850.
30. Redline, S.; Yenokyan, G.; Gottlieb, D.J.; Shahar, E.; O'Connor, G.; Resnick, H.E.; Diener-West, M.; Sanders, M.H.; Wolf, P.A.; Geraghty, E.M.; et al. Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. *Am. J. Respir. Crit. Care Med.* 2010, 182, 269–277.
31. Yaggi, H.K.; Concato, J.; Kernan, W.N.; Lichtman, J.H.; Brass, L.M.; Mohsenin, V. Obstructive sleep apnea as a risk factor for stroke and death. *N. Engl. J. Med.* 2005, 353, 2034–2041.

32. Tietjens, J.R.; Claman, D.; Kezirian, E.J.; De Marco, T.; Mirzayan, A.; Sadroonri, B.; Goldberg, A.N.; Long, C.; Gerstenfeld, E.P.; Yeghiazarians, Y. Obstructive Sleep Apnea in Cardiovascular Disease: A Review of the Literature and Proposed Multidisciplinary Clinical Management Strategy. *J. Am. Heart Assoc.* 2019, 8, e010440.
33. Peppard, P.E.; Young, T.; Palta, M.; Skatrud, J. Prospective study of the association between sleep-disordered breathing and hypertension. *N. Engl. J. Med.* 2000, 342, 1378–1384.
34. O'Donnell, C.; O'Mahony, A.M.; McNicholas, W.T.; Ryan, S. Cardiovascular manifestations in obstructive sleep apnea: Current evidence and potential mechanisms. *Pol. Arch. Intern. Med.* 2021, 131, 550–560.
35. Parati, G.; Lombardi, C.; Hedner, J.; Bonsignore, M.R.; Grote, L.; Tkacova, R.; Lévy, P.; Riha, R.L.; Bassetti, C.; Narkiewicz, K.; et al. Recommendations for the management of patients with obstructive sleep apnoea and hypertension. *Eur. Respir. J.* 2013, 41, 523–538.
36. Mehra, R.; Benjamin, E.J.; Shahar, E.; Gottlieb, D.J.; Nawabit, R.; Kirchner, H.L.; Sahadevan, J.; Redline, S. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. *Am. J. Respir. Crit. Care Med.* 2006, 173, 910–916.
37. Platek, A.E.; Szymanski, F.M.; Filipiak, K.J.; Dudzik-Plocica, A.; Krzowski, B.; Karpinski, G. Stratification of cardiovascular risk in patients with atrial fibrillation and obstructive sleep apnea-validity of the 2MACE score. *Sleep Breath.* 2017, 21, 601–606.
38. Monahan, K.; Brewster, J.; Wang, L.; Parvez, B.; Goyal, S.; Roden, D.M.; Darbar, D. Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter. *Am. J. Cardiol.* 2012, 110, 369–372.
39. Brown, D.L.; Khorassani, F.S.; Kim, S.; Chervin, R.D.; Case, E.; Morgenstern, L.B.; Yadollahi, A.; Tower, S.; Lisabeth, L.D. Sleep-Disordered Breathing Is Associated with Recurrent Ischemic Stroke. *Stroke* 2019, 50, 571–576.
40. McEvoy, R.D.; Antic, N.A.; Heeley, E.; Luo, Y.; Ou, Q.; Zhang, X.; Mediano, O.; Chen, R.; Drager, L.F.; Liu, Z.; et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N. Engl. J. Med.* 2016, 375, 919–931.
41. Yaranov, D.M.; Smyrlis, A.; Usatii, N.; Butler, A.; Petrini, J.R.; Mendez, J.; Warshofsky, M.K. Effect of obstructive sleep apnea on frequency of stroke in patients with atrial fibrillation. *Am. J. Cardiol.* 2015, 115, 461–465.
42. Aaronson, J.A.; Van Bennekom, C.A.M.; Hofman, W.F.; Van Bezeij, T.; Aardweg, J.G.V.D.; Groet, E.; Kylstra, W.A.; Schmand, B. Obstructive Sleep Apnea is Related to Impaired Cognitive and Functional Status after Stroke. *Sleep* 2015, 38, 1431–1437.
43. Peres, B.U.; Hirsch, A.A.; Fox, N.; Laher, I.; Hanly, P.; Skomro, R.; Almeida, F.; Ayas, N.T.; Canadian Sleep and Circadian Network. Circulating biomarkers to identify cardiometabolic complications in patients with Obstructive Sleep Apnea: A systematic review. *Sleep Med. Rev.* 2019, 44, 48–57.
44. Xie, W.; Zheng, F.; Song, X. Obstructive sleep apnea and serious adverse outcomes in patients with cardiovascular or cerebrovascular disease: A PRISMA-compliant systematic review and meta-analysis. *Medicine* 2014, 93, e336.
45. Salari, N.; Khazaie, H.; Abolfathi, M.; Ghasemi, H.; Shabani, S.; Rasoulpoor, S.; Mohammadi, M.; Khaledi-Paveh, B. The effect of obstructive sleep apnea on the increased risk of cardiovascular disease: A systematic review and meta-analysis. *Neurol. Sci.* 2022, 43, 219–231.
46. Lee, C.-H.; Sethi, R.; Li, R.; Ho, H.-H.; Hein, T.; Jim, M.-H.; Loo, G.; Koo, C.-Y.; Gao, X.-F.; Chandra, S.; et al. Obstructive Sleep Apnea and Cardiovascular Events After Percutaneous Coronary Intervention. *Circulation* 2016, 133, 2008–2017.
47. Correia, L.C.L.; Souza, A.C.; Garcia, G.; Sabino, M.; Brito, M.; Maraux, M.; Rabelo, M.M.N.; Esteves, J.P. Obstructive sleep apnea affects hospital outcomes of patients with non-ST-elevation acute coronary syndromes. *Sleep* 2012, 35, 1241–1245.
48. Gong, F.F.; Jelinek, M.V.; Castro, J.M.; Collier, J.M.; McGrady, M.; Boffa, U.; Shiel, L.; Liew, D.; Wolfe, R.; Stewart, S.; et al. Risk factors for incident heart failure with preserved or reduced ejection fraction, and valvular heart failure, in a community-based cohort. *Open Heart* 2018, 5, e000782.
49. Zhou, X.; Liu, F.; Zhang, W.; Wang, G.; Guo, D.; Fu, W.; Wang, L. Obstructive sleep apnea and risk of aortic dissection: A meta-analysis of observational studies. *Vascular* 2018, 26, 515–523.
50. Drager, L.F.; Santos, R.B.; Silva, W.A.; Parise, B.K.; Giatti, S.; Aiello, A.N.; Souza, S.P.; Furlan, S.F.; Lorenzi-Filho, G.; Lotufo, P.A.; et al. OSA, Short Sleep Duration, and Their Interactions with Sleepiness and Cardiometabolic Risk Factors in Adults: The ELSA-Brasil Study. *Chest* 2019, 155, 1190–1198.
51. Jelic, S.; Le Jemtel, T.H. Inflammation, oxidative stress, and the vascular endothelium in obstructive sleep apnea. *Trends Cardiovasc. Med.* 2008, 18, 253–260.

52. Fletcher, E.C.; Bao, G.; Li, R. Renin activity and blood pressure in response to chronic episodic hypoxia. *Hypertension* 1999, 34, 309–314.
53. Karakaş, M.S.; Altekin, R.E.; Baktır, A.O.; Küçük, M.; Cilli, A.; Yalçınkaya, S. Association between mean platelet volume and severity of disease in patients with obstructive sleep apnea syndrome without risk factors for cardiovascular disease. *Türk Kardiyol. Dern. Ars.* 2013, 41, 14–20.
54. Drager, L.F.; Bortolotto, L.A.; Lorenzi, M.C.; Figueiredo, A.C.; Krieger, E.M.; Lorenzi-Filho, G. Early signs of atherosclerosis in obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* 2005, 172, 613–618.
55. Paschou, S.A.; Anagnostis, P.; Vryonidou, A.; Goulis, D.G. Diabetes and Atherosclerosis: Old Players in a New Field, Osteoporosis. *Curr. Vasc. Pharmacol.* 2018, 16, 524–527.
56. Oikonomou, E.; Siasos, G.; Tsigkou, V.; Bletsa, E.; Panoilia, M.-E.; Oikonomou, I.N.; Simanidis, I.; Spinou, M.; Papastavrou, A.; Kokosias, G.; et al. Coronary Artery Disease and Endothelial Dysfunction: Novel Diagnostic and Therapeutic Approaches. *Curr. Med. Chem.* 2020, 27, 1052–1080.
57. Antonopoulos, A.S.; Siasos, G.; Oikonomou, E.; Gouliopoulos, N.; Konsola, T.; Tsigkou, V.; Moschos, M.; Tentolouris, N.; Kassi, E.; Paschou, S.A.; et al. Arterial stiffness and microvascular disease in type 2 diabetes. *Eur. J. Clin. Investig.* 2021, 51, e13380.
58. Paschou, S.A.; Siasos, G. Diabetes and the Heart: New Clinical Trials and Recent Recommendations. *Curr. Pharm. Des.* 2020, 26, 4685–4686.
59. Peracaula, M.; Torres, D.; Poyatos, P.; Luque, N.; Rojas, E.; Obrador, A.; Orriols, R.; Tura-Ceide, O. Endothelial Dysfunction and Cardiovascular Risk in Obstructive Sleep Apnea: A Review Article. *Life* 2022, 12, 537.
60. Kato, M.; Roberts-Thomson, P.; Phillips, B.G.; Haynes, W.G.; Winnicki, M.; Accurso, V.; Somers, V.K. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 2000, 102, 2607–2610.
61. Gjørup, P.H.; Sadauskiene, L.; Wessels, J.; Nyvad, O.; Strunge, B.; Pedersen, E.B. Abnormally increased endothelin-1 in plasma during the night in obstructive sleep apnea: Relation to blood pressure and severity of disease. *Am. J. Hypertens.* 2007, 20, 44–52.
62. Von Känel, R.; Lored, J.S.; Ancoli-Israel, S.; Mills, P.J.; Natarajan, L.; Dimsdale, J.E. Association between polysomnographic measures of disrupted sleep and prothrombotic factors. *Chest* 2007, 131, 733–739.
63. Otto, M.E.; Belohlavek, M.; Romero-Corral, A.; Gami, A.S.; Gilman, G.; Svatikova, A.; Amin, R.S.; Lopez-Jimenez, F.; Khandheria, B.K.; Somers, V.K. Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea. *Am. J. Cardiol.* 2007, 99, 1298–1302.
64. Digby, G.C.; Baranchuk, A. Sleep apnea and atrial fibrillation; 2012 update. *Curr. Cardiol. Rev.* 2012, 8, 265–272.
65. Shi, H.; Jiang, X. Correlation between QTc Prolongation and Obstructive Sleep Apnea in Patients with Type 2 Diabetes Mellitus. *Med. Sci. Monit.* 2020, 26, e926954.
66. Abboud, F.; Kumar, R. Obstructive sleep apnea and insight into mechanisms of sympathetic overactivity. *J. Clin. Investig.* 2014, 124, 1454–1457.
67. Whitsel, E.A.; Boyko, E.J.; Siscovick, D.S. Reassessing the role of QTc in the diagnosis of autonomic failure among patients with diabetes: A meta-analysis. *Diabetes Care* 2000, 23, 241–247.
68. Nadeem, R.; Harvey, M.; Singh, M.; Khan, A.A.; Albustani, M.; Baessler, A.; Madbouly, E.M.; Sajid, H.; Khan, M.; Navid, N. Patients with obstructive sleep apnea display increased carotid intima media: A meta-analysis. *Int. J. Vasc. Med.* 2013, 2013, 839582.
69. Kent, B.D.; Garvey, J.F.; Ryan, S.; Nolan, G.; Dodd, J.D.; McNicholas, W.T. Severity of obstructive sleep apnoea predicts coronary artery plaque burden: A coronary computed tomographic angiography study. *Eur. Respir. J.* 2013, 42, 1263–1270.
70. Lyons, O.D.; Chan, C.T.; Elias, R.M.; Bradley, T.D. Relationship of left atrial size to obstructive sleep apnea severity in end-stage renal disease. *Sleep Med.* 2014, 15, 1314–1318.
71. Lu, M.; Wang, Z.; Zhan, X.; Wei, Y. Obstructive sleep apnea increases the risk of cardiovascular damage: A systematic review and meta-analysis of imaging studies. *Syst. Rev.* 2021, 10, 212.