OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS). WHAT'S NEW?

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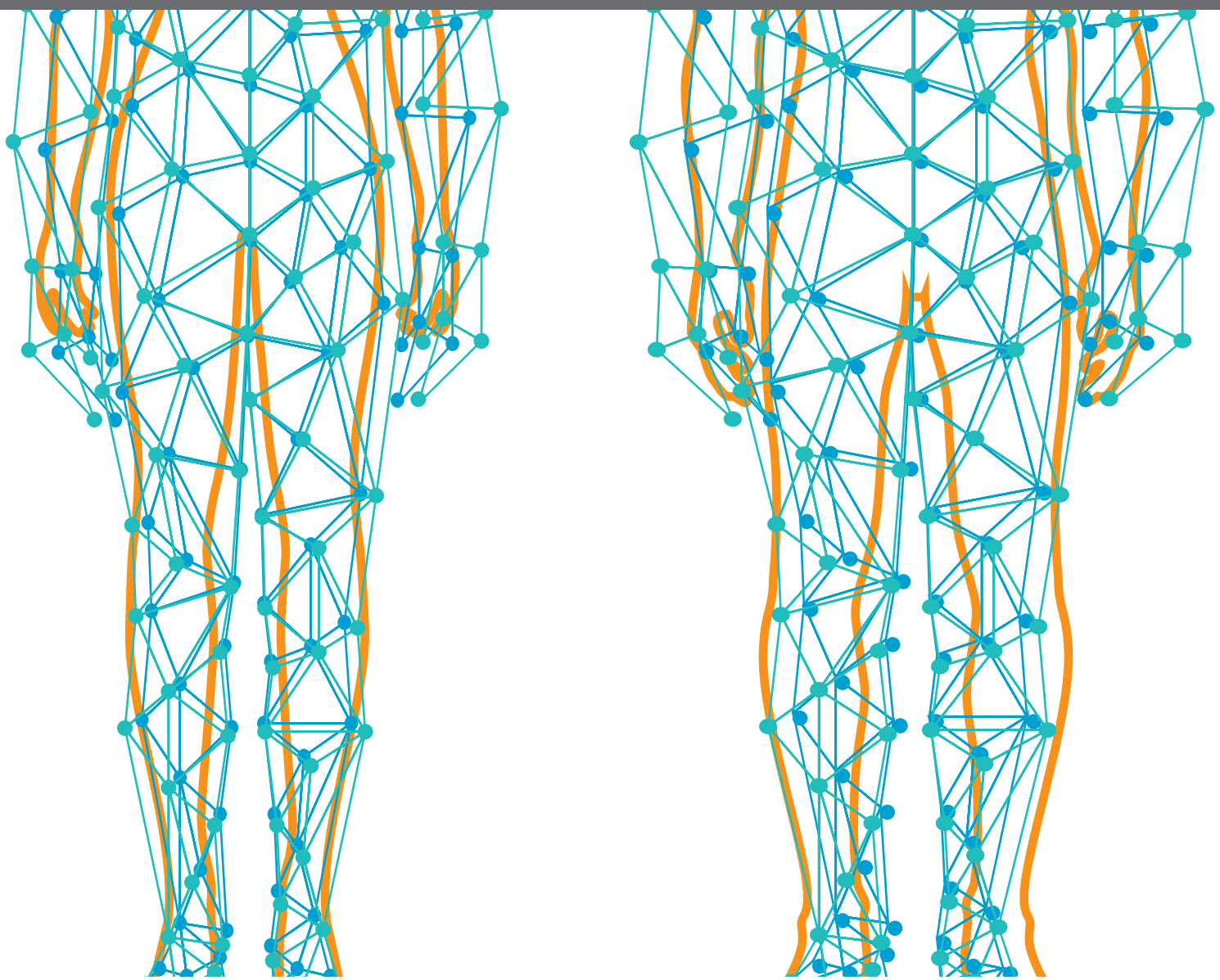

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OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS). WHAT'S NEW?

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Editorial: Obstructive sleep apnea syndrome (OSAS). What's new?

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KEYWORDS

OSAS, CPAP, polysomnography, sleep disorders, apnea syndrome

Editorial on the Research Topic
Obstructive sleep apnea syndrome (OSAS). What's new?

This Research Topic entitled *"Obstructive sleep apnea syndrome (OSAS). What's new?"*, involving authors from different specializations and numerous countries, confirms that OSAS is a hot topic. OSA syndrome is an airway obstruction (i.e. complete or partial) with numerous etiologies (1–4). Different papers have demonstrated that the prevalence of OSAS is 2–4% in men and 1–2% in women of average age. The reference tools for OSAS diagnosis are clinical polysomnography or nocturnal portable multi-channel monitoring. Frequently, continuous positive airway pressure (CPAP) therapy is the first treatment for a patient (5, 6). Long-term CPAP treatment may present limited compliance, and there is no unanimous opinion on other alternative treatments for OSAS in literature on the subject. This special issue discusses several of these "unmet needs".

In the first article (Braghiroli et al.) of the collection, the authors compared 118 OSAS patients with different disease severity, using a standard monitoring system (Nox T3) and a low-cost device (AirgoTM) with an elastic band and a small recorder, which is lightweight and comfortable for the patient. The data showed that AirgoTM has an excellent level of sensitivity, specificity, positive and negative predicted value, and accuracy. The authors reported that AirgoTM is a reliable tool for screening suspected OSAS patients, the device was well tolerated by the subjects, and that it is based on an automatic analysis that can help physicians to increase the selection of possible candidates for treatment.

The second article (Conte et al.) evaluates a simplified non-invasive screening system for improving the diagnosis of OSAS. The authors used the original Berlin Questionnaire, simplified to a set of questions specifically included by the authors' group that complemented the socio-demographic, clinical, and medical history framework of the participants, to investigate the impact of OSAS on health care systems. In conclusion, the authors demonstrated that their reduced version of the Berlin questionnaire seems

capable of reproducing the outcome of the original questionnaire. Furthermore, the decrease in the number of questions may be useful for screening possible cases of OSAS in situations where the time it takes to complete the questionnaire needs to be as short as possible.

In another article (Cai et al.) the researchers selected 74 OSAS patients and classified them into mild, moderate, and severe diseases. In addition, the authors selected 20 subjects as a control group. The investigators evaluated the serum levels of liver fibrosis markers using electrochemiluminescence immunoassay. The researchers exposed hepatic stellate cells to intermittent hypoxia (IH) or normoxia (RA). The authors observed that serum liver fibrosis markers were positively correlated with the apnea-hypopnea index (AHI) but negatively correlated with lowest saturation oxygen (LSaO2) respectively. Lastly, the experiments support the view that OSAS might either directly or indirectly trigger or exacerbate liver fibrosis by IH-related pathways.

The aim of the fourth study (Stavrou, Koutedakis et al.) was to investigate the effect of different pillows [own pillow (OP), foam-memory pillow (MFP), generic laboratory pillow (LP)] on selected polysomnography (PSG) evaluations in 32 OSAS patients. Interestingly, the study indicates that pillow type and use, which is often uncontrolled in OSAS assessments, correlates with several PSG parameters and a snoring subtype of the syndrome.

In the fifth paper (Chung et al.) the authors demonstrated in 62 OSAS patients with overnight oxygen desaturation (sPO2 $<$ 90%) that neck CT with computational fluid dynamics evaluation of airway pressure and airflow velocity may offer a quick prediction of moderate to severe OSAS.

The sixth article undertakes an evaluation of possible correlations between brain-derived neurotrophic factor (BDNF), OSAS, and endothelial dysfunction (Makhout et al.). This study included 103 children, of which 20 had OSAS, all with obesity, aged 8 to 18 years. The authors also investigated the possible effect of weight loss on serum BDNF levels, as BDNF has a significant part in the regulation of food intake and body weight. In conclusion, the authors demonstrated that BDNF levels were similar in children with obesity, with and without OSA, indicating that BDNF concentration is not influenced by OSAS. The authors observed an effect of OSAS and endothelial function on BDNF levels.

The seventh article (Gao et al.) is a review that explores the evidence of duration and quality of sleep as evaluated by multiple health outcomes. The authors included 85 meta-analyses and 36 health outcomes. The researchers underlined the association between short sleep and an improvement in the risk of becoming overweight and/or obese; and poor sleep quality and an increased risk of both mellitus and gestational diabetes. They reported that the correlation of long sleep with increased risk of all-cause mortality (stroke, dyslipidaemia, mortality of coronary heart disease, stroke mortality, and the developing or dying of stroke) were graded as highly suggestive.

The eighth study (Hu et al.) evaluated the prognostic factors and survival rates of 90 lung cancer patients with OSAS by nomogram. There were significant differences in sex, apnea hypopnea index (AHI), Tumor Node Metastasis (TNM), coronary heart disease, lowest arterial oxygen saturation, and oxygen desaturation index (ODI4) between the lung cancer subgroup and lung cancer with the OSAS subgroup. In the lung cancer group with OSAS, six factors (i.e. age, AHI, TNM, cancer types, BMI, and ODI4) were independent prognostic factors, and a nomogram model was established based on these parameters. The authors demonstrated that the nomogram could predict the prognosis of patients and guide personalized treatment regimes.

The ninth paper (Stavrou, Astara et al.) reviews literature on the altered systematic pathophysiologic mechanisms in OSAS subjects and proposes a correct exercise program for all subjects. The interesting results of this study indicate that exercise prevents a dysregulation of both daytime and nighttime cardiovascular autonomic function, reduces body weight, and halts the onset and progress of insulin resistance, while it ameliorates excessive daytime sleepiness, cognitive decline, and mood disturbances, resulting in an improvement in the quality of sleep and life.

The tenth article (Duan et al.) examined the correlations of OSAS risk with depression, anxiety, and life events in 10,287 Chinese subjects. The Berlin Questionnaire (BQ) was used to ascertain the level of OSAS, while Depression Scale (CES-D) and Zung's self-rating anxiety scale (SAS) were used to define depression and anxiety. The results indicated that depression and anxiety, especially when both co-occur at high levels, were correlated with an increased risk of OSAS. However, adverse life events were not correlated with any risk of OSAS. The authors advised increasing attention on depression and anxiety in OSAS patients.

In the last article, the authors (Chen et al.) illustrate a strategy for realizing a systematic review, exploring the association between sleep-disordered breathing and periodontal diseases, a topic of controversy and clinical significance. The authors underline that the results can provide evidence for the development of relevant prevention and treatment strategies.

Overall, this collection of papers underlines the importance of assessing the risk of obstructive sleep apnea syndrome, as this syndrome is linked with a high risk of hypertension, cardiovascular diseases, daytime sleepiness, home and work-related accidents, and a consequent worsening of life quality. Numerous studies stress the importance of praecox

diagnosis and a multidisciplinary approach in addressing all these situations.

Author contributions

BR, EB, and FS compiled the manuscript. MC and CA undertook final amendments and approved the final version. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Levrini L, Sacchi F, Milano F, Polimeni A, Cozza P, Bernkopf E, et al. Italian recommendations on dental support in the treatment of adult obstructive sleep apnea syndrome (OSAS). *Ann Stomatol (Roma).* (2016) 6:81–6. doi: 10.11138/ads/2015.6.3.081

2. Ma B, Li Y, Wang X, Du L, Wang S, Ma H, et al. Association between abdominal adipose tissue distribution and obstructive sleep apnea in Chinese obese patients. *Front Endocrinol (Lausanne).* (2022) 13:847324. doi: 10.3389/fendo.2022.847324

3. Ruaro B, Salton F, Braga L, Wade B, Confalonieri P, Volpe MC, et al. The history and mystery of alveolar epithelial type ii cells: focus on their physiologic and pathologic role in lung. *Int J Mol Sci.* (2021) 22:2566. doi: 10.3390/ijms22052566

4. Antonaglia C, Passuti G, Giudici F, Salton F, Ruaro B, Radovanovic D, et al. Low arousal threshold: a common pathophysiological trait in patients with obstructive sleep apnea syndrome and asthma. *Sleep Breath.* (2022). doi: 10.1007/s11325-022-02665-4. [Epub ahead of print].

5. Portel L, Parrat E, Nocent-Ejnaini C, Mangiapan G, Prud'homme A, Oster JP, et al. Phenotyping to target obstructive sleep apnoea syndrom (OSAS) in adults patients with severe asthma. *Respir Med Res.* (2022) 82:100888. doi: 10.1016/j.resmer.2022.100888

6. Tingting X, Danming Y, Xin C. Non-surgical treatment of obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol.* (2018) 275:335–46. doi: 10.1007/s00405-017-4818-y

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REVIEW
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Obstructive Sleep Apnea Syndrome: The Effect of Acute and Chronic Responses of Exercise

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Obstructive Sleep Apnea Syndrome (OSAS) is a sleep disorder with high prevalence in general population, but alarmingly low in clinicians' differential diagnosis. We reviewed the literature on PubMed and Scopus from June 1980–2021 in order to describe the altered systematic pathophysiologic mechanisms in OSAS patients as well as to propose an exercise program for these patients. Exercise prevents a dysregulation of both daytime and nighttime cardiovascular autonomic function, reduces body weight, halts the onset and progress of insulin resistance, while it ameliorates excessive daytime sleepiness, cognitive decline, and mood disturbances, contributing to an overall greater sleep quality and quality of life.

Keywords: cardiopulmonary function, metabolism, cognitive decline, physical activity, pulmonary rehabilitation

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OBSTRUCTIVE SLEEP APNEA SYNDROME

Obstructive Sleep Apnea Syndrome (OSAS) is a disorder of sleep breathing characterized by prolonged periods of complete or partial obstruction of the upper airway (1). OSAS demonstrates increasing prevalence, as it is conjoined with obesity, ranging in 9–37% in men and 4–50% in women, regardless of race and nationality (2). Despite being easily recognized, it tends to elude clinicians' attention, as in only 10% of the population the definitive diagnosis is established (3). Obstructive episodes accompanied by respiratory effort, cause a decrease of the airflow in the upper airway by at least 30% for 10 s and oxygen desaturation in blood by at least 4% (hypopnea) or complete cessation (apnea) for 10 s, resulting in desaturation of oxyhemoglobin and fragmentation of sleep.

The severity of OSAS is evaluated mainly through the Apnea - Hypopnea Index (AHI), representing the number of apneas and hypopneas per hour sleep. Normal values in adults are AHI $\leq$5, 6-to-15 are characterized as mild, 16-to-29 moderate and $\geq$30 severe OSAS (1). The gold standard for diagnosis and severity evaluation is via polysomnography (PSG). PSG offers a systematic collection of various systematic parameters at the same time during sleep. It utilizes electroencephalogram, electro-oculogram and electromyogram for the discrimination of sleep stages and underlying conditions of the nervous system. In addition, electrocardiogram and pulse oximetry estimate heart rate and rhythm and O_2 tissue supply, unveiling any disruptions in oxygenation; a hallmark of the pathophysiology of OSAS (4).

Almost 80% of OSAS patients report excessive daytime sleepiness, signifying declining performance at work as well as increased risk for labor and traffic accidents (5). Daytime sleepiness, lack of concentration, fatigue, social and emotional difficulties are likely to cause frictions in

relationships with other people and render them susceptible for rather lonely and sedentary lifestyle, as well as for anxiety and depressive disorders (6, 7).

Exercise, along with sleep, offers a wide variety of benefits and constitutes a fundamental element for prosperity and longevity. For the general population, it is a necessary constituent of daily life, while in patients, based on their underlying condition, it is crucial to prescribe exercise adjunctively to the main treatment, depending on their capabilities. OSAS patients are faced with crucial systematic consequences, which exercise could ameliorate. They can benefit from exercise, as it improves (**Figure 1**) cardiopulmonary, cognitive and metabolic profile as well as quality of life, regardless with CPAP therapy and BMI management (8). Oftentimes, CPAP therapy may be insufficient or not tolerated by patients. We added a note to clarify that we examined exercise adjunctively to main therapies, like CPAP, or when such therapies fail or are not tolerated by patients. Therefore, we aimed to review the literature, to describe the acute and chronic systematic detrimental consequences of OSAS with focus on exercise effects, as well as to stress the importance of an exercise program for these patients, adjunctively to main therapy. In **Table 1** present a typical exercise program as a strategy to improve health of patients with OSAS.

METHODS

The choice of literature was done aiming at a comprehensive coverage of the topic during the period January 2019 to July 2021 with keywords: "Obstructive Sleep Apnea Syndrome," "Sleep disorders," "Exercise," "Cogition," "Oxidative stress," "Cardiopulmonary Exercise Testing," "6-minute walk test," "Fatigue," "Anxiety," and "adults" and combinations between of them in Pub Med and Scopus database. The studies selected involved adult patients and included patients with co-morbidities, review articles and meta-analyses while the articles used were in English.

ASSESSMENT OF THE ABILITY TO EXERCISE

Cardiopulmonary Exercise Testing

Cardiopulmonary Exercise Testing (CPET) and/or otherwise ergospirometry, is analogous to PSG in terms of systematically collecting information simultaneously. It is a non-invasive test that evaluates the function not only of the heart and lungs, but also of the whole body, both at rest but mainly during exercise. The test is performed on a cycle-ergometer and/or on treadmill and measurements are recorded from the cardiovascular, respiratory, circulatory and musculoskeletal systems. Specifically, within a strictly predetermined protocol with either a steady project increase in stages or with a continuous gradual project increase the ability of exercise and it is used in a wide range of clinical situations as it concerns all stages of each disease including diagnosis, severity assessment, disease progression, prognosis and response to treatment, to answer specific questions that arise after a basic clinical assessment (9).

Contraindications to CPET

Contraindications to the assessment of the ability to exercise through the CPET (10) relate to the inability to perform a valid and satisfactory maximum/submaximal effort with an increased

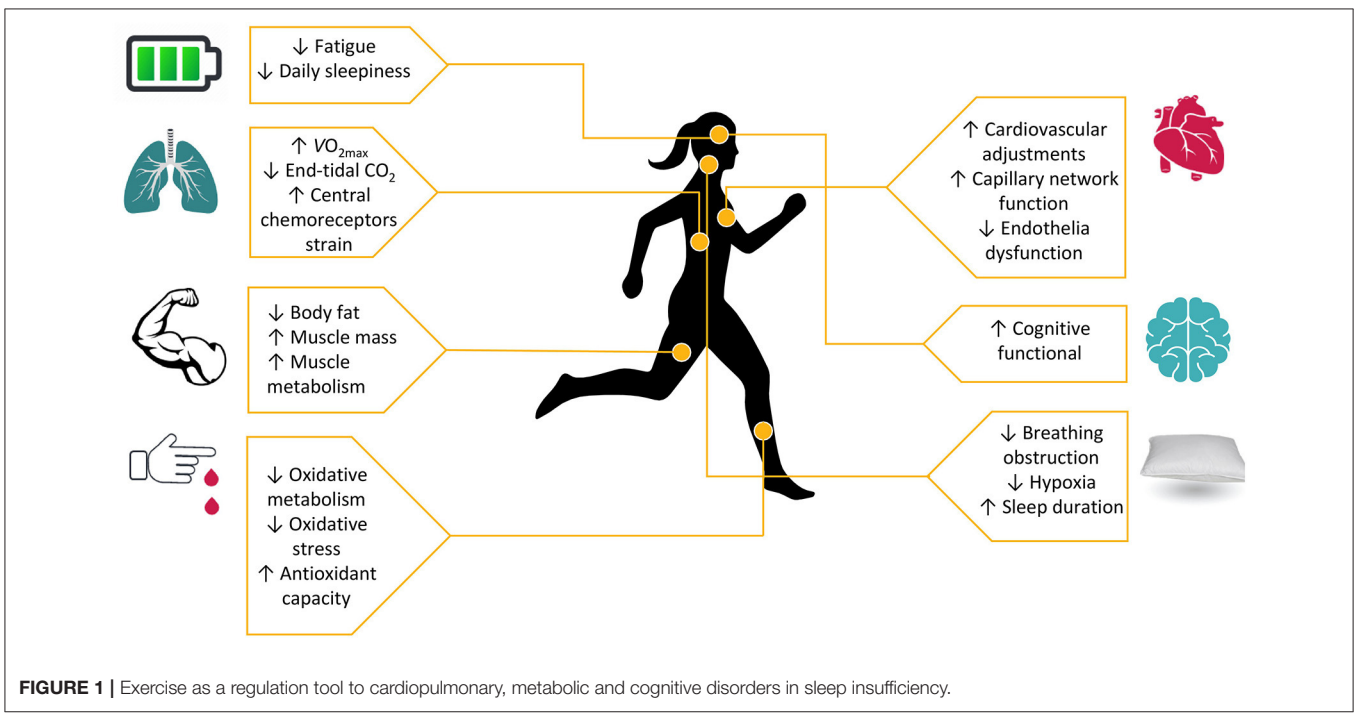

FIGURE 1 | Exercise as a regulation tool to cardiopulmonary, metabolic and cognitive disorders in sleep insufficiency.

TABLE 1 | Recommended exercise program for patients with OSAS.

Duration	**3–9 months**	
Frequency	3–5 session per week	
Session duration	45–60 min	
Warm-up	15% of each session	30–50% of VO_{2max} and/or 50–60% of HR_{max}
Aerobic exercises	60% of each session	Intermittent exercise on 70–80% of VO_{2max} and/or on 75–85% of HR_{max}
Strength exercise	15% of each session	Multi-joint exercise (large muscle mass), 2–8 sets to 6–12 repetitions on 60–70% of 1 RM
Mobility-Flexibility	10% of each session	Static or dynamic. Stretch to the point of feeling tightness or slight discomfort, 2–4 sets to 6–12 repetitions at 10–30 s
Cool-down	15% of each session	40–50% $\tau\eta\varsigma$ VO_{2max} and/or 50–60% $\tau\eta\varsigma$ HR_{max}

1 RM, one-repetition maximum; HR, heart rate; VO_{2max}, maximal oxygen uptake.

likelihood of the occurrence of an unpleasant incident during exercise (**Supplementary Material**).

Six-Minute Walk Test

Six-minute walk test (6 MWT) is an additional assessment tools in patients with OSAS (11). 6 MWT is a non-invasive sub-maximal test it reviews the responses of exercise and evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism (12). The test is performed on 30-m on a flat hallway with hard surface, no exercise equipment and measures the distance that a patient can quickly walk in a period of 6 min (the 6 MWD). During 6 MWT are recorded the total of meters (m), arterial O_2 saturation (SpO_2), heart rate (HR), blood pressure (BP) and self-assessed lower extremity fatigue with dyspnea Borg Scale CR10 (13).

ACUTE RESPONSES TO EXERCISE IN OSAS PATIENTS

Cardiopulmonary Alterations

OSAS is a determinant of cardiovascular morbidity and mortality, with its most prominent cardiovascular complications involving drug-resistant hypertension, ischemic heart disease, cardiac arrhythmias and vascular stroke, while increased risk for sinus bradycardia, atrial and ventricular fibrillation, non-persistent ventricular tachycardia, activation of parasympathetic nervous system and bradyarrhythmias exist (14).OSAS patients showed altered hemodynamic response during exercise, while in the presence of comorbidities, the hemodynamic response to exercise is further impaired (15). Patients with OSAS experience a blunt chronotropic response to graded exercise due to variable dysregulation of cardiac β-receptors and/or baroreflex regulation site, resulting in impaired autonomic cardiovascular response (16, 17). Sleep apnea is conjoined with sleep fragmentation that creates a noxious environment prone to sympathetic excitation (18). As a result, alpha and beta – 2 receptors become desensitized, inducing vasoconstriction and endothelial dysfunction, as well as increasing heart rate (HR) and blood pressure (BP) (19, 20). This adrenergic blunted response becomes prominent during exercise, in which normally the operating point of baroreflex is set above mean arterial pressure, which is reset after exercise (21). In OSAS, the variability of baroreflex is attenuated and set centrally to higher operating point (22). OSAS patients who have undergone a CPET (**Table 2**) exhibit lower aerobic and anaerobic capacity compared to healthy individuals (27). According to Aron et al. (37), despite CPET being widely utilized for the evaluation and diagnosis of patients with coronary disease, studies have indicated significant differences in cardiorespiratory responses in OSAS patients. The authors observed that these patients demonstrate reduced ability to exercise and a reduced response of the heart rate (HR) to exercise compared to healthy individuals and concluded that these responses (low oxygen uptake and low heart rate) indicate a chronotropic disability. Moreover, OSAS patients have increased systolic and diastolic blood pressure during exercise and permanently elevated systolic blood pressure during the first minutes of the post-exercise recovery phase. These differences may be due to cardiac dysfunction, decreased muscle metabolism, chronic overactivation of the sympathetic nervous system (SNS) and endothelial dysfunction (17).

Heart failure arises due to repeated hypoxia-re-oxygenation and results in instability of the Autonomic Nervous System (ANS) (38). ANS instability is associated with endothelial dysfunction, vasoconstriction induced by SNS and enhanced response of β-2 receptor (23). According to Mansukhani et al. (38), there are several mechanisms by which blood pressure changes can occur during exercise in patients with OSAS. Disordered breathing with recurrent hypoxia-re-oxygenation circles has an impact on blood pressure response associated with endothelial dysfunction and ANS instability, while during polysomnography (PSG) in OSAS patients, arrythmias are reported (38). Decreased exercise capacity may indicate early cardiovascular dysfunction in these patients (23), while other factors contributing to reduced exercise may include weakened muscles and/or metabolic disorders (25).

Patients with OSAS have reduced pulmonary ventilation activity (reduced ERV relate to the cross-sectional area of the pharyngeal airway which decreases as lung volume decreases from FRC to residual volume suggesting the contribution of lung volumes). It is related to the severity of AHI and desaturation during sleep, interpreting an increased airway resistance during sleep, which is not sufficiently related with body composition (17). In addition, regulation of breathing during sleep is principally under the control of the chemoreceptors. The ventilatory feedback control system of chemoreflex is based on fluctuations of PaO_2, which are more prominent in OSAS patients, making it vulnerable to instability (17). OSAS consists of repetitive episodes of apneas and hypopneas which activate the circle of intermittent hypoxia—hypercapnia, resulting in increased end-tidal CO_2 while bicarbonate buffer

TABLE 2 | Acute responses to exercise in patients with OSAS.

References	Protocol	Results after exercise protocol	
		Increase	**Decrease**
Grote et al. (23)	50 watts per 2 min^{-1}	BP	HR
Tryfon et al. (24)	10, 15, or 20 watts per 1 min^{-1}	BP	VO_{2max}
Bonnani et al. (25)	3 min^{-1} submaximal test		VO_{2max}, La
Oztruk et al. (26)	20 watts per 2 min^{-1}		VO_{2max}
Lin et al. (27)	1 min on 100 kpm		VO_{2max}, anaerobic threshold
Kaleth et al. (28)	15 watts per 1 min^{-1}		VO_{2max}, HR, SBP
Vanhecke et al. (29)	Bruce test	BP	VO_{2max}, HR
Ucok et al. (30)	Wingate test	% body fat	VO_{2max}
Cintra et al. (31)	CPET maximal test	BP, LV	HDL
Rizzi et al. (32)	10–15 watts per 1 min^{-1}	DBP	VO_{2max}
Stavrou et al. (33)	15–20 watts per 1 min^{-1}		VO_{2max}, V_E/MVV, VO_2/HR
Stavrou et al. (34)	15–20 watts per 1 min^{-1}	$P_{ET}CO_2$, BP	
Stavrou et al. (35)	15–20 watts per 1 min^{-1}	Leg Fatigue	VO_{2max}, HR
Stavrou et al. (36)	6 MWT	Dyspnea, Oxidative stress	Distance, HR

CPET, cardiopulmonary exercise test; HDL, high-density lipoprotein; La, lactate acid; LV, left ventricular; MVV, maximum volunteer ventilation; $P_{ET}CO_2$, end-tidal carbon dioxide pressure, V_E, ventilation; VO_{2max}, maximal oxygen uptake; W, watts; BP, blood pressure (systolic / diastolic); DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; LV, left ventricular; 6MWT, 6 minute walk test.

system will attempt compensation by generating bicarbonate ions in addition to hydrogen ions, resulting in metabolic acidosis and alkalosis (17, 36, 39). Moreover, in patients with OSAS were observed higher values in maximum inspiratory pressure, which is associated with the severity of AHI (11). Concomitant with training programs in athletes, the intermittent breath holding during hypoxia-re-oxygenation, in patients with OSAS increases the intrathoracic pressure with successive alteration in the transmural pressure of the cardiac cavities, resulting increased respiratory muscles strength (11).

Insulin - Resistant Syndromes and Pro-inflammatory Proneness

It is well-known that OSAS is related to other, beyond cardiopulmonary comorbidities such as type II diabetes and metabolic syndrome (40), as well as pro – inflammatory susceptibility. As far as diabetes mellitus and metabolic syndrome in relation to OSAS are concerned, researches have attributed their correlation to sleep fragmentation and particularly to sympathetic excitation and hypoxemia (Stavrou et al., 2019) (41). Sympathetic activity halts insulin secretion in islet beta cells, leading to OSAS patients often displaying impaired insulin sensitivity and increased plasma glucose levels (42), while studies have shown a significant statistical relationship between the severity of OSAS and insulin resistance (43). Furthermore, pancreatic beta cells require high supply of oxygen to support insulin secretion, rendering them sensitive to hypoxia (44). Hence, hypoxemia induced by sleep apnea, paves a direct and plausible relationship with insulin—resistant syndromes. Exercise could reverse such detrimental effects, as it restores vascular function by increasing NO bioavailability and balancing autonomic function, while it increases insulin sensitivity (45).

Sleep restriction, based on laboratory studies, is associated with a pre-inflammatory condition, which includes increase in inflammatory cytokines such as interleukins, Tumor Necrosis Factor (TNF) and C-reactive protein (CRP), regardless of obesity (46). Particularly, patients with OSAS due to hypoxia during sleep may experience low-grade systemic inflammation, which in turn may contribute to the onset and/or acceleration of the process of a widely prevalent inflammatory disease, atherosclerosis (47). According to Ruchała et al. (48), neurosteroids are synthesized in nervous system from cholesterol, steroid precursors and sex steroids, circulating in the blood stream and indirectly modulate breathing through gamma-aminobutyric acid (GABA) or N-methyl-D-aspartate (NMDA) signaling pathways. Testosterone is secreted on sleep patterns in particular first REM phase and plasma prolactin (PRL) concentrations show a sleep-dependent pattern, with increased secretion during sleep, while sleep deprivation can lead to lower levels. In addition, CPAP therapy is associated with a significant regulation of hormones serum level such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), PRL, and testosterone. Moreover, Steiropoulos et al. (49) showed that in OSAS patients the night-time hypoxia can affect fasting insulin levels, even in non-diabetic OSAS patients, both a long-term Continuous Positive Airway Pressure (CPAP) treatment and short-term exercise without CPAP treatment (Stavrou et al., 2019) can significantly reduce HbA1c levels. Finally, OSAS patients present low vitamin-D levels. The low vitamin-D levels have been associated with multiple cardiovascular disorders, nervous system disorders (multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's, and Alzheimer's), while CPAP treatment may increase vitamin-D levels OSAS patients (50, 51).

Therefore, exercise is expected to have an anti—inflammatory impact. However, only one study by Cavagnolli et al. (52), aimed

to distinguish the anti - inflammatory effect of exercise in OSAS from its comorbidities and found C-RP was not significantly different between control and non-obese OSAS group. In a recent clinical trial by Jurado-García et al. (53), demonstrated that metabolic profile of obese OSAS patients improved after low—intensity exercise. Therefore, it becomes apparent that exercise acts indirectly through obesity in the amelioration of the systemic inflammatory environment. However, more studies are required to replicate the results.

Oxidative Stress

Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of Reactive Oxygen Species (ROS) or Reactive Oxygen Molecules (ROM) in cells and tissues and the ability of a biological system to detoxify these reactive products. ROS can play, and in fact they do it, several physiological roles (i.e., cell signaling), and they are normally generated as by-products of oxygen metabolism; despite this, environmental stressors (i.e., UV, ionizing radiations, pollutants, and heavy metals) and xenobiotics (i.e., antiblastic drugs) contribute to greatly increase ROS production, therefore causing the imbalance that leads to cell and tissue damage (oxidative stress) (54). Antioxidants are molecules that can donate an electron to a free radical without making themselves unstable, as this causes the free radical to stabilize and become less reactive. Several antioxidants have been exploited in recent years for their actual or supposed beneficial effect against oxidative stress. While we tend to describe oxidative stress as harmful for human body, it could as well be exploited as a therapeutic approach to treat clinical conditions (55).

It is a fact that oxidative stress has been associated with increased values in various diseases and therefore in diseases of the respiratory system (56). Thus, we can conclude that oxidative stress is also directly related to sleep disorders, and especially with obstructive sleep apnea according to studies. Obstructive sleep apnea syndrome can cause free oxygen radicals to be produced, due to the hypoxia/reoxygenation phenomenon, as reoxygenation can causes the production of these reactive oxygen species. Patients with severe OSAS have reduced values of antioxidant capacity, while antioxidant capacity is an index of excessive oxidative stress (57). OSAS itself can increase significantly the values of oxidative stress, given the fact that its patients have no other comorbidities or factors (58). In addition, patients with severe obstructive sleep apnea syndrome who presented increased oxidative stress, reduced the levels of oxidative stress after nasal CPAP treatment (59), but the antioxidant defense was not affected (60), while the values of ROMs in blood samples was associated with the severity of OSAS (61). It is worth emphasizing that sleep-disordered breathing has been recognized as a common, often unrecognized, comorbidity in patients with heart failure that is associated with increased mortality. Intermittent hypoxia in patients with sleep-disordered breathing could resemble ischemia–reperfusion injury, resulting in reactive oxygen species (ROS) generation during the reoxygenation period. Thus, sleep-disordered breathing is independently associated with enhanced oxidative stress in patients with heart failure (62).

Exercise itself is, also, linked to oxidative stress. Although acute exercise elevates ROS, systematic training prompts the organism to adapt to repetitive stimuli by increasing mitochondria biogenesis and antioxidant capacity (63). Hence, exercise brings additional benefits to OSAS patients, making a training program essential to supplement disease management.

MENTAL FUNCTION ALTERATIONS

Fatigue

Sleep disturbances prompt to an underestimated notion of one's exercise capabilities. Patients with OSAS demonstrate leg fatigue during mild exercise and/or physical activity, resulting in early cessation due to intolerance to exercise (64). According to Vanuxem et al. (65), leg fatigue reflects an impairment of muscle metabolism due to decreased peripheral O_2 uptake, increased maximal lactate concentration and delayed lactate elimination in exercising muscles, resulting the occurrence of mitochondrial abnormalities in skeletal myofibres and the increased production of reactive O_2 species exhibited in the neutrophils (25). In addition, the overestimation of the perceived sense of the leg fatigue is associated with cognitive decline, particularly with distinctive domains, in the framework of apneic episodes in OSAS patients (66). Such symptoms seem to promote a rather sedentary lifestyle, but they tend to ameliorate after treatment for OSAS (67).

Sleep disturbances influence acutely athletic performance. Chase et al. demonstrated that a single night of sleep restriction had a significant negative impact on athletic performance the following morning (68), while Rae et al. showed that even recovery from exercise was diminished after a single night of sleep deprivation (69). Concomitantly, two - night sleep deprivation affects executive function, as it causes central fatigue, signifying fewer high threshold motor units that can be recruited and, therefore, fewer muscle fibers will be activated to produce work (70).

Cognition

OSAS as well as the severity of the syndrome can cause mental, cognitive and executive dysfunction, inability to concentrate, memory impairment and reduced activation of areas of the brain associated with knowledge. Some epidemiological studies have suggested a pathophysiological link between OSAS and Alzheimer's disease, which remains to be elucidated (5). According to Vanek et al. (71) attention, working memory, episodic memory, and executive functions are decreased in OSAS, due to different regions of the brain involved in cognition processes such as frontal cortex and hippocampus. Cerebral perfusion is altered during obstructive episodes, predisposing several brain areas relevant to cognitive performance to hypoxia (72). Nevertheless, the brain areas affected by apneic episodes have not been extrapolated to phenotypes of cognitive impairment, yet. Poor sleep quality is related to lower reaction time, after exhaustive exercise, in athletes due to compromised transmission velocity of neuronal impulses from the brain to working muscles (73). Perceptual ability (e.g., motor

TABLE 3 | Chronic responses to exercise in patients with OSAS.

References	Protocol	Results after exercise intervention period	
		Increase	**Decrease**
Norman et al. (83)	6 months (3 sessions/week) aerobic PA >3 METs + resistance exercise training + dietary consultation	VO_{2max}, profile of mood states scores	AHI, Body fat, BP, ESS, Fatigue
Hambrecht et al. (84)	4 weeks, 3 times daily for 10 min on row ergometer and 3 times daily for 10 min on bicycle ergometer (warm-up 5 min, warm-down: 5 min). Workload exercise, so that did not experience chest pain and any signs of ischemia in the ECG	Vessel diameter, mean peak blood flow velocity, endothelium-dependent vasodilatation in LIMA	
Barnes et al. (85)	16 weeks aerobic exercise, resistance training, diet program (follow-up at 12 months).	VO_{2max}, strength, quality of life	AHI, Body fat, HR in maximal effort, ESS, Cardiometabolic indexes
Kline et al. (86)	12 weeks (4 sessions/week), 150 min/week aerobic exercise on 60% of HRR and resistance exercises (4 sessions/week), 2 sets, 10–12 rep	Daily unsupervised activity, Sleep quality (PSQI)	AHI, Body fat
Yang et al. (87)	12 weeks (3 sessions/week), 30 min aerobic exercise on AT	SpO_2	AHI, BMI, HRR
Servantes et al. (88)	3/week for 3 months, 30–70 years, NYHA class II to III, AHI ≥ 5/h with symptoms or AHI ≥15/h, randomized four groups (A: control, B: exercise, C: CPAP, D: exercise + CPAP) B + C group: warm-up: 10-min, aerobic training: ±10 bpm form HR_{AT} of CPET (treadmill and cycloergometer; 1 month 30 min, 2 months 45-min) and strength training (three exercises for upper limbs and four exercises for lower limbs, 1-min rest period, free weights) 50–60% of 1 RM	VO_{2max}	AHI, ESS, Quality of life
Yilmaz et al. (89)	12 weeks (5 sessions/week), 60-min Tai-Chi & Qigong (3 sessions/week in rehabilitation center and 2 sessions/week self-selected)	SpO_2, Sleep quality (PSQI)	AHI, ESS
Stavrou et al. (39)	4 weeks (3 sessions/week), 4 set for 5 min with 1 min rest on 70% of VO_{2max}	VO_{2max}	AHI, BP, HbA1-c, LDL
Berger et al. (90)	9 months 3 h/week supervised community physical activity program (Nordic walking, gymnastics, and aqua gym), 40–80 years, 15–30 AHI/h, warm-up 10-min, 40-min combined resistance and aerobic exercises at the anaerobic threshold, and cooldown 10-min stretches	VO_{2max}	AHI, Nighttime HRV, Cardiovascular risk

1 RM, one-repetition maximum; AHI, apnea-hypopnea index; AT, anaerobic threshold; avergSpO$_2$, mean oxygen saturation during polysomnography study; BMI, body mass index; BP, blood pressure; CPAP, Continuous positive airway pressure; CPET, cardiopulmonary exercise test; ECG, Electrocardiography; ESS, Epworth sleepiness scale; HbA1-c, hemoglobin A1c; HRR, heart rate reserve; LDL, low-density lipoprotein; LIMA, left internal mammary artery; NYHA, New York Heart Association; PA, physical activity; PSQI, Pittsburgh Sleep Quality Index; VO$_{2max}$, oxygen uptake in maximal effort.

coordination), as well as attention and memory consolidation are hindered by acutely restricted sleep (36).

Exercise, particularly aerobic, along with a healthy and balanced diet, have been strongly linked to enhancing cognitive skills, as it increases cerebral perfusion (74). Executive function (75) and memory consolidation (76) have been indicated as examples of cognitive skills honed by exercise. However, further studies remain to fully elucidate the exact pathogenetic relationship of OSAS and cognitive impairment, especially in the context of exercise.

Anxiety and Mood Disorders

Several studies have adequately associated OSAS with mood and anxiety disorders (17). Sleep deprivation (chronic and/or acute) has a negative impact on cognitive performance, such as increased general anxiety, anxiety for failure, memory impairment, reduced concentration, and dysfunctional affective regulation (77, 78). According to Daabis and Gharraf (79), anxiety coexisting with depression in patients with OSAS and no CPAP treatment is associated with the general population, while depressive symptoms are highly prevalent in patients with moderate to severe OSAS and high BMI (80). Moreover, depression relate to functional decrease of serotoninergic neurotransmission, responsible for the alterations in sleep (79). Serotonin delivery to upper airway dilatator motor neurons reduce in dependency of the vigilance state, and lead to reductions in dilator muscle activity specifically during sleep (81).

CHRONIC RESPONSES TO EXERCISE

Physical activity is considered to be one of the greatest lifestyle behaviors promoting health and is closely related to sleep quality, while there is a two-way relationship between sleep quality and physical activity (82). The low levels of physical activity in patients with OSAS, are due to early fatigue, daytime drowsiness and increased BMI. Pulmonary rehabilitation program (**Table 3**), with exercise being the main feature, in patients with OSAS show results that are associated with reduced AHI and ESS (91), while, at the same time, exercise has been shown to reduce the severity of other disorders or/and other OSAS related diseases, such as diabetes mellitus, cardiovascular disease, hypertension and obesity. The way exercise reduces the symptoms of OSAS is not fully understood, but studies have shown that the effect

of exercise in patients with OSAS is not related to weight loss or BMI, but is possibly related to other mechanisms not yet understood (92). One possible explanation given, for exercise to reduce mild to severe AHI, focuses on the comorbidity of obesity and the obesity - hypoventilation syndrome, due to increased adipose tissue to the upper respiratory tract, leading to increased number of events of sleep apnea and/or hypopnea (93).

In addition, physical activity in patients with OSAS has been observed to present a protective role in the course of the disease, without, however, representing a reduction in maximal oxygen uptake, an indicator associated with health status (35). A supervised physical activity may prevent a decline in nighttime cardiac autonomic function (CAF) and may be cardioprotective in OSAS patients with bradycardia, CAF preservation, and increase O_2 uptake in maximal effort (90). According to Servantes et al. (88), both exercise and CPAP treatment improved subjective excessive daytime sleepiness, quality of life, and the NYHA functional class distribution. Furthermore, peak O_2 consumption, as health indicator, can be improved only with exercise (strength and endurance) while exercise can reduce AHI and have important implications in the management of patients with HF and OSAS (88).

Exercise can lead to a reduction in body weight and BMI and therefore a reduction in adipose tissue in the upper tract and in the pharyngeal region (94), while at the same time exercise improves the levels of physical activity and in combination with application of CPAP machine, there is additional improvement in patients' sleep symptoms and quality of life. The increase of physical activity improves patients' health indicators and can significantly reduce the cardiovascular risk factors associated with OSAS (39). Finally, exercise in patients with OSAS, improves quality of life and mood, reduces levels of anger, depression, bodily pain, and total mood disturbances, and increased participation in social activities (95). Exercise contributes positive biological and psychological effects that affect the brain and the cognitive functioning and promote a condition of well-being, while triggers potent neuroplastic phenomena, partly mediated by epigenetic mechanisms (96).

CONCLUSION

Patients with OSAS exhibit systematic detrimental effects, with tremendous impact on quality of life, if left untreated. Cardiopulmonary implications, as well as endocrine dysregulation and cognitive impairment consist of the main consequences. Patients with OSAS exhibit acute exercise responses related to OSAS such as reduced ability to exercise, lower aerobic and anaerobic capacity compared to healthy individuals. They also exhibit chronic responses such as prolonged physical inactivity. As a result, a specific exercise program targeting patients with OSAS is described in detail, in order to ameliorate the systematic consequences of OSAS, as well as to propose the prescription of an exercise program as a supplementary therapeutic intervention for these patients.

AUTHOR CONTRIBUTIONS

VS and KG conceived of the presented idea and designed the study. VS, KT, GV, EP, KA, and SB contributed to the writing the paper. VS designed the figures and tables. ZD and KG supervised the study. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.806924/full#supplementary-material

REFERENCES

1. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. *Am J Respir Crit Care Med*. (1996) 153:855–78. doi: 10.1164/ajrccm.153.2.8564147
2. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. *J Thorac Dis*. (2015) 7:1311–22. doi: 10.3978/j.issn.2072-1439.2015.06.11
3. Cai A, Zhou Y, Zhang J, Zhong Q, Wang R, Wang L. Epidemiological characteristics and gender-specific differences of obstructive sleep apnea in a Chinese hypertensive population: a cross-sectional study. *BMC Cardiovasc Disord*. (2017) 17:8. doi: 10.1186/s12872-016-0447-4
4. Kushida AC, Littner RM, Morgenthaler T, Alessi AC, Bailey D, Coleman J, et al. Practice Parameters for the Indications for Polysomnography and Related Procedures: An Update for 2005. *Sleep* (2005) 28:499–523. doi: 10.1093/sleep/28.4.499
5. Valgimigli M, Ceconi C, Malagutti P, Merli E, Soukhomovskaia O, Francolini G, et al. Tumor necrosis factor-alpha receptor 1 is a major predictor of mortality and new-onset heart failure in patients with acute myocardial infarction: the cytokine-activation and long-term prognosis in myocardial infarction (C-ALPHA) study. *Circulation*. (2005) 111:863–70. doi: 10.1161/01.CIR.0000155614.35441.69
6. Mattis J, Sehgal A. Circadian rhythms, sleep, and disorders of aging. *Trends Endocrinol Metab*. (2016) 27:192–203. doi: 10.1016/j.tem.2016.02.003
7. Simpson L, McArdle N, Eastwood PR, Ward KL, Cooper MN, Wilson AC, et al. Physical inactivity is associated with moderate-severe obstructive sleep apnea. *J Clin Sleep Med*. (2015) 11:1091–9. doi: 10.5664/jcsm.5078
8. Iftikhar IH, Kline CE, Youngstedt SD. Effects of exercise training on sleep apnea: a meta-analysis. *Lung*. (2014) 192:175–84. doi: 10.1007/s00408-013-9511-3
9. Stavrou VT, Astara K, Tourlakopoulos KN, Daniil Z, Gourgoulianis KI, Kalabakas K, et al. Sleep quality's effect on vigilance and perceptual ability in adolescent and adult athletes. *J Sports Med*. (2021) 2021:9. doi: 10.1155/2021/5585573
10. Levett DZH, Jack S, Swart M, Carlisle J, Wilson J, Snowden C, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *Br J Anaesth*. (2018) 120:484–500. doi: 10.1016/j.bja.2017.10.020
11. Stavrou VT, Astara K, Karetsi E, Daniil Z, Gourgoulianis KI. Respiratory muscle strength as an indicator of the severity of apnea hypopnea index: stepping towards the distinction between sleep apnea and breath holding. *Cureus*. (2021) 13:e14015. doi: 10.7759/cureus.14015

12. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. (2002) 166:111–7. doi: 10.1164/ajrccm.166.1.at1102
13. Borg E, Borg G, Larsson K, Letzter M, Sundblad BM. An index for breathlessness and leg fatigue. *Scand J Med Sci Sports*. (2010) 20:644–50. doi: 10.1111/j.1600-0838.2009.00985.x
14. Natsios G, Pastaka C, Vavougios G, Zarogiannis SG, Tsolaki V, Dimoulis A, et al. Age, body mass index, and daytime and nocturnal hypoxia as predictors of hypertension in patients with obstructive sleep apnea. *J Clin Hypertens*. (2016) 18:146–52. doi: 10.1111/jch.12645
15. Abdeyrim A, Zhang Y, Li N, Zhao M, Wang Y, Yao X, et al. Impact of obstructive sleep apnea on lung volumes and mechanical properties of the respiratory system in overweight and obese individuals. *BMC Pulm Med*. (2015) 15:76. doi: 10.1186/s12890-015-0063-6
16. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med*. (1993) 328:303–7. doi: 10.1056/NEJM199302043280502
17. Stavrou V, Bardaka F, Karetsi E, Daniil Z, Gourgoulianis KI. Brief review: ergospirometry in patients with obstructive sleep apnea syndrome. *J Clin Med*. (2018) 7:191. doi: 10.3390/jcm7080191
18. Goff EA, Nicholas CL, Simonds AK, Trinder J, Morrell MJ. Differential effects of waking from non-rapid eye movement versus rapid eye movement sleep on cardiovascular activity. *J Sleep Res*. (2010) 19(1 Pt 2):201–6. doi: 10.1111/j.1365-2869.2009.00783.x
19. Grote L, Kraiczi H, Hedner J. Reduced alpha- and beta(2)-adrenergic vascular response in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. (2000) 162 (4 Pt 1):1480–7. doi: 10.1164/ajrccm.162.4.9912028
20. Mills PJ, Dimsdale JE, Coy TV, Ancoli-Israel S, Clausen JL, Nelesen RA. Beta 2-adrenergic receptor characteristics in sleep apnea patients. *Sleep*. (1995) 18:39–42. doi: 10.1093/sleep/18.1.39
21. DiCarlo SE, Bishop VS. Central baroreflex resetting as a means of increasing and decreasing sympathetic outflow and arterial pressure. *Ann N Y Acad Sci*. (2001) 940:324–37. doi: 10.1111/j.1749-6632.2001.tb03688.x
22. Cooper VL, Elliott MW, Pearson SB, Taylor CM, Mohammed MM, Hainsworth R. Daytime variability of baroreflex function in patients with obstructive sleep apnoea: implications for hypertension. *Exp Physiol*. (2007) 92:391–8. doi: 10.1113/expphysiol.2006.035584
23. Grote L, Hedner J, Peter H. The heart rate response to exercise is blunted in patients with sleep-related breathing disorder. *Cardiology*. (2004) 102:93–9. doi: 10.1159/000077911
24. Tryfon S, Stanopoulos I, Dascalopoulou E, Argyropoulou P, Bouros D, Mavrofridis E. Sleep apnea syndrome and diastolic blood pressure elevationduring exercise. *Respiration*. (2004) 71:499–504. doi: 10.1159/000080635
25. Bonanni E, Pasquali L, Manca ML, Maestri M, Prontera C, Fabbrini M, et al. Lactate production and catecholamine profile during aerobic exercise in normotensive OSAS patients. *Sleep Med*. (2004) 5:137–45. doi: 10.1016/j.sleep.2003.08.009
26. Ozturk LM, Metin G, Cuhadaroglu C, Utkusavas A, Tutluoglu B. Cardiopulmonary responses to exercise in moderate- to-severe obstructive sleep apnea. *Tuberk Toraks*. (2005) 53:10–9.
27. Lin CC, Hsieh WY, Chou CS, Liaw SF. Cardiopulmonary exercise testing in obstructive sleep apnea syndrome. *Respir Physiol Neurobiol*. (2006) 150:27–34. doi: 10.1016/j.resp.2005.01.008
28. Kaleth AS, Chittenden TW, Hawkins BJ, Hargens TA, Guill SG, Zedalis D, et al. Unique cardiopulmonary exercise test responses in overweight middle-aged adults with obstructive sleep apnea. *Sleep Med*. (2007) 8:160–8. doi: 10.1016/j.sleep.2006.08.005
29. Vanhecke T, Franklin B, Zalesin K, Sangal B, deJong A, Agrawal V, et al. Cardiorespiratory fitness and obstructive sleep apnea syndrome in morbidly obese patients. *Chest*. (2008) 134:539–45. doi: 10.1378/chest.08-0567
30. Ucok K, Aycicek A, Sezer M, Genc A, Akkaya M, Caglar V, et al. Aerobic and anaeroc exercise capacities in obstructive sleep apnea and associations with subcutaneous fat distributions. *Lung*. (2009) 187:29–36. doi: 10.1007/s00408-008-9128-0
31. Cintra FD, Tufik S, Paola AD, Feres MC, Melo-Fujita L, Oliveira W, Rizzi C, et al. Cardiovascular profile in patients with obstructive sleep apnea. *Arq Bras Cardiol*. (2011) 96:293–9. doi: 10.1590/S0066-782X2011005000030
32. Rizzi CF, Cintra F, Mello-Fujita L, Rios LF, Mendonca ET, Feres MC, et al. Does obstructive sleep apnea impair the cardiopulmonary response to exercise? *Sleep*. (2013) 36:547–53. doi: 10.5665/sleep.2542
33. Stavrou V, Vavougios G, Pastaka CH, Daniil Z, Gourgoulianis K, Karetsi E. The cardiopulmonary exercise testing as a novel predictive tool of sleep apnea syndrome. *ERS Int Congr*. (2015) 46(Suppl. 59):PA2321. doi: 10.1183/13993003.congress-2015.PA2321
34. Stavrou V, Boutou AK, Vavougios GD, Pastaka C, Gourgoulianis KI, Koutedakis Y, et al. The use of cardiopulmonary exercise testing in identifying the presence of obstructive sleep apnea syndrome in patients with compatible symptomatology. *Respir Physiol Neurobiol*. (2019) 262:26–31. doi: 10.1016/j.resp.2019.01.010
35. Stavrou V, Bardaka F, Karetsi E, Seitanidis G, Daniil Z, Gourgoulianis KI. The effect of physical strain on breeders patients with obstructive sleep apnea syndrome. *Respir Physiol Neurobiol*. (2019) 260:137–9. doi: 10.1016/j.resp.2018.11.009
36. Stavrou VT, Vavougios GD, Astara K, Siachpazidou DI, Papayianni E, Gourgoulianis KI. The 6-minute walk test and anthropometric characteristics as assessment tools in patients with Obstructive Sleep Apnea Syndrome. A preliminary report during the pandemic. *J Personal Med*. (2021) 11:563. doi: 10.3390/jpm11060563
37. Aron A, Zedalis D, Gregg JM, Gwazdauskas FC, Herbert WG. Potential clinical use of cardiopulmonary exercise testing in obstructive sleep apnea hypopnea syndrome. *Int J Cardiol*. (2009) 132:176–86. doi: 10.1016/j.ijcard.2008.11.014
38. Mansukhani MP, Allison TG, Lopez-Jimenez F, Somers VK, Caples SM. Functional aerobic capacity in patients with sleep-disordered breathing. *Am J Cardiol*. (2013) 111:1650–4. doi: 10.1016/j.amjcard.2013.02.008
39. Stavrou V, Karetsi E, Daniil Z, Gourgoulianis KI. 4 weeks exercise in obstructive sleep apnea syndrome patient with type 2 diabetes mellitus and without continuous positive airway pressure treatment: a case report. *Sleep Med Res*. (2019) 10:1–5. doi: 10.17241/smr.2019.00374
40. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med*. (2015) 3:310–8. doi: 10.1016/S2213-2600(15)00043-0
41. Murphy AM, Thomas A, Crinion SJ, Kent BD, Tambuwala MM, Fabre A, et al. Intermittent hypoxia in obstructive sleep apnoea mediates insulin resistance through adipose tissue inflammation. *Eur Respir J*. (2017) 49:1601731. doi: 10.1183/13993003.01731-2016
42. Ryan S. Adipose tissue inflammation by intermittent hypoxia: mechanistic link between obstructive sleep apnoea and metabolic dysfunction. *J Physiol*. (2017) 595:2423–30. doi: 10.1113/JP273312
43. Iftikhar IH, Hoyos CM, Phillips CL. Meta-analyses of the association of sleep apnea with insulin resistance, and the effects of CPAP on HOMA-IR, adiponectin, and visceral adipose fat. *J Clin Sleep Med*. (2015) 11:475–85. doi: 10.5664/jcsm.4610
44. Olsson R, Olerud J, Pettersson U, Carlsson PO. Increased numbers of low-oxygenated pancreatic islets after intraportal islet transplantation. *Diabetes*. (2011) 60:2350–3. doi: 10.2337/db09-0490
45. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. (2011) 43:1334–59. doi: 10.1249/MSS.0b013e318213fefb
46. Perelis M, Ramsey KM, Marcheva B, Bass J. Circadian transcription from beta cell function to diabetes path-ophysiology. *J Biol Rhythms*. (2016) 31:323–36. doi: 10.1177/0748730416656949
47. Jordan A, McSharry D, Malhotra A. Adult obstructive sleep apnoea. *Lancet*. (2014) 22:736–47. doi: 10.1016/S0140-6736(13)60734-5
48. Ruchała M, Bromińska B, Cyrańska-Chyrek E, Kuznar-Kamińska B, Kostrzewska M, Batura-Gabryel H. Obstructive sleep apnea and hormones

- a novel insight. *Arch Med Sci.* (2017) 13:875–84. doi: 10.5114/aoms.2016.61499
49. Steiropoulos P, Papanas N, Nena E, Tsara V, Fitili C, Tzouvelekis A, et al. Markers of glycemic control and insulin resistance in non-diabetic patients with obstructive sleep apnea hypopnea syndrome: does adherence to CPAP treatment improve glycemic control? *Sleep Med.* (2009) 10:887–91. doi: 10.1016/j.sleep.2008.10.004
50. Siachpazidou DI, Stavrou V, Zouridis S, Gogou E, Economou NT, Pastaka C, et al. 25-hydroxyvitamin D levels in patients with obstructive sleep apnea and continuous positive airway pressure treatment: a brief review. *Sleep Sci.* (2020) 13:78–83. doi: 10.1007/s11325-020-02146-6
51. Siachpazidou DI, Stavrou VT, Astara K, Pastaka C, Gogou E, Hatzoglou C, et al. Alzheimer disease in patients with obstructive sleep apnea syndrome. *Tanaffos.* (2020) 19:176–85.
52. Cavagnolli DA, Esteves AM, Ackel-D'Elia C, Maeda MY, de Faria AP, Tufik S, et al. Aerobic exercise does not change C-reactive protein levels in non-obese patients with obstructive sleep apnoea. *Eur J Sport Sci.* (2014) 14(Suppl. 1):S142–7. doi: 10.1080/17461391.2012.663412
53. Jurado-García A, Molina-Recio G, Feu-Collado N, Palomares-Muriana A, Gómez-González AM, Márquez-Pérez FL, et al. Effect of a graduated walking program on the severity of obstructive sleep apnea syndrome. A randomized clinical trial. *Int J Environ Res Public Health.* (2020) 17:6334. doi: 10.3390/ijerph17176334
54. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative stress: harms and benefits for human health. *Oxid Med Cell Longev.* (2017) 2017:8416763. doi: 10.1155/2017/8416763
55. Betteridge DJ. What is oxidative stress? *Metabolism.* (2000) 49(2 Suppl. 1):3–8. doi: 10.1016/S0026-0495(00)80077-3
56. Papageorgiou E, Kostikas K, Kiropoulos T, Karetsi E, Mpatavanis G, Gourgoulianis KI. Increased oxidative stress in exudative pleural effusions: a new marker for the differentiation between exudates and transudates? *Chest.* (2005) 128:3291–7. doi: 10.1378/chest.128.5.3291
57. Christou K, Markoulis N, Moulas AN, Pastaka C, Gourgoulianis KI. Reactive oxygen metabolites (ROMs) as an index of oxidative stress in obstructive sleep apnea patients. *Sleep Breath.* (2003) 7:105–10. doi: 10.1007/s11325-003-0105-9
58. Ntalapascha M, Makris D, Kyparos A, Tsilioni I, Kostikas K, Gourgoulianis K, et al. Oxidative stress in patients with obstructive sleep apnea syndrome. *Sleep Breath.* (2013) 17:549–55. doi: 10.1007/s11325-012-0718-y
59. Christou K, Kostikas K, Pastaka C, Tanou K, Antoniadou I, Gourgoulianis KI. Nasal continuous positive airway pressure treatment reduces systemic oxidative stress in patients with severe obstructive sleep apnea syndrome. *Sleep Med.* (2009) 10:87–94. doi: 10.1016/j.sleep.2007.10.011
60. Alzoghaibi MA, Bahammam AS. The effect of one night of continuous positive airway pressure therapy on oxidative stress and antioxidant defense in hypertensive patients with severe obstructive sleep apnea. *Sleep Breath.* (2012) 16:499–504. doi: 10.1007/s11325-011-0531-z
61. Christou K, Moulas AN, Pastaka C, Gourgoulianis KI. Antioxidant capacity in obstructive sleep apnea patients. *Sleep Med.* (2003) 4:225–8. doi: 10.1016/S1389-9457(02)00253-8
62. Kondo M, Kohno T, Kohsaka S, Fukuoka R, Shiraishi Y, Sawano M, et al. Enhanced oxidative stress is associated with sleep-disordered breathing and obesity in patients with heart failure. *Int J Cardiol.* (2016) 15:133–5. doi: 10.1016/j.ijcard.2016.02.042
63. Kawamura T, Muraoka I. Exercise-induced oxidative stress and the effects of antioxidant intake from a physiological viewpoint. *Antioxidants.* (2018) 7:119. doi: 10.3390/antiox7090119
64. Aguillard RN, Riedel BW, Lichstein KL, Grieve FG, Johnson CT, Noe SL. Daytime functioning in obstructive sleep apnea patients: exercise tolerance, subjective fatigue, and sleepiness. *Appl Psychophysiol Biofeedback.* (1998) 23:207–17. doi: 10.1023/A:1022257514209
65. Vanuxem D, Badier M, Guillot C, Delpierre S, Jahjah F, Vanuxem P. Impairment of muscle energy metabolism in patients with sleep apnoea syndrome. *Respir Med.* (1997) 91:551–7. doi: 10.1016/S0954-6111(97)90089-5
66. Astara K, Stavrou VT, Vavougios GD, Siachpazidou DI, Papayianni E, Gourgoulianis KI. Fitness indicators and cognitive performance in patients with obstructive sleep apnea syndrome. A preliminary report. *ERJ Open Res.* (2021) 7(Suppl. 7):52. doi: 10.1183/23120541.sleepandbreathing,-2021.52
67. Chotinaiwattarakul W, O'Brien LM, Fan L, Chervin RD. Fatigue, tiredness, and lack of energy improve with treatment for OSA. *J Clin Sleep Med.* (2009) 5:222–7. doi: 10.5664/jcsm.27490
68. Chase JD, Roberson PA, Saunders MJ, Hargens TA, Womack CJ, Luden ND. One night of sleep restriction following heavy exercise impairs 3-km cycling time-trial performance in the morning. *Appl Physiol Nutr Metab.* (2017) 42:909–15. doi: 10.1139/apnm-2016-0698
69. Rae DE, Chin T, Dikgomo K, Hill L, McKune AJ, Kohn TA, et al. One night of partial sleep deprivation impairs recovery from a single exercise training session. *Eur J Appl Physiol.* (2017) 117:699–712. doi: 10.1007/s00421-017-3565-5
70. Skurvydas A, Kazlauskaite D, Zlibinaite L, Cekanauskaite A, Valanciene D, Karanauskiene D, et al. Effects of two nights of sleep deprivation on executive function and central and peripheral fatigue during maximal voluntary contraction lasting 60s. *Physiol Behav.* (2021) 229:113226. doi: 10.1016/j.physbeh.2020.113226
71. Vanek J, Prasko J, Genzor S, Ociskova M, Kantor K, Holubova M, et al. Obstructive sleep apnea, depression and cognitive impairment. *Sleep Med.* (2020) 72:50–8. doi: 10.1016/j.sleep.2020.03.017
72. O'Donoghue FJ, Wellard RM, Rochford PD, Dawson A, Barnes M, Ruehland WR, et al. Magnetic resonance spectroscopy and neurocognitive dysfunction in obstructive sleep apnea before and after CPAP treatment. *Sleep.* (2012) 35:41–8. doi: 10.5665/sleep.1582
73. Fullagar HH, Skorski S, Duffield R, Hammes D, Coutts AJ, Meyer T. Sleep and athletic performance: the effects of sleep loss on exercise performance, and physiological and cognitive responses to exercise. *Sports Med.* (2015) 45:161–86. doi: 10.1007/s40279-014-0260-0
74. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2011) 42:2672–713. doi: 10.1161/STR.0b013e3182299496
75. Kleinloog JPD, Mensink RP, Ivanov D, Adam JJ, Uludag K, Joris PJ. Aerobic exercise training improves cerebral blood flow and executive function: a randomized, controlled cross-over trial in sedentary older men. *Front Aging Neurosci.* (2019) 11:333. doi: 10.3389/fnagi.2019.00333
76. Maass A, Düzel S, Goerke M, Becke A, Sobieray U, Neumann K, et al. Vascular hippocampal plasticity after aerobic exercise in older adults. *Mol Psychiatry.* (2015) 20:585–93. doi: 10.1038/mp.2014.114
77. Matsumoto Y, Mishima K, Satoh K, Shimizu T, Hishikawa Y. Physical activity increases the dissociation between subjective sleepiness and objective performance levels during extended wakefulness in human. *Neurosci Lett.* (2002) 326:133–6. doi: 10.1016/S0304-3940(02)00335-X
78. Kamphuis J, Meerlo P, Koolhaas JM, Lancel M. Poor sleep as a potential causal factor in aggression and violence. *Sleep Med.* (2012) 13:327–34. doi: 10.1016/j.sleep.2011.12.006
79. Daabis R, Gharraf H. Predictors of anxiety and depression in patients with obstructive sleep apnea. *Egypt J Chest Dis Tuberculosis.* (2012) 61:171–7. doi: 10.1016/j.ejcdt.2012.10.032
80. Rezaeitalab F, Moharrari F, Saberi S, Asadpour H, Rezaeetalab F. The correlation of anxiety and depression with obstructive sleep apnea syndrome. *J Res Med Sci.* (2014) 19:205–10.
81. Veasey SC. Serotonin agonists and antagonists in obstructive sleep apnea: therapeutic potential Am. *J Respir Med.* (2003) 2:21–9. doi: 10.1007/BF03256636
82. Mendelson M, Bailly S, Marillier M, Flore P, Borel JC, Vivodtzev I, et al. Obstructive sleep apnea syndrome, objectively measured physical activity and exercise training interventions: a systematic review and meta-analysis. *Front Neurol.* (2018) 9:73. doi: 10.3389/fneur.2018.00073
83. Norman JF, Von Essen SG, Fuchs RH, McElligott M. Exercise training effect on obstructive sleep apnea syndrome. *Sleep Res Online.* (2000) 3:121–9.
84. Hambrecht R, Adams V, Erbs S, Linke A, Kränkel N, Shu Y, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation

of endothelial nitric oxide synthase. *Circulation.* (2003) 107:3152–8. doi: 10.1161/01.CIR.0000074229.93804.5C
85. Barnes M, Goldsworthy UR, Cary BA, Hill CJ. A diet and exercise program to improve clinical outcomes in patients with obstructive sleep apnea–a feasibility study. *J Clin Sleep Med.* (2009) 5:409–15. doi: 10.5664/jcsm.27594
86. Kline CE, Crowley EP, Ewing GB, Burch JB, Blair SN, Durstine JL, et al. The effect of exercise training on obstructive sleep apnea and sleep quality: a randomized controlled trial. *Sleep.* (2011) 34:1631–40. doi: 10.5665/sleep.1422
87. Yang H, Liu Y, Zheng H, Liu G, Mei A. Effects of 12 weeks of regular aerobic exercises on autonomic nervous system in obstructive sleep apnea syndrome patients. *Sleep Breath.* (2018) 22:1189–95. doi: 10.1007/s11325-018-1736-1
88. Servantes DM, Javaheri S, Kravchychyn ACP, Storti LJ, Almeida DR, de Mello MT, et al. Effects of exercise training and CPAP in patients with Heart Failure and OSA: a preliminary study. *Chest.* (2018) 154:808–17. doi: 10.1016/j.chest.2018.05.011
89. Yilmaz GG, Akkoyunlu ME, Kikic L, Algun C. The effect of T'ai Chi and Qigong training on patients with obstructive sleep apnea: a randomized controlled study. *J Altern Complement Med.* (2019) 25:317–25. doi: 10.1089/acm.2018.0197
90. Berger M, Raffin J, Pichot V, Hupin D, Garet M, Labeix P, et al. Effect of exercise training on heart rate variability in patients with obstructive sleep apnea: a randomized controlled trial. *Scand J Med Sci Sports.* (2019) 29:1254–62. doi: 10.1111/sms.13447
91. Aiello AE, Feinstein L, Dowd JB, Pawelec G, Derhovanessian E, Galea S, et al. Income and markers of immunological cellular aging. *Psychosom Med.* (2016) 78:657–66. doi: 10.1097/PSY.0000000000000320
92. Awad KM, Malhotra A, Barnet JH, Quan SF, Peppard PE. Exercise is associated with a reduced incidence of sleep-disordered breathing. *Am J Med.* (2012) 125:485–90. doi: 10.1016/j.amjmed.2011.11.025
93. Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnea?: the rational clinical examination systematic review. *JAMA*. (2016) 310:731e741. doi: 10.1001/jama.2013.276185
94. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. *Am J Med.* (2009) 122:535e542. doi: 10.1016/j.amjmed.2008.10.037
95. Butner KL, Hargens TA, Kaleth AS, Miller LE, Zedalis D, Herbert WG. Association of obstructive sleep apnea severity with exercise capacity and health-related quality of life. *N Am J Med Sci.* (2013) 5:362–6. doi: 10.4103/1947-2714.114168
96. Mandolesi L, Polverino A, Montuori S, Foti F, Ferraioli G, Sorrentino P, et al. Effects of physical exercise on cognitive functioning and wellbeing: biological and psychological benefits. *Front Psychol.* (2018) 27:509. doi: 10.3389/fpsyg.2018.00509

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The Role of Brain-Derived Neurotrophic Factor in Obstructive Sleep Apnea and Endothelial Function in a Pediatric Population With Obesity

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Background: Childhood obesity has increased worldwide, becoming a significant public health concern. Brain-derived neurotrophic factor (BDNF) plays an important role in the central regulation of food intake and body weight, but little is known regarding its role in childhood obesity. Next to obesity, BDNF has been linked to obstructive sleep apnea (OSA) and endothelial dysfunction, two obesity-related comorbidities. The aim of this study is to investigate how BDNF, OSA and endothelial dysfunction interact in children with obesity and to determine the effect of weight loss on serum BDNF levels.

Methods: Children and adolescents with obesity aged 8–18 years who were enrolled in a multidisciplinary obesity treatment (MOT) in a tertiary hospital, were prospectively included. Several examinations were conducted during this MOT; at baseline, after 6 months and after 12 months, including the assessment of endothelial function, body composition measurements and a polysomnography. BDNF levels were measured on a serum sample by means of ELISA.

Results: A total of 103 patients with obesity was included, of which 20 had OSA (19.4%). BDNF levels were comparable in children with obesity and OSA and children with obesity but without OSA (26.75 vs. 27.87 ng/ml, $p = 0.6$). No correlations were found between BDNF and sleep-related variables or between BDNF and endothelial function parameters nor between BDNF and adiposity measures. To investigate if the interaction between OSA and endothelial dysfunction had an influence on BDNF levels, a general linear model was used. This model revealed that a diagnosis of OSA, as well as the interaction between OSA and maximal endothelial dilatation, contributed significantly ($p = 0.03$, $p = 0.04$, respectively) to BDNF levels. After 1 year of weight loss therapy, BDNF levels did not change (26.18 vs. 25.46 ng/ml, $p = 0.7$) in our population.

Conclusion: BDNF concentrations were comparable in children with obesity, both with and without OSA, indicating that BDNF levels are not affected by OSA. However, we did find an interaction effect of OSA and endothelial function on BDNF levels.

Keywords: brain-derived neurotrophic factor, pediatric obesity, obstructive sleep apnea, endothelial function, weight loss treatment, multidisciplinary obesity treatment

INTRODUCTION

The pediatric obesity epidemic has been expanding in both developed and developing countries at an alarming rate over the past decades. According to the World Health Organization, 340 million children and adolescents worldwide had overweight or obesity in 2016 (1). Multiple cardiovascular risk factors are associated with childhood obesity, which can all detrimentally affect the endothelium, leading to endothelial dysfunction (2–4), highly prognostic of later cardiovascular morbidity and mortality. Another important obesity-related comorbidity is obstructive sleep apnea (OSA) which is characterized by recurrent breathing pauses during sleep. Several complications are associated with OSA in childhood, including cardiovascular and neurocognitive complications (5, 6). Studies show that the recurrent episodes of arousal and hypoxemia, occurring in OSA patients, can result in increased sympathetic activity, oxidative stress and inflammation, again contributing to endothelial dysfunction (7, 8). This implies that inflammatory processes leading to endothelial dysfunction can play an important role in the association between OSA and cardiovascular disease. Since obesity is a leading cause of OSA in adults and an increasing etiology of childhood OSA, there is concern that the two concurrent conditions may create an environment that further induces endothelial dysfunction and cardiovascular morbidity (9). This was confirmed by a study that showed that both OSA and obesity are independently associated with an increased risk for endothelial dysfunction in prepubertal children, and that these effects are magnified when both obesity and OSA are present (10). Indeed, our research group recently showed that even after weight loss treatment endothelial dysfunction improved less in the presence of OSA (11). This highlights the need for effective long-term weight-loss programs to prevent OSA and the ongoing epidemic of obesity.

Brain-derived neurotrophic factor (BDNF) is one of the neurotrophic factors that support differentiation, maturation and survival of neurons in the nervous system. Besides its neuroprotective effect, BDNF plays a major role in feeding behavior, food intake regulation, energy metabolism and weight control (12, 13). However, the association between circulating levels of BDNF and obesity is still unclear. Only a limited number of studies have looked at the relationship between BDNF and obesity in children, with conflicting results (14, 15). No studies have investigated the effect of OSA and obesity on BDNF in a pediatric population. Animal studies have shown that exposure to chronic intermittent hypoxia can lead to a decrease in BDNF expression (16). As BDNF has an important role in cognitive function (17), this could indicate a crucial role for this protein in the neurocognitive complications seen in childhood OSA. Since it has been suggested that neurocognitive deficits and endothelial dysfunction as seen in children with OSA are linked (18), BDNF could play an important role in this association (19). Indeed, numerous reports have uncovered critical roles for neurotrophins such as BDNF and their receptors on non-neural cells, including endothelial cells (20). Therefore, this is the first study that examines the relationship between OSA, endothelial function and BDNF in a pediatric population with obesity. Additionally, the effect of a multidisciplinary obesity weight loss treatment program on BDNF levels in this population is also investigated.

Abbreviations: AHI, apnea-hypopnea index; BDNF, brain-derived neurotrophic factor; BMI, body mass index; BMI z, BMI standard deviation score; ELISA, Enzyme-Linked Immunosorbent Assay; MOT, multidisciplinary obesity treatment; OAI, obstructive apnea index; oAHI, obstructive apnea–hypopnea index; OSA, obstructive sleep apnea; ODI, oxygen desaturation index; PWA, pulse wave amplitude; PSG, polysomnography; RHI, reactive hyperemia index; SaO2, oxygen saturation; TPR, time to peak response; TST, total sleep time; TST 95, total sleep time with saturation under 95%; WHR, waist-to-hip ratio.

MATERIALS AND METHODS

Study Design

In this prospective study, children and adolescents with obesity aged 8–18 years were consecutively included through the pediatric obesity clinic of the Antwerp University Hospital. Patients were excluded in case of an acute inflammatory process; use of non-steroidal anti-inflammatory drugs or immunosuppressive drugs; structural heart disease or other cardiac diseases; active malignant hematological disease; an underlying syndromic disorder; and a genetic or endogenous cause of obesity. Part of the study population was included via a randomized controlled trial (n°ISRCTN14722584) of which the results were previously reported (21, 22).

All patients were asked to complete three study visits: a baseline visit at the moment of inclusion, a second visit after 6 months of treatment (Follow-up 1) and a third visit after 1 year of weight loss treatment (Follow-up 2).

The ethics committee of the Antwerp University Hospital approved this study (EC no. 19/45/519 and 17/10/112) and a written informed consent was obtained from patients and their parents or legal guardian.

Multidisciplinary Obesity Treatment

Each participant in this study received a treatment program based on an evidence-based multidisciplinary obesity treatment protocol (MOT) at the pediatric obesity clinic of the Antwerp University Hospital. The multidisciplinary team consists of an experienced pediatrician and pediatric dietician. Personal psychological support is provided on request. Briefly, the

program consists of a first contact after which a 2-day inpatient stay in the hospital is planned. During this hospitalization the severity of obesity and its associated co-morbidities (such as cardiovascular disease, OSA, insulin resistance and liver steatosis) are further objectified. Results are discussed with patients and their parents. After this, a routine follow-up is established where the dietician is seen on a 4 weekly basis and works on a step-by-step approach to establish a sustainable healthy food pattern. The pediatrician is seen on a 3-monthly basis and monitors the evolution of the obesity severity and its related co-morbidities. Throughout the sessions, physical activity with a minimum of 30 min a day is highly encouraged.

Anthropometry

Height was accurately measured to 0.1 cm using a standing stadiometer and weight was measured to the nearest 0.05 kg using a digital weighing scale. Waist circumference and waist-to-hip ratio were measured by standardized techniques, using an inelastic, retractable tape measuring the smallest circumference between the lowest ribs and highest hip comb ∼1 cm above the umbilicus. Body mass index (BMI) was calculated as weight in kilograms over height in m^2 and was further analyzed as *z*-scores using the Flemish growth study as a reference population (23). Overweight and obesity were defined according to the International Obesity Task Force criteria (24).

Blood Pressure

The arterial blood pressure was each visit measured by an automated validated oscillometric device at the right upper arm with an adjusted cuff. The blood pressure was measured three times and an average of these measurements was used. Systolic and diastolic blood pressure percentiles were calculated specified for age, height and sex (25, 26).

Body Composition

The body composition was measured by a body composition monitor® (Fresenius Medical Care, St. Wendel, Germany) relying on the technique of bioimpedance spectroscopy. Each measurement was performed in the morning after an overnight fast, with the patient lying supine. Electrodes were attached following the wrist-ankle approach, in a tetrapolar arrangement with two electrodes placed on the hands and two on the feet. To guarantee good contact of the electrodes with the skin, degreasing with diethylether was performed before placement of the electrodes. Age, sex, height, weight and blood pressure were registered by the device before starting the measurement. If the quality calculated by the BCM was below 75%, the measurement was repeated and only good quality measurements were used (27). All guidelines for the use of the BCM were as follows: non-electrical bed, no cell phones and no electrical devices within 1 m of the device.

Endothelial Function

Peripheral microvascular endothelial function was non-invasively measured at the distal phalanx of the index finger using the Endo-PAT 2000 (Itamar Medical Ltd., Israel). Measurements were performed in the morning after an overnight fast in a temperature-controlled room (21–24°C). Briefly, finger probes were placed at the fingertips of both hands to measure arterial pulse wave amplitudes. After a 5-min baseline measurement, the brachial artery in the non-dominant arm was occluded using a manometer cuff to supra-systolic pressures (≥200 mmHg). After 5 min of occlusion, the cuff was released to allow recording of the reactive hyperemia for 5 min. Measurements were performed according to manufacturers' guidelines and recommendations in children (28). Parameters of interest are reactive hyperemia index (RHI), mean baseline pulse wave amplitude (PWA), maximal dilation and time to peak response.

Sleep Assessment

At baseline, all children underwent standard nocturnal polysomnography evaluation in the child sleep laboratory of the Antwerp University Hospital with assessment of following variables that were continuously measured and recorded by a computerized polysomnograph (Brain RT, OSG, Rumst, Belgium): electroencephalography (C4/Al and C3/A2); electro-oculography; electromyography of anterior tibialis and chin muscles; and electrocardiography. Respiratory effort was measured by respiratory inductance plethysmography and oxygen saturation by a finger probe connected to a pulse oximeter (Xpod, Nonin, Minnesota, USA). Airflow was measured by means of a nasal pressure cannula and thermistor, and snoring was detected by means of a microphone at suprasternal notch. Children were also monitored on audio/videotape using an infrared camera (29, 30).

An apnea was defined as the absence of airflow lasting at least two breaths, a hypopnea as a ≥30% decrease in amplitude of the airflow signal, lasting for ≥2 breaths and with a concurrent desaturation of ≥3% or a concurrent arousal. An obstructive apnea was diagnosed in the presence of continued or increased respiratory effort. In the absence of respiratory effort, the apnea was labeled as a central apnea. The number of obstructive apneas and hypopneas per hour of sleep were quantified in the obstructive apnea-hypopnea index (oAHI). OSA is classified as mild (oAHI 2–5/h), moderate (>5 and up to 10/h) and severe (oAHI > 10 events/h) (29, 30). All desaturations of ≥3% from the baseline SaO_2 were quantified and the oxygen desaturation index was calculated as the total of desaturations divided by the total sleep time (31, 32).

Weight loss was seen as the initial treatment for OSA, and therefore no extra treatment was given between study visits. Severe cases of OSA were referred to an ENT specialist for further evaluation.

Determination of Human Free Serum BDNF Concentrations

A fasting venous blood sample was drawn to determine BDNF levels using a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) (Quantikine; R&D Systems, Inc., Minneapolis, MN), according to the manufacturers' guidelines. The detection limit of the assay was 20 pg/ml, the intra-assay coefficient of variation was 13.85% and the intra-assay coefficient of variation was <10% for all samples.

Statistical Analysis

All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 27, NY, USA). Normality was tested using a Kolmogorov–Smirnov test. Normally distributed data were presented as mean and standard deviation and skewed data were reported as median and range (minimum–maximum). Patients were distributed in groups based on their oAHI. Groups with OSA and groups without OSA were compared using the independent samples *T*-test for normally distributed data and the Mann-Whitney U test for skewed data. To look for correlations between parameters, the Pearson correlation was used for normally distributed data and the Spearman correlation for skewed data. Afterwards, general linear models were used to investigate if the interaction between OSA and endothelial function had an effect on BDNF levels. For all analyses, $p < 0.05$ was considered statistically significant. Based on a previous study that found a significant correlation between oxygen desaturation index (ODI) and BDNF ($r = 0.65$, $p < 0.001$) (33), a sample size was calculated that would need 16 subjects with OSA to achieve adequate statistical power (power goal of 80% and a type I error rate of 5%).

RESULTS

Baseline Assessment

A total of 103 children with overweight or obesity were included with an average BMI of 31.14 kg/m^2 (range 21.89–40.89 kg/m^2) corresponding to a mean *z*-score of 2.45 (range 1.70–3.20). The mean age was 12.02 ± 2.17 years, and 51.5% of subjects were female. OSA was detected in 20 patients (19.4%): 12 children had mild OSA (60%) and 8 children had moderate-to-severe OSA (20%). Characteristics of obese patients with (oAHI ≥ 2) and without (oAHI < 2) OSA are presented in **Table 1**. Both groups were comparable in age and body composition. In our population, more boys were diagnosed with OSA ($p = 0.03$) and the diastolic blood pressure percentile ($p = 0.03$) was higher in patients with OSA. As expected, several sleep-related variables were significantly higher in the OSA group. **Table 2** shows that the mean baseline PWA (416.60 vs. 411.51, $p = 0.002$) was significantly higher in the OSA group. No significant differences were found in BDNF levels between subjects with and without OSA (**Figure 1**).

To investigate the impact of OSA and endothelial dysfunction on BDNF levels, a correlation analysis was performed. No

TABLE 2 | Endothelial function parameters of patients with (oAHI ≥ 2) and without (oAHI < 2) obstructive sleep apnea at baseline.

	OSA (oAHI ≥ 2)	Non-OSA (oAHI < 2)	*p*-value
RHI	1.37 (0.92–2.45)	1.59 (0.80–3.03)	0.1
Mean baseline PWA	416.60 ± 200.11	411.51 ± 192.26	0.002
TPR (seconds)	202 (75–285)	195 (45–285)	0.7
Maximal dilation	1.49 (1.12–2.64)	1.29 (0.84–2.47)	0.2

RHI, reactive hyperemia index; mean baseline PWA, mean baseline pulse wave amplitude; TPR, time to peak response.

TABLE 1 | Characteristics and sleep assessment data of patients with (oAHI ≥ 2) and without (oAHI < 2) obstructive sleep apnea at baseline.

	OSA (oAHI ≥ 2)	Non-OSA (oAHI < 2)	*p*-value
N	20	83	
Sex (male/female)	14/6	36/47	0.03
Age (years)	12.8 ± 2.6	12.3 ± 2.1	0.4
Weight (kg)	84.33 ± 19.58	78.92 ± 19.99	0.3
Height (cm)	159.35 ± 11.85	158.49 ± 12.18	0.8
BMI (kg/m^2)	32.76 ± 4.06	30.74 ± 4.18	0.06
BMI *z* score	2.50 (1.90–3.20)	2.40 (1.70–3.10)	0.1
Waist (cm)	95.8 (73.5–117.0)	91.0 (65.0–118.0)	0.1
WHR	0.90 (0.73–1.00)	0.87 (0.74–1.06)	0.1
Systolic blood pressure (mmHg)	116.20 ± 11.76	111.14 ± 11.02	0.07
Diastolic blood pressure (mmHg)	69 (58–87)	63 (46–88)	0.04
Systolic blood pressure percentile	79 (6–99)	66 (3–99)	0.08
Diastolic blood pressure percentile	72 (21–98)	46 (4–99)	0.03
Lean % (%)	45.59 ± 5.58	47.56 ± 6.40	0.5
Fat % (%)	41.71 ± 4.15	40.49 ± 4.44	0.3
oAHI (events/h)	3.15 (2.00–14.40)	0.48 (0.00–1.70)	< 0.001
ODI (events/h)	1.65 (0.00–6.90)	0.20 (0.00–5.10)	< 0.001
TST 95 (%)	0.10 (0.00–2.60)	0.00 (0.00–3.90)	0.003
Mean SaO_2 (%)	96.84 ± 0.77	97.08 ± 0.74	0.2
Number of desaturations	55 (1–268)	11 (0–136)	< 0.001

BMI, body mass index; BMI z, BMI standard deviation; WHR, waist-to-hip ratio; oAHI, obstructive apnea-hypopnea index; ODI, oxygen desaturation index; TST, total sleep time; TST 95, total sleep time with saturation under 95%; mean SaO_2, mean oxygen saturation.

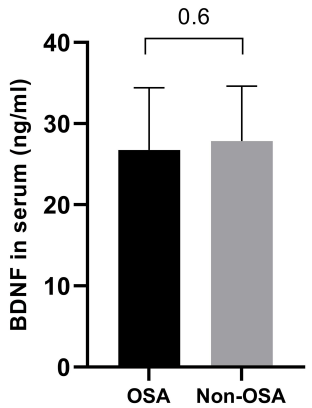

FIGURE 1 | Comparison of BDNF levels between patients with (oAHI ≥ 2) and without OSA (oAHI < 2). The BDNF level is comparable in both groups (26.75 ± 7.66 ng/ml vs. 27.87 ± 6.77 ng/ml, $p = 0.6$).

TABLE 3 | General linear model for BDNF with OSA diagnosis, BMI *z* score and maximal dilatation as factors.

	r^2	*p*-value
BDNF	0.07	
OSA diagnosis		0.03
BMI *z* score		0.1
Maximal dilatation		0.1
OSA diagnosis * maximal dilatation		0.04

*BDNF, brain-derived neurotrophic factor; OSA, obstructive sleep apnea; *indicates an interaction effect.*

correlations were found between BDNF and any of the sleep-related variables ($p > 0.2$), nor between BDNF and endothelial function ($p > 0.1$). Furthermore, BDNF was not associated with any obesity-related parameter or patient characteristics. To investigate whether the interaction between OSA and endothelial function had an effect on BDNF levels, a general linear model with OSA diagnosis as a categorical variable and maximal dilatation was made. This model (**Table 3**) shows that a diagnosis of OSA ($p = 0.03$) and the interaction between OSA and maximal endothelial dilatation ($p = 0.04$) both contributed significantly to BDNF levels. The maximal dilatation and BMI *z* score separately did not have an effect on BDNF levels (both $p = 0.1$).

Follow-Up Assessment

Of the 103 patients that participated at baseline, 82 (79%) attended the first follow-up visit and 73 patients (71%) attended the second follow-up visit. The average interval between baseline and follow-up visit 1 was 8.00 ± 1.18 months and between baseline and follow-up visit 2 was 15.00 ± 1.54 months. Patient characteristics at the different study visits are shown in **Table 4**. The mean BMI *z*-score at the start of treatment was 2.43 ± 0.36 and decreased significantly to 2.25 ± 0.43 at the first follow-up visit and to 2.22 ± 0.49 at the second follow-up visit ($p < 0.001$). The mean absolute decrease in BMI *z* score after 1 year was 0.21 ± 0.14.

Anthropometric data and their evolution in time are shown in **Table 4**. BDNF levels remained stable during weight loss (26.18 ng/ml at baseline vs. 25.46 ng/ml after 1 year, $p = 0.4$) (**Figure 2**). Changes in body weight (BMI *z* score) and changes in BDNF levels (BDNF) between baseline and after 1 year did not correlate ($r = 0.22$, $p = 0.09$), also no relationship was found between BMI *z* score and final BDNF levels measured after 1 year ($r = -0.14$, $p = 0.27$). The endothelial function parameters were not significantly different between baseline and the follow-up visits (**Table 5**), except for the maximum dilatation that significantly decreased between baseline and the first follow-up visit (1.52 vs. 1.47, $p < 0.001$) and remained stable between the first and second follow-up visit (1.47 and 1.46, $p = 0.1$). Also, no correlations were found between (BDNF) and differences in maximal dilatation after 1 year ($r = 0.007$, $p = 0.9$) nor between maximal dilatation and final BDNF levels measured after one year ($r = -0.09$, $p = 0.7$).

DISCUSSION

In this prospective study, no difference in BDNF levels could be found between children with obesity, both with and without OSA. However, an interaction of endothelial function and OSA on BDNF levels was found in this pediatric population with obesity. This interaction suggests that BDNF levels decrease in the context of endothelial dysfunction and OSA. Furthermore, 1 year of weight loss therapy did not have an effect on BDNF levels in this clinical cohort.

We could not detect a difference in serum BDNF levels between obese children with and without OSA. Limited studies in children have investigated the relationship between BDNF and OSA and to the best of our knowledge, we are the first to investigate BDNF levels in a solely obese pediatric population. The study by Wang et al. investigated BDNF levels in children with OSA and healthy volunteers (34). They found no difference in BDNF levels between the two groups, which is in agreement with our results. In this study, the authors also studied the effect of adenotonsillectomy on BDNF levels and found that BDNF levels decreased 3 months after adenotonsillectomy which was associated with the improvement in sleep-disordered breathing. This indicates an effect of OSA on BDNF levels. However, this decrease disappeared again 12-months post-adenotonsillectomy, as BDNF levels were then similar between control subjects and OSA patients. A number of studies also investigated the relationship between OSA and BDNF in adults. Flores et al. reported that adults with obesity and untreated OSA had significantly higher BDNF serum levels compared to adults with obesity but without OSA. This study also showed a positive correlation between the ODI and BDNF levels in adult OSA patients (33). As OSA in adults is often more severe compared to childhood OSA, this could indicate that patients with more pronounced intermittent hypoxia are more likely to have higher levels of circulating BDNF (33). This could be explained by the neuroprotective role of BDNF following hypoxic events, as

TABLE 4 | Patient characteristics and body composition measurements of baseline and follow-up visits.

	Baseline	Follow-up visit 1	Follow-up visit 2	*p*-value
N	103	82	73	
Sex (male/female)	50/53	40/42	38/35	
Age (years)	12.41 ± 2.21	13.00 ± 2.22	13.49 ± 2.35	<0.001*#◦
Weight (kg)	80.54 ± 20.63	79.90 ± 20.90	83.07 ± 20.67	0.004*#◦
Height (cm)	158.66 ± 12.06	161.29 ± 11.87	163.93 ± 11.48	<0.001*#◦
BMI (kg/m^2)	31.45 ± 4.73	30.25 ± 5.24	30.53 ± 5.46	<0.001* # ◦
BMI *z* score	2.40 (1.10–3.30)	2.30 (1.40–3.70)	2.29 (0.96–3.70)	<0.001*#
Waist (cm)	92.00 (65.00–128.50)	87.00 (68.00–125.00)	87.05 (67.50–118.00)	<0.001*#
WHR	0.87 ± 0.06	0.84 ± 0.07	0.83 ± 0.07	<0.001*#
Systolic blood pressure (mmHg)	112.13 ± 11.29	116.91 ± 14.97	117.01 ± 13.71	<0.001*#
Diastolic blood pressure (mmHg)	63.00 (46.00–88.00)	72.00 (51.00–100.00)	72.00 (53.00–95.00)	< 0.001*#
Systolic blood pressure percentile	72 (3–99)	80 (8–99)	73 (1–99)	0.8
Diastolic blood pressure percentile	50 (4–99)	77 (14–99)	73 (11–99)	<0.001*#
Lean % (%)	46.80 ± 6.73	47.59 ± 8.01	46.47 ± 8.52	0.9
Fat % (%)	40.69 ± 5.28	39.70 ± 6.29	40.55 ± 6.72	0.4

BMI, body mass index; BMI z, BMI standard deviation; WHR, waist-to-hip ratio.
**Significant difference between baseline and follow-up visit 2.*
#Significant difference between baseline and follow-up visit 1.
◦significant difference between follow-up visit 1 and follow-up visit 2.

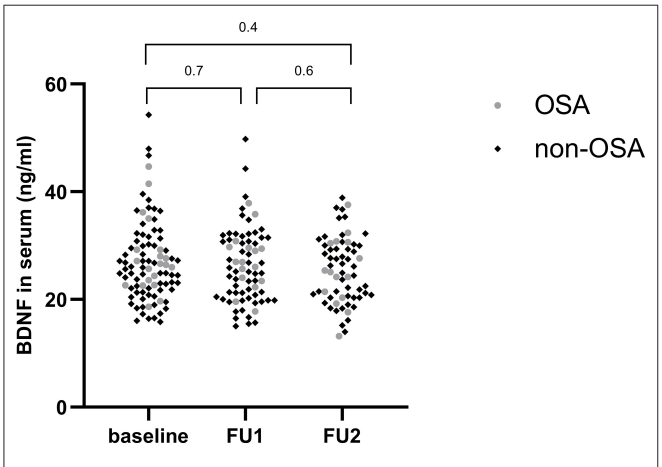

FIGURE 2 | Evolution of BDNF levels during weight loss. FU1, Follow-up visit 1; FU2, follow-up visit 2.

studies have shown increased BDNF levels after acute ischemic stroke or repeated hypoxic stimulation in animal studies (35, 36). In this study, OSA was indeed more severe in their adult population than our pediatric population. In contrast, Staats et al. did not find any difference in BDNF levels at baseline between adult patients with untreated OSA and healthy controls. However, after CPAP treatment a decrease in BDNF levels was seen, again indicating an association between OSA and BNDF levels (37).

Children with obesity are known to exhibit impaired endothelial function (38). In our population, no difference in endothelial function between children with OSA and without OSA was found. Endothelial function did improve after weight loss in our population. However, the improvement of endothelial function did not have an effect on BDNF levels after 1 year of weight loss treatment.

At baseline, no correlations were found between BDNF and endothelial function parameters for our obese population or between BDNF and sleep-related variables. However, a general linear model for BDNF showed that the interaction between OSA and endothelial function contributed significantly to BDNF levels. Studies have shown that OSA and endothelial function are independently associated (39–42). Recently, our research group has also shown that OSA has an important influence on the improvement of endothelial function in a pediatric population with obesity (11). This study further demonstrates that the coexistence of OSA and endothelial function can have detrimental effects on the health of these children. BDNF levels are essential in the survival, growth and differentiation of new neurons during early brain development and are involved in the plasticity changes related to learning, memory, and higher cognitive function (17). Lower BDNF levels have also been linked with poorer neurocognitive function in children with type I diabetes (43). Our results indicate a possible role for BDNF in the neurocognitive complications seen in pediatric OSA. In the study by Gozal et al. a degree of concordance between endothelial function and the presence of cognitive deficits was found, suggesting a shared pathogenetic mechanism between endothelial dysfunction and neurocognitive deficits as both these disorders are more likely to coexist in children with OSA (18). It is possible that BDNF plays a role in the common pathophysiological pathways of neurocognition and endothelial function in pediatric OSA.

One year of weight loss treatment had no significant effect on BDNF levels over time in our study cohort. This result is comparable to a study by Lee et al., where BDNF levels remained stable after 12 weeks of weight loss. However, a significant

TABLE 5 | Endothelial function parameters during weight loss treatment.

	Baseline	Follow-up visit 1	Follow-up visit 2	*p*-value
N	103	82	73	
RHI	1.52 (0.80–2.87)	1.47 (0.95–4.47)	1.48 (1.00–3.00)	0.5
Mean baseline PWA	443.73 ± 207.50	413.31 ± 207.23	426.35 ± 193.485	0.4
TPR (seconds)	195 (45–285)	165 (75–285)	165 (45–285)	0.4
Maximal dilation	1.52 (0.80–3.03)	1.47 (0.95–4.47)	1.46 (1.00–3.00)	<0.001[#*]

RHI, reactive hyperemia index; mean baseline PWA, mean baseline pulse wave amplitude; TPR, time to peak response.
[#]Significant difference between baseline and follow-up visit 1.
[*]Significant difference between baseline and follow-up visit 2.

increase in BDNF levels was found after the 12-week weight loss program (44). In contrast, Glud et al. showed that in both men and women a decrease in BDNF levels was caused after a 12-week weight-loss intervention (45). Since changes in body weight in humans have been shown to affect BDNF levels (46, 47), it is suggested that the effect of weight loss on circulating BDNF might depend on the level of exercise and dietary energy restriction (48). In contrast to a previous study in children with obesity where plasma concentrations of BDNF increased after weight loss and an adequate carbohydrate intake (15), we did not find a relationship between body weight changes and changes in BDNF levels after a weight-loss treatment of 1 year. The difference could be explained by the high variation in body weight change in our population. Also, in adults with overweight and obesity similar findings were found by Araya et al., as BDNF levels increased after a 3-month reduced-caloric diet, suggesting that BDNF levels can be regulated by food intake (47). It would be interesting to further investigate the potential dose-response relationship between BDNF levels and energy restriction and for the existence of a possible weight loss/energy restriction threshold.

This study has some strengths and limitations. The major strengths include the prospective design and the large study population with obesity. The measurement of BDNF in serum is an asset as previous studies have shown that measuring circulating BDNF in serum has several advantages compared to plasma or whole blood measurements (49, 50). Several study limitations need to be taken into consideration. First, the majority of our population consisted out of patients without OSA or with only mild OSA (7.8% of all patients were diagnosed with moderate to severe OSA). However, our population is representative of a pediatric obesity clinic since all patients with obesity were consecutively included and not only those suspected of sleep-disordered breathing. Second, we observed heterogeneous weight trajectories, limiting the average weight loss, as result that it was more difficult to detect a significant effect of weight than e.g., in a residential cohort. Third, as we did not assess cognitive function in our study, it was not possible to investigate the relationship between BDNF and cognitive function directly. Lastly, because of the COVID pandemic, appointments had to be rescheduled, which resulted in more variation in time between the different visits.

For future research it would be interesting to include a normal-weight control group to get a better understanding of the relationship between obesity and BDNF. Additionally, as polysomnography data was only available at baseline, it would be of interest to investigate the long-term association between OSA and BDNF and also include follow-up sleep data in future research.

To conclude, BDNF concentrations of children with obesity with and without OSA are comparable in our cohort, suggesting that BDNF levels are not affected by OSA. An univariate association between BDNF and sleep-related variables or between BDNF and endothelial function parameters could not be determined. However, a general linear model showed that the interaction between OSA and endothelial function affects BDNF levels, indicating an indirect link between BDNF, OSA and endothelial function. Lastly, weight loss did not have an effect on BDNF levels. Future research with emphasis on longitudinal studies is necessary to investigate the possible role of BDNF in OSA and endothelial function, as it is complicated in children with conflicting data in current literature.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Antwerp University Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

The current study was conceptualized by AV, SV, and KVH. AV, EV, SV, KVH, and BD designed the methodology. The formal analysis was done by SM. The experiments were performed by SM, EV, KVDM, and AV. The original draft was prepared by SM and AV. EV, KVDM, LB, BD, KVH, and SV reviewed the original version. AV supervised the whole research activity together with SV, KVH, and BD. The project administration was executed by AV. The funding for this research project was obtained by SV, LB, and BD. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Di Cesare M, Soric M, Bovet P, Miranda JJ, Bhutta Z, Stevens GA, et al. The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. *BMC Med*. (2019) 17:212. doi: 10.1186/s12916-019-1449-8
2. Budhiraja R, Parthasarathy S, Quan SF. Endothelial dysfunction in obstructive sleep apnea. *J Clin Sleep Med*. (2007) 3:409–15. doi: 10.5664/jcsm.26864
3. Ip MS, Tse HF, Lam B, Tsang KW, Lam WK. Endothelial function in obstructive sleep apnea and response to treatment. *Am J Respir Crit Care Med*. (2004) 169:348–53. doi: 10.1164/rccm.200306-767OC
4. Nieto FJ, Herrington DM, Redline S, Benjamin EJ, Robbins JA. Sleep apnea and markers of vascular endothelial function in a large community sample of older adults. *Am J Respir Crit Care Med*. (2004) 169:354–60. doi: 10.1164/rccm.200306-756OC
5. Konstantinopoulou S, Tapia IE. Neurocognitive and behavioural outcomes following intervention for obstructive sleep apnoea syndrome in children. *Paediatr Respir Rev*. (2016) 20:51–4. doi: 10.1016/j.prrv.2016.05.004
6. Berger S, Polotsky VY. Leptin and leptin resistance in the pathogenesis of obstructive sleep apnea: a possible link to oxidative stress and cardiovascular complications. *Oxid Med Cell Longev*. (2018) 2018:5137947. doi: 10.1155/2018/5137947
7. Lavie L, Vishnevsky A, Lavie P. Evidence for lipid peroxidation in obstructive sleep apnea. *Sleep*. (2004) 27:123–8.
8. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev*. (2010) 90:47–112. doi: 10.1152/physrev.00043.2008
9. Katz SL, Pillar G. Obstructive sleep apnea, obesity, and endothelial dysfunction in children. *Am J Respir Crit Care Med*. (2016) 194:1046–7. doi: 10.1164/rccm.201605-0911ED
10. Bhattacharjee R, Kim J, Alotaibi WH, Kheirandish-Gozal L, Capdevila OS, Gozal D. Endothelial dysfunction in children without hypertension: potential contributions of obesity and obstructive sleep apnea. *Chest*. (2012) 141:682–91. doi: 10.1378/chest.11-1777
11. Jacobs S, Mylemans E, Ysebaert M, Vermeiren E, De Guchtenaere A, Heuten H, et al. The impact of obstructive sleep apnea on endothelial function during weight loss in an obese pediatric population. *Sleep Med*. (2021) 86:48–55. doi: 10.1016/j.sleep.2021.08.002
12. Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. *Arch Med Sci*. (2015) 11:1164–78. doi: 10.5114/aoms.2015.56342
13. Skledar M, Nikolac M, Dodig-Curkovic K, Curkovic M, Borovecki F, Pivac N. Association between brain-derived neurotrophic factor Val66Met and obesity in children and adolescents. *Prog Neuropsychopharmacol Biol Psychiatry*. (2012) 36:136–40. doi: 10.1016/j.pnpbp.2011.08.003
14. Roth CL, Elfers C, Gebhardt U, Muller HL, Reinehr T. Brain-derived neurotrophic factor and its relation to leptin in obese children before and after weight loss. *Metabolism*. (2013) 62:226–34. doi: 10.1016/j.metabol.2012.08.001
15. Corripio R, Gonzalez-Clemente JM, Jacobo PS, Silvia N, Lluis G, Joan V, et al. Plasma brain-derived neurotrophic factor in prepubertal obese children: results from a 2-year lifestyle intervention programme. *Clin Endocrinol*. (2012) 77:715–20. doi: 10.1111/j.1365-2265.2012.04431.x
16. Xie H, Leung KL, Chen L, Chan YS, Ng PC, Fok TF, et al. Brain-derived neurotrophic factor rescues and prevents chronic intermittent hypoxia-induced impairment of hippocampal long-term synaptic plasticity. *Neurobiol Dis*. (2010) 40:155–62. doi: 10.1016/j.nbd.2010.05.020
17. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. *Front Cell Neurosci*. (2019) 13:363. doi: 10.3389/fncel.2019.00363
18. Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Spruyt K. Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea. *Pediatrics*. (2010) 126:e1161–7. doi: 10.1542/peds.2010-0688
19. Monnier A, Prigent-Tessier A, Quirie A, Bertrand N, Savary S, Gondcaille C, et al. Brain-derived neurotrophic factor of the cerebral microvasculature: a forgotten and nitric oxide-dependent contributor of brain-derived neurotrophic factor in the brain. *Acta Physiol*. (2017) 219:790–802. doi: 10.1111/apha.12743
20. Kermani P, Hempstead B. Brain-derived neurotrophic factor: a newly described mediator of angiogenesis. *Trends Cardiovasc Med*. (2007) 17:140–3. doi: 10.1016/j.tcm.2007.03.002
21. Naets T, Vervoort L, Ysebaert M, Van Eyck A, Verhulst S, Bruyndonckx L, et al. WELCOME: improving WEight controL and CO-Morbidities in children with obesity via Executive function training: study protocol for a randomized controlled trial. *BMC Public Health*. (2018) 18:1075. doi: 10.1186/s12889-018-5950-3
22. Vermeiren E, Naets T, Van Eyck A, Vervoort L, Ysebaert M, Baeck N, et al. Improving treatment outcome in children with obesity by an online self-control training: a randomized controlled trial. *Front Pediatr*. (2021) 9:794256. doi: 10.3389/fped.2021.794256
23. Roelants M, Hauspie R, Hoppenbrouwers K. References for growth and pubertal development from birth to 21 years in Flanders, Belgium. *Ann Hum Biol*. (2009) 36:680–94. doi: 10.3109/03014460903049074
24. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. (2000) 320:1240–3. doi: 10.1136/bmj.320.7244.1240
25. Barba G, Buck C, Bammann K, Hadjigeorgiou C, Hebestreit A, Marild S, et al. Blood pressure reference values for European non-overweight school children: the IDEFICS study. *Int J Obes*. (2014) 38(Suppl. 2):S48–56. doi: 10.1038/ijo.2014.135
26. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. (2017) 140:e20171904. doi: 10.1542/peds.2017-1904
27. Vermeiren E, Ysebaert M, Van Hoorenbeeck K, Bruyndonckx L, Van Dessel K, Van Helvoirt M, et al. Comparison of bioimpedance spectroscopy and dual energy X-ray absorptiometry for assessing body composition changes in obese children during weight loss. *Eur J Clin Nutr*. (2020) 75:73–84. doi: 10.1038/s41430-020-00738-9
28. Bruyndonckx L, Radtke T, Eser P, Vrints CJ, Ramet J, Wilhelm M, et al. Methodological considerations and practical recommendations for the application of peripheral arterial tonometry in children and adolescents. *Int J Cardiol*. (2013) 168:3183–90. doi: 10.1016/j.ijcard.2013.07.236
29. Standards and indications for cardiopulmonary sleep studies in children. American Thoracic Society. *Am J Respir Crit Care Med*. (1996) 153:866–78. doi: 10.1164/ajrccm.153.2.8564147
30. Verhulst SL, Schrauwen N, Haentjens D, Suys B, Rooman RP, Van Gaal L, et al. Sleep-disordered breathing in overweight and obese children and adolescents: prevalence, characteristics and the role of fat distribution. *Arch Dis Child*. (2007) 92:205–8. doi: 10.1136/adc.2006.101089
31. Van Eyck A, De Guchtenaere A, Van Gaal L, De Backer W, Verhulst SL, Van Hoorenbeeck K. Clinical predictors of residual sleep apnea after weight loss therapy in obese adolescents. *J Pediatr*. (2018) 196:189–93 e1. doi: 10.1016/j.jpeds.2017.12.056

32. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K, et al. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. *Eur Respir J*. (2016) 47:69–94. doi: 10.1183/13993003.00385-2015
33. Flores KR, Viccaro F, Aquilini M, Scarpino S, Ronchetti F, Mancini R, et al. Protective role of brain derived neurotrophic factor (BDNF) in obstructive sleep apnea syndrome (OSAS) patients. *PLoS ONE*. (2020) 15:e0227834. doi: 10.1371/journal.pone.0227834
34. Wang Y, Wang JJ, Zhao MQ, Liu, Li YZ. Changes of serum brain-derived neurotrophic factor in children with obstructive sleep apnoea-hypopnoea syndrome following adenotonsillectomy. *J Int Med Res*. (2010) 38:1942–51. doi: 10.1177/147323001003800607
35. Vermehren-Schmaedick A, Jenkins VK, Knopp SJ, Balkowiec A, Bissonnette JM. Acute intermittent hypoxia-induced expression of brain-derived neurotrophic factor is disrupted in the brainstem of methyl-CpG-binding protein 2 null mice. *Neuroscience*. (2012) 206:1–6. doi: 10.1016/j.neuroscience.2012.01.017
36. Stanzani L, Zoia C, Sala G, Appollonio I, Frattola L, De Simoni MG, et al. Nerve growth factor and transforming growth factor-beta serum levels in acute stroke patients. Possible involvement of neurotrophins in cerebrovascular disease. *Cerebrovasc Dis*. (2001) 12:240–4. doi: 10.1159/000047710
37. Staats R, Stoll P, Zingler D, Virchow JC, Lommatzsch M. Regulation of brain-derived neurotrophic factor (BDNF) during sleep apnoea treatment. *Thorax*. (2005) 60:688–92. doi: 10.1136/thx.2004.038208
38. Mahmud FH, Hill DJ, Cuerden MS, Clarson CL. Impaired vascular function in obese adolescents with insulin resistance. *J Pediatr*. (2009) 155:678–82. doi: 10.1016/j.jpeds.2009.04.060
39. Azuma M, Chihara Y, Yoshimura C, Murase K, Hamada S, Tachikawa R, et al. Association between endothelial function (assessed on reactive hyperemia peripheral arterial tonometry) and obstructive sleep apnea, visceral fat accumulation, and serum adiponectin. *Circ J*. (2015) 79:1381–9. doi: 10.1253/circj.CJ-14-1303
40. Zhang F, Wu Y, Feng G, Ni X, Xu Z, Gozal D. Polysomnographic correlates of endothelial function in children with obstructive sleep apnea. *Sleep Med*. (2018) 52:45–50. doi: 10.1016/j.sleep.2018.07.023
41. Namtvedt SK, Hisdal J, Randby A, Agewall S, Stranden E, Somers VK, et al. Impaired endothelial function in persons with obstructive sleep apnoea: impact of obesity. *Heart*. (2013) 99:30–4. doi: 10.1136/heartjnl-2012-303009
42. Atkeson A, Yeh SY, Malhotra A, Jelic S. Endothelial function in obstructive sleep apnea. *Prog Cardiovasc Dis*. (2009) 51:351–62. doi: 10.1016/j.pcad.2008.08.002
43. Chen HJ, Lee YJ, Huang CC, Lin YF, Li ST. Serum brain-derived neurotrophic factor and neurocognitive function in children with type 1 diabetes. *J Formos Med Assoc*. (2021) 120(1 Pt 1):157–64. doi: 10.1016/j.jfma.2020.04.011
44. Lee SS, Yoo JH, Kang S, Woo JH, Shin KO, Kim KB, et al. The effects of 12 weeks regular aerobic exercise on brain-derived neurotrophic factor and inflammatory factors in juvenile obesity and type 2 diabetes mellitus. *J Phys Ther Sci*. (2014) 26:1199–204. doi: 10.1589/jpts.26.1199
45. Glud M, Christiansen T, Larsen LH, Richelsen B, Bruun JM. Changes in circulating BDNF in relation to Sex, Diet, and exercise: a 12-week randomized controlled study in overweight and obese participants. *J Obes*. (2019) 2019:4537274. doi: 10.1155/2019/4537274
46. Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, et al. The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiol Aging*. (2005) 26:115–23. doi: 10.1016/j.neurobiolaging.2004.03.002
47. Araya AV, Orellana X, Espinoza J. Evaluation of the effect of caloric restriction on serum BDNF in overweight and obese subjects: preliminary evidences. *Endocrine*. (2008) 33:300–4. doi: 10.1007/s12020-008-9090-x
48. Mattson MP. The impact of dietary energy intake on cognitive aging. *Front Aging Neurosci*. (2010) 2:5. doi: 10.3389/neuro.24.005.2010
49. Maffioletti E, Zanardini R, Gennarelli M, Bocchio-Chiavetto L. Influence of clotting duration on brain-derived neurotrophic factor (BDNF) dosage in serum. *Biotechniques*. (2014) 57:111–4. doi: 10.2144/000114204
50. Polacchini A, Metelli G, Francavilla R, Baj G, Florean M, Mascaretti LG, et al. A method for reproducible measurements of serum BDNF: comparison of the performance of six commercial assays. *Sci Rep*. (2015) 5:17989. doi: 10.1038/srep17989

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frontiers in Medicine

SYSTEMATIC REVIEW
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Sleep Duration/Quality With Health Outcomes: An Umbrella Review of Meta-Analyses of Prospective Studies

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Background: To quantitatively evaluate the evidence of duration and quality of sleep as measured by multiple health outcomes.

Methods: This review is registered with PROSPERO, number CRD42021235587. We systematically searched three databases from inception until November 15, 2020. For each meta-analysis, the summary effect size using fixed and random effects models, the 95% confidence interval, and the 95% prediction interval were assessed; heterogeneity, evidence of small-study effects, and excess significance bias were also estimated. According to the above metrics, we evaluated the credibility of each association.

Results: A total of 85 meta-analyses with 36 health outcomes were included in the study. We observed highly suggestive evidence for an association between long sleep and an increased risk of all-cause mortality. Moreover, suggestive evidence supported the associations between long sleep and 5 increased risk of health outcomes (stroke, dyslipidaemia, mortality of coronary heart disease, stroke mortality, and the development or death of stroke); short sleep and increased risk of overweight and/or obesity; poor sleep quality and increased risk of diabetes mellitus and gestational diabetes mellitus.

Conclusions: Only the evidence of the association of long sleep with an increased risk of all-cause mortality was graded as highly suggestive. Additional studies are needed to be conducted.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/, identifier: CRD42021235587

Keywords: health outcomes, meta-analysis, sleep duration, sleep quality, umbrella review

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INTRODUCTION

Sleep is an important and complex physiological process for maintaining optimal health. The National Sleep Foundation recommends 7–9 h of sleep for people aged 26–64 years and 7–8 h of sleep for people aged ≥65 years (1). However, because of irregular working, shift-work patterns, and unhealthy sleeping habits, the quantity and quality of sleep may be abnormal in modern society. Over the last few decades, there has been growing evidence to suggest that self-reported short or long sleep duration (often defined as <6 or 7 and >8 or 9 h, respectively) and poor sleep quality

[Pittsburgh Sleep Quality Index (PSQI) > 5] may be consistently associated with adverse health outcomes [e.g., short sleep and increased risk of hypertension (2), long sleep and increased risk of chronic kidney disease (3), poor sleep quality and increased risk of preterm birth (4), etc.].

Although previous studies have examined this topic using various methodologies, a quantitative appraisal of epidemiological credibility is lacking, as are examinations of the potential bias between the quantity and quality of sleep and health-related outcomes and assessments of the most influential outcomes. Therefore, in the present study, we conducted an umbrella review of the evidence between the quantity and quality of sleep and the multiple health outcomes in systematic reviews and meta-analyses, assessed the diverse bias, and quantitatively evaluated the strength and credibility of the evidence.

METHODS

We strictly followed standardized guidelines to perform an umbrella review, which is the systematic collection and evaluation of multiple systematic reviews and meta-analyses conducted on a specific research topic (5). The umbrella review was conducted according to the Preferred Reporting Items for Systematic Reviews, Meta-Analyses guidelines (**Supplementary Table S1**) (6), and the guidance of the Meta-analysis of Observational Studies in Epidemiology statement (**Supplementary Table S2**) (7). The study protocol was registered in the PROSPERO database for systematic reviews and meta-analyses (registration number: CRD42021235587).

Search Strategy

The electronic databases, PubMed, EMBASE, and the Web of Science were searched systematically from inception until November 15, 2020, to identify related systematic reviews and meta-analyses of observational studies. A predefined search strategy was used, which is presented in **Supplementary Table S3**. In addition, we performed a manual check of reference lists from the retrieved articles for further potentially relevant articles.

Eligibility Criteria and Appraisal of Included Studies

Two authors (CG and X-YL) independently scrutinized articles based on titles and abstracts. If needed, full articles were retrieved for a final decision. Disagreements between the two reviewers were resolved by discussion and consensus with a senior advisor (T-TG). Articles were included according to the following criteria: (A) systematic reviews and meta-analyses of prospective studies on the associations between duration and quality of sleep and any health-related outcome, (B) studies that relied on data from human studies with any type of health-related outcome measure, and (C) studies that reported effect sizes such as odds ratios (ORs), relative risk (RRs), or hazard ratios (HRs) at follow-up. We included information that we were interested in in each study, such as subgroup analysis and dose–response analysis. If a systematic review or meta-analysis performed a subgroup analysis stratified by the study design, then the results for prospective studies were included (8–10).

We excluded individual studies according to the following criteria: (A) meta-analyses of case-control or cross-sectional studies, (B) studies in which sleep measures were not the exposure of interest (such as sleep-disordered breathing, restless leg syndrome, or napping), (C) meta-analyses or systematic reviews that did not present study-specific data [effect sizes, 95% confidence intervals (CIs) and numbers of cases/population)], (D) systematic reviews without a quantitative synthesis, or (E) other types of papers (e.g., review, abstract, non-English, or editorial). For the main analysis, whenever an eligible meta-analysis included a lower number of component studies compared to other meta-analyses related to the same association, we retained the one with the largest number of primary studies (8–10).

Exposure Identification

For exposures, the studies of sleep duration included "short sleep duration" and "long sleep duration." In most studies, "sleep duration" was defined as hours per day or minutes per night. "Short sleep duration" was defined as ≤5, <5, ≤6, <6, ≤5–6 or <7, and "long sleep duration" was defined as >7, ≥8, ≥9 or ≥8–9 h. The reference categories for sleep duration in the studies, in h per night, were 7, 7–8, 6–8 or 7–9 h. In this umbrella review, "poor sleep quality," "good sleep quality" and "not-poor sleep quality" were separately characterized as PSQI > 5, PSQI < 5 and PSQI ≤ 5.

Data Extraction

Two investigators (X-YL and F-HL) independently extracted the related data from the included studies using a custom-made data extraction form. In the case of discrepancies, the data were subsequently verified by a third author (CG). The data-collection form included the first author, year of publication, journal of publication, exposure, outcome examined, number of included studies, case number, and study population. For each of the included studies in each eligible meta-analysis, we extracted the first author, year of publication, epidemiological design, number of cases and total population, and the maximally adjusted relative risk (ORs, RRs or HRs) along with the corresponding 95% CI.

Data Analysis

For each exposure and outcome pair, we evaluated the summary effect size and the 95% CI through both fixed and random effects models (11, 12). The heterogeneity between studies was assessed with the I^2 metric of inconsistency and its 95% CI (13). The I^2 ranges between 0 and 100% and quantifies the variability in effect estimates that it is due to heterogeneity rather than sampling error. Values exceeding 50% were indicative of high heterogeneity, whereas values >75% implied very high heterogeneity (14). We also calculated the 95% prediction interval (PI), which further accounted for heterogeneity between studies and estimated the uncertainty of the association if future studies examine that same association (15).

We used Egger's regression asymmetry test to identify small-study effects (16) to evaluate whether smaller studies tend to give higher risk estimates compared with larger studies, which can indicate publication, other reporting biases, or other reasons for differences between small and large studies (17). We calculated the standard error of the effect size for the largest data set of each meta-analysis to determine whether larger estimates of effect size were predicted by small studies compared to large studies (10). Indication of small study effects was based on the *P* value for Egger's test was smaller than 0.10 and the largest study had a smaller effect size than the summary effect size (17).

We applied the excess significance test to evaluate whether the observed number of studies (O) with statistically significant results among those included in a meta-analysis was larger than the expected number of studies (E) with statistically significant results (18). E is calculated by the sum of the statistical power estimates for each component study. The statistical power of each study was calculated with an algorithm using a non-central *t* distribution (19). The excess significance test for single meta-analyses was considered positive at $P < 0.10$, given that O > E as previously proposed (10). When standardized mean differences were reported, we planned to transform these estimates into ORs (20). The statistical analysis and the power calculations were conducted in STATA version 15.0, and all *P* values were two-tailed.

Methodological Quality Appraisal

To study the quality of the reporting of the included systematic reviews and meta-analyses, two investigators (CG and X-YL) independently rated the methodological quality with the Assessment of Multiple Systematic Reviews (AMSTAR-1) tool. Higher scores imply greater quality, ranging from 0 to 11. The AMSTAR-1 tool involves dichotomous scoring (0 or 1) of 11 related items to assess the methodological rigor of the included articles, such as a comprehensive search strategy or publication bias assessment. AMSTAR-1 scores are graded as high (8–11), medium (4–7), and low quality (0–3) (21).

Grading the Evidence

Statistically significant meta-analyses ($P < 0.05$) were rated into four levels (convincing, highly suggestive, suggestive, and weak) using specific criteria. For convincing evidence: $P < 10^{-6}$, number of cases >1,000, $I^2 < 50\%$, $P < 0.05$ of the largest component study in the meta-analysis, 95% PI excludes the null value, absence of small-study effects ($P > 0.1$ for Egger's test), and no excess significance bias ($P > 0.1$). For highly suggestive evidence: $P < 10^{-6}$, number of cases >1,000, and $P < 0.05$ of the largest study. For suggestive evidence: $P < 10^{-3}$, and number of cases >1,000. For weak evidence, the sole criterion was $P < 0.05$ (22). When $P > 0.05$, there was no association (10). All analyses were conducted in STATA, version 15.0.

RESULTS

Study Selection

As reported in **Figure 1**, 15,669 records were retrieved across three electronic databases search, and 7,958 records were identified unduplicated through the parallel reviews. A total of 7,728 records were excluded after title and abstract screening, and 201 were excluded through assessment of the full-text (**Figure 1**). Ultimately, 36 articles were included in our umbrella review for analysis.

Characteristics of Included Meta-Analyses

The characteristics of these 36 articles are summarized in **Table 1**. All articles were published between 2009 and 2020. These included studies covered 85 meta-analyses, which reported associations between duration and quality of sleep and 36 different outcomes. The median number of original studies in each meta-analysis was 7 (range from 3 to 27), while the median number of cases was 4,848 (range from 156 to 219,518), and the median number of the total participants was 113,226 (range from 1,230 to 2,311,390). The case number exceeded 1,000 in 81 meta-analyses.

Summary Effect Size

Of the 78 meta-analyses from 32 articles regarding sleep duration, the summary random effects estimates were significant at $P < 1 \times 10^{-6}$ in 10 (13%) meta-analyses, and the summary fixed effects estimates were significant in 28 (36%) meta-analyses (**Supplementary Table S4**). Thirty-nine (50%) meta-analyses reported that the largest study effect was nominally statistically significant, with a $P < 0.05$, and a more conservative effect than the summary random effects was observed in 57 (73%) meta-analyses. The studies with the smallest SE for each association suggested that 30 of 78 were significant at $P < 0.05$.

Out of the 7 meta-analyses from 5 articles regarding sleep quality, the summary fixed-effects and random-effects estimates were significant at $P < 0.05$. However, when we used ($P < 1 \times 10^{-6}$) as a threshold for significance, the summary random effects estimates were not significant in any meta-analyses, and 3 (43%) meta-analyses produced significant summary results using the fixed-effects methods (**Supplementary Table S4**). The studies with the smallest standard error for each association suggested that 5 of 7 were significant at $P < 0.05$, and a more conservative effect than the summary random effects was observed in 5 (71%) meta-analyses. The studies with the smallest SE for each association suggested that two of 7 were significant at $P < 0.05$.

Heterogeneity and Prediction Intervals

In all the included studies regarding sleep duration, approximately 44 (56%) studies had a lower heterogeneity, with $I^2 \leq 50\%$; approximately 28 (36%) studies had substantial heterogeneity estimates, with I^2 between 50 and 75%; and 6 (8%) studies had considerable heterogeneity estimates, with $I^2 > 75\%$ (**Table 2**). When 95% PIs were evaluated, we found that 10 meta-analyses [cognitive disorders, stroke, diabetes, all cancer mortality, all-cause mortality, mortality (both all-cause and cause-specific), stroke mortality, obesity, overweight and/or obesity, and the development or death of stroke] excluded the null value (**Table 2**).

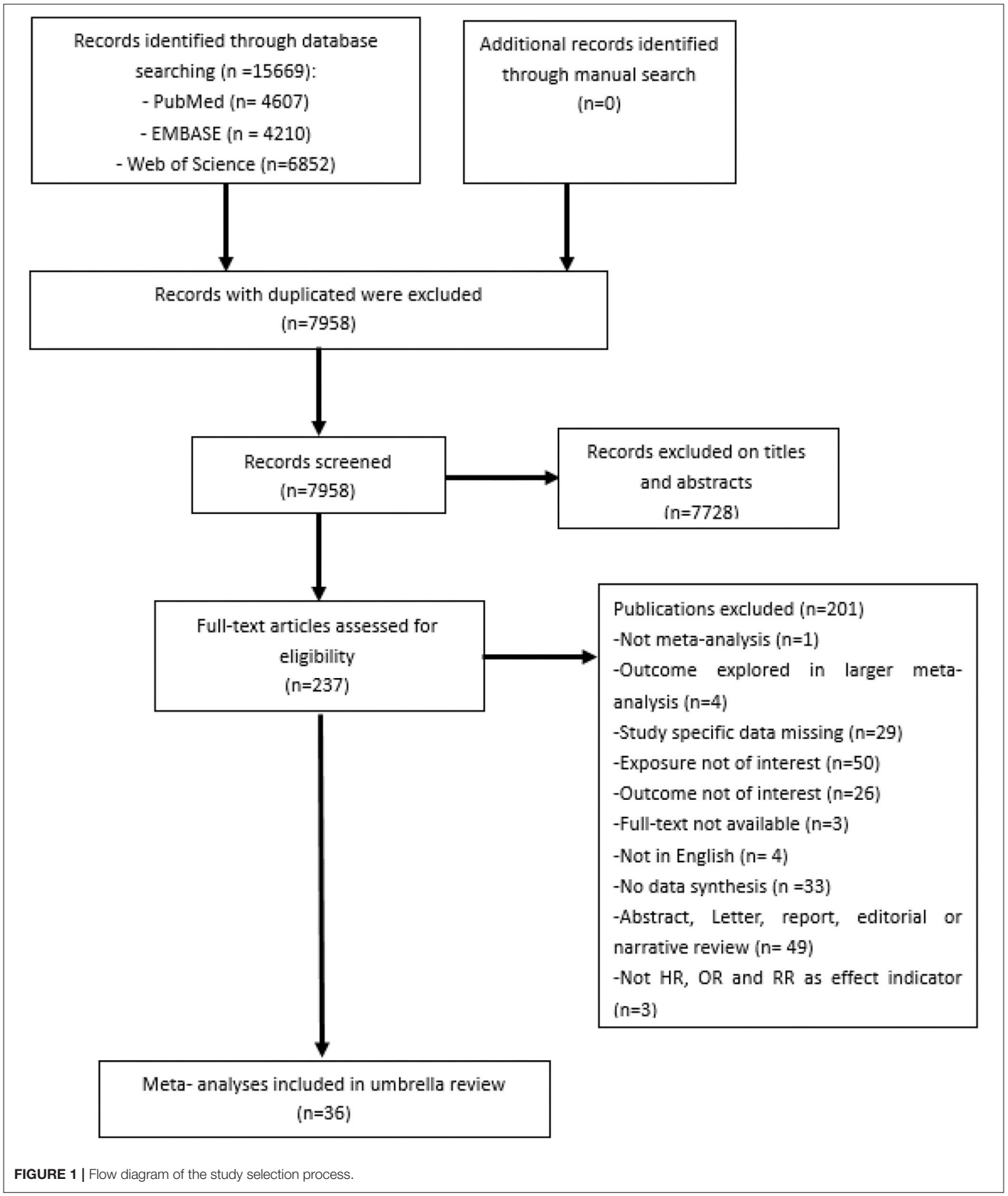

FIGURE 1 | Flow diagram of the study selection process.

Of the 7 meta-analyses about sleep quality, 3 (42%) showed low heterogeneity ($I^2 < 50\%$), and 2 (29%) separately showed substantial heterogeneity ($I^2 > 50\%$ and $I^2 \leq 75\%$) and considerable heterogeneity ($I^2 > 75\%$; **Table 2**). When 95% PIs were evaluated, we found that no meta-analysis excluded the null value (**Table 2**).

TABLE 1 | Main characteristics of included systematic reviews or meta-analyses that evaluate sleep duration/quality and health outcome risk.

Outcomes	Individual study	No. of studies	Effect metric	Level of comparison	Summary effect size (95% CI)	
					Random effects	Fixed effects
Sleep duration						
Diseases of the circulatory system						
Atrial fibrillation	Chokesuwattanaskul et al. (23), 2018	3	OR	Not-short vs. Short	1.20 (0.93–1.55)	1.13 (1.01–1.28)
Coronary artery disease	Yang et al. (24), 2015	10	RR	Short vs. Ref	1.10 (1.04–1.17)	1.07 (1.03–1.12)
		10	RR	Long vs. Ref	1.03 (0.91–1.16)	1.00 (0.93–1.08)
Coronary heart disease	Yin et al. (25), 2017	14	RR	Per 1-h reduction	1.07 (1.03–1.12)	1.05 (1.03–1.08)
		12	RR	Per 1-h increment	1.05 (1.00–1.10)	1.07 (1.04–1.09)
Hypertension	Meng et al. (26), 2013	5	RR	Long vs. Ref	0.96 (0.76–1.21)	1.03 (0.92–1.15)
	Li et al. (27), 2019	7	RR	$\leq$ 5 vs. 7 h	1.33 (1.04–1.70)	1.20 (1.13–1.26)
		3	RR	6 vs. 7 h	1.09 (1.04–1.14)	1.09 (1.04–1.14)
		6	RR	9 vs. 7 h	0.93 (0.85–1.01)	0.94 (0.90–0.97)
		4	RR	> 9 vs. 7 h	0.96 (0.75–1.24)	0.89 (0.80.0.99)
Total cardiovascular disease	Yin et al. (25), 2017	16	RR	Per 1-h reduction	1.06 (1.03–1.09)	1.04 (1.03–1.06)
		17	RR	Per 1-h increment	1.12 (1.08–1.16)	1.10 (1.09–1.12)
	Kwok et al. (28), 2018	5	RR	Short vs. Ref	1.16 (0.95–1.40)	1.08 (0.99–1.17)
Diseases of the nervous system						
Dementia	Fan et al. (29), 2019	7	HR	Long vs. Normal	1.77 (1.32–2.37)	1.55 (1.35–1.77)
		7	HR	Short vs. Normal	1.20 (0.91–1.59)	1.01 (0.94–1.09)
Alzheimer's disease	Fan et al. (29), 2019	6	HR	Long vs. Normal	1.63 (1.24–2.13)	1.59 (1.36–1.85)
		6	HR	Short vs. Normal	1.18 (0.91–1.54)	1.02 (0.94–1.10)
Cognitive decline	Wu et al. (30), 2017	3	RR	Shortest vs. Ref	1.37 (1.18–1.60)	1.37 (1.18–1.60)
		3	RR	Longest vs. Ref	1.17 (0.97–1.41)	1.17 (0.97–1.41)
Cognitive disorders	Wu et al. (30), 2017	9	RR	Shortest vs. Ref	1.33 (1.16–1.54)	1.32 (1.19–1.47)
		9	RR	Longest vs. Ref	1.20 (1.06–1.36)	1.20 (1.06–1.36)
Mild cognitive impairment/Dementia	Wu et al. (30), 2017	6	RR	Shortest vs. Ref	1.27 (0.97–1.66)	1.23 (1.05–1.44)
Mild cognitive impairment/Dementia	Wu et al. (30), 2017	6	RR	Longest vs. Ref	1.19 (1.00–1.42)	1.19 (1.01–1.41)
	Liang et al. (31), 2018	4	RR	Per 1-h increment	0.98 (0.97–1.00)	0.98 (0.97. 1.00)
Stroke	Leng et al. (32), 2015	12	RR	Short vs. Average	1.15 (1.07–1.24)	1.15 (1.07–1.24)
		12	RR	Long vs. Average	1.44 (1.26–1.65)	1.41 (1.32–1.52)
	He et al. (33), 2016	12	RR	Every 1-h reduction	1.10 (0.98–1.23)	1.05 (0.98–1.14)
		12	RR	Every 1-h increment	1.38 (1.23–1.55)	1.34 (1.25–1.44)
Endocrine diseases						
Diabetes	Holliday et al. (34), 2013	10	OR	Short vs. Ref	1.35 (1.19–1.53)	1.33 (1.20–1.48)
Type 2 diabetes	Cappuccio et al. (35), 2010	7	RR	Short vs. Ref	1.29 (1.03–1.60)	1.14 (1.02–1.27)
		6	RR	Long vs. Ref	1.48 (1.12–1.96)	1.38 (1.17–1.63)
	Shan et al. (36), 2015	9	RR	Per 1-h reduction	1.09 (1.04–1.15)	1.06 (1.04–1.08)
Mortality						
All cancer mortality	Li et al. (37), 2019	14	RR	Short vs. Ref	1.02 (0.99–1.05)	1.02 (0.99–1.05)
		14	RR	Long vs. Ref	1.05 (1.02–1.08)	1.05 (1.02–1.08)
	Stone et al. (38), 2019	18	HR	Lowest vs. Ref	1.04 (1.00–1.08)	1.03 (1.00–1.06)
		20	HR	Longest vs. Ref	1.09 (1.04–1.15)	1.08 (1.04–1.13)
All-cause mortality	Yin et al. (25), 2017	24	RR	Per 1-h reduction	1.06 (1.04–1.07)	1.04 (1.03–1.04)
		27	RR	Per 1-h increment	1.13 (1.11–1.15)	1.12 (1.11–1.13)
	Francesco et al. (39), 2010	16	RR	Long vs. Ref	1.29 (1.22–1.38)	1.24 (1.21–1.26)
Cardiovascular mortality	Kwok et al. (28), 2018	3	RR	Short vs. Ref	1.18 (0.90–1.53)	1.18 (0.90–1.53)
Mortality of coronary artery disease	Yang et al. (24), 2015	5	RR	Short vs. Ref	1.25 (1.06–1.47)	1.25 (1.12–1.41)
		5	RR	Long vs. Ref	1.26 (1.11–1.42)	1.24 (1.13–1.35)

(Continued)

TABLE 1 | Continued

Outcomes	Individual study	No. of studies	Effect metric	Level of comparison	Summary effect size (95% CI)	
					Random effects	Fixed effects
Mortality of coronary heart disease	Kwok et al. (28), 2018	3	RR	Short vs. Ref	1.44 (0.74–2.83)	1.51 (1.05–2.16)
	Kwok et al. (28), 2018	5	RR	Short vs. Ref	1.29 (1.10–1.51)	1.29 (1.17–1.43)
	Kwok et al. (28), 2018	4	RR	Short vs. Ref	1.12 (0.98–1.27)	1.12 (1.01–1.24)
	Kwok et al. (28), 2018	6	RR	Long vs. Ref	1.36 (1.17–1.59)	1.39 (1.26–1.53)
Mortality of coronary heart disease	Kwok et al. (28), 2018	3	RR	Long vs. Ref	1.24 (1.00–1.53)	1.24 (1.00–1.53)
Mortality (all-cause and cause-specific)	Gallicchio et al. (40), 2009	16	RR	Short vs. Ref	1.10 (1.06–1.15)	1.10 (1.08–1.12)
Prostate cancer mortality	Liu et al. (41), 2020	6	RR	Short vs. Ref	0.99 (0.91–1.07)	0.99 (0.91–1.07)
		6	RR	Long vs. Ref	0.88 (0.75–1.04)	0.94 (0.87–1.02)
Stroke mortality	Li et al. (42), 2016	4	RR	Per 1-h reduction	1.05 (0.99–1.11)	1.05 (0.99–1.11)
		11	RR	Per 1-h increment	1.17 (1.13–1.20)	1.17 (1.13–1.20)
Neoplasms						
Breast cancer	Wong et al. (43), 2020	15	RR	Short vs. Ref	0.99 (0.97–1.01)	0.99 (0.98–1.01)
		15	RR	Long vs. Ref	1.00 (0.96–1.04)	1.01 (0.98–1.04)
Cancer	Lu et al. (44), 2013	9	RR	Short vs. Ref	1.05 (0.90–1.24)	1.02 (0.93–1.11)
		9	RR	Long vs. Ref	0.92 (0.76–1.12)	0.97 (0.88–1.06)
	Zhao et al. (45), 2013	9	HR	Per 1-h reduction	1.06 (0.92–1.22)	1.01 (0.94–1.09)
		12	HR	Per 1-h increment	0.91 (0.78–1.07)	0.98 (0.91–1.06)
Nutritional diseases						
Obesity	Miller et al. (46), 2020	13	RR	Per an additional hour	1.54 (1.33–1.77)	1.51 (1.43–1.60)
	Wu et al. (47), 2015	13	OR	Short vs. Ref	1.71 (1.36–2.14)	2.18 (2.13–2.22)
Overweight	Ruan et al. (48), 2015	7	OR	Lowest vs. Highest	1.79 (1.39–2.31)	2.22 (2.17–2.26)
Overweight and obesity	Fatima et al. (49), 2015	11	OR	Short vs. Ref	1.56 (1.24–1.98)	2.20 (2.16–2.25)
Overweight or obesity	Miller et al. (50), 2018	7	RR	Highest vs. Lowest	1.40 (1.18–1.65)	1.28 (1.16–1.41)
		8	RR	Highest vs. Lowest	1.57 (1.40–1.76)	1.61 (1.51–1.72)
Other outcomes						
Depression	Zhai et al. (51), 2015	6	RR	Short vs. Ref	1.30 (1.04–1.64)	1.30 (1.04–1.64)
		4	RR	Long vs. Ref	1.41 (1.04–1.92)	1.41 (1.04–1.92)
Dyslipidaemia	Kruisbrink et al. (52), 2017	6	RR	Short vs. Ref	1.01 (0.92–1.11)	1.05 (0.99–1.10)
		6	RR	Long vs. Ref	0.98 (0.87–1.10)	0.94 (0.88–1.00)
Gestational diabetes mellitus	Zhang et al. (53), 2020	4	RR	Long vs. Normal	1.19 (1.05–1.35)	1.19 (1.05–1.35)
Gestational diabetes mellitus	Zhang et al. (53), 2020	4	RR	Short vs. Not-short	2.02 (1.31–3.11)	2.02 (1.31–3.11)
	Xu et al. (54), 2018	5	OR	Short vs. Ref	1.58 (0.99–2.52)	1.37 (1.05–1.80)
		3	OR	Long vs. Ref	1.28 (1.10–1.49)	1.28 (1.10–1.49)
The developing or dying of coronary heart disease	Cappuccio et al. (55), 2011	7	RR	Short vs. Ref	1.48 (1.22–1.80)	1.48 (1.31–1.68)
		7	RR	Long vs. Ref	1.38 (1.15–1.66)	1.41 (1.26–1.59)
The developing or dying of stroke	Cappuccio et al. (55), 2011	4	RR	Short vs. Ref	1.15 (1.00–1.32)	1.15 (1.00–1.32)
		4	RR	Long vs. Ref	1.65 (1.45–1.87)	1.65 (1.45–1.87)
The developing or dying of total cardiovascular disease	Cappuccio et al. (55), 2011	7	RR	Short vs. Ref	1.03 (0.93–1.15)	1.03 (0.93–1.15)
		8	RR	Long vs. Ref	1.41 (1.20–1.67)	1.42 (1.30–1.54)
Sleep quality						
All-cause mortality	Kwok et al. (28), 2018	10	RR	Poor vs. Good	1.03 (0.93–1.14)	1.03 (0.98–1.09)
Cardiovascular mortality	Kwok et al. (28), 2018	4	RR	Poor vs. Good	0.96 (0.82–1.13)	0.96 (0.82–1.13)
Coronary heart disease	Kwok et al. (28), 2018	4	RR	Poor vs. Good	1.44 (1.09–1.90)	1.32 (1.12–1.56)
Diabetes mellitus	Anothaisintawee et al. (56), 2015	11	RR	Poor vs. Not- Poor	1.40 (1.21–1.63)	1.32 (1.28–1.36)
Gestational diabetes mellitus	Zhang et al. (53), 2020	4	RR	Poor vs. Not- Poor	1.27 (1.11–1.44)	1.27 (1.11–1.44)
Inflammatory bowel disease	Hao et al. (57), 2020	3	OR	Poor vs. Not- Poor	2.54 (1.37–4.71)	2.38 (1.71–3.31)
Preterm birth	Wang et al. (58), 2020	5	RR	Poor vs. Good	1.54 (1.18–2.00)	1.26 (1.15–1.38)

CI, confidence interval; OR, odds ratio; RR, relative risk; HR: hazard ratio.
All statistical tests were two-sided.

TABLE 2 | Level of evidence for the association of sleep duration/quality for health outcomes.

Outcomes	Level of comparison	Features used for classification of level of evidence								
		Significance threshed reached*	I^2 (95% CI)	95% prediction interval	Egger's *P* value	Excess significance§		Largest study Significant	Small-study effect/Excess significant bias	Evidence class
						O/E#	*P* value¶			
Sleep duration										
Diseases of the circulatory system										
Atrial fibrillation	Not-short vs. Short	>0.05	66.1 (0–90)	(0.07–20.51)	0.607	1/0.86	0.860	No	No/No	No association
Coronary artery disease	Short vs. Ref	<0.001 but $>10^{-6}$	24.9 (0–62)	(0.98–1.25)	0.019	4/3.01	0.495	No	Yes/No	Suggestive
	Long vs. Ref	>0.05	45.8 (0–72)	(0.75–1.42)	0.477	3/4.22	0.435	Yes	No/No	No association
Coronary heart disease	Per 1-h reduction	<0.05 but >0.001	58 (29–75)	(0.93–1.23)	0.097	5/5.09	0.961	No	Yes/No	Weak
	Per 1-h increment	<0.05 but >0.001	64.5 (39–79)	(0.89–1.23)	0.186	6/4.20	0.275	Yes	No/No	Weak
Hypertension	Long vs. Ref	>0.05	48.2 (0–79)	(0.52–1.76)	0.147	1/1.42	0.677	No	No/No	No association
	≤ 5 vs. 7 h	<0.05 but >0.001	79.2 (57–90)	(0.63–2.84)	0.450	4/2.93	0.413	Yes	No/No	Weak
	6 vs. 7 h	<0.001 but $>10^{-6}$	0 (0–90)	(0.82–1.45)	0.872	1/0.17	0.041	Yes	No/Yes	Suggestive
	9 vs. 7 h	>0.05	6.5 (0–76)	(0.78–1.10)	0.445	2/0.93	0.228	Yes	No/No	No association
	> 9 vs. 7 h	>0.05	63 (0–88)	(0.36–2.60)	0.547	1/1.04	0.960	Yes	No/No	No association
Total cardiovascular disease	Per 1-h reduction	<0.001 but $>10^{-6}$	51.4 (20–71)	(0.98–1.14)	0.050	8/4.98	0.103	Yes	Yes/No	Suggestive
	Per 1-h increment	$<10^{-6}$	75.5 (63–84)	(0.97–1.29)	0.239	12/12.70	0.696	No	No/No	Weak
	Short vs. Ref	>0.05	54.6 (0–82)	(0.70–1.91)	0.100	2/1.55	0.648	No	Yes/No	No association
Diseases of the nervous system										
Dementia	Long vs. Normal	<0.001 but $>10^{-6}$	68.3 (30–86)	(0.74–4.20)	0.206	5/2.32	0.032	Yes	No/Yes	Suggestive
	Short vs. Normal	>0.05	62.2 (14–83)	(0.54–2.66)	0.212	2/2.02	0.990	No	No/No	No association
Alzheimer's disease	Long vs. Normal	<0.001 but $>10^{-6}$	45.1 (0–78)	(0.79–3.33)	0.761	4/1.37	0.011	Yes	No/Yes	Suggestive
	Short vs. Normal	>0.05	57.8 (0–83)	(0.57–2.47)	0.148	0/1.78	0.112	No	No/No	No association
Cognitive decline	Shortest vs. Ref	<0.001 but $>10^{-6}$	0 (0–90)	(0.51–3.71)	0.652	2/0.34	0.003	Yes	No/Yes	Suggestive
	Longest vs. Ref	>0.05	0 (0–90)	(0.35–3.92)	0.714	0/0.18	0.662	No	No/No	No association
Cognitive disorders	Shortest vs. Ref	<0.001 but $>10^{-6}$	25.6 (0–63)	(0.98–1.81)	0.304	4/1.89	0.084	Yes	No/Yes	Suggestive
	Longest vs. Ref	<0.05 but >0.001	0 (0–60)	(1.04–1.39)	0.048	1/1.59	0.608	No	Yes/No	Weak
Mild cognitive impairment/ Dementia	Shortest vs. Ref	>0.05	46.3 (0–79)	(0.64–2.53)	0.605	2/1.28	0.476	Yes	No/No	No association
	Longest vs. Ref	<0.05 but >0.001	2.7 (0–75)	(0.91–1.56)	0.241	0/0.96	0.284	No	No/No	Weak
	Per 1-h increase	>0.05	0 (0–85)	(0.95–1.02)	0.872	1/0.87	0.879	No	No/No	No association
Stroke	Short vs. Average	<0.001 but $>10^{-6}$	0 (0–50)	(1.06–1.25)	0.082	2/2.43	0.759	No	Yes/No	Suggestive
	Long vs. Average	$<10^{-6}$	68 (42–82)	(0.93–2.23)	0.486	9/2.73	0.000	Yes	No/Yes	Highly suggestive
	Every 1-h decrease	>0.05	44.2 (0–70)	(0.80–1.52)	0.080	2/4.56	0.128	No	Yes/No	No association
	Every 1-h increase	$<10^{-6}$	56.3 (22–75)	(0.95–2.00)	0.089	10/11.55	0.018	No	Yes/No	Weak
Endocrine diseases										
Diabetes	Short vs. Ref	<0.001 but $>10^{-6}$	16.6 (0–58)	(1.06–1.71)	0.021	5/1.84	0.010	Yes	Yes/Yes	Suggestive
Type 2 diabetes	Short vs. Ref	<0.05 but >0.001	57.5 (11–80)	(0.72–2.29)	0.141	3/3.47	0.722	No	No/No	Weak
	Long vs. Ref	<0.05 but >0.001	37.9 (0–74)	(0.77–2.84)	0.421	3/1.56	0.180	Yes	No/No	Weak
	Per 1-h reduction	<0.001 but $>10^{-6}$	61.8 (21–82)	(0.97–1.24)	0.083	7/2.43	0.001	Yes	Yes/Yes	Suggestive
Mortality										
All cancer mortality	Short vs. Ref	>0.05	0 (0–52)	(0.99–1.05)	0.819	0/2.08	0.118	No	No/No	No association
	Long vs. Ref	<0.001 but $>10^{-6}$	0 (0–52)	(1.02–1.08)	0.001	2/3.01	0.511	No	Yes/No	Suggestive
All cancer mortality	Lowest vs. Ref	>0.05	19.5 (0–54)	(0.95–1.14)	0.136	2/5.41	0.080	No	No/No	No association
	Longest vs. Ref	<0.001 but $>10^{-6}$	18.8 (0–53)	(0.98–1.21)	0.096	4/3.87	0.942	Yes	Yes/No	Suggestive
All-cause mortality	Per 1-h reduction	$<10^{-6}$	57.4 (36–71)	(1.01–1.11)	0.001	15/9.02	0.012	Yes	Yes/Yes	Highly suggestive
	Per 1-h increment	$<10^{-6}$	77.4 (69–83)	(1.05–1.22)	0.423	27/12.36	1.557×10^{8}	Yes	No/Yes	Highly suggestive

(Continued)

TABLE 2 | Continued

Outcomes	Level of comparison	Features used for classification of level of evidence								
		Significance threshold reached*	I^2 (95% CI)	95% prediction interval	Egger's *P* value	Excess significance§		Largest study Significant	Small-study effect/Excess significant bias	Evidence class
						O/E#	*P* value¶			
	Long vs. Ref	$<10^{-6}$	71 (57–80)	(1.03–1.62)	0.160	15/8.96	0.002	Yes	No/Yes	Highly suggestive
Cardiovascular mortality	Short vs. Ref	>0.05	0 (0–90)	(0.21–6.44)	0.028	0/0.25	1.000	No	Yes/No	No association
Mortality of coronary artery disease	Short vs. Ref	<0.05 but >0.001	42.6 (0–75)	(0.82–1.90)	0.644	4/1.88	0.050	Yes	No/Yes	Weak
	Long vs. Ref	<0.001 but $>10^{-6}$	38.9 (0–73)	(0.93–1.70)	0.493	3/3.13	0.901	No	No/No	Suggestive
Mortality of coronary heart disease	Short vs. Ref	>0.05	55.5 (0–87)	(0.00–1,535.63)	0.667	1/0.73	0.569	No	No/No	No association
	Short vs. Ref	<0.05 but >0.001	55.2 (0–81)	(0.83–2.01)	0.907	3/2.40	0.676	Yes	No/No	Weak
	Short vs. Ref	>0.05	24.3 (0–68)	(0.84–1.49)	0.851	1/1.10	1.000	No	No/No	No association
	Long vs. Ref	<0.001 but $>10^{-6}$	53.3 (1.0–78)	(0.89–2.09)	0.706	5/3.99	0.671	Yes	No/No	Suggestive
	Long vs. Ref	>0.05	0 (0–90)	(0.31–4.97)	0.291	1/0.50	0.419	Yes	No/No	No association
Mortality (all-cause and cause-specific)	Short vs. Ref	<0.001 but $>10^{-6}$	20.5 (0–56)	(1.01–1.21)	0.712	4/2.95	0.500	Yes	No/No	Suggestive
Prostate cancer mortality	Short vs. Ref	>0.05	0 (0–75)	(0.88–1.10)	0.466	0/0.86	0.316	No	No/No	No association
	Long vs. Ref	>0.05	55.6 (0–82)	(0.56–1.40)	0.241	2/1.52	0.651	No	No/No	No association
Stroke mortality	Per 1-h reduction	>0.05	0 (0–71)	(0.98–1.12)	0.996	1/1.27	0.774	No	No/No	No association
	Per 1-h increase	$<10^{-6}$	1.5 (0–61)	(1.12–1.21)	0.490	8/1.92	1.001×10^{7}	Yes	No/Yes	Highly suggestive
Neoplasms										
Breast cancer	Short vs. Ref	>0.05	7.5 (0–44)	(0.96–1.03)	0.347	2/2.57	0.695	No	No/No	No association
	Long vs. Ref	>0.05	11.2 (0–49)	(0.93–1.07)	0.065	0/2.69	0.070	No	Yes/No	No association
Cancer	Short vs. Ref	>0.05	57.6 (14–79)	(0.67–1.66)	0.349	3/3.10	0.944	No	No/No	No association
	Long vs. Ref	>0.05	68.9 (40–84)	(0.52–1.66)	0.374	4/3.51	0.740	No	No/No	No association
	Per 1-h reduction	>0.05	63.8 (28–82)	(0.69–1.62)	0.374	3/3.33	0.820	No	No/No	No association
	Per 1-h increase	>0.05	67.6 (42–82)	(0.55–1.52)	0.071	5/4.80	0.908	No	Yes/No	No association
Nutritional diseases										
Obesity	Per an additional hour	$<10^{-6}$	68.6 (44–82)	(1.00–2.37)	0.710	9/3.53	0.001	Yes	No/Yes	Highly suggestive
	Short vs. Ref	<0.001 but $>10^{-6}$	91.3 (87–94)	(0.73–4.00)	0.067	10/5.62	0.014	Yes	Yes/Yes	Suggestive
Overweight	Lowest vs. Highest	<0.001 but $>10^{-6}$	76.5 (53–88)	(0.85–3.78)	0.167	7/3.09	0.003	Yes	No/Yes	Suggestive
Overweight and obesity	Short vs. Ref	<0.001 but $>10^{-6}$	87.1 (80–92)	(0.69–3.56)	0.026	10/5.75	0.010	Yes	Yes/Yes	Suggestive
Overweight or obesity	Highest vs. Lowest	<0.001 but $>10^{-6}$	40.5 (0–75)	(0.94–2.09)	0.002	5/2.00	0.012	Yes	Yes/Yes	Suggestive
	Highest vs. Lowest	$<10^{-6}$	22.7 (0–64)	(1.23–2.00)	0.521	6/1.49	4.063×10^{5}	Yes	No/Yes	Highly suggestive
Other outcome										
Depression	Short vs. Ref	<0.05 but >0.001	0 (0–71)	(0.97–1.76)	0.965	1/1.09	0.925	No	No/No	Weak
	Long vs. Ref	<0.05 but >0.001	0 (0–79)	(0.86–2.32)	0.526	0/0.77	0.328	No	No/No	Weak
Dyslipidaemia	Short vs. Ref	>0.05	62.2 (29–80)	(0.75–1.36)	0.147	4/4.57	0.585	Yes	No/No	No association
	Long vs. Ref	>0.05	63.9 (38–79)	(0.65–1.48)	0.249	3/5.79	6.291×10^{10}	No	No/No	No association
Gestational diabetes mellitus	Long vs. Normal	<0.05 but >0.001	0 (0–85)	(0.90–1.58)	0.883	1/0.67	0.657	Yes	No/No	Weak
	Short vs. Not-short	<0.001 but $>10^{-6}$	0 (0–85)	(0.78–5.19)	0.003	1/0.58	0.545	No	Yes/No	Weak
	Short vs. Ref	>0.05	57.1 (0–83)	(0.42–5.93)	0.031	3/1.90	0.312	No	Yes/No	No association
	Long vs. Ref	<0.001 but $>10^{-6}$	0 (0–85)	(0.92–1.78)	0.771	1/0.36	0.260	Yes	No/No	Suggestive
The developing or dying of coronary heart disease	Short vs. Ref	<0.001 but $>10^{-6}$	43.3 (0–72)	(0.91–2.41)	0.962	6/3.23	0.036	Yes	No/Yes	Suggestive
	Long vs. Ref	<0.001 but $>10^{-6}$	49 (1–74)	(0.84–2.29)	0.913	5/4.96	0.976	Yes	No/No	Suggestive

(Continued)

TABLE 2 | Continued

Outcomes	Level of comparison	Features used for classification of level of evidence								
		Significance threshold reached*	I^2 (95% CI)	95% prediction interval	Egger's *P* value	Excess significance§		Largest study Significant	Small-study effect/Excess significant bias	Evidence class
						O/E#	*P* value¶			
The developing or dying of stroke	Short vs. Ref	<0.05 but >0.001	0 (0–75)	(0.95–1.39)	0.304	0/0.82	0.310	No	No/No	Weak
	Long vs. Ref	$<10^{-6}$	0 (0–75)	(1.38–1.97)	0.955	4/0.47	4.725×10^{8}	Yes	No/Yes	Highly suggestive
The developing or dying of total cardiovascular disease	Short vs. Ref	>0.05	0 (0–60)	(0.92–1.16)	0.470	0/1.01	0.279	No	No/No	No association
	Long vs. Ref	<0.001 but $>10^{-6}$	59.8 (26–78)	(0.86–2.31)	0.794	6/2.89	0.022	Yes	No/Yes	Suggestive
Sleep quality										
All-cause mortality	Poor vs. Good	>0.05	0.6 (14–79)	(0.79–1.35)	0.917	3/2.89	1.000	Yes	No/No	No association
Cardiovascular mortality	Poor vs. Good	>0.05	0 (0–85)	(0.67–1.37)	0.303	0/0.31	1.000	No	No/No	No association
Coronary heart disease	Poor vs. Good	<0.05 but >0.001	53.2 (0–85)	(0.51–4.10)	0.075	1/1.08	1.000	No	Yes/No	Weak
Diabetes mellitus	Poor vs. Not- Poor	<0.001 but $>10^{-6}$	84.1 (73–91)	(0.89–2.22)	0.679	8/4.04	0.013	Yes	No/Yes	Suggestive
Gestational diabetes mellitus	Poor vs. Not- Poor	<0.001 but $>10^{-6}$	0 (0–85)	(0.95–1.68)	0.807	2/0.50	0.024	Yes	No/Yes	Suggestive
Inflammatory bowel disease	Poor vs. Not- Poor	<0.05 but >0.001	62.3 (0–89)	(0–1,940.14)	0.683	2/0.87	0.148	Yes	No/No	Weak
Preterm birth	Poor vs. Good	<0.001 but $>10^{-6}$	76.7 (43–90)	(0.67–3.51)	0.039	5/1.73	0.002	Yes	Yes/Yes	Weak

CI, confidence interval.

§*Expected number of statistically significant studies using the point estimate of the largest study (smallest standard error) as the plausible effect size.*

**P value under the random-effects model.*

#*Observed/Expected number of statistically significant studies.*

¶*P value of the excess statistical significance test.*

All statistical tests two sided.

Small-Study Effects and Excess Significance Bias

According to Egger's test, evidence of small-study effects was observed in 21 (27%) of 78 meta-analyses and 2 (29%) of 7 meta-analyses about duration and quality of sleep, respectively (**Table 2**). When taking the largest study estimate as to the plausible effect size, 22 (28%) of 78 meta-analyses and 3 (43%) of 7 meta-analyses about duration and quality of sleep respectively showed evidence of excess significance (**Table 2**).

Methodological Quality of the Meta-Analyses

The methodological quality of the included studies regarding sleep duration (n = 33) and sleep quality (n = 5) was assessed by AMSTAR-1, which contained 11 items for scoring. **Figure 2** provides a breakdown of AMSTAR-1 levels for studies representing each study. For sleep duration, the median AMSTAR-1 score achieved across all studies was 6 out of 11 (range from 2 to 9). The studies were rated at three levels: 15% were rated as "high," 79% were rated as "moderate," and 6% were classified as "low." For sleep quality, the median AMSTAR-1 score achieved across all studies was 7 (range from 5 to 8). Approximately 40% were rated as being of "high," 60% as "moderate" quality, and no meta-analysis was categorized into low quality according to the AMSTAR-1 criteria. The common flaws were that gray literature was not considered in the literature search (item 4), and the list of excluded studies was not presented (item 5).

Evidence Grading

For sleep duration, no association presented convincing evidence, the only evidence of long sleep duration with an increased risk of all-cause mortality was categorized as highly suggestive, and the methodological quality was moderate (**Table 2**). Moreover, suggestive evidence supported the associations between long sleep and increased risk of 5 health outcomes (stroke, dyslipidaemia, mortality of coronary heart disease, stroke mortality, and the development or death of stroke); short sleep duration and increased risk of overweight and/or obesity. Moreover, 14 associations were supported by weak evidence. The remaining 31 associations were not confirmed. The detailed results of the analyses on which the evidence ratings were based are shown in **Table 2**.

For sleep quality, no association presented convincing or highly suggestive evidence, whereas suggestive evidence suggested that poor sleep quality was associated with an increased risk of diabetes mellitus and gestational diabetes mellitus. Moreover, 3 associations were supported by weak evidence and 2 associations were not confirmed.

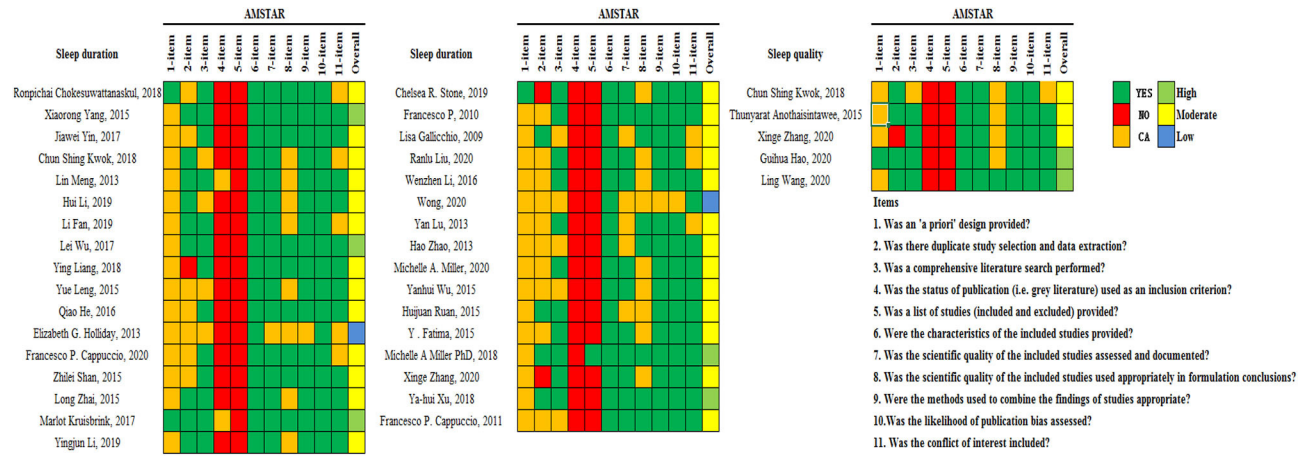

FIGURE 2 | Detailed evaluation of the methodological quality with AMSTAR-1.

DISCUSSION

In this umbrella review, to objectively assess the strength of associations between duration and quality of sleep and health outcomes, we performed a comprehensive overview by incorporating evidence from the current systematic reviews and meta-analyses of prospective studies. Overall, 85 published meta-analyses were included, and 52 (61%) were nominally statistically significant at $P < 0.05$ under the random-effects models. Although the study confirmed that short/long sleep duration or poor sleep quality was associated with an increase in the important health outcomes, the mechanisms do not seem straightforward.

In this umbrella review, evidence of the association of long sleep duration with an increased risk of all-cause mortality (25), was the only one categorized as highly suggestive, and the methodological quality was moderate in the above outcome. An association between long sleep and an increased risk of all-cause mortality was reported previously in studies with high quality and large sample sizes (59–62), which was consistent with our results. Heslop and colleagues (63), however, analyzed data from a workplace-based study of Scottish men and women who were followed over a 25-year period and found that long sleep was associated with decreased risk of all-cause mortality in men. However, this study reported RRs with only 3 quantitative categories of sleep duration. Meanwhile, long sleep duration was defined as >8 h, which may result in inaccurate evaluation of extremely long sleep. To date, no published studies have demonstrated a possible mechanism mediating the effect of long sleep as a cause of mortality. The association between a long duration of sleep and mortality may be explained by residual confounding and comorbidities (64). In particular, depressive symptoms, low socioeconomic status, low level of physical activity, unemployment, undiagnosed health conditions, poor general health, and cancer-related fatigue have all been shown to be associated with long sleep (64).

Suggestive evidence has shown that long sleep duration is positively linked with the morbidity of stroke (32) and mortality of stroke per 1-h increase in sleep duration (42). At present, the biological mechanisms of the relationship between long sleep and stroke are not clear. One important biological pathway is inflammation, as long sleep periods have been associated with an increased level of inflammatory biomarkers, such as C-reactive protein and interleukin-6 (65–68). Interestingly, a number of studies have associated long sleep with cardiovascular conditions including atrial fibrillation, carotid artery atherosclerosis, and left ventricular mass, which might have predisposed one to the risk of stroke (69–73). Meanwhile, some studies suggested an association for long sleep and stroke only among those with limited physical function (74) or with a history of hypertension (75). Another possible biological pathway is due to sleep disorders such as sleep-disordered breathing (76). Decreased cerebral blood flow and raised intracranial pressure occurred during apneic events in some studies (77, 78), and cerebral hypoperfusion may also occur during wakefulness in sleep apnea patients (79). Klingelhofer et al. (80) found that blood flow in the middle cerebral artery during apneic showed rapid increases and decreases in velocity. Such changes could incline vulnerable individuals to ischemic or hemorrhagic events (76). Several epidemiological studies have explored this association. A previous meta-analysis indicated that long sleep duration was associated with an increased risk of stroke (55), but they did not use a dose–response analysis to determine the association (55). A meta-analysis by Ge showed a significantly increased risk of stroke incidence and mortality at long sleep durations in both cohort and cross-sectional studies. Their subgroup analysis also showed that long sleep duration was a statistical stroke risk in both sexes and in Asians (81). Those results were in accordance with ours. However, the relationship between sleep duration and stroke may be related to stroke types (82), age (83), gender and race (84), and high-quality studies are therefore needed to explore this matter.

We also found suggestive evidence that long sleep duration is associated with an increased risk of mortality of coronary heart disease (28). Khan et al. (85) found that there is a significant association of coronary heart disease in the top

quartile of sleep duration compared to those in the bottom quartile. Those results were in accordance with ours. However, further adjustment for risk factors including systolic blood pressure, history of cardiovascular disease, diabetes, smoking, alcohol use, renal function and serum Low-Density Lipoprotein cholesterol attenuated the associations with fatal coronary heart disease. However, the average sleep duration in Khan's study was 9.1 h with the lowest quartile being 8.2 h. This is longer than previously reported data from Western populations. Long sleep duration has been related to systemic inflammation, an increase in cytokines and changes in several metabolic pathways (68). The lack of physiological challenge due to increased sleep has also been proposed as a mechanism that may increase mortality (86). Longer sleep duration has also been linked to depression and other psychiatric disorders, which are known to be associated with increased cardiovascular disease events (51, 87). However, all these proposed mechanisms are speculative at best and require more research.

Suggestive evidence also showed that short sleep duration is linked with the increased risk of overweight or obesity only observed in children (50). There are several lines of evidence to suggest plausible mechanisms. Sleep deprivation is associated with various hormonal responses that may affect both hunger and satiety, leading to appetite dysregulation. These include lower leptin and higher ghrelin levels (88, 89), which would increase appetite. Sleep deprivation has effects on endocannabinoids which regulate a variety of central nervous system processes including appetite (90). Changes in factors that affect metabolism, including insulin and glucose metabolism, cortisol, growth hormone and thyroid stimulating hormone are also important (48, 91–95). In turn, obesity predisposes individuals to metabolic dysfunction that can cause sleep apnea, which leads to short sleep duration (96). Activation of inflammatory pathways by short sleep periods may be implicated in the development of obesity (97) and it can up and downregulate the expression of genes involved in oxidative stress and metabolism (98). Finally, insufficient sleep is associated with alterations in attention, impulse control, mood, motivation, and judgment, and all of these factors could potentially influence eating behaviors, energy intake, and ultimately BMI in children (99).

Regarding sleep quality, we found that poor sleep quality is associated with an increased risk of diabetes mellitus (56) and gestational diabetes mellitus (53). This result is consistent with the results of a previous meta-analysis, which concluded that sleep quality may be a novel and independent risk factor for poorer glycemic control in type 2 diabetes patients (100). Poor sleep quality as defined by the presence of one or more insomnia symptoms included in the Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria was associated with a 40% increase in the risk of developing diabetes. Poor self-reported sleep quality may also be linked with other comorbid conditions, such as depression, undiagnosed obstructive sleep apnea and sleep deprivation, which are risk factors for diabetes. Adjusting for these covariates still resulted in a significant association between poor sleep quality and incident diabetes in several studies (101, 102). Pregnant women with poor sleep quality had an increased risk of gestational diabetes mellitus (GDM). In addition to its direct effect on GDM, sleep quality has been considered a moderator of the association between sleep duration and GDM risk (103). The potential pathophysiological mechanisms between poor sleep quality and glucose intolerance have been well established, including decreased brain glucose utilization (104–106), sympathetic nervous system overactivity (107, 108), alterations in the hypothalamic–pituitary–adrenal axis and growth hormone (109–111), elevated systemic inflammatory response (112, 113), reduction in the percentage of slow wave sleep (114), adipocyte dysfunction (115), changes in appetite-regulating hormones (88), and increased obesity risk (95).

To our knowledge, the present study is the first umbrella review to quantitatively evaluate the existing evidence of the associations between duration and quality of sleep and health outcomes. The main strength of our umbrella review was to provide a comprehensive summary and evaluation of the credibility and validity of evidence of duration and quality of sleep and health outcomes according to the assessment results of a series of statistical analyses. In addition, we searched three databases through a rigorous strategy, and two authors independently extracted the information. Moreover, we followed the AMSTAR-1 criteria to assess the methodological quality of selected studies in our umbrella review, and most of the investigated meta-analyses achieved a moderate-to-high quality score. We used standardized criteria to explore the extent of heterogeneity and potential bias among the included studies and further assessed the strength of claimed associations to identify which was the most credible evidence. We also used the criteria of evidence grading to evaluate the evidence categorization.

Nevertheless, several limitations should be noted when interpreting the results. Firstly, we failed to find convincing evidence for the relation of sleep and health outcomes. In addition, the quality of the evidence was rated weak or not confirmed for 39% of the associations (n = 33). Thus, further research is needed for outcomes for which the certainty of evidence was rated weak or not confirmed. Secondly, owing to the limited studies, we failed to conduct subgroup analysis (e.g., exploring by age, sex, geographical location), or sensitive analysis (e.g., excluding studies with high risks), and other relevant factors might have been missed. Many meta-analyses lacked dose-response information and compared high vs. low sleep duration without defining thresholds for these categories. Thirdly, we only evaluated published meta-analyses of prospective studies with available data, therefore, meta-analyses of randomized controlled trials were not included in our study. Fourthly, for sleep quality, only systematic reviews and meta-analyses assessing sleep quality by the PSQI questionnaire were included in this umbrella review. The PSQI is currently the only standardized clinical instrument that covers a broad range of indicators relevant to sleep quality (116). Lastly, we did not examine any error of the meta-analyses or the quality of the primary studies, as these were beyond the scope of our umbrella review. Our findings appear to be very convincing, but one may need to practice caution in terms of considering the implications of the results in the community. Although long or

short sleep is associated with an increased risk of some health outcomes, there is no rigorous evidence that lengthening or shortening sleep duration can lead to a smaller frequency of these outcomes.

In conclusion, abnormal duration or quality of sleep was significantly associated with an extensive range of adverse health-related outcomes. Based on our umbrella review, although 36 studies explored 36 unique associations, the highly suggestive evidence only supported that long sleep duration was associated with an increased risk of all-cause mortality. The relationship between abnormal duration or quality of sleep and other outcomes could be genuine, but there is still limited evidence for them. Overall, this article assessed the associations between duration and quality of sleep and health outcomes based on previous studies, which is helpful for identifying at-risk groups and developing prevention strategies to counteract the effect of sleep discrepancies. Abnormal duration or quality of sleep is harmful to human health, but further high-quality prospective studies and better designed trials are needed to generate definite conclusions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

T-TG and Q-JW contributed to the study design. CG and X-YL conducted the literature search. JG, J-LL, X-YL, F-HL, and MZ extracted the data and conducted the analyses. CG, JG, T-TG, J-LL, Y-TS, and Y-HZ wrote the first draft of the manuscript and edited the manuscript. All authors read and approved the final manuscript and accept responsibility for the integrity of the data analyzed.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.813943/full#supplementary-material

REFERENCES

1. Foundation NS. *How Much Sleep Do We Really Need?* (2018). Available online at: https://www.sleepfoundation.org/how-sleep-works/how-much-sleep-do-we-really-need (accessed June 27, 2018).
2. Roncoroni J, Dong Y, Owen J, Wippold G. The association of sleep duration and feeling rested with health in US Hispanic women. *Sleep Med.* (2021) 83:54–62. doi: 10.1016/j.sleep.2021.03.044
3. Park S, Lee S, Kim Y, Lee Y, Kang MW, Kim K. Short or long sleep duration and CKD: a Mendelian Randomization Study. *J Am Soc Nephrol.* (2021) 31:2937–47. doi: 10.1681/ASN.2020050666
4. Blair LM, Porter K, Leblebicioglu B, Christian LM. Poor sleep quality and associated inflammation predict preterm birth: heightened risk among African Americans. *Sleep.* (2015) 38:1259–67. doi: 10.5665/sleep.4904
5. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc.* (2015) 13:132–40. doi: 10.1097/XEB.0000000000000055
6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097
7. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA.* (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008
8. Liu FH, Liu C, Gong TT, Gao S, Sun H, Jiang YT. Dietary inflammatory index and health outcomes: an umbrella review of systematic review and meta-analyses of observational studies. *Front Nutr.* (2021) 8:647122. doi: 10.3389/fnut.2021.647122
9. Marx W, Veronese N, Kelly JT, Smith L, Hockey M, Collins S, et al. The dietary inflammatory index and human health: an umbrella review of meta-analyses of observational studies. *Adv Nutr.* (2021) 12:1681–90. doi: 10.1093/advances/nmab037
10. Sun H, Gong TT, Xia Y, Wen ZY, Zhao LG, Zhao YH, et al. Diet and ovarian cancer risk: an umbrella review of systematic reviews and meta-analyses of cohort studies. *Clin. Nutr.* (2021) 40:1682–90. doi: 10.1016/j.clnu.2020.11.032
11. Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med.* (2000) 19:3127–31. doi: 10.1002/1097-0258(20001130)19:22<3127::AID-SIM784>3.0.CO;2-M
12. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med.* (1997) 127:820–6. doi: 10.7326/0003-4819-127-9-199711010-00008
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557
14. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *BMJ.* (2007) 335:914–6. doi: 10.1136/bmj.39343.408449.80
15. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ.* (2011) 342:d549. doi: 10.1136/bmj.d549
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629
17. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ.* (2011) 343:d4002. doi: 10.1136/bmj.d4002
18. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials.* (2007) 4:245–53. doi: 10.1177/1740774507079441
19. Tsilidis KK, Panagiotou OA, Sena ES, Aretouli E, Evangelou E, Howells DW. Evaluation of excess significance bias in animal studies of neurological diseases. *PLoS Biol.* (2013) 11:e1001609. doi: 10.1371/journal.pbio.1001609
20. da Costa BR, Rutjes AW, Johnston BC, Reichenbach S, Nüesch E, Tonia T, et al. Methods to convert continuous outcomes into odds ratios of treatment response and numbers needed to treat: meta-epidemiological study. *Int J Epidemiol.* (2012). 41:1445–59. doi: 10.1093/ije/dys124

21. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* (2007) 7:10. doi: 10.1186/1471-2288-7-10
22. Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Mitra A. Obesity and gynaecological and obstetric conditions: umbrella review of the literature. *BMJ.* (2017) 359:j4511. doi: 10.1136/bmj.j4511
23. Chokesuwattanaskul R, Thongprayoon C, Sharma K, Congrete S, Tanawuttiwat T, Cheungpasitporn W. Associations of sleep quality with incident atrial fibrillation: a meta-analysis. *Intern Med J.* (2018) 48:964–72. doi: 10.1111/imj.13764
24. Yang X, Chen H, Pan LiS, Jia L, C. Association of sleep duration with the morbidity and mortality of coronary artery disease: a meta-analysis of prospective studies. *Heart Lung Circ.* (2015) 24:1180–90. doi: 10.1016/j.hlc.2015.08.005
25. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc.* (2017) 6:e005947. doi: 10.1161/JAHA.117.005947
26. Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertens Res.* (2013) 36:985–95. doi: 10.1038/hr.2013.70
27. Ren LiH, Wu Y, Zhao Y, X. Correlation between sleep duration and hypertension: a dose-response meta-analysis. *J Hum Hypertens.* (2019) 33:218–28. doi: 10.1038/s41371-018-0135-1
28. Kwok CS, Kontopantelis E, Kuligowski G, Gray M, Muhyaldeen A, Gale CP. Self-reported sleep duration and quality and cardiovascular disease and mortality: a dose-response meta-analysis. *J Am Heart Assoc.* (2018) 7:e008552. doi: 10.1161/JAHA.118.008552
29. Fan L, Xu W, Cai Y, Hu Y, Wu C. Sleep duration and the risk of dementia: a systematic review and meta-analysis of prospective cohort studies. *J Am Med Directors Assoc.* (2019). 20:1480–7.e5. doi: 10.1016/j.jamda.2019.06.009
30. Wu L, Sun D, Tan Y. A systematic review and dose-response meta-analysis of sleep duration and the occurrence of cognitive disorders. *Sleep Breath.* (2018) 22:805–14. doi: 10.1007/s11325-017-1527-0
31. Liang Y, Qu LB, Liu H. Non-linear associations between sleep duration and the risks of mild cognitive impairment/dementia and cognitive decline: a dose-response meta-analysis of observational studies. *Aging Clin Exp Res.* (2019) 31:309–20. doi: 10.1007/s40520-018-1005-y
32. Leng Y, Cappuccio FP, Wainwright NW, Surtees PG, Luben R, Brayne C. Sleep duration and risk of fatal and nonfatal stroke: a prospective study and meta-analysis. *Neurology.* (2015) 84:1072–9. doi: 10.1212/WNL.0000000000001371
33. He Q, Sun H, Wu X, Zhang P, Dai H, Ai C, et al. Sleep duration and risk of stroke: a dose-response meta-analysis of prospective cohort studies. *Sleep Med.* (2017) 32:66–74. doi: 10.1016/j.sleep.2016.12.012
34. Holliday EG, Magee CA, Kritharides L, Banks E, Attia J. Short sleep duration is associated with risk of future diabetes but not cardiovascular disease: a prospective study and meta-analysis. *PLoS ONE.* (2013) 8:e82305. doi: 10.1371/journal.pone.0082305
35. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care.* (2010) 33:414–20. doi: 10.2337/dc09-1124
36. Shan Z, Ma H, Xie M, Yan P, Guo Y, Bao W. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care.* (2015) 38:529–37. doi: 10.2337/dc14-2073
37. Cai LiY, Ling S, Mi Y, Fan S, Zhong CY, et al. Association between total sleep time and all cancer mortality: non-linear dose-response meta-analysis of cohort studies. *Sleep Med.* (2019) 60:211–8. doi: 10.1016/j.sleep.2019.03.026
38. Stone CR, Haig TR, Fiest KM, McNeil J, Brenner DR, Friedenreich CM. The association between sleep duration and cancer-specific mortality: a systematic review and meta-analysis. *Cancer Causes Control.* (2019). 30:501–25. doi: 10.1007/s10552-019-01156-4
39. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep.* (2010) 33:585–92. doi: 10.1093/sleep/33.5.585
40. Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *J Sleep Res.* (2009) 18:148–58. doi: 10.1111/j.1365-2869.2008.00732.x
41. Liu R, Wu S, Zhang B, Guo M, Zhang Y. The association between sleep duration and prostate cancer: A systematic review and meta-analysis. *Medicine.* (2020) 99:e21180. doi: 10.1097/MD.0000000000021180
42. Wang LiW, Cao D, Yin S, Gong X, Gan YY, et al. Sleep duration and risk of stroke events and stroke mortality: a systematic review and meta-analysis of prospective cohort studies. *Int J Cardiol.* (2016) 223:870–6. doi: 10.1016/j.ijcard.2016.08.302
43. Wong ATY, Heath AK, Tong TYN, Reeves GK, Floud S, Beral V, et al. Sleep duration and breast cancer incidence: results from the Million Women Study and meta-analysis of published prospective studies. *Sleep.* (2021) 44:166. doi: 10.1093/sleep/zsaa166
44. Lu Y, Tian N, Yin J, Shi Y, Huang Z. Association between sleep duration and cancer risk: a meta-analysis of prospective cohort studies. *PLoS ONE.* (2013) 8:e74723. doi: 10.1371/journal.pone.0074723
45. Zhao H, Yin JY, Yang WS, Qin Q, Shi Li TT. Sleep duration and cancer risk: a systematic review and meta-analysis of prospective studies. *Asian Pac J Cancer Prev.* (2013) 14:7509–15. doi: 10.7314/APJCP.2013.14.12.7509
46. Miller MA, Bates S, Cappuccio Ji C. Systematic review and meta-analyses of the relationship between short sleep and incidence of obesity and effectiveness of sleep interventions on weight gain in preschool children. *Obes Rev.* (2021) 22:e13113. doi: 10.1111/obr.13113
47. Wu Y, Gong Q, Zou Z, Zhang LiH. Short sleep duration and obesity among children: A systematic review and meta-analysis of prospective studies. *Obes Res Clin Pract.* (2017) 11:140–50. doi: 10.1016/j.orcp.2016.05.005
48. Ruan H, Xun P, Cai W, He K, Tang Q. Habitual sleep duration and risk of childhood obesity: systematic review and dose-response meta-analysis of prospective cohort studies. *Sci Rep.* (2015) 5:16160. doi: 10.1038/srep16160
49. Fatima Y, Doi SA, Mamun AA. Longitudinal impact of sleep on overweight and obesity in children and adolescents: a systematic review and bias-adjusted meta-analysis. *Obes Rev.* (2015) 16:137–49. doi: 10.1111/obr.12245
50. Miller MA, Kruisbrink M, Wallace J, Ji C, Cappuccio FP. Sleep duration and incidence of obesity in infants, children, and adolescents: a systematic review and meta-analysis of prospective studies. *Sleep.* (2018) 41:18. doi: 10.1093/sleep/zsy018
51. Zhai L, Zhang H, Zhang D. Sleep duration and depression among adults: a meta-analysis of prospective studies. *Depress Anxiety.* (2015) 32:664–70. doi: 10.1002/da.22386
52. Kruisbrink M, Robertson W, Miller JiC, Geleijnse MA, Cappuccio JM. Association of sleep duration and quality with blood lipids: a systematic review and meta-analysis of prospective studies. *BMJ Open.* (2017) 7:e018585. doi: 10.1136/bmjopen-2017-018585
53. Zhang X, Zhang R, Cheng L, Wang Y, Ding X, Fu J. The effect of sleep impairment on gestational diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Sleep Med.* (2020) 74:267–77. doi: 10.1016/j.sleep.2020.05.014
54. Xu YH, Shi L, Bao YP, Chen SJ, Shi J, Zhang RL. Association between sleep duration during pregnancy and gestational diabetes mellitus: a meta-analysis. *Sleep Med.* (2018) 52:67–74. doi: 10.1016/j.sleep.2018.07.021
55. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J.* (2011) 32:1484–92. doi: 10.1093/eurheartj/ehr007
56. Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. *Sleep Med Rev.* (2016) 30:11–24. doi: 10.1016/j.smrv.2015.10.002
57. Hao G, Zhu B, Wang LiY, Li P, Hou L, L. Sleep quality and disease activity in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Sleep Med.* (2020) 75:301–8. doi: 10.1016/j.sleep.2020.08.032
58. Wang L, Jin F. Association between maternal sleep duration and quality, and the risk of preterm birth: a systematic review and meta-analysis of observational studies. *BMC Preg Childbirth.* (2020) 20:125. doi: 10.1186/s12884-020-2814-5

59. Bellavia A, Åkerstedt T, Bottai M, Wolk A, Orsini N. Sleep duration and survival percentiles across categories of physical activity. *Am J Epidemiol.* (2014) 179:484–91. doi: 10.1093/aje/kwt280
60. Magee CA, Holliday EG, Attia J, Kritharides L, Banks E. Investigation of the relationship between sleep duration, all-cause mortality, and preexisting disease. *Sleep Med.* (2013) 14:591–6. doi: 10.1016/j.sleep.2013.02.002
61. Xiao Q, Keadle SK, Hollenbeck AR, Matthews CE. Sleep duration and total and cause-specific mortality in a large US cohort: interrelationships with physical activity, sedentary behavior, and body mass index. *Am J Epidemiol.* (2014) 180:997–1006. doi: 10.1093/aje/kwu222
62. Yeo Y, Ma SH, Park SK, Chang SH, Shin HR, Kang D. A prospective cohort study on the relationship of sleep duration with all-cause and disease-specific mortality in the Korean Multi-center Cancer Cohort study. *J Prev Med Public Health.* (2013) 46:271–81. doi: 10.3961/jpmph.2013.46.5.271
63. Chen HC, Su TP, Chou P. A nine-year follow-up study of sleep patterns and mortality in community-dwelling older adults in Taiwan. *Sleep.* (2013) 36:1187–98. doi: 10.5665/sleep.2884
64. Stranges S, Dorn JM, Shipley MJ, Kandala NB, Trevisan M, Miller MA. Correlates of short and long sleep duration: a cross-cultural comparison between the United Kingdom and the United States: the Whitehall II Study and the Western New York Health Study. *Am J Epidemiol.* (2008) 168:1353–64. doi: 10.1093/aje/kwn337
65. Grandner MA, Buxton OM, Jackson N, Sands-Lincoln M, Pandey A, Jean-Louis G. Extreme sleep durations and increased C-reactive protein: effects of sex and ethnoracial group. *Sleep.* (2013) 36:769–79e. doi: 10.5665/sleep.2646
66. Grandner MA, Sands-Lincoln MR, Pak VM, Garland SN. Sleep duration, cardiovascular disease, and proinflammatory biomarkers. *Nat Sci Sleep.* (2013) 5:93–107. doi: 10.2147/NSS.S31063
67. Patel SR, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R. Sleep duration and biomarkers of inflammation. *Sleep.* (2009) 32:200–4. doi: 10.1093/sleep/32.2.200
68. Prather AA, Vogelzangs N, Penninx BW. Sleep duration, insomnia, and markers of systemic inflammation: results from the Netherlands Study of Depression and Anxiety (NESDA). *J Psychiatr Res.* (2015) 60:95–102. doi: 10.1016/j.jpsychires.2014.09.018
69. Abe T, Aoki T, Yata S, Okada M. Sleep duration is significantly associated with carotid artery atherosclerosis incidence in a Japanese population. *Atherosclerosis.* (2011) 217:509–13. doi: 10.1016/j.atherosclerosis.2011.02.029
70. Khawaja O, Sarwar A, Albert CM, Gaziano JM, Djoussé L. Sleep duration and risk of atrial fibrillation (from the Physicians' Health Study). *Am J Cardiol.* (2013) 111:547–51. doi: 10.1016/j.amjcard.2012.10.038
71. Ramos AR, Dong C, Rundek T, Elkind MS, Boden-Albala B, Sacco RL. Sleep duration is associated with white matter hyperintensity volume in older adults: the Northern Manhattan Study. *J Sleep Res.* (2014) 23:524–30. doi: 10.1111/jsr.12177
72. Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology.* (1978) 28:973–7. doi: 10.1212/WNL.28.10.973
73. Wolff B, Völzke H, Schwahn C, Robinson D, Kessler C, John U. Relation of self-reported sleep duration with carotid intima-media thickness in a general population sample. *Atherosclerosis.* (2008) 196:727–32. doi: 10.1016/j.atherosclerosis.2006.12.023
74. Kakizaki M, Kuriyama S, Nakaya N, Sone T, Nagai M, Sugawara Y. Long sleep duration and cause-specific mortality according to physical function and self-rated health: the Ohsaki Cohort Study. *J Sleep Res.* (2013) 22:209–16. doi: 10.1111/j.1365-2869.2012.01053.x
75. Pan A, De Silva DA, Yuan JM, Koh WP. Sleep duration and risk of stroke mortality among Chinese adults: Singapore Chinese health study. *Stroke.* (2014). 45:1620–5. doi: 10.1161/STROKEAHA.114.005181
76. Qureshi AI, Giles WH, Croft JB, Bliwise DL. Habitual sleep patterns and risk for stroke and coronary heart disease: a 10-year follow-up from NHANES I. *Neurology.* (1997) 48:904–11. doi: 10.1212/WNL.48.4.904
77. Fischer AQ, Chaudhary BA, Taormina MA, Akhtar B. Intracranial hemodynamics in sleep apnea. *Chest.* (1992) 102:1402–6. doi: 10.1378/chest.102.5.1402
78. Jennum P, Børgesen SE. Intracranial pressure and obstructive sleep apnea. *Chest.* (1989) 95:279–83. doi: 10.1378/chest.95.2.279
79. Daly JAGR, Miller B, Garret K. Impaired awake cerebral perfusion in sleep apnea [abstract]. *Am Rev Respir Dis.* (1990) 141:A376.
80. Klingelhöfer J, Hajak G, Sander D, Schulz-Varszegi M, Rüther E, Conrad B. Assessment of intracranial hemodynamics in sleep apnea syndrome. *Stroke.* (1992) 23:1427–33. doi: 10.1161/01.STR.23.10.1427
81. Ge B, Guo X. Short and long sleep durations are both associated with increased risk of stroke: a meta-analysis of observational studies. *Int J Stroke.* (2015) 10:177–84. doi: 10.1111/ijs.12398
82. Titova OE, Michaëlsson K, Larsson SC. Sleep duration and stroke: prospective cohort study and mendelian randomization analysis. *Stroke.* (2020) 51:3279–85. doi: 10.1161/STROKEAHA.120.029902
83. Leng Y, Wainwright NW, Cappuccio FP, Surtees PG, Luben R, Wareham N. Self-reported sleep patterns in a British population cohort. *Sleep Med.* (2014) 15:295–302. doi: 10.1016/j.sleep.2013.10.015
84. Petrov ME, Howard G, Grandner MA, Kleindorfer D, Molano JR, Howard VJ. Sleep duration and risk of incident stroke by age, sex, and race: the REGARDS study. *Neurology.* (2018) 91:e1702–e9. doi: 10.1212/WNL.0000000000006424
85. Khan H, Kella D, Kunutsor SK, Savonen K, Laukkanen JA. Sleep duration and risk of fatal coronary heart disease, sudden cardiac death, cancer death, and all-cause mortality. *Am J Med.* (2018) 131:1499–505.e2. doi: 10.1016/j.amjmed.2018.07.010
86. Grandner MA, Drummond SP. Who are the long sleepers? Towards an understanding of the mortality relationship. *Sleep Med Rev.* (2007) 11:341–60. doi: 10.1016/j.smrv.2007.03.010
87. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *Eur Heart J.* (2014) 35:1365–72. doi: 10.1093/eurheartj/eht462
88. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med.* (2004) 141:846–50. doi: 10.7326/0003-4819-141-11-200412070-00008
89. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med.* (2004) 1:e62. doi: 10.1371/journal.pmed.0010062
90. Cedernaes J, Fanelli F, Fazzini A, Pagotto U, Broman JE, Vogel H. Sleep restriction alters plasma endocannabinoids concentrations before but not after exercise in humans. *Psychoneuroendocrinology.* (2016) 74:258–68. doi: 10.1016/j.psyneuen.2016.09.014
91. Taheri S. The link between short sleep duration and obesity: we should recommend more sleep to prevent obesity. *Arch Dis Child.* (2006) 91:881–4. doi: 10.1136/adc.2005.093013
92. Chen X, Beydoun MA, Wang Y. Is sleep duration associated with childhood obesity? A systematic review and meta-analysis. *Obesity.* (2008) 16, 265–74. doi: 10.1038/oby.2007.63
93. Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat Rev Endocrinol.* (2009) 5:253–61. doi: 10.1038/nrendo.2009.23
94. Beccuti G, Pannain S. Sleep and obesity. *Curr Opin Clin Nutr Metab Care.* (2011) 14:402–12. doi: 10.1097/MCO.0b013e3283479109
95. Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. *Ann Intern Med.* (2012) 157:549–57. doi: 10.7326/0003-4819-157-8-201210160-00005
96. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol.* (2013) 62:569–76. doi: 10.1016/j.jacc.2013.05.045
97. Miller MA, Cappuccio FP. Inflammation, sleep, obesity and cardiovascular disease. *Curr Vasc Pharmacol.* (2007) 5:93–102. doi: 10.2174/157016107780368280
98. Möller-Levet CS, Archer SN, Bucca G, Laing EE, Slak A, Kabiljo R. Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. *Proc Natl Acad Sci USA.* (2013) 110:E1132–41. doi: 10.1073/pnas.1217154110
99. Taveras EM, Rifas-Shiman SL, Bub KL, Gillman MW, Oken E. Prospective study of insufficient sleep and neurobehavioral functioning among school-age children. *Acad Pediatr.* (2017) 17:625–32. doi: 10.1016/j.acap.2017.02.001

100. Lee SWH, Ng KY, Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: a systematic review and meta-analysis. *Sleep Med Rev.* (2017) 31:91–101. doi: 10.1016/j.smrv.2016.02.001
101. Boyko EJ, Seelig AD, Jacobson IG, Hooper TI, Smith B, Smith TC. Sleep characteristics, mental health, and diabetes risk: a prospective study of US military service members in the Millennium Cohort Study. *Diab Care.* (2013) 36:3154–61. doi: 10.2337/DC13-0042
102. Lai YJ, Lin CL, Lin MC, Lee ST, Sung FC, Chang YJ. Population-based cohort study on the increase in the risk for type 2 diabetes mellitus development from nonapnea sleep disorders. *Sleep Med.* (2013) 14:913–8. doi: 10.1016/j.sleep.2013.03.024
103. Zhong C, Chen R, Zhou X, Xu S, Cui LiQ. Poor sleep during early pregnancy increases subsequent risk of gestational diabetes mellitus. *Sleep Med.* (2018) 46:20–5. doi: 10.1016/j.sleep.2018.02.014
104. Rafalson L, Donahue RP, Stranges S, Lamonte MJ, Dmochowski J, Dorn J. Short sleep duration is associated with the development of impaired fasting glucose: the Western New York Health Study. *Ann Epidemiol.* (2010) 20:883–9. doi: 10.1016/j.annepidem.2010.05.002
105. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. (1999) 354:1435–9. doi: 10.1016/S0140-6736(99)01376-8
106. Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R. Neural basis of alertness and cognitive performance impairments during sleepiness. I Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res.* (2000) 9:335–52. doi: 10.1046/j.1365-2869.2000.00225.x
107. Grassi, G. Dell'Oro R, Quarti-Trevano F, Scopelliti F, Seravalle G, Paleari F, et al. (2005). Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. *Diabetologia.* 48:1359–65. doi: 10.1007/s00125-005-1798-z
108. Tentolouris N, Argyrakopoulou G, Katsilambros N. Perturbed autonomic nervous system function in metabolic syndrome. *Neuromolecular Med.* (2008) 10:169–78. doi: 10.1007/s12017-008-8022-5
109. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes.* (2010) 59:2126–33. doi: 10.2337/db09-0699
110. Leproult R, Van Cauter E. Role of sleep and sleep loss in hormonal release and metabolism. *Endocr Dev.* (2010) 17:11–21. doi: 10.1159/000262524
111. Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP. Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. *Clin Endocrinol.* (1999) 51:205–15. doi: 10.1046/j.1365-2265.1999.00763.x
112. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation.* (2002) 106:2067–72. doi: 10.1161/01.CIR.0000034509.14906.AE
113. Larkin EK, Rosen CL, Kirchner HL, Storfer-Isser A, Emancipator JL, Johnson NL. Variation of C-reactive protein levels in adolescents: association with sleep-disordered breathing and sleep duration. *Circulation.* (2005) 111:1978–84. doi: 10.1161/01.CIR.0000161819.76138.5E
114. Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci USA.* (2008) 105:1044–9. doi: 10.1073/pnas.0706446105
115. Broussard J, Brady MJ. The impact of sleep disturbances on adipocyte function and lipid metabolism. Best practice and research. *Clin Endocrinol Metab.* (2010) 24:763–73. doi: 10.1016/j.beem.2010.08.007
116. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. *Sleep Med Rev.* (2016) 25:52–73. doi: 10.1016/j.smrv.2015.01.009

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Prediction of Moderate to Severe Obstructive Sleep Apnea Using Neck Computed Tomography With Computational Fluid Dynamics Study

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Background: Moderate to severe obstructive sleep apnea (OSA) is associated with cardiovascular disease. Polysomnography is time intensive and difficult to access for diagnosis of OSA. Neck computed tomography (CT) provides upper airway delineation but not diagnostic criteria for moderate to severe OSA. We explored neck CT with computational fluid dynamics (CFD) study for airway pressure and airflow velocity to predict moderate to severe OSA.

Methods: Enrolled from February 1, 2020, to June 30, 2021, patients with OSA with overnight oxygen desaturation (sPO2 <90%) received awake neck CT with a CFD study of their airway pressure and airflow velocity. CTL12 and CTL34 were defined as airflow velocity <3 and ≥3 m/s, respectively, and airway pressure <10 and ≥10 pa, respectively, in the narrowest upper airway.

Results: Sixty-two patients (42 male and 20 female; mean age: 50.4 ± 14.6 years) were included; 12 and 50 patients had mild OSA and moderate to severe OSA, respectively. The minimum sPO2 in the supine position was 80.7 ± 9.1%. The total time of sPO2 <90% at overnight oximetry was 29.3 ± 51.1 min. Most (85.5%) neck CT examinations with CFD study presented CTL34. Patients with CTL34 had a lower minimum sPO2 in the supine position (78.4 vs. 88.1%, $P = 0.004$) and longer duration of sPO2 <90% at overnight oximetry (33.9 vs. 1.9 min, $P = 0.001$) than those with CTL12. The values of the area under the receiver operating characteristic curves of airway pressure and of airflow velocity at the narrowest upper airway were 0.788 and 0.733, respectively.

Conclusion: Neck CT with CFD study of airway pressure and airflow velocity may provide a quick prediction of moderate to severe OSA.

Keywords: obstructive sleep apnea, overnight oxygen desaturation, computed tomography, computational fluid dynamics, airway pressure, airflow velocity

INTRODUCTION

Obstructive sleep apnea (OSA) is a so-called invisible killer disorder characterized by repetitive pauses of airflow through the upper airway with hypoxia during sleep (1). Intermittent hypoxemia may lead to systemic inflammation, which may play a vital role for risk of cardiovascular disease (CVD), diabetes, and cancer (1–4). A Swiss study observed that the prevalence of moderate to severe sleep apnea (apnea-hypopnea index [AHI] ≥ 15 episodes per hour) was 49.7% in men and 23.4% in women (5). Evidence has indicated that approximately 1 billion adults worldwide aged between 30 and 60 years may have OSA, which carries risks of major morbidity and mortality (2–4, 6). Patients with OSA may experience considerably worse health and quality of life (7).

The reference standard for diagnosis of OSA is a full-night polysomnography, a level 1 study, in a sleep center. However, patients with OSA experience substantial wait time (2–36 months) for sleep studies because OSA has become increasingly prevalent and diagnostic capacity remains limited (8–11). A full polysomnographic examination in a sleep center features data collection using electroencephalography, electrocardiography, electrooculography, chin and leg electromyography, thoracoabdominal bands, and snoring sensors and regarding body position, airflow, and saturation of pulse oxyhemoglobin (sPO2) (11). Therefore, many patients take sleeping pills to help overcome distraction and achieve sleep in their study. However, these medications may affect the sleep stages. Benzodiazepines may produce an increase and decrease in polysomnography readings at stage 2 and stage 3 sleep, respectively (12). Clinicians should be cognizant of a patient's medication before making a diagnosis in the sleep study.

The pathogenesis of OSA may result from pharyngeal collapse during sleep. Pharyngeal collapse can occur at the retropalatal level (uvula), the retroglossal level (tongue base), and at the oropharyngeal lateral walls and the hypopharynx (epiglottis) (13). Identification of the upper airway obstruction site is essential for an effective and nuanced treatment of OSA; current polysomnography for determining AHI cannot provide such necessary anatomic information. Although drug-induced sleep endoscopy (DISE) is an alternative modality for examining the obstruction site in patients with OSA, DISE requires sedation and may result in aspiration, laryngospasm, and deep desaturation (14, 15). Multidetector neck CT is a fast modality for scanning. Castro et al. (16) used computational fluid dynamics (CFD) simulations to construct the complex 3-dimensional airflow pattern in the human nasal passageways using the CT scan. Yu et al. (17) used neck CT with 3-dimensional models and reported substantial difference between the minimum cross-sectional area and the pressure gradient of the upper airway among patients with OSA and patients without OSA. Chousangsuntorn et al. reported that the presence of complete obstruction and complete concentric collapse in neck CT were associated with increased AHI for patients with OSA (18). Our study used a multidetector neck CT to reconstruct a 3-dimensional model of upper airway geometry as well as utilize CFD computations to evaluate airflow velocity and airway pressure of the upper airway. Relevant studies have indicated that having untreated moderate to severe OSA is correlated with increased cardiovascular morbidity and mortality (19–21). Therefore, we further used the results of the CFD study of airflow velocity and airway pressure to predict the moderate to severe OSA.

TABLE 1 | Demographic characteristics of study participants.

Variables	*N* = 62	
	N (mean)	% (SD)
Sex		
Male	42	67.7
Female	20	32.3
Age	(54.0)	(14.6)
Epworth sleepiness scale	(8.1)	(4.3)
Berlin questionnaire high risk	17	29.8
Body mass index (kg/m^2)	(27.6)	(4.0)
Neck circumferences (cm)	(38.5)	(3.5)
Waist circumferences (cm)	(96.9)	(8.7)
AHI (/h)	(34.7)	(24.1)
Mild severity of OSA	12	19.4
Moderate to severe severity of OSA	50	80.6
Minimum sPO2 of overnight oximetry (%)	(80.3)	(8.9)
Minimum sPO2 in supine position (%)	(80.7)	(9.1)
sPO2 <90% (min) at overnight oximetry	(29.3)	(51.1)
N1 + N2 phase of TST (%)	(70.6)	(13.0)
N3 phase of TST (%)	(9.7)	(8.4)
Airway pressure (pa)	(40.3)	(55.9)
Airflow velocity at the narrowest upper airway (m/s)	(9.7)	(7.3)
CTL12	9	14.5
CTL34	53	85.5

SD, standard deviation; AHI, apnea-hypopnea index; REM, rapid eye movement; RDI, respiratory disturbance index; sPO2, pulse oxygen saturation; PSG, polysomnography; TST, total sleep time; CTL12, airflow velocity <3 m/s and airway pressure <10 Pa in the narrowest upper airway by neck CT; CTL34, Airflow velocity ≥ 3 m/s or airway pressure ≥10 Pa in the narrowest upper airway by neck CT.

MATERIALS AND METHODS

Study Participants

The patients in the study were diagnosed as having OSA (AHI ≥ 5 episodes per hour) with overnight oxygen desaturation (sPO2 < 90%) in a full-night level-1 polysomnography session in a sleep center of the Taichung Hospital from February 1, 2020, to June 30, 2021. All patients received awake neck CT to evaluate the obstruction level of the upper airway from the skull base to the thoracic inlet by using a 160-slice Toshiba AQUILION PRIME scanner (Canon Medical Systems, Otawara-Shi, Tochigi-ken, Japan) with the following settings: 120 kVp, automatic mA, 1-mm slice thickness, 5-mm reconstruction interval, 1:1 helical pitch, and 30-cm display field of view with an

approximately 5-s scan time (approximately 5 mGy of radiation exposure). We further constructed a 3-dimensional mesh model and geometry of upper airway from CT Digital Imaging and Communications in Medicine (DICOM) (Innolitics, Austin, TX, USA) images (image size 512 × 512). We excluded those patients who slept for <4 h. All personally identifiable information was digitally encrypted by a system used in the hospital. The study was approved by the Institutional Review Board of Tsaotun Psychiatric Center, Ministry of Health and Welfare (110008).

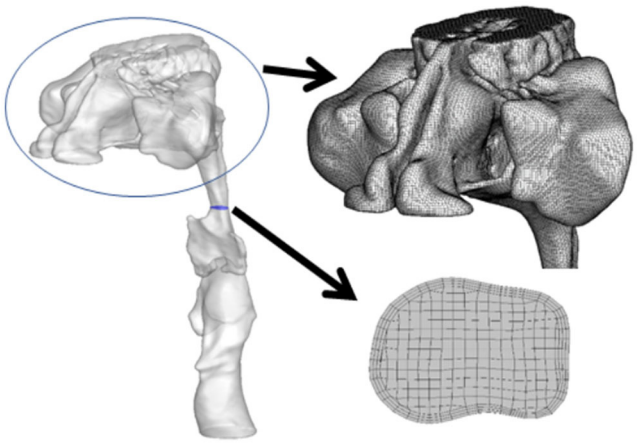

FIGURE 1 | Geometry of upper airway and corresponding computational mesh arrangement.

Construction of Geometry and Mesh

The generation of an unstructured surface mesh, which was then saved in a stereolithography file, required the delineation of the upper airway and importation of the images into Soteria OPZ (Soteria Biotech, Taipei, Taiwan) and further construction of CFD airflow simulation (**Figure 1**). The unstructured tetrahedral meshes on the surface, structured hexahedral meshes in the core of the upper airway, and pentahedral meshes inside the transition region were generated by snappyHexMesh software (OpenFOAM, London, UK).

Numerical Model and Method

The 3-dimensional incompressible flows in turbulence were determined by the Reynolds-averaged Navier–Stokes equations (RANS) inside the upper airway. The gravitational effect, heat source, heat transfer, phase change, and chemical reactions were disregarded. Turbulence closure was obtained using the standard shear stress transport k–ω model (22). The velocity profile as a function of time (t) was imposed at the inlet of the airway as

$$U = U_i \sin(2\pi ft) \tag{1}$$

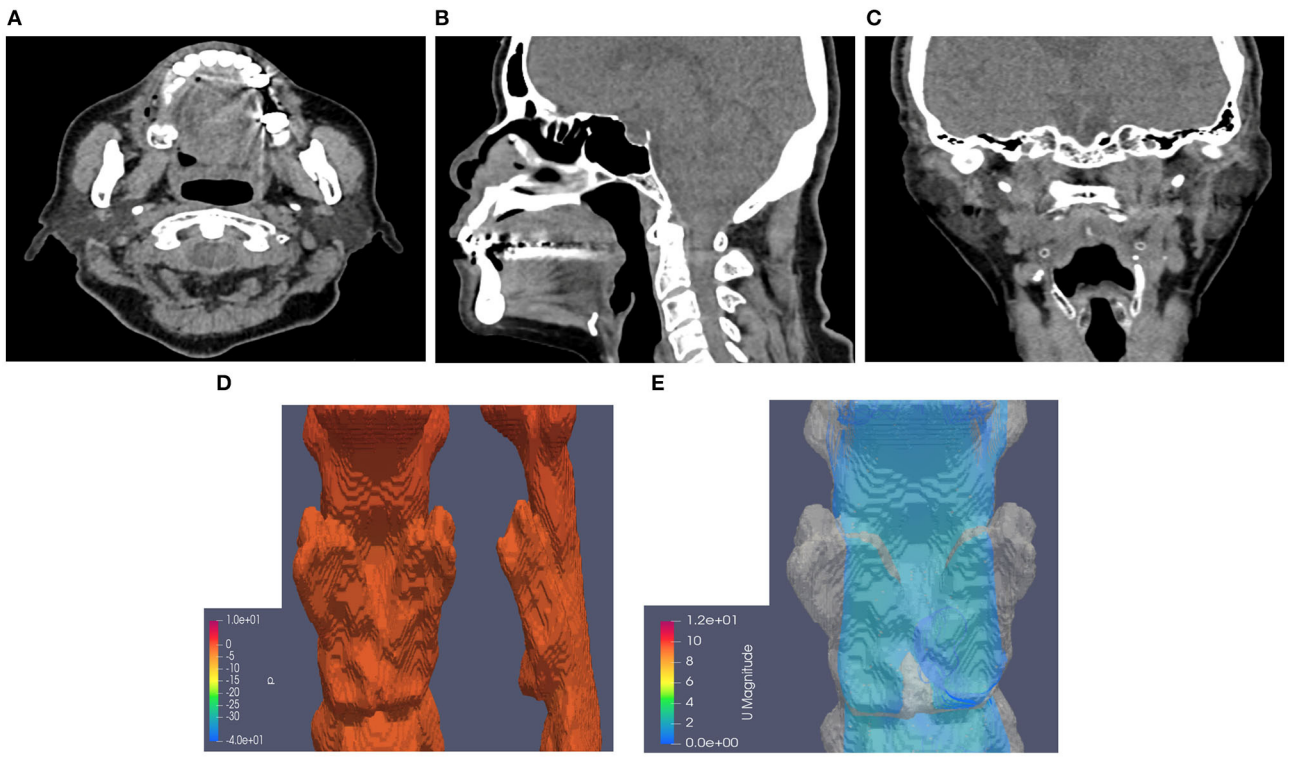

FIGURE 2 | Neck CT with computational fluid dynamics study of the 82-year-old female showed CTL12. **(A)** Axial view. **(B)** Sagittal view. **(C)** Coronal view. **(D)** Airway pressure of 1.28 Pa. **(E)** Airflow velocity of 0.8 m/s.

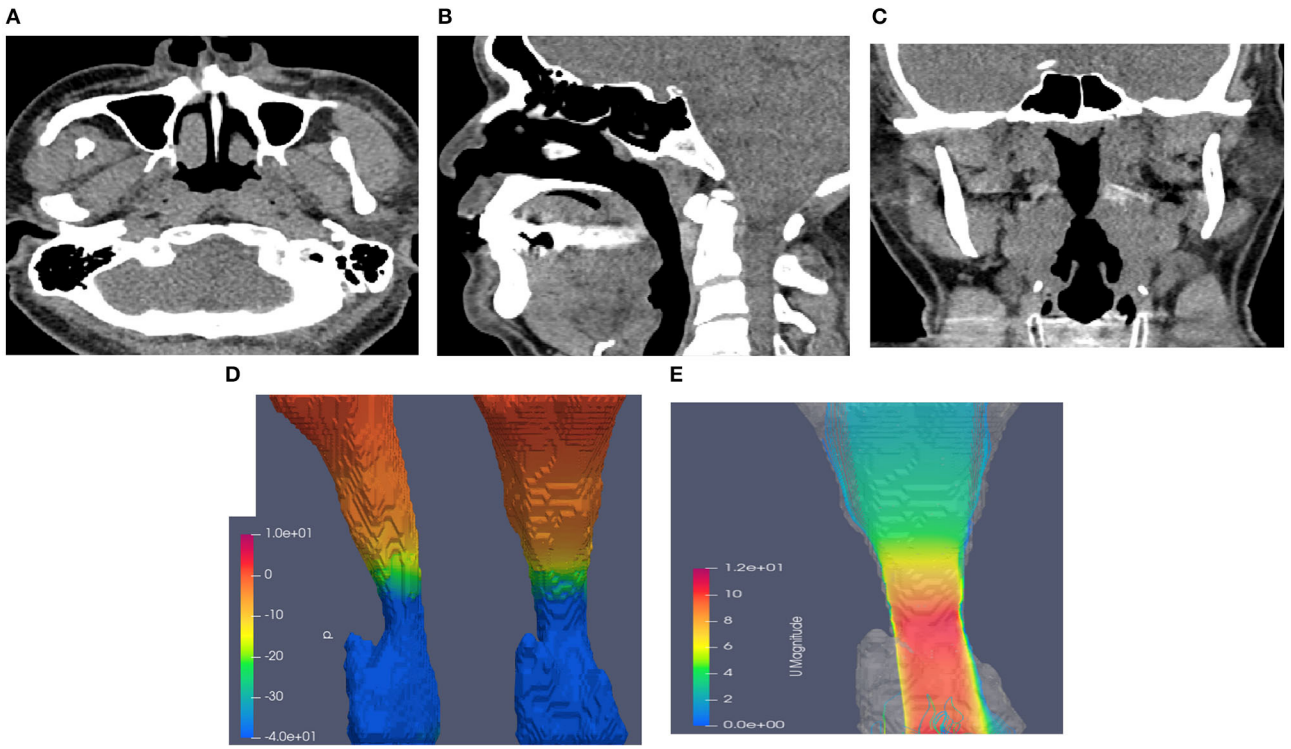

FIGURE 3 | Neck CT with computational fluid dynamics study of the 44-year-old male showed CTL34. **(A)** Axial view. **(B)** Sagittal view. **(C)** Coronal view. **(D)** Airway pressure of 51.88 Pa. **(E)** Airflow velocity of 10.7 m/s.

where Ui and f are the amplitude and frequency, respectively, of the variation in velocity (17). The transient calculation of the upper airway included four cycles of respiration.

The density and dynamic viscosity of inhaled fluid were set at 1.1614 kg/m3 and 1.846e−5 kg/ms, respectively, because we expected normal air inhalation from the nose. The inlet boundary was located at the nasopharynx and the velocity of the flow was variably set to represent normal breathing; the outlet boundary was positioned at the hypopharynx where the pressure was set at 0 Pa with the reference pressure of 1 atm. A no-slip condition was imposed on the surface of the trachea. Null initial velocity and pressure were set in the trachea. The simulation condition involved a breathing period (T = 1/f) of 3.75 s and a tidal volume of 500 ml. The RANS was solved using the finite volume method in Soteria OPZ software.

Working Definition of CFD Study

Airflow velocity was used to indicate a normal (<1 m/s), mild severity (1–3 m/s), moderate severity (3–5 m/s), or severe severity (>5 m/s) condition. Airway pressure was used to indicate a normal (<3 pa), mild severity (3–10 pa), moderate severity (10–20 pa), or severe severity (>20 pa) condition. We defined CTL12 and CTL 34 as airflow velocity <3 and ≥3 m/s, respectively, and airway pressure <10 and ≥10 pa, respectively, in the narrowest upper airway. We evaluated airway pressure and airflow velocity by using area under the receiving operating characteristic curve (AUROC) to predict moderate to severe OSA.

Statistical Analyses

We conducted statistical analyses by using SPSS Version 22.0 (IBM, Armonk, NY, USA). The Chi-square test was used to compare and test the differences in categorical variables between both groups. The Mann–Whitney *U* test was used to compare the continuous variables of both groups. The $P < 0.05$ was represented as a statistical significance level for all tests. We also computed the AUROC for a determination of prediction discrimination of airway pressure and airflow velocity for diagnosing moderate to severe OSA.

RESULT

The participants were 70 patients with OSA and overnight oxygen desaturation who received awake neck CT with a CFD study of airflow velocity and airway pressure. We excluded 8 patients who slept for <4 h. No substantial differences between demographics and OSA severity were present between the individuals included and excluded. The remaining 62 patients (42 male and 20 female) were included in the analyses. Most of the study patients (51, 82.3%) were never smokers. Seven patients were current smokers and four patients were ex-smokers. Their mean age was 50.4 ± 14.6 years. Their body

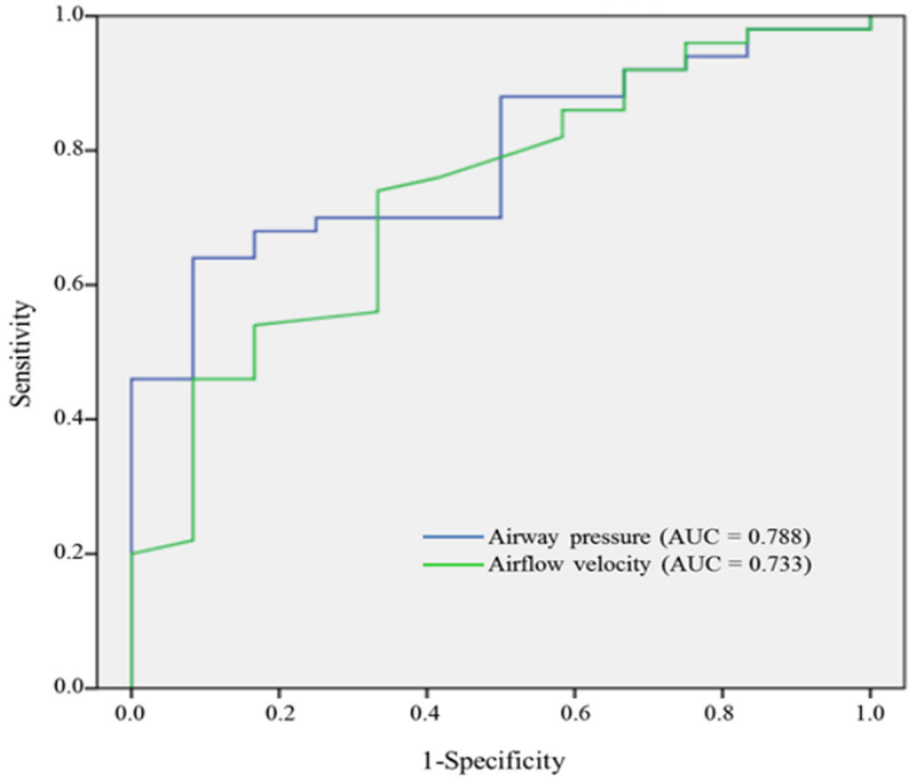

FIGURE 4 | AUROC curves of airway pressure and airflow velocity for predicting moderate to severe OSA.

mass index (BMI), neck circumference, and waist circumference were 27.6 ± 4.0 kg/m^2, 38.5 ± 3.5 cm, and 96.9 ± 8.7 cm, respectively. The average AHI was 34.7 ± 24.1 episodes per hour. In total, 12 patients with mild OSA and 50 patients with moderate to severe OSA participated. The minimum sPO2 of overnight oximetry was 80.3 ± 8.9%. The minimum sPO2 in the supine position was 80.7 ± 9.1%. The total duration of sPO2 < 90% at overnight oximetry for each participant was 29.3 ± 51.1 min. The mean airway pressure was 40.3 ± 55.9 Pa and the mean airflow velocity was 9.7 ± 7.3 m/s. Most (85.5%) neck CT examinations with CFD study were of CTL34 (**Table 1**).

Table 2 presents the results of patients with mild OSA and those with moderate to severe OSA for comparison. Patients with mild OSA and those with moderate to severe OSA did not substantially differ with respect to BMI, neck circumference, or waist circumference. The patients with moderate to severe OSA exhibited considerably less deep sleep (8.2 vs. 16.2%, $P = 0.004$) and more shallow sleep (72.2 vs. 63.8%, $P = 0.023$) than did the patients with mild OSA. Furthermore, patients with moderate to severe OSA had substantially lower sPO2 (78.8 vs. 88.7%, $P < 0.001$) and a longer duration of sPO2 < 90% at overnight oximetry (36.2 vs. 0.4 min, $P < 0.001$) than did the patients with mild OSA. The patients with moderate to severe OSA carried substantially higher airway pressure (47.0 vs. 13.0 pa, $P = 0.005$) and airflow velocity (10.7 vs. 5.9 m/s, $P = 0.023$) in the narrowest upper airway than did the patients with mild OSA.

Table 3 presents the results of CTL12 and CTL34 for comparison. The patients with CTL34 exhibited a larger waist circumference (97.9 vs. 90.8 cm, $P = 0.037$) and higher AHI (38.0 vs. 16.1 per hour, $P = 0.003$) than did the patients with CTL12. The patients with CT34 had lower minimum sPO2 in the supine position (78.4 vs. 88.1%, $P = 0.004$) and longer duration of sPO2 < 90% at overnight oximetry (33.9 vs. 1.9 min, $P = 0.001$) than did the patients with CTL12. We illustrated neck CT with CFD study for CTL12 in the (**Figure 2**) and for CTL34 in the (**Figure 3**).

As depicted in (**Figure 4**), the values of the AUROC for airway pressure and airflow velocity at the narrowest upper airway for predicting moderate to severe OSA were 0.788 and 0.733, respectively. Our definition of CTL34 for the prediction discrimination of moderate to severe OSA yielded a sensitivity of 92%, specificity of 42%, positive predictive value of 87%, and negative predictive value of 56%.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the effectiveness of using awake neck CT with a CFD study of both airway pressure and airflow velocity to predict moderate

TABLE 2 | Results for patients with mild OSA and patients with moderate to severe OSA.

Variables	Mild OSA ($N = 12$) M ± SD (*n*, %)	Moderate to severe OSA ($N = 50$) M ± SD (*n*, %)	*P*-value
Male	(6, 14.3%)	(36, 85.7%)	0.177
Age (y)	46.2 ± 18.3	55.9 ± 13.1	0.066
ESS	8.5 ± 5.1	8.0 ± 4.1	0.95
Berlin questionnaire high risk	(2, 18.2%)	(15, 32.6%)	0.476
BMI (kg/m^2)	27.1 ± 4.2	27.8 ± 3.9	0.575
Neck circumference (cm)	38.0 ± 4.2	38.6 ± 3.4	0.430
Waist circumference (cm)	94.4 ± 9.2	97.5 ± 8.6	0.378
RDI in REM phase (/h)	18.0 ± 11.8	50.8 ± 21.1	<0.001
RDI in NREM phase (/h)	6.4 ± 3.0	38.3 ± 24.5	<0.001
Minimum sPO2 at overnight oximetry (%)	88.1 ± 2.0	78.4 ± 8.9	<0.001
Minimum sPO2 in supine position (%)	88.7 ± 1.9	78.8 ± 9.1	<0.001
Total time of sPO2 < 90% (min) at overnight oximetry	0.4 ± 0.5	36.2 ± 54.8	<0.001
N1+N2 phase of TST (%)	63.8±11.6	72.2±12.9	0.023
N3 phase of TST (%)	16.2 ± 9.9	8.2 ± 7.3	0.004
Airway pressure (pa)	13.0 ± 8.3	47.0 ± 60.5	0.005
Airflow velocity at the narrowest upper airway (m/s)	5.9 ± 3.9	10.7 ± 7.6	0.023

OSA, obstructive sleep apnea; Mann–Whitney U test.
M, mean; SD, standard deviation; ESS, Epworth sleepiness scale; BMI, body mass index; REM, rapid eye movement; RDI, respiratory disturbance index; sPO2, pulse oxygen saturation; PSG, polysomnography; TST, total sleep time.

TABLE 3 | Results for patients with CTL12 or CTL34 as determined using awake neck CT with CFD study.

Variables	CTL12 ($N = 9$) M ± SD (*n*, %)	CTL34 ($N = 53$) M±SD (*n*, %)	*P*-value
Male	(6, 14.3%)	(36, 85.7%)	0.941
Age (y)	59.3 ± 15.5	53.1 ± 14.4	0.142
BMI (kg/m^2)	25.2 ± 3.6	28.0 ± 3.9	0.060
Neck circumference (cm)	38.1 ± 3.9	38.6 ± 3.5	0.430
Waist circumference (cm)	90.8 ± 7.9	97.9 ± 8.5	0.037
AHI (/h)	16.1 ± 12.6	38.0 ± 23.9	0.003
RDI in REM phase (/h)	25.0 ± 15.7	47.8 ± 23.1	0.007
RDI in NREM phase (/h)	13.1 ± 13.7	35.4 ± 25.6	0.003
Minimum sPO2 at overnight oximetry (%)	88.1 ± 2.0	78.4 ± 8.9	0.004
Minimum sPO2 in supine position (%)	88.7 ± 1.9	78.8 ± 9.1	0.012
Total time of sPO2 < 90% (min) at overnight oximetry	1.9 ± 3.2	33.9 ± 54.0	0.001
N1+N2 phase of TST (%)	71.5 ± 14.6	70.4 ± 12.9	0.772
N3 phase of TST (%)	10.1 ± 8.4	9.7 ± 8.5	0.803

CT, computed tomography; CFD, computational fluid dynamics; Mann–Whitney U test; CTL12, airflow velocity < 3 m/s and airway pressure < 10 Pa in the narrowest upper airway; CTL34, Airflow velocity ≥3 m/s or airway pressure ≥10 Pa in the narrowest upper airway; M, mean; SD, standard deviation; BMI, body mass index; AHI, apnea-hypopnea index; REM, rapid eye movement; RDI, respiratory disturbance index; sPO2, pulse oxygen saturation; PSG, polysomnography; TST, total sleep time.

to severe OSA. Airway pressure and airflow velocity through a CFD study of neck CT at the narrowest upper airway provided acceptable discrimination for moderate to severe OSA (AUROC = 0.788 for airway pressure and AUROC = 0.733 for airflow velocity, respectively). Concomitant airway pressure and airflow velocity provided a sensitivity of 92% and a specificity of 42%. Awake neck CT provides a quick screening modality not only for moderate to severe OSA but also for the anatomic obstruction site of the upper airway. However, awake CT may not completely reveal upper airway collapse caused by decreased muscle tone during sleep, and this limitation may result in relatively low specificity. Albeit previous studies indicated that Berlin questionnaire and Epworth sleepiness scale may be helpful to screen OSA (23, 24). However, neither Berlin questionnaire nor Epworth sleepiness scale can predict moderate to severe OSA in the current study.

Barkdull et al. reported that patients with OSA exhibited smaller cross-sectional areas in the retroglossal airway and a larger distance between the mandible and hyoid (25). Although AHI is correlated with the retroglossal airway and distance between the mandible and hyoid, a clear threshold is not available for demarcating moderate to severe OSA. Chousangsuntorn et al. suggested that patients with severe OSA were likely to have complete concentric collapse of the upper airway in neck CT examination after they took 10 mg of zolpidem hemitartrate (18). Our study participants received awake neck CT examinations without the use of sedatives because the overall examination periods lasted only approximately 5 min. Furthermore, we utilized CFD computations to calculate concomitant airflow velocity and airway pressure at the narrowest upper airway, which indicated acceptable predictors of moderate to severe OSA.

Although overnight polysomnography in a sleep center is considered a diagnostic standard for OSA (26), the method is time consuming and cannot determine the anatomic obstruction site of the upper airway. BMI, neck circumference, and waist circumference were not found to be factors contributing to mild OSA and moderate to severe OSA in our study. **Table 2** demonstrates that the patients with moderate to severe OSA exhibited substantially lower overnight minimum sPO2 and longer overnight hypoxemia than did the patients with mild OSA. Overnight hypoxemia may result in oxidative stress, systemic and vascular inflammation, vasoconstriction, and endothelial dysfunction, which become pivotal risk factors that contribute to the development of OSA-related comorbidities (27). Patients with OSA with hypoxemia carry risk of developing not only comorbid CVD but also worsened CVD-related outcomes

(28). Thus, we selected patients diagnosed with OSA with overnight oxygen desaturation and searched for a potential quick-examination modality.

We further evaluated patients by using neck CT with a CFD study of airway pressure and airflow velocity and categorized the readings as indicating CTL12 or CTL34. The patients with CTL34 exhibited a larger waist circumference than did the patients with CTL12. Waist circumference was strongly correlated with total amount of visceral fat, which may result in increased adipose tissue within the airway and a reduced upper airway size (29, 30). **Table 3** demonstrates that the patients with CTL34 had substantially decreased minimum sPO2 in the supine position, increased AHI, and prolonged overnight hypoxemia compared with the patients with CTL12. The patients in the awake neck CT with CFD study that exhibited airflow velocity $\geq$ 3 m/s or airway pressure $\geq$ 10 Pa are highly suggestive of moderate to severe OSA and require prompt treatment. Untreated OSA with overnight hypoxemia increases risks of CVD and mortality (28).

A primary strength of this study is that it is the first to conduct an awake neck CT with CFD study of airway pressure and airflow velocity that provides acceptable diagnosis of moderate to severe OSA. This study's findings suggest that awake neck CT shortens examination wait time ($\sim$5-s scan time) and reduces the need for sedative medications. Relevant studies have used DISE to evaluate the upper airway condition of patients with OSA (31, 32). Both sedative medication and the depth of sedation simulating natural sleep should be considered. However, several limitations must be considered when interpreting these findings. First, repetitive episodes of upper airway collapse during sleep may be masked by awake neck CT. This can explain why a CFD study of airway pressure and airflow velocity by awake neck CT provides relatively low specificity. Additionally, the patients with overnight oxygen desaturation must receive a comprehensive sleep study even if awake neck CT with CFD study of airway pressure and airflow velocity did not meet the criteria of CTL34. Second, this retrospective study might have produced biased results (e.g., OSA prevalence) because the data were collected from a single sleep center.

CONCLUSION

This study reports that neck CT with a CFD study of airway pressure and airflow velocity may provide an acceptable prediction of moderate to severe OSA. Moreover, neck CT can shorten diagnostic examination wait time and provide good measurements of upper airway anatomy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Tsaotun Psychiatric Center, Ministry of Health and Welfare (110008), Taiwan. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

W-SC: conception and design and administrative support. All authors collected, assembly of data, data analysis, interpretation, manuscript writing and final approval of manuscript.

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REFERENCES

1. Gabryelska A, Łukasik ZM, Makowska JS, Białasiewicz P. Obstructive sleep apnea: from intermittent hypoxia to cardiovascular complications via blood platelets. *Front Neurol.* (2018) 9:635. doi: 10.3389/fneur.2018.00635
2. Dong JY, Zhang YH, Qin LQ. Obstructive sleep apnea and cardiovascular risk: meta-analysis of prospective cohort studies. *Atherosclerosis.* (2013) 229:489–95. doi: 10.1016/j.atherosclerosis.2013.04.026
3. Iftikhar IH, Hoyos CM, Phillips CL, Magalang UJ. Meta-analyses of the association of sleep apnea with insulin resistance, and the effects of CPAP on HOMA-IR, adiponectin, and visceral adipose fat. *J Clin Sleep Med.* (2015) 11:475–85. doi: 10.5664/jcsm.4610
4. Kendzerska T, Povitz M, Leung RS, Boulos MI, McIsaac DI, Murray BJ, et al. Obstructive sleep apnea and incident cancer: a large retrospective multicenter clinical cohort study. *Cancer Epidemiol Biomarkers Prev.* (2021) 30:295–304. doi: 10.1158/1055-9965.EPI-20-0975
5. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med.* (2015) 3:310–8. doi: 10.1016/S2213-2600(15)00043-0
6. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med.* (2019) 7:687–98. doi: 10.1016/S2213-2600(19)30198-5
7. Waldman LT, Parthasarathy S, Villa KF, Bron M, Bujanover S, Brod M. Understanding the burden of illness of excessive daytime sleepiness associated with obstructive sleep apnea: a qualitative study. *Health Qual Life Outcomes.* (2020) 18:128. doi: 10.1186/s12955-020-01382-4
8. Flemons WW, Douglas NJ, Kuna ST, Rodenstein DO, Wheatley J. Access to diagnosis and treatment of patients with suspected sleep apnea. *Am J Respir Crit Care Med.* (2004) 169:668–72. doi: 10.1164/rccm.200308-1124PP
9. Chen N-H, Hang L-W, Lin C-M. Sleep medicine in Taiwan. *Sleep Biol Rhythms.* (2016) 14:11–9. doi: 10.1007/s41105-015-0007-9
10. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. *J Thorac Dis.* (2015) 7:1311–22. doi: 10.3978/j.issn.2072-1439.2015.06.11

11. Chai-Coetzer CL, Antic NA, Hamilton GS, McArdle N, Wong K, Yee BJ, et al. Physician decision making and clinical outcomes with laboratory polysomnography or limited-channel sleep studies for obstructive sleep apnea: a randomized trial. *Ann Intern Med.* (2017) 166:332–40. doi: 10.7326/M16-1301
12. Roehrs T, Roth T. Drug-related sleep stage changes: functional significance and clinical relevance. *Sleep Med Clin.* (2010) 5:559–70. doi: 10.1016/j.jsmc.2010.08.002
13. Marques M, Genta PR, Azarbarzin A, Sands SA, Taranto-Montemurro L, Messineo L, et al. Retropalatal and retroglossal airway compliance in patients with obstructive sleep apnea. *Respir Physiol Neurobiol.* (2018) 258:98–103. doi: 10.1016/j.resp.2018.06.008
14. Cavaliere M, Russo F, Iemma M. Awake versus drug-induced sleep endoscopy: evaluation of airway obstruction in obstructive sleep apnea/hypopnoea syndrome. *Laryngoscope.* (2013) 123:2315–8. doi: 10.1002/lary.23881
15. Shallik N. Anesthetic management for drug induced sleep endoscopy. *Middle East J Anaesthesiol.* (2015) 23:131–5.
16. Castro Ruiz P, Castro Ruiz F, Costas López A, Cenjor Español C. [Computational fluid dynamics simulations of the airflow in the human nasal cavity]. *Acta Otorrinolaringol Esp.* (2005) 56:403–10. doi: 10.1016/S0001-6519(05)78638-6
17. Yu CC, Hsiao HD, Tseng TI, Lee LC, Yao CM, Chen NH, et al. Computational fluid dynamics study of the inspiratory upper airway and clinical severity of obstructive sleep apnea. *J Craniofac Surg.* (2012) 23:401–5. doi: 10.1097/SCS.0b013e318240feed
18. Chousangsuntorn K, Bhongmakapat T, Apirakkittikul N, Sungkarat W, Supakul N, Laothamatas J. Computed tomography characterization and comparison with polysomnography for obstructive sleep apnea evaluation. *J Oral Maxillofac Surg.* (2018) 76:854–72. doi: 10.1016/j.joms.2017.09.006
19. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, et al. CPAP versus oxygen in obstructive sleep apnea. *N Engl J Med.* (2014) 370:2276–85. doi: 10.1056/NEJMoa1306766
20. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med.* (2010) 182:269–77. doi: 10.1164/rccm.200911-1746OC
21. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S. Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. *Circulation.* (2017) 136:1840–50. doi: 10.1161/CIRCULATIONAHA.117.029400
22. Zhao M, Barber T, Cistulli P, Sutherland K, Rosengarten G. Computational fluid dynamics for the assessment of upper airway response to oral appliance treatment in obstructive sleep apnea. *J Biomech.* (2013) 46:142–50. doi: 10.1016/j.jbiomech.2012.10.033
23. Tan A, Yin JD, Tan LW, van Dam RM, Cheung YY, Lee CH. Using the Berlin questionnaire to predict obstructive sleep apnea in the general population. *J Clin Sleep Med.* (2017) 13:427–32. doi: 10.5664/jcsm.6496
24. Rosenthal LD, Dolan DC. The Epworth sleepiness scale in the identification of obstructive sleep apnea. *J Nerv Ment Dis.* (2008) 196:429–31. doi: 10.1097/NMD.0b013e31816ff3bf
25. Barkdull GC, Kohl CA, Patel M, Davidson TM. Computed tomography imaging of patients with obstructive sleep apnea. *Laryngoscope.* (2008) 118:1486–92. doi: 10.1097/MLG.0b013e3181782706
26. Hamilton GS, Gupta R, Vizcarra D, Insalaco G, Escobar F, Kadotani H. Endorsement of: "clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American academy of sleep medicine clinical practice guideline" by the World Sleep Society. *Sleep Med.* (2021) 79:152–4. doi: 10.1016/j.sleep.2020.12.044
27. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. *Chest.* (2015) 147:266–74. doi: 10.1378/chest.14-0500
28. Tietjens JR, Claman D, Kezirian EJ, De Marco T, Mirzayan A, Sadroonri B, et al. Obstructive sleep apnea in cardiovascular disease: a review of the literature and proposed multidisciplinary clinical management strategy. *J Am Heart Assoc.* (2019) 8:e010440. doi: 10.1161/JAHA.118.010440
29. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care.* (2008) 31(Suppl. 2):S303–9. doi: 10.2337/dc08-s272
30. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, et al. Waist circumference as a vital sign in clinical practice: a consensus statement from the IAS and ICCR working group on visceral obesity. *Nat Rev Endocrinol.* (2020) 16:177–89. doi: 10.1038/s41574-019-0310-7
31. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. *Eur Arch Otorhinolaryngol.* (2011) 268:1233–6. doi: 10.1007/s00405-011-1633-8
32. De Vito A, Carrasco Llatas M, Ravesloot MJ, Kotecha B, De Vries N, et al. European position paper on drug-induced sleep endoscopy: 2017 Update. *Clin Otolaryngol.* (2018) 43:1541–52. doi: 10.1111/coa.13213

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Increased Levels of CHI3L1 and HA Are Associated With Higher Occurrence of Liver Damage in Patients With Obstructive Sleep Apnea

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Background: Obstructive sleep apnea-hypopnea syndrome (OSA) may cause liver fibrosis, and liver fibrosis serum biomarkers plays an important role on the diagnosis of liver fibrosis. In addition, this study aimed to observe the changes of 4 serum markers and Chitinase 3-like protein 1 (CHIl3L1) levels in OSA patients with different disease severity and explore their interactions. And then, we examined whether intermittent hypoxia (IH) exposure can activate hepatic stellate cell.

Methods: 74 OSA patients in Second Xiangya hospital from January 2021 to October 2021 was selected and categorized into mild, moderate, and severe groups according to AHI. In addition, 20 subjects were selected as the control group. Serum levels of liver fibrosis markers were determined by electrochemiluminescence immunoassay. Hepatic stellate cells were exposed to intermittent IH or normoxia (RA). Results were analyzed using the SPSS software.

Results: There was a significant increase in serum hyaluronic acid (HA), collagen type IV (CIV) and CHI3L1 levels in OSA patients compared with control group. Specifically, serum liver fibrosis markers HA, CIV and CHI3L1 levels were positively correlated with apnea-hypopnea index (AHI), but negatively correlated with the lowest saturation oxygen ($LSaO_2$) respectively. The LX-2 cells (human hepatic stellate cell line) exposed to IH showed significant increases in fibrotic protein expression.

Conclusion: OSA might either directly or indirectly trigger or exacerbate liver fibrosis, possibly via IH-related pathways.

Keywords: obstructive sleep apnea-hypopnea syndrome, liver damage, Chitinase 3-like protein 1, hyaluronic acid, biomarker, liver fibrosis

INTRODUCTION

Obstructive sleep apnea-hypopnea syndrome (OSA) is a common disorder that affects all age groups, especially middle-aged and elderly people (1). It is characterized by intermittent episodes of upper airway obstruction during sleep, resulting in increased respiratory effort, recurrent decreased arterial oxygen saturation and sleep disruption (2). Various evidence suggests that the prevalence of OSA is increasing worldwide, which may be due to increased living standards and rising obesity rates (3). Therefore, it is of great interest to explore the parthenogenesis of OSA, which could lay the foundation for effective treatment of OSA.

Epidemiological studies have shown that OSA subjects have more than a 5-fold higher risk of developing liver disease compared to non-OSA subjects (4). There are some experimental and clinical data have suggested that OSA may contribute to the development and exacerbation of liver fibrosis, which occurs in response to any etiology of almost all chronic liver diseases (5, 6). Biopsy has long been touted as the gold standard for the assessment of liver fibrosis. However, it has been limited by its invasiveness, cost, associated complications, sampling variability, and potential risks of clinical application (7). In view of these limitations, it has been suggested that non-invasive methods should be developed to greatly facilitate the clinical management of liver fibrosis and reduce the need for biopsy. In recent years, serum marker levels have been introduced as a non-invasive method to assess liver fibrosis (8). Hyaluronic acid (HA), procollagen type III N-terminal peptide (PIIINP), collagen type IV (CIV), and laminin (LN) are four common markers of liver fibrosis. Their diagnostic properties have been confirmed by many studies (9). However, it is difficult to determine the stage of liver fibrosis based on the results of these four serum fibrosis markers alone.

Chitinase 3-like 1 (CHI3L1) is a novel biomarker to diagnosis of liver fibrosis. Based on RNA sequencing data, CHI3L1 expression in liver is higher than that in other tissues like heart, brain, kidney and so on (9). In other words, CHI3L1 is a highly liver-enriched gene which may be a good marker of liver disease (10). Immunohistochemical studies have shown that CHI3L1 is expressed in fibrotic areas of the liver (11, 12). And it also has a strong correlation with the degree of liver fibrosis. Huang et al. showed CHI3L1 outperforms CIV, HA, LN and PCIII in diagnosing liver fibrosis (13). Based on these supporting evidence, serum CHI3L1 has been assumed to be a useful biomarker for liver fibrosis and prognosis (14).

However, the correlation between OSA and liver fibrosis is not well defined, but chronic intermittent hypoxia (CIH), as quantified by oxygen saturation, has been shown to be an important causal factor (15, 16). Hepatic stellate cells (HSCs) are now considered to be one of the key cell types involved in the progression of liver fibrosis and associated pathophysiological and clinical complications (17). Following liver tissue damage, hematopoietic stem cells undergo an activation process characterized by a phenotype of proliferation, motility, contraction, and synthesis of ECM components to promote the formation of liver fibrosis (18).

Therefore, the aim of our study was to investigate changes in the levels of four serum markers and CHII3L1 in OSA patients with different disease severity and to explore their interactions. We then examined whether CIH exposure could activate hepatic stellate cells. These results will contribute to a better understanding of the pathogenic mechanisms of OSA.

MATERIALS AND METHODS

Human Subjects

Ninty-four Patients Were Recruited at the Second Xiangya Hospital of Central South University (Changsha, China) between January 2021 and October 2021. The Diagnosis of OSA Was Determined According to the Relevant Clinical Practice Guidelines by American Academy of Sleep Medicine (AASM) (19). A Total of 20 Healthy Volunteers Served as Matched Controls who Were Matched for age and BMI to Patients With OSA to Minimize Confounding Factors. Inclusion and Exclusion Criteria Were the Same for all the Study Groups.

Inclusion Criteria

A. Age 18–65 years old.
B. No gender limitation.

Exclusion Criteria

A. Age $<$ 18 years old or $>$ 65 years old.
B. History of or active cancer.
C. Severe cardiopulmonary disease.
D. Infectious disease.
E. History of acute upper respiratory tract infection in the past month: nasal congestion, sneezing, salivation, etc.
F. History of any prescribed medications.
G. Did not obtain the consent of the subject.

Polysomnography

Apnea-hypopnea index (AHI) was calculated as the number of apneas and hypoventilation per hour during sleep time. We also recorded the lowest saturation oxygen ($LSaO_2$) as an indicator of nocturnal hypoxemia. Based on the AHI, subjects were divided into control group (AHI $<$ 5, $n = 20$) and OSA group (AHI $>$ 5, $n = 74$). The OSA group was assigned as follows: Mild, AHI: 5-14.9 ($n = 15$), moderate AHI:15.0–29.9 ($n = 24$), and severe, AHI $\geq$ 30 ($n = 35$).

Human Serum Samples Collection

Serum samples (approximately 3 mL) were collected from the antecubital inferior caval vein, allowed to clot for 30 min, and centrifuged at 3,000 g for 10 min at 25°C. The resulting serum was aliquoted and frozen at −80°C for further analysis.

All experimental procedures were approved by the Second Xiangya Hospital of Central South University and were in accordance with the laboratory guidelines.

Clinical Laboratory Measurements

Clinical laboratory parameters including age, sex, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), globulin (Glo), and hemoglobin (HGB) were measured and recorded on admission.

Biochemical tests were performed using a routine automated analyzer (HItachi 7180). The concentrations of the four serum fibrosis markers PIIINP, CIV, LN, and HA were determined by electrochemiluminescence immunoassay (Mindray CL-i2000). Serum Chitinase 3-like protein 1 was measured by electrochemiluminescence immunoassay (YHLO iFlash 3000-H).

Cell Culture

LX-2, human immortalized hepatic stellate cell line (Hunan, China) was cultured in high glucose DMEM supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin. The cells were starved for 10 h in DMEM medium containing 1% FBS before treatment.

LX-2 Intermitted Hypoxia *in vitro*

LX-2 were grown and maintained in growth medium (EGM-2-MV; Clonetics) containing depleted fetal bovine serum and further cultured at 37°C and 5% CO_2 in a cell culture incubator. Cells were grown in T-25 flasks and incubated in hypoxia (0.1–21% O_2, equilibrated N_2) or normoxia (21–21% O_2) every 5 min for 3–7 days.

Western Blotting

Intracellular proteins were Extracted employing RIPA buffer and PMSF (Beyotime, Shanghai, China) at 99:1 ratio. And total protein was quantified with a BCA kits (Thermos Fisher Scientific, USA). Then, equal amounts of protein were separated by SDS-PAGE (10% gels), and transferred to PVDF membranes (Sigma-Aldrich, USA). After blocking with 5% skim milk for 1 h, the membranes were incubated with the primary antibodies overnight at 4°C. The next day, the membranes were incubated at room temperature for 1 h with specific secondary antibodies. The membranes were rinsed following by chemiluminescence imaging. Quantitative analysis of Western blots was conducted by ImageJ software. Antibodies: FN (Abcam, #ab45688, 1:1000), COL1A1 (CST, #72026, 1:1000), MMP9 (Abcam, #EP1254, 1:1000), CHI3L1 (Abcam, # ab255297, 1:1000), beta-actin (Sangon, #D110001, 1:2500). Image J was used to quantify the gray values for each target proteins bands.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) software version 23.0 was used for statistical analysis. Patient characteristics were expressed as mean ± standard deviation, median, and range or proportion. One-way ANOVA was used to compare all continuous variables between groups, and Student's test was performed to assess the significance of differences between the two groups. The Wilcoxon rank sum test was used for non-parametric data. Correlations were assessed using Spearman's correlation coefficient for continuous variables and Kendall's correlation coefficient for categorical variables. For 95% confidence interval, a p-value < 0.05 considered to be statistically significant.

RESULTS

Demographic, Clinical, and Biochemical Profile

The clinical characteristics and biochemical parameters of the study subjects have been summarized in **Table 1**. It could be found that the control group and the OSA groups did not have significant differences in anthropometric data including age, male-female ratio, and BMI. Mean values of AHI ($p =$

TABLE 1 | Demographics characteristics and biochemical profiles of study subjects.

Variables	Control ($n = 20$)	OSA ($n = 74$)		
		Mild OSA ($n = 15$)	Moderate OSA ($n = 24$)	Severe OSA ($n = 35$)
Age (years)	45.08 ± 13.73	46.12 ± 8.3	45.45 ± 9.51	44.2 ± 11.47
Sex (male/female)	17/3	12/3	20/4	29/6
BMI (kg/m^2)	28.74 ± 11.43	29.21 ± 8.99	29.45 ± 7.52	30.27 ± 12.53
AHI (events/h)	2.1 (1.5, 3)	11.35 (8.2, 18.6)*	24.2 (21.1, 31.5)*#	59.4 (47.35, 76.1)*#&
$LSaO_2$ (%)	94.8 ± 2.9	81.5 ± 4.3*	74.5 ± 11.8*#	55.2 ± 5.9*#&
ALT (U/L)	11 (9.3, 20)	12.1 (4.3, 34.1)	24.6 (19, 37.4)*#	30.91 (15.1, 45.8)*#
AST (U/L)	14.9 (13.4, 21.3)	15.4 (10.2, 24.3)	19.5 (16.7, 25.2)*#	22.6 (10.1, 30.5)*#
ALT/AST	1.22 (0.71, 1.38)	1.12 (0.61, 1.54)	0.74 (0.58, 1.01)*#	0.72 (0.51, 1.54)*#
TP (g/L)	63 (60.45, 67.65)	64.1 (59.2, 68.5)	67.5 (64.8, 71)	66.2 (59.8, 75.2)
ALB (g/L)	38.4 (36.5, 42.4)	39.2 (35.1, 43.2)	41.75 (39.38, 43.7)*	40.15 (38.12, 45.3)*
Globulin (g/L)	24.9 (22.75, 28.43)	25.3 (21.45, 29.22)	26.3 (23.5, 29.1)	26.2 (24.5, 30.5)
A/G	1.6 ± 0.23	1.59 ± 0.21	1.61 ± 0.27*	1.62 ± 0.25*
HGB (g/L)	133.3 ± 19.63	134.2 ± 12.21	147.6 ± 14.48*#	152.9 ± 13.52*#

AHI, apnea-hypopnea index; BMI, body mass index; $LSaO_2$, lowest saturation oxygen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; HGB, Hemoglobin.

**$p < 0.05$, compared with the control group.*

#$p < 0.05$, compared with the mild OSA group.

&$p < 0.05$, compared with the moderate OSA group.

0.001), $LSaO_2$ ($p = 0.003$) were significantly different in all subject groups.

Comparison of hepatic function index between four groups: The concentrations of serum ALT, AST, ALT/AST, plasma HGB in moderate OSA patients, severe OSA groups was significantly higher than control and mild OSA groups. However, the ALB, A/G concentration in moderate OSA, severe OSA groups was significantly higher than control group.

Four Serum Liver Fibrosis Markers and CHI3L1 Levels in Patients With OSA and Control Subjects

Serum HA levels were significantly higher in the OSA group compared with the control group ($p < 0.05$) (**Table 2**). In addition, serum HA levels progressively increased with increasing severity of OSA (33.12 ± 10.6 ng/mL for mild OSA, 34.53 ± 13.2 ng/mL for moderate OSA, and 35.44 ± 10.7 ng/mL for severe OSA) (**Table 3**).

A similar trend was observed for serum CIV and CHI3L1 levels. serum CIV and CHI3L1 levels were higher in the OSA group ($n = 74$) than in the control group, with a significant difference between the severe OSA and control groups (41.78 ± 8.72 vs. 45.52 ± 2.45 ng/ml, 34.79 ± 12.08 ng/ml vs. 60.9 ± 7.2 ng/ml, $p < 0.05$).

Correlations Between Serum Markers of Liver Fibrosis and Polysomnographic Parameters

Based on the foregoing results, we found that the HA, CIV and CHI3L1 may be used as an indicator of liver fibrosis in OSA patients. By analyzing the total population of OSA patients ($n = 74$), significant correlations were observed between three liver fibrosis serum markers levels and several polysomnographic parameters including AHI, $LSaO_2$, as shown in **Table 4**, **Figures 1**, **2**. Specifically, serum liver fibrosis markers HA ($r = 0.2694$, $p = 0.008$) and CIV ($r = 0.2693$, $p = 0.03$) levels were positively correlated with AHI, but negatively correlated with $LSaO_2$ ($r = -0.4081$, $p = 0.01$; $r = -0.426$, $p = 0.007$) respectively. Similarly, serum CHI3L1 levels showed positive correlation with AHI ($r = 0.221$, $p = 0.02$), and negative correlation with $LSaO_2$ ($r = -0.3814$, $p = 0.01$), respectively.

Effect of Intermittent Hypoxia on Fibrotic Markers

LX-2 cell exposed to IH for 3, 5 days showed significant FN, Collagen, MMP9 increase in compared to normoxia. Similarly, IH exposures for 5 days resulted in significant increases in CHI3L1 expression (**Figure 3**).

TABLE 2 | Serum levels of 4 serum markers and CHI3L1 in the subjects.

Variables	Control ($n = 20$)	OSA ($n = 74$)	p value
HA (ng/ml)	23.62 ± 5.93	34.42 ± 8.47	0.001*
PIIINP (ng/ml)	7.384 ± 1.69	7.69 ± 2.75	0.524
CIV (ng/ml)	41.78 ± 8.72	49.65 ± 6.43	0.004*
LN (ng/ml)	27.29 ± 6.39	28.63 ± 7.68	0.341
CHI3L1 (ng/ml)	34.45 (26.7, 41.3)	39.64 (31.2, 55.9)	0.03*

*HA, hyaluronan; PIIINP, procollagen type III N-terminal peptide; CIV, type IV collagen; LN, laminin; CHI3L1, Chitinase-3-like protein 1. *p < 0.05, OSA group compared with the control group.*

TABLE 4 | Correlation analysis between different parameters in OSA patients.

	AHI		$LSaO_2$	
	r	*P*-value	*r*	*P*-value
HA	0.2694	0.008	−0.4081	0.01
CIV	0.2693	0.03	−0.426	0.007
CHI3L1	0.221	0.02	−0.3814	0.01

AHI, apnea-hypopnea index; $LSaO_2$, lowest saturation oxygen; HA, hyaluronan; PIIINP, procollagen type III N-terminal peptide; CIV, type IV collagen; LN, laminin; CHI3L1, Chitinase-3-like protein 1.

TABLE 3 | Four serum markers and CHI3L1 in the control and OSA subgroups.

Variables	Control ($n = 20$)	OSA ($n = 74$)		
		Mild OSA ($n = 15$)	Moderate OSA ($n = 24$)	Severe OSA ($n = 35$)
HA (ng/ml)	23.62 ± 5.93	33.12 ± 10.6*	34.53 ± 13.2*	35.44 ± 10.7**
PIIINP (ng/ml)	7.384 ± 1.69	7.12 ± 2.28	7.368 ± 2.24	8.32 ± 3.1
CIV (ng/ml)	41.78 ± 8.72	37.41 ± 4.57	39.55 ± 3.46	45.52 ± 2.45*
LN (ng/ml)	27.29 ± 6.39	27.37 ± 7.69	29.12 ± 7.92	30.48 ± 7.4
CHI3L1 (ng/ml)	34.45 (26.7, 41.3)	35.42 (29.42, 41.2)	37.88 (29.9, 51.2)	40.35 (31.9, 54.9)*

HA, hyaluronan; PIIINP, procollagen type III N-terminal peptide; CIV, type IV collagen; LN, laminin; CHI3L1, Chitinase-3-like protein 1.
**p < 0.05, compared with the control group. **p < 0.001, compared with the control group.*

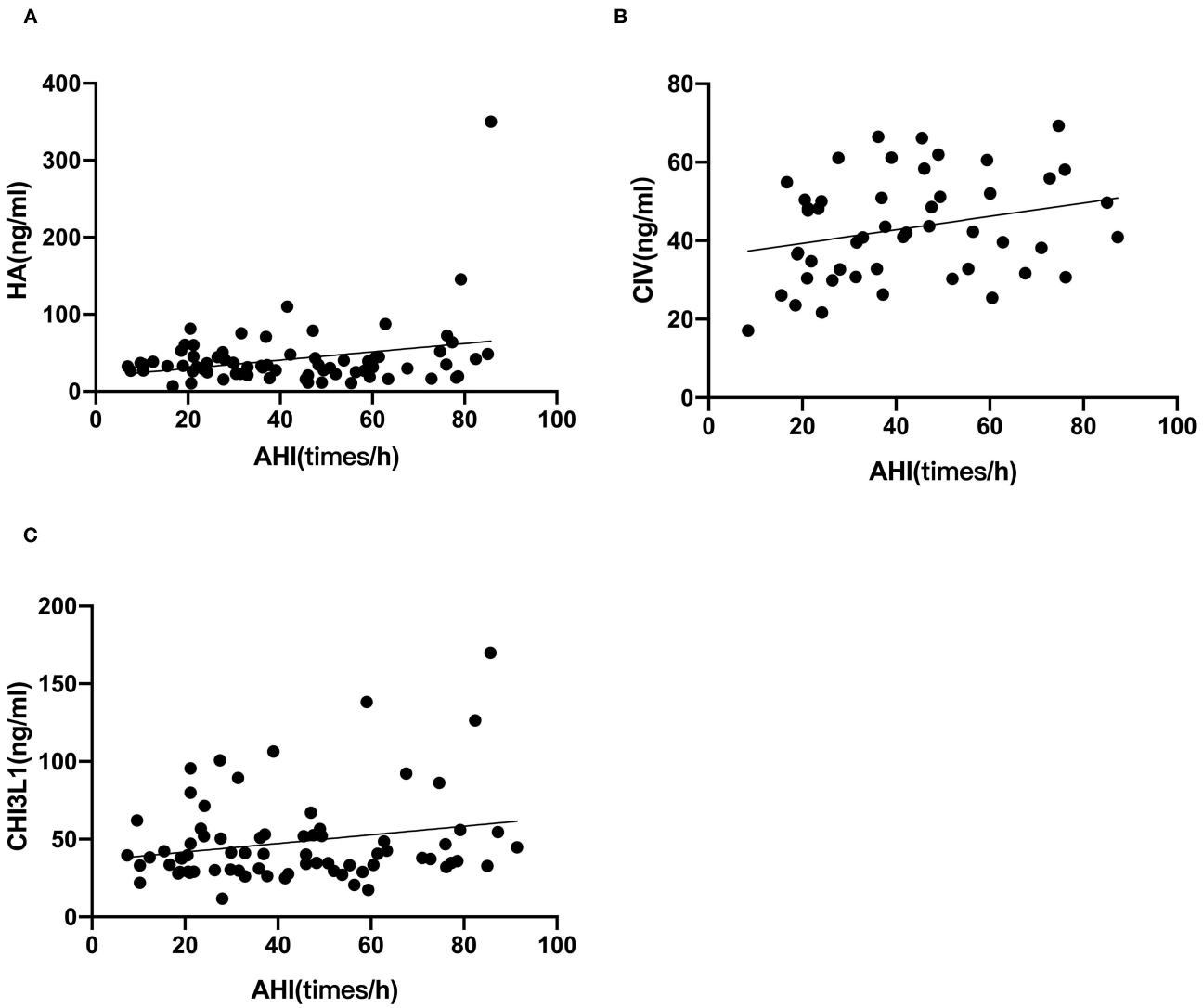

FIGURE 1 | AHI correlated with liver fibrosis serum biomarkers in patients with OSA. The correlations between AHI and each marker **(A)** HA; **(B)** CIV; **(C)** CHI3L1 were assessed by Spearman's rank correlation coefficient. The *p*-values and correlation coefficients are shown in each plot.

DISCUSSION

In the present study, we investigated changes in the levels of five serum liver fibrosis markers in patients with OSA and found that serum HA, CIV and CHI3L1 levels were significantly increased in patients with compared with healthy volunteers. In addition, serum HA, CIV and CHI3L1 levels were strongly correlated with AHI and $LSaO_2$ in OSA patients, which suggested that three serum markers levels were related to OSA severity. In addition, intermittent hypoxia *in vitro* can increase expression of fibrotic markers in hepatic stellate cell. Therefore, OSA might either directly or indirectly trigger or exacerbate liver fibrosis, possibly via oxidative stress-related pathways.

As shown **Table 2**, it is obviously appeared that OSA patients have hepatic impairment. And as the degree of OSA increases, the more severe the liver function impairment. But as liver damage gets worse, the hepatitis can progress to liver fibrosis. There are some experimental and clinical data have suggested that OSA may contribute to the development and exacerbation of liver fibrosis (5, 6). However, the diagnosis of liver fibrosis mainly based on liver biopsy, which is regarded as the gold standard. However, liver biopsy requires coarse needle puncture, which is invasive (20). It is necessary to substitute liver biopsy with non-invasive techniques. Until now, there are two methods used in clinical scenario: one is ultrasound detection the other is serum indicators. However, transient ultrasound elastography (Fibro scan) and shear wave elastography (SWE) are influenced by many factors, such as ascites, obesity, operator experience, etc., Therefore, non-invasive serum fibrosis markers were chosen in this study. Serum HA, LN, PIIINP, and CIV have been used as serological markers to diagnose hepatic fibrosis, estimate

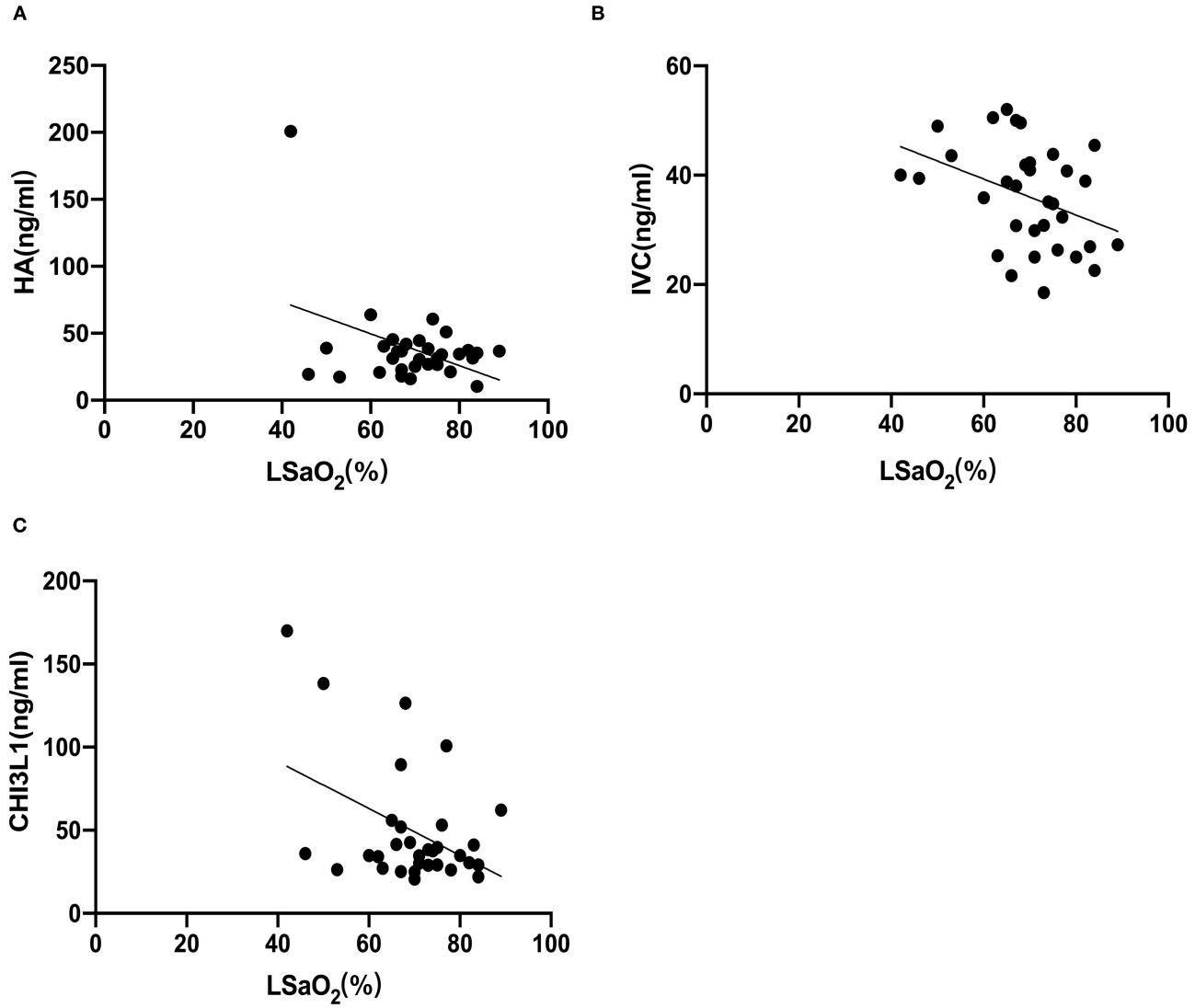

FIGURE 2 | $LSaO_2$ correlated with liver fibrosis serum biomarkers in patients with OSA. The correlations between $LSaO_2$ and each marker **(A)** HA; **(B)** CIV; **(C)** CHI3L1 were assessed by Spearman's rank correlation coefficient. The *p*-values and correlation coefficients are shown in each plot.

the severity of the condition, and assess the prognosis for patients with chronic hepatic disease with better specificity and sensitivity (21).

From **Figure 4** and **Table 2** it is clear that HA is the most sensitive index among the five liver fibrosis serum markers. Cai et al. suggested that HA has a strong positive correlation with the degree of hepatic fibrosis compared with LN, PIIINP, and CIV (22). This is consistent with the results of our previous study on the relationship between serum fibrosis markers and liver histological changes (23). The concentration of CIV might increase during the early stages of hepatic fibrosis and could promote capillarization of hepatic sinuses. Specifically, serum liver fibrosis markers HA, CIV levels were positively correlated with AHI, but negatively correlated with $LSaO_2$, respectively. Therefore, HA, CIV can reflect to some extent that OSA patients may tend to have liver fibrosis, and it will deepen with the degree of OSA. To our knowledge, this is the first study on changes in serum liver fibrosis marker levels in patients with OSA, and these results suggest that HA, CIV may serve as a potential surrogate biomarker for the severity of various chronic hypoxic liver diseases.

In present study, we found that PIIINP and LN these two serological markers were not significantly different in healthy subjects vs. OSA patients (**Table 3**). Compared with other two serological indexes, these two indexes have poor sensitivity and specificity in diagnosing liver damage. It is reported that PIIINP has reached a limited clinical application with 76–78% sensitivity and 71–81% specificity (24). Moreover, LN could only be a predictor of portal hypertension (25), which is not a liver specific biomarker and has not gained widespread acceptance.

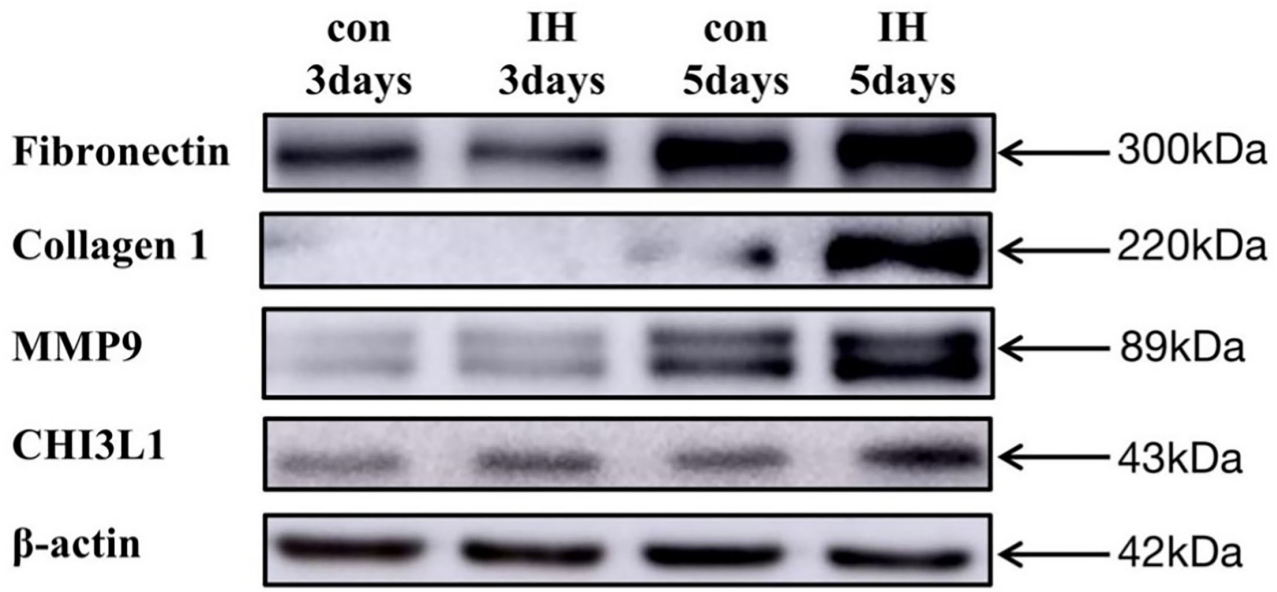

FIGURE 3 | LX-2 cell changes in FN, Collagen 1, MMP9, CHI3L1 expression *in vitro* exposures to IH (1–21% O_2) or to RA (21–21% O_2) for 1–5 days.

CHI3L1 is a novel serological marker for the assessment of liver fibrosis compared to the other four traditional serological markers. It is involved in physiological and pathophysiological processes and has been shown to be a common inflammatory cytokine that contributes to OSA (11). It is also reported that plasm CHI3L1 levels are associated with hypertension in patients with OSA (26). However, CHI3L1 is not only important in inflammation and cardiovascular disease but also plays a role in liver fibrosis. Some studies demonstrated that CHI3L1 is liver-enriched and has better application value in staging liver fibrosis than platelet ratio index (APRI) and fibrosis-4 index (FIB-4). Therefore, our study used CHI3L1 to evaluate the extent of liver fibrosis in OSA patients.

In addition, there was a positive correlation between CHI3L1 levels and AHI and a negative correlation between CHI3L1 levels and $LSaO_2$. These results suggest that serum CHI3L1 levels may be a modifying factor in the development of OSA and may serve as a potential biomarker of OSA severity.

The above results suggest that clinicians should monitor serum HA, CIV, CHI3L1 levels in OSA patients and judge the liver damage by combining the levels of AHI and $LaSO_2$, to select the appropriate treatment plan as soon as possible.

Since previous studies have shown that OSA and its associated intermittent hypoxia (IH) induce oxidative stress. Therefore, we speculated that OSA may be inducing liver fibrosis through IH. Several studies have shown that intermittent hypoxemia caused by OSA can accelerate the progression of liver fibrosis. For example, chronic intermittent hypoxia accelerates hepatic fibrosis in rats with combined hypoxia and non-alcoholic steatohepatitis through angiogenesis (27). Another study also revealed that TLR4 mediates inflammation and hepatic fibrosis induced by chronic intermittent hypoxia in rats (28). Previous studies have investigated the effects of IH on liver fibrosis in animal models, but hepatic stellate cells also play critical roles in the development of liver fibrosis. To the best of our knowledge, this is the first study on LX-2 exposed to IH. Another important result of our study is LX-2 exposed to IH showed significant increases in FN, MMP9, COL1A1 expression. All three of the above proteins are conventional proteins associated with liver fibrosis. In contrast, CHI3L1 is a relatively novel protein, and its elevated expression in IH exposure is consistent with the previous clinical findings. Thus, it is highly likely that OSA, a systemic disease which activates a multiplicity of pathophysiological pathways, will exert its detrimental endo-organ effects via a large number of mechanisms.

The above results suggest that CHI3L1 may be useful as a biomarker of liver fibrosis in patients with OSA. Although CHI3L1 appears promising as a serum biomarker in this limited trial and may also provide a mechanistic link to the pathogenesis of liver fibrosis, further testing is needed to validate its use in the routine management of patients with liver fibrosis.

Our findings have several limitations. The first and most significant limitation of our study revolves around the small sample size. Obviously, in this context we advocate caution in interpreting our data and studying these findings further in a larger cohort. Second, the evaluation of liver fibrosis severity in our experiment only has serum testing, it is also necessary to prepare a combined ultrasound as well as CT for imaging aspects of the test and to rigorously design liver puncture examinations in patients with OSA. Finally, our study only analysis the role of intermittent hypoxia *in vitro*, without performing any *in vivo* experiments. But the strength of the vitro experiments in our study could be considered as a starting observation for *in vivo* studies. Therefore, further basic mechanistic studies are needed.

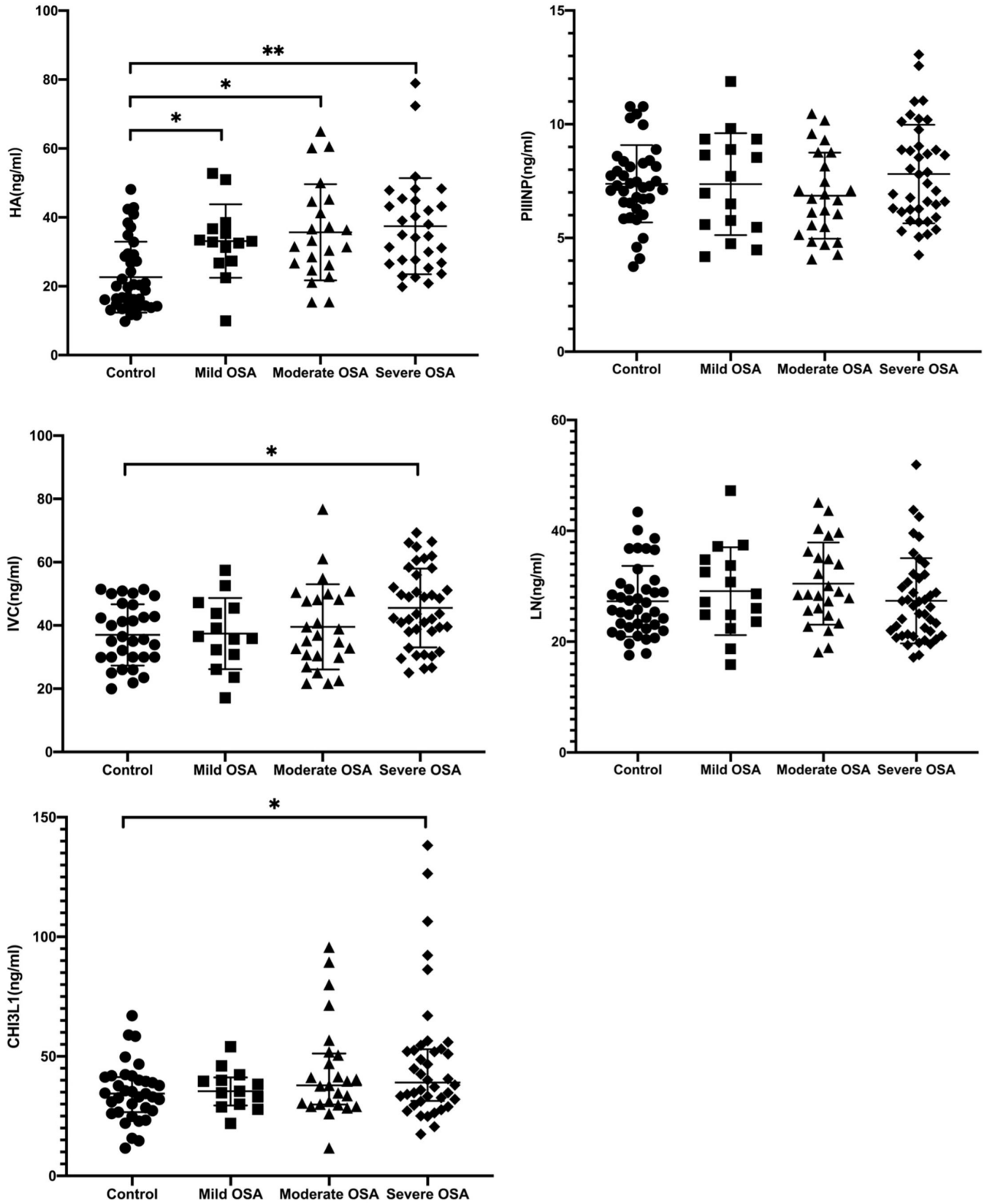

FIGURE 4 | Serum HA, PIIINP, CIV, LN, and CHI3L1 levels in patients with OSA. *$p < 0.05$, **$p < 0.001$, by Kruskal-Wallis test with Dunn's multiple comparison test.

CONCLUSION

In conclusion, our findings suggest that serum HA, CIV, CHI3L1 levels are related to the severity of OSA in patients. Moreover, hepatic stellate cell LX-2 *in vitro* data demonstrate that IH causes fibrotic protein over-expression. These findings indicate that OSA may induce liver fibrosis, which may be through IH. Although the detailed mechanisms and clinical implications remain to be elucidated in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Second Xiangya Hospital of Central South University (No. 2021168). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JC: formal analysis, investigation, and writing—original draft. XL: methodology and data curation. PH: data curation and software. SL and FW: investigation. RC: data curation. ZC and LZ: visualization. MS: software. MH: supervision and writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.854570/full#supplementary-material

REFERENCES

1. Qaseem A, Holty JE, OwensDK, Dallas P, Starkey M, Shekelle P. Clinical guidelines committee of the American college of: management of obstructive sleep apnea in adults: a clinical practice guideline from the American college of physicians. *Ann Intern Med*. (2013) 159:471–83. doi: 10.7326/0003-4819-159-7-201310010-00704
2. McNicholas WT, Bonsigore MR, Management Committee of EU COST ACTION B26. Management Committee of: Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J*. (2007) 29:156–78. doi: 10.1183/09031936.00027406
3. Young T, Peppard PE, Taheri S: Excess weight and sleep-disordered breathing. *J Appl Physiol (1985)*. (2005) 99:1592–9. doi: 10.1152/japplphysiol.00587.2005
4. Chou TC, Liang WM, Wang CB, Wu TN, Hang LW. Obstructive sleep apnea is associated with liver disease: a population-based cohort study. *Sleep Med*. (2015) 16:955–60. doi: 10.1016/j.sleep.2015.02.542
5. Krolow GK, Garcia E, Schoor F, Araujo FBS, CoralPG. Obstructive sleep apnea and severity of nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol*. (2021) 33:1104–9. doi: 10.1097/MEG.0000000000001920
6. Agrawal S, Duseja A, Aggarwal A, Das A, Mehta M, Dhiman RK, et al. Obstructive sleep apnea is an important predictor of hepatic fibrosis in patients with nonalcoholic fatty liver disease in a tertiary care center. *Hepatol Int*. (2015) 9:283–91. doi: 10.1007/s12072-015-9615-3
7. J. Boursier, de Ledinghen V, Leroy V, Anty R, Francque S, Salmon D, et al. A stepwise algorithm using an at-a-glance first-line test for the non-invasive diagnosis of advanced liver fibrosis and cirrhosis. *J Hepatol*. (2017) 66:1158–65 (2017) doi: 10.1016/j.jhep.2017.01.003
8. Agbim U, Asrani KS. Non-invasive assessment of liver fibrosis and prognosis: an update on serum and elastography markers. *Expert Rev Gastroenterol Hepatol*. (2019) 13:361–74. doi: 10.1080/17474124.2019.1579641
9. Liu W, Yang YJ, An Q. LINC00963 promotes ovarian cancer proliferation, migration and EMT via the miR-378g /CHI3L1 axis. *Cancer Manag Res*. (2020) 12:463–73. doi: 10.2147/CMAR.S229083
10. Johansen JS. Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodelling, fibroses and cancer. *Dan Med Bull*. (2006) 53:172–209.
11. Mutlu LC, Tulubas F, Alp R, Kaplan G, Yildiz ZD, Gurel A. Serum YKL-40 level is correlated with apnea hypopnea index in patients with obstructive sleep apnea sindrome. *Eur Rev Med Pharmacol Sci*. (2017) 21:4161–6.
12. Johansen JS, Christoffersen P, Moller S, Price PA, Henriksen JH, Garbarsch C, et al. Serum YKL-40 is increased in patients with hepatic fibrosis. *J Hepatol*. (2000) 32:911–20. doi: 10.1016/S0168-8278 (00)80095-1
13. Huang H, Wu T, Mao J, Fang Y, Zhang J, Wu L, et al. CHI3L1 is a liver-enriched, noninvasive biomarker that can be used to stage and diagnose substantial hepatic fibrosis. *J. Integr. Biol*. (2015) 19:339–45. doi: 10.1089/omi.2015.0037
14. Berres ML, Papen S, Pauels K, Schmitz P, Zaldivar MM, Hellerbrand C, et al. A functional variation in CHI3L1 is associated with severity of liver fibrosis and YKL-40 serum levels in chronic hepatitis C infection. *J Hepatol*. (2009) 50:370–6. doi: 10.1016/j.jhep.2008.09.016
15. Aron-Wisnewsky J, Minville C, Tordjman J, Levy P, Bouillot JL, Basdevant A, et al. Chronic intermittent hypoxia is a major trigger for non-alcoholic fatty liver disease in morbid obese. *J Hepatol*. (2012) 56:225–33. doi: 10.1016/j.jhep.2011.04.022
16. Savransky V, Nanayakkara A, Vivero A, Li J, Bevans S, Smith PL, et al. Chronic intermittent hypoxia predisposes to liver injury. *Hepatology*. (2007) 45:1007–13. doi: 10.1002/hep.21593
17. Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. *Nat Rev Gastroenterol Hepatol*. (2021) 18:151–66. doi: 10.1038/s41575-020-00372-7
18. Cai J, Hu M, Chen Z, Ling Z: The roles and mechanisms of hypoxia in liver fibrosis. *J Transl Med*. (2021) 19:186. doi: 10.1186/s12967-021-02854-x
19. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. 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. doi: 10.5664/jcsm.6506
20. Deeken-Draisey, Rao SM, Yang YG. Pathology in patients with chronic liver disease: a practical approach to liver biopsy interpretation in patients with acute and chronic liver diseases. *Clin Liver Dis*. (2020) 24:361–72. doi: 10.1016/j.cld.2020.04.001
21. Q G. Research progress on serologic assays for clinical tests of liver fibrosis. *Jilin Medicine*. (2011) 6:1198–9. Available online at: https://d.wanfangdata.com.cn/periodical/ChlQZXJpb2RpY2FsQ0hJTmV3UzIwMjExMjMwEhBqaWxpbnl4MjAxMTA2MTMwGgh0bjNwbGt5Mg%3D%3D

22. T. J. Cai W, Weng H. Influencing factor analysis of serum fibrosis indicators. *Chinese Journal of Liver Disease*. (2003) 1:23–5. Available online at: https://d.wanfangdata.com.cn/periodical/ChlQZXJpb2RpY2FsQ0hJTmV3UzIwMjExMjMwEhB6aGd6Ynp6MjAwMzAxMDA3GghsaGd2bWdjNw%3D%3D
23. Parise ER, Oliveira AC, Figueiredo-Mendes C, Lanzoni V, Martins J, Nader H, et al. Noninvasive serum markers in the diagnosis of structural liver damage in chronic hepatitis C virus infection. *Liver Int*. (2006) 26:1095–9. doi: 10.1111/j.1478-3231.2006.01356.x
24. Collazos J, Diaz F. Role of the measurement of serum procollagen type III N-terminal peptide in the evaluation of liver diseases. *Clin Chim Acta*. (1994) 227:37–43. doi: 10.1016/0009-8981 (94)90133-3
25. Kropf J, Gressner AM, Tittor W. Logistic-regression model for assessing portal hypertension by measuring hyaluronic acid (hyaluronan) and laminin in serum. *Clin Chem*. (1991) 37:30–5. doi: 10.1093/clinchem/37.1.30
26. Li K, Chen Z, Qin Y, Wei XY. Plasm YKL-40 levels are associated with hypertension in patients with obstructive sleep apnea. *Biomed Res Int*. (2019) 2019:5193597. doi: 10.1155/2019/5193597
27. Wu W, Li W, Wei J, Wang C, Yao Y, Zhu W, et al. Chronic intermittent hypoxia accelerates liver fibrosis in rats with combined hypoxia and nonalcoholic steatohepatitis via angiogenesis rather than endoplasmic reticulum stress. *Acta Biochim Biophys Sin*. (2019) 51:159–67. doi: 10.1093/abbs/gmy169
28. Lin ZP, Lin HL, Yu XP, Zheng YJ, Cheng YS. TLR4 mediates inflammation and hepatic fibrosis induced by chronic intermittent hypoxia in rats. *Mol Med Rep*. (2020) 22:651–60. doi: 10.3892/mmr.2020.11134

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frontiers in Medicine

ORIGINAL RESEARCH
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Memory Foam Pillow as an Intervention in Obstructive Sleep Apnea Syndrome: A Preliminary Randomized Study

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Specific pillow use is a seldom studied or controlled factor in the setting of sleep disordered breathing. The aim of this study was to investigate the effect of different pillows [own pillow (OP), memory foam pillow (MFP), generic laboratory pillow (LP)] on polysomnography (PSG)-derived parameters in patients with Obstructive Sleep Apnea Syndrome (OSAS). Thirty-two consecutive patients with OSAS were randomly allocated into two groups with randomized pillow usage [Group A: 3 h with LP and 3 h with OP (Age: 53.8 ± 12.5 years, BMI: 32.1 ± 4.6 kg/m^2); Group B: 3 h with LP and 3 h with MFP (Age: 52.0 ± 6.3 years, BMI: 30.6 ± 2.2 kg/m^2)]. Statistically significant differences between pillow types were detected in desaturation index and heart rate. In Group B (with MFP), a statistically significant decrease of 47.0 ± 15.9% was observed in snoring events ($p < 0.05$) and 10.6 ± 6.7% in their duration ($p < 0.05$) compared to LP. On the other hand, group A with OP recorded a decrease of 29.1 ± 32.1% in snoring events and 32.5 ± 33.1% in duration, but these values were not statistically significant ($p > 0.05$) compared to LP. These findings indicate that pillow type and usage, often uncontrolled in OSAS studies (contribution to the field), may impact several PSG parameters and are related to a snoring subtype of the syndrome. Secondly, they indicate that a focus on the treatment of the snoring OSAS subtype warrants further dedicated investigation.

Keywords: pillow, memory foam pillow, sleep quality, snoring, desaturation

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INTRODUCTION

Pillows affect sleep quality by maintaining the natural curvature of the spine, thus ensuring optimal sleep posture (1). In patients with mild sleep-disordered breathing, optimal pillow usage may reduce snoring and improves sleep quality efficiency and, by extent, depth (2). Conversely, incorrect pillow placement, such as that occurs during travel, may be detrimental to sleep health (3). Considering Obstructive Sleep Apnea Syndrome's (OSAS's) heterogeneity (4) and the implication of other overlapping symptoms, such as snoring (5), it is necessary to assess the biological context of potential interventions.

Previous studies on pillow usage are limited in number and focus on the role of cervical positional therapy, collectively reporting an improvement on snoring (6–9). Previous research has suggested that the use of custom fitted pillows may represent an efficacious and cost-effective treatment option in mild to moderate OSAS (10), filling a niche where continuous positive airway pressure (CPAP) would not be indicated (11). Considering that pillow design can be guided (12, 13) to alleviate specific symptoms, an evaluation of pillow type impact on sleep health may be directly relevant to their efficacious implementation.

In this context, two major research questions regarding the implementation of specific pillows as a possible OSAS treatment arise: who will benefit and how? As a heterogeneous disease, OSAS' treatment goals extend from severity to phenomenology (4, 14). Toward this end, the effect of pillow usage should be evaluated in order to determine how it shapes polysomnography (PSG)-captured parameters and its implication in sleep disordered breathing phenotypes.

The aim of our study was to investigate the effect of different pillows [own pillow (OP), memory foam pillow (MFP), generic laboratory pillow (LP)] on PSG parameters in patients with OSAS.

MATERIALS AND METHODS

Study Population

This was a single-center, randomized prospective study. Participants were recruited from the province of Thessaly region (Greece). The inclusion criteria were as follows: patients referred for potential sleep disordered breathing following a polysomnography study, an apnea-hypopnea index (AHI) of $\geq$5 events/h with LP, age between 20 and 80 years, BMI $<$ 40 kg/m^2, waist to hip ratio $<$1, and neck circumferences $<$40 cm. Exclusion criteria were as follows: neurological and psychiatric disorders, musculoskeletal disorders, and awakening during changing pillows.

The study was approved by the Institutional Ethics Committee of the University of Thessaly, Greece (No. 21/09-01-2017) and informed consents were obtained from all participants, in accordance with the Helsinki declaration.

Full Night Polysomnography

Overnight PSG was performed in accordance with the American Academy of Sleep Medicine (AASM) guidelines (15). PSG-included electroencephalography, electrooculography, submental electromyography, anterior tibialis electromyography, nasal cannula airflow signal using a nasal cannula/pressure transducer system, oral thermistor, electrocardiography, and body position (16). Respiratory efforts were monitored with abdominal and thoracic bands. Arterial SaO_2 was measured using SpO_2. Apnea was defined as complete cessation of airflow for at least 10 s in duration. Hypopnea was defined as one of the following three: (1) $>$50% reduction in airflow, (2) $<$50% reduction in airflow associated with a desaturation of $>$3%, or (3) a moderate reduction in airflow with associated arousal by electroencephalography. Apneas were classified as obstructive, central, or mixed according to the presence or absence of respiratory efforts. Snoring was measured by a microphone. Patients with predominant obstructive sleep apneas and AHI $\geq$ 5 events/h were diagnosed with the OSAS. PSG was performed at the Laboratory of Sleep Disorders (Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, Greece) using an Alice®4 computer system (Philips Respironics, PA, USA). PSG scoring was performed by specialists blinded to pillow usage and group allocation.

Learning Effect Attenuation

In an attempt to eliminate any PSG learning effect, volunteers were randomly divided into two groups, (Group A: 3 h with LP and 3 h with their OP; Group B: 3 h with LP and 3 h with MFP). The replacement of the pillow during PSG was (a) conducted by a sleep technician in a randomized order and (b) at the awaking phase.

Epworth Sleep Scale Questionnaire

Sleepiness was assessed using the validated Greek version of the Epworth Sleepiness Scale (ESS), (17) a self-administered questionnaire evaluating the possibility of dozing in a variety of situations (18).

Pillow Characteristics

The dimensions of the LPs were 12.0 $\times$ 60.0 $\times$ 36.0 cm (Height $\times$ Length $\times$ Width) and was made with microfiber. The pillows owned by patients had variant dimensions (14.2 $\pm$ 0.8 $\times$ 55.0 $\pm$ 3.4 $\times$ 44.2 $\pm$ 3.6 cm; Height x Length $\times$ Width) and were made of polyester (34%), foam shredded (29%), and goose feather (37%). The MFPs had dimensions of 16.0 $\times$ 70.0 $\times$ 40.0 cm (Height $\times$ Length $\times$ Width) and was made of memory foam with aloe vera extract (Media Strome®, Greece).

Statistical Analyses

Pairwise comparisons per group (Group A: LP vs. OP and Group B: LP vs. MFP) were performed with the dependent samples *t*-test. We calculated the standardized rates of change between sequential measurements via the formula [(Post-Pre)/Pre], where "post" refers to post-intervention and "pre" refers to pre-intervention. These rates were compared between intervention groups via the independent Samples *t*-test. Data are presented as absolute numbers, percentages, or mean values $\pm$Sd where applicable. For all statistical analyses, a p-value $<$ 0.05 was considered statistically significant. All analyses were performed via the IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA) software package.

RESULTS

Out of the 147 individuals who were assessed for eligibility, 32 were included in the study (**Figure 1**). Demographic characteristics were not significantly different between groups (**Table 1**). **Table 2** illustrates statistical differences in Heart Rate (HR) values between two types of pillows (LP vs. MFP) in

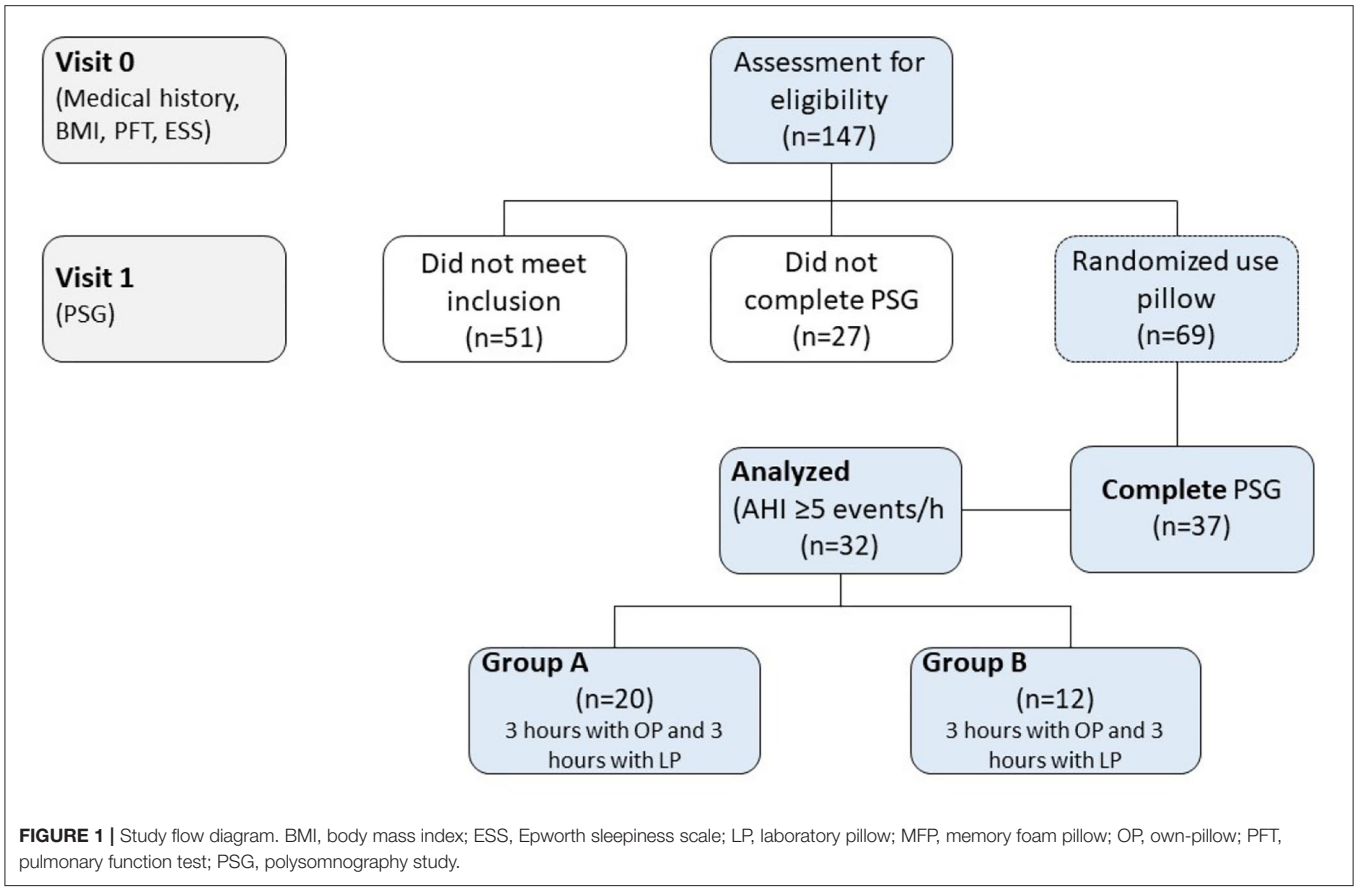

FIGURE 1 | Study flow diagram. BMI, body mass index; ESS, Epworth sleepiness scale; LP, laboratory pillow; MFP, memory foam pillow; OP, own-pillow; PFT, pulmonary function test; PSG, polysomnography study.

awakening phase ($p = 0.003$), REM stage ($p = 0.003$), and non-REM stage ($p = 0.003$). The group with the MFP pillow showed higher values in HR during awakening phase and non-REM stage compared to the group with OP ($p < 0.05$). There were statistically significant differences between pillow types and the standardized rate of change for the arousal index and the number of snoring events ($p < 0.05$). **Table 2** provides information on snoring duration and snoring events during PSG. Unlike Group A which demonstrated no statistical differences in snoring parameters, Group B recorded significantly lower number of snoring events by 47.0 ± 15.9 % (106.0 ± 17.8 vs. 55.8 ± 23.7 events, $p = 0.002$) and snoring duration by 10.6 ± 6.7% (42.2 ± 5.0 vs. 37.5 ± 3.7 min, $p = 0.002$) with MFP compared to LP.

TABLE 1 | Patient characteristics.

	Total ($n = 32$)	Group A ($n = 20$)	Group B ($n = 12$)	*P* value
Age, yrs	53.1 ± 10.5	53.8 ± 12.5	52.0 ± 6.3	0.685
Body mass index, kg/m^2	31.6 ± 3.9	32.1 ± 4.6	30.6 ± 2.2	0.287
Gender, (Male/Female)	24/8	16/4	8/4	0.272
Smokers, %	31	35	25	0.569
Hypercholesterolemia, %	38	45	25	-
Gastroesophageal reflux disease, %	6	10	-	-
Hypertension (Stage I), %	6	10	-	-
Asthma, %	6	-	17	-
Comorbidity-free, %	44	35	58	-
Epworth sleepiness scale, score	9.3 ± 4.2	9.2 ± 4.6	9.3 ± 3.7	0.656

Data are expressed as mean ± standard deviation or percentages.

DISCUSSION

Our study aimed to investigate the effect of pillow type (OP and/or MFP vs. LP) in patients with OSAS and its effects on polysomnographic and phenotypic parameters of the syndrome. We report on preliminary results from our ongoing study, indicating that MFP improved several PSG-captured parameters in patients with OSAS, mainly the snoring phenotype. Reduction of quantity and intensity of snoring events, along with improved oxygenation relative to body position, were among the significant PSG-captured effects of MFP usage. These findings indicate that pillow type and usage, often uncontrolled in OSAS studies, impacts several PSG parameters and is related to a snoring subtype of the syndrome. Secondly, they indicate that a focus on the treatment of the snoring OSAS subtype warrants further, dedicated investigation.

In general, the supine position has been implicated in the exacerbation of apneic episodes in OSAS (19), whereas prone

TABLE 2 | Polysomnography parameters results.

	Total ($n = 32$)	Group A ($n = 20$)			Group B ($n = 12$)			*P* value between groups
		LP	OP	*P value*	LP	MFP	*P* value	
AHI, events/h	34.9 ± 22.6	39.0 ± 27.7	42.2 ± 32.5	0.279	28.0 ± 5.9	26.6 ± 9.0	0.301	0.173
Non-REM, %	34.8 ± 24.3	40.2 ± 29.1	41.5 ± 33.8	0.514	26.0 ± 8.4	27.0 ± 10.6	0.340	0.498
REM, %	40.8 ± 22.5	38.3 ± 24.6	44.3 ± 26.8	0.247	44.9 ± 18.9	35.1 ± 15.4	0.032	0.946
Body position distribution desaturation at								
Left, %	31.1 ± 34.2	28.0 ± 11.4	16.7 ± 8.6	0.001	68.9 ± 27.4	46.2 ± 29.3	0.013	<0.001
Right, %	51.9 ± 43.8	47.2 ± 54.3	14.3 ± 5.1	0.001	59.8 ± 14.3	59.5 ± 21.3	0.875	0.934
Up, %	51.3 ± 68.4	67.1 ± 83.2	83.4 ± 88.1	0.274	25.0 ± 5.5	6.5 ± 3.1	0.005	0.145
Averages values in HR during awakening, bpm	77.1 ± 10.2	75.2 ± 12.0	78.5 ± 22.9	0.247	80.4 ± 4.0	84.6 ± 5.2	0.003	0.799
Averages values in HR non-REM stage, bpm	66.6 ± 9.3	68.0 ± 8.3	69.4 ± 7.7	0.305	64.3 ± 10.8	72.2 ± 4.7	0.003	0.051
Averages values in HR REM stage, bpm	72.1 ± 10.2	69.8 ± 11.7	72.1 ± 16.3	0.191	75.8 ± 6.0	80.3 ± 9.1	0.003	0.459
Desaturation index during sleep	34.8 ± 25.0	40.3 ± 29.9	43.7 ± 35.3	0.296	25.6 ± 8.9	23.3 ± 8.6	0.017	0.140
Desaturation duration, min	14.4 ± 9.9	16.0 ± 12.5	16.3 ± 12.9	0.747	11.8 ± 3.5	10.9 ± 3.8	0.054	0.253
Averages values in SaO_2 per respiratory event, %	90.0 ± 3.8	89.6 ± 4.7	88.7 ± 4.9	0.038	90.8 ± 1.2	90.7 ± 1.1	0.011	0.143
Minimum SaO_2 per respiratory event, %	83.0 ± 7.2	83.2 ± 8.7	81.6 ± 8.8	0.192	82.7 ± 3.7	84.8 ± 2.9	0.006	0.159
Awakening index, n/h	37.5 ± 24.6	41.5 ± 30.1	53.9 ± 29.8	<0.001	31.0 ± 7.9	30.0 ± 10.0	0.301	0.031
Snoring duration, min	36.8 ± 21.2	33.6 ± 26.2	30.2 ± 17.2	0.911	42.2 ± 5.0	37.5 ± 3.7	0.002	0.356
Snoring events	100.3 ± 48.8	96.8 ± 60.6	94.5 ± 55.6	0.852	106.0 ± 17.8	55.8 ± 23.7	0.002	0.058

Data are expressed as mean ± standard deviation or percentages changes. AHI, apnea-hypopnea index; HR, heart rate; Left: Desaturation during sleep in left body position; LP, laboratory pillow; MFP, memory foam pillow; OP, own-pillow; REM, rapid eye movement during sleep; Right: Desaturation during sleep in right body position; Up: Desaturation during sleep in supine body position.

position may be alleviating (20). Our findings indicate that this alleviation may be captured by the improvement of desaturation index and snoring events, and thus may be more relevant to the snoring phenotype (21).

The use of different pillow types showed HR changes in both groups of patients with OSAS. However, the MFP sub-group showed higher values in HR around apneic episodes as recorded by awakening phase and minimum SaO_2 per respiratory event compared to the OP sub-group. Before apneic episodes, bradycardia occurs, followed by HR increase that may or may not produce cortical arousals (22). The lower the HR variability, the lower the arousals that occur, leading to less sleep fragmentation and sleep quality. OSAS severity is associated with the abnormal adaptability of the autonomic nervous system (ANS), and this association is reversible up to an extent as the treatment of OSAS is implemented (23). The application of a more suitable pillow could reinforce the therapeutic effects.

The characteristics of snoring were also significantly ameliorated when the MFP was applied. Snoring is elicited by a Bernoulli effect on the soft palate, as negative pressure induces its vibration during an obstructive respiratory event (24). Maintaining airway patency via positional therapy could therefore be expected to reduce snoring events. The use of "smart" pillows for positional therapy in OSAS have reported a reduction of snoring events and overall better sleep quality (6) – findings that are similar to our own.

Positional therapy in OSAS phenotypes where obstructive events and snoring are central features has been previously proposed as a simple and effective intervention (25). Similarly, pillows designed to address cervical positioning and, by extension, airway patency have been associated with a reduction of snoring events and duration (7, 10).

Limitations

It is reasonable to assume that the present study might have been influenced by methodological limitations such as the lack of information on allergenic effects of synthetic pillows (26), although such effects were not diagnosed or reported in our study. Furthermore, longer follow-up studies are needed in order to determine whether the effects noted in our study are sustained. Another important limitation is that measurements of the mandibular plane-hyoid distance, the small posterior airway space diameters, and tongue volume were not included in our study (27). Finally, the production of groups via randomization process may have created groups with the potential to exhibit greater improvement following the implementation of different pillow types. This has been addressed with both between and within-group subject comparisons in order to simultaneously assess the effect of pillow placement and different pillow type. The randomization involved patient allocation rather than pillow placement post-allocation. In order to detect sequence effects, we would have to deploy a different design, i.e., MFP-LP-MFP vs. LP-MFP-LP, and then determine sequences within and then across groups. We did not deploy this aforementioned design on the premises of introducing additional disruption in the PSG that would correspondingly need to be accounted for.

CONCLUSIONS

Compared to either own or regular LPs, MFP seems to be more effective in decreasing snoring events and snoring duration. As a relatively easy to implement intervention, large studies should focus on the role of appropriate pillows as an adjunctive treatment modality of OSAS. Furthermore, our study indicates that the usage of the patient's OP rather than LPs may give a closer-to-life laboratory investigation of OSAS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Ethics Committee of the University of Thessaly, Greece, No. 21/09-01-2017. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VTS, YK, and KIG conceived and designed the experiments. VTS, GDV, EP, and FB analyzed the data. VTS, YK, KA, IS, and GDV wrote the paper. VTS, YK, GDV, and KIG edited the paper. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Lin XY, Wu FG. Pillow shape design to enhance the sleep quality of middle-aged groups. *Procedia Manuf.* (2015) 3:4429–35. doi: 10.1016/j.promfg.2015.07.476
2. Liu SF, Lee YL, Liang JC. Shape design of an optimal comfortable pillow based on the analytic hierarchy process method. *J Chiropr Med.* (2011) 10:229–39. doi: 10.1016/j.jcm.2011.04.002
3. Stavrou VT, Astara K, Daniil Z, Gourgoulianis KI, Kalabakas K, Karagiannis D, et al. The reciprocal association between fitness indicators and sleep quality in the context of recent sport injury. *Int J Environ Res Public Health.* (2020) 17:4810. doi: 10.3390/ijerph17134810
4. Vavougios GD, George DG, Pastaka C, Zarogiannis SG, Gourgoulianis KI. Phenotypes of comorbidity in OSAS patients: combining categorical principal component analysis with cluster analysis. *J Sleep Res.* (2016) 25:31–8. doi: 10.1111/jsr.12344
5. Sowho M, Sgambati F, Guzman M, Schneider H, Schwartz A. Snoring: a source of noise pollution and sleep apnea predictor. *Sleep*. (2020) 15:zsz305. doi: 10.1093/sleep/zsz305
6. Chung TT, Lee MT, Ku MC, Yang KC, Wei CY. Efficacy of a smart antisnore pillow in patients with obstructive sleep apnea syndrome. *Behav Neurol.* (2021) 2021:8824011. doi: 10.1155/2021/8824011
7. Zuberi NA, Rekab K, Nguyen HV. Sleep apnea avoidance pillow effects on obstructive sleep apnea syndrome and snoring. *Sleep Breath.* (2004) 8:201–7. doi: 10.1055/s-2004-860897
8. Kushida CA, Rao S, Guilleminault C, Giraudo S, Hsieh J, Hyde P, et al. Cervical positional effects on snoring and apneas. *Sleep Res Online.* (1999) 2:7–10.
9. Chen WC, Lee LA, Chen NH, Fang TJ, Huang CG, Cheng WN Li HY. Treatment of snoring with positional therapy in patients with positional obstructive sleep apnea syndrome. *Sci Rep.* (2015) 11:18188. doi: 10.1038/srep18188
10. Kushida CA, Sherrill CM, Hong SC, Palombini L, Hyde P, Dement WC. Cervical positioning for reduction of sleep-disordered breathing in mild-to-moderate OSAS. *Sleep Breath.* (2001) 5:71–8. doi: 10.1055/s-2001-15797
11. Srijithesh PR, Aghoram R, Goel A, Dhanya J. Positional therapy for obstructive sleep apnoea. *Cochrane Database Syst Rev.* (2019) 1:CD010990. doi: 10.1002/14651858.CD010990.pub2
12. Son J, Jung S, Song H, Kim J, Bang S, Bahn S, et al. Survey of koreans on sleep habits and sleeping symptoms relating to pillow comfort and support. *Int J Environ Res Public Health.* (2020) 17:302. doi: 10.3390/ijerph17010302
13. Li Y, Wu J, Lu C, Tang Z, Li C. Pillow support model with partitioned matching based on body pressure distribution matrix. *Healthcare (Basel).* (2021) 9:571. doi: 10.3390/healthcare9050571
14. Al-Hussaini A, Berry S. An evidence-based approach to the management of snoring in adults. *Clin Otolaryngol.* (2015) 40:79–85. doi: 10.1111/coa.12341
15. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. 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. doi: 10.5664/jcsm.6506
16. Wolpert EA. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. *Arch Gen Psychiatry.* (1969) 20:246–7.
17. Tsara V, Serasli E, Amfilochiou A, Constantinidis T, Christaki P. Greek Version of the Epworth Sleepiness Scale. *Sleep Breath.* (2004) 8:91–5. doi: 10.1055/s-2004-829632
18. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. American Academy of Sleep Medicine. In: *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications.* 1st ed. Westchester, IL: American Academy of Sleep Medicine. (2017).
19. Oksenberg A, Khamaysi I, Silverberg DS, Tarasiuk A. Association of body position with severity of apneic events in patients with severe nonpositional obstructive sleep apnea. *Chest.* (2000) 118:1018–24. doi: 10.1378/chest.118.4.1018
20. Afrashi A, Ucar ZZ. Effect of prone positioning in mild to moderate obstructive sleep apnea syndrome. *Sleep Breath.* (2015) 19:1027–34. doi: 10.1007/s11325-014-0985-x
21. Labarca G, Gower J, Lamperti L, Dreyse J, Jorquera J. Chronic intermittent hypoxia in obstructive sleep apnea: a narrative review from pathophysiological pathways to a precision clinical approach. *Sleep Breath.* (2000) 24:751–60. doi: 10.1007/s11325-019-01967-4
22. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Bradycardia during sleep apnea. Characteristics and mechanism. *J Clin Invest.* (1982) 69:1286–92. doi: 10.1172/JCI110568
23. Sequeira VCC, Bandeira PM, Azevedo JCM. Heart rate variability in adults with obstructive sleep apnea: a systematic review. *Sleep Sci.* (2019) 12:214–21. doi: 10.5935/1984-0063.20190082
24. Fajdiga I. Snoring imaging: could Bernoulli explain it all? *Chest.* (2005) 128:896–901. doi: 10.1378/chest.128.2.896
25. Newell J, Mairesse O, Neu D. Can positional therapy be simple, effective and well tolerated all together? A prospective study on treatment response and compliance in positional sleep apnea with a positioning pillow. *Sleep Breath.* (2018) 22:1143–51. doi: 10.1007/s11325-018-1650-6

26. Shusterman D, Baroody FM, Craig T, Friedlander S, Nsouli T, Silverman B. American academy of allergy, asthma & immunology's rhinitis, rhinosinusitis and ocular allergy committee work group on rhinitis and sleep-disordered breathing. Role of the allergist-immunologist and upper airway allergy in sleep-disordered breathing. *J Allergy Clin Immunol Pract.* (2017) 5:628–39. doi: 10.1016/j.jaip.2016.10.007
27. Barrera JE, Pau CY, Forest VI, Holbrook AB, Popelka GR. Anatomic measures of upper airway structures in obstructive sleep apnea. *World J Otorhinolaryngol Head Neck Surg.* (2017) 3:85–91. doi: 10.1016/j.wjorl.2017.05.002

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Development and Validation of a Prognostic Nomogram in Lung Cancer With Obstructive Sleep Apnea Syndrome

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To analyze the prognostic factors and survival rate of lung cancer patients with obstructive sleep apnea (OSA) by nomogram. The nomogram was established by a development cohort ($n = 90$), and the validation cohort included 38 patients. Factors in the nomogram were identified by Cox hazard analysis. We tested the accuracy of the nomograms by discrimination and calibration, and plotted decision curves to assess the benefits of nomogram-assisted decisions. There were significant difference in sex, apnea hypopnea index (AHI), Tumor Node Metastasis (TNM), coronary heart disease, lowest arterial oxygen saturation [LSpO2 (%)], oxygen below 90% of the time [T90% (min)], the percentage of the total recorded time spend below 90% oxygen saturation (TS90%) and oxygen desaturation index (ODI4) between lung cancer subgroup and lung cancer with OSA subgroup ($P < 0.05$). Lung cancer patients with OSA age, AHI, TNM, cancer types, BMI and ODI4 were independent prognostic factor. Based on these six factors, a nomogram model was established. The c-index of internal verification was 0.802 (95% CI 0.767–0.885). The ROC curve analysis for the nomogram show 1-year survival (AUC = 0.827), 3-year survival (AUC = 0.867), 5-year survival (AUC = 0.801) in the development cohort were good accuracy. The calibration curve shows that this prediction model is in good agreement. Decision curve analysis (DCA) suggests that the net benefit of decision-making with this nomogram is higher, especially in the probability interval of <20% threshold. The nomogram can predict the prognosis of patients and guide individualized treatment.

Keywords: obstructive sleep apnea syndrome, lung cancer, prognosis, nomogram, development

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INTRODUCTION

Lung cancer is the leading cause of cancer death in the world, at present, the pathogenesis of lung cancer is not clearly. Sleep apnea syndrome (SAS) is a disease with high incidence rate and serious harm to patient's health, obstructive sleep apnea (OSA) accounts for more than 90% of SAS (1). OSA is an independent risk factor of multiple system chronic diseases such as hypertension, coronary heart disease, arrhythmia and stroke (2), which also effects the development of chronic obstructive

pulmonary disease (3). OSA also plays an important role in the occurrence and development of tumors (4), lung cancer is the malignant tumor which most closely related with OSA (5).

Through there are comprehensive treatments of lung cancer, the survival rate has been significantly improved, improving the quality of life, especially sleep quality were important for lung cancer patients. It's not only helps to accelerate the physical and mental recovery, but also increases the body's immunity and resistance. Lung cancer is the most common cancer in OSA patients, OSA is usually develop moderate or severe when diagnosis, lung cancer and intermittent hypoxia, apnea, daytime sleepiness forming a vicious cycle, decreased the quality of life and survival time significantly (6).

Currently, nomogram have been developed in the majority of cancer types (7–9), in this study, we aimed to develop and validate a prognostic nomogram which uses widely available general data and laboratory indicators to improve our ability to predict survival time of lung cancer patients with OSA.

METHODS

Patient Selection

The retrospectively study included 410 lung cancer patients from 2013 to 2016 in Renmin Hospital of Wuhan University and Tongji Hospital, all subjects received philips YZB/USA 1575-2013 portable sleep recorder to monitor patients' sleep for at least 7 h per night, there are 128 cases diagnosis of OSA, the inclusion criteria were as follows: (1) the pathological diagnosis was confirmed as lung malignant tumor; (2) normal range of blood pressure in patients with hypertension after use of antihypertensive treatment and no hypertension-related complications; after symptomatic treatment, the patients with CHD were stable without complications; the blood glucose level in patients with type 2 diabetes without complications; (3) no drugs possibly influencing the sleep patterns was currently being taken.

Patients suffering from the following diseases or lesions were excluded: respiratory infectious disease, intracranial lesions, pulmonary embolism, rheumatic diseases and other chronic disease diseases that may cause abnormal blood oxygen saturation (10, 11). This study was conducted in accordance with the Declaration of *Helsinki*.

Laboratory Measurements

All subjects received philips YZB/USA 1575-2013 portable sleep recorder to monitor patients' sleep for at least 7 h per night, all data previously listed was send back, analyzed by computer and corrected artificially. The data about apnea hypopnea index (AHI), oxygen desaturation index (ODI4), lowest arterial oxygen saturation [LSpO2 (%)], oxygen below 90% of the time [T90% (min)], and the percentage of the total recorded time spend below 90% oxygen saturation (TS90%) were obtained. All the data was recorded when the first time of hospitalizations, clinical information was extracted from Electronic Medical Record system. All the patients received routine tests at the first time visit in hospital.

Follow-Up

Patients were advised to receive regular follow-ups after completion of the primary therapy according to clinical guidelines. Patients were generally follow-up every 3 months in the first 2 years and annually thereafter for patients without evidence of recurrence in the following 3–5 years. OS was defined as the time from the diagnosis of lung cancer to the time of the last follow-up or death, the follow-up deadline was November 1, 2020.

Statistical Analysis

Statistical analyses were performed by SPSS 25.0 (IBM, Chicago, IL, USA) and R for Windows (version3.4.2, http://www.r-project.org/). The optimal cut-off points in our study were evaluated by minimum *P*-value from log-rank $\times 2$ statistics using the X-tile program (12) and continuous variables were transformed to categorical variables, regression analysis was used to analyze the risk factors in the development cohort, nomogram was formulated based on the results of univariate and multivariate analysis by the package of rms. Study tested the accuracy of the nomograms by discrimination and calibration both in primary and externa validation cohort. The discrimination of the nomogram was measured by Harrell's C-index (C-index). The calibration curve of the nomogram model for the overall survival were formulated. The total points of each patient were calculated according to the established Cox regression model. Survival curves were depicted by the Kaplan–Meier method. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Clinical Characteristics of All Patients

The clinical characteristics of all patients were evaluated. The characteristics of the 282 lung cancer patients and 128 lung cancer patients with OSA are showed in **Table 1**. The median age was 59.98 years and only 172 patients (42.0%) were female. Among the 410 patients, there were 73 patients with the small cell carcinoma (17.8%) and 337 patients with the non-small cell carcinoma (82.2%). There was significant difference in sex, AHI, TNM stage, coronary heart disease, LSpO2, T90%, TS90%, and ODI4 between lung cancer subgroup and lung cancer with OSA subgroup ($P < 0.05$).

Clinical Characteristics of Lung Cancer Patients With OSA

The clinical characteristics of the training and validation sets were evaluated. The characteristics of the 90 patients in the development cohort and 38 patients in the validation cohort are showed in **Table 2**. The majority of patients are men and the TNM stages were represented, there were no statistically significant difference between development cohort and validation cohort.

Biomarker Selection

All the available information including general data, clinical characteristics and biomarkers were included for univariate and multivariate analysis (**Table 3**). In univariate analyses age, AHI,

TABLE 1 | Baseline clinical features of all patients [Mean ± SD/No (%)].

Characteristics	Total ($n = 410$)	Lung cancer ($n = 282$)	Lung cancer with OSA ($n = 128$)	Statistics	*P*
Age, year	59.98 ± 3.22	59.53 ± 3.53	60.98 ± 2.45	1.432*	0.853
Sex				6.382†	0.011
Male	238 (58.0)	152 (53.9)	86 (67.2)		
Female	172 (42.0)	130 (46.1)	42 (32.8)		
AHI	4.35 ± 2.01	2.54 ± 2.03	9.87 ± 1.98	0.637*	0.001
TNM stage				11.860†	0.008
I	129 (31.5)	95 (33.7)	34 (26.6)		
II	147 (35.9)	102 (36.2)	45 (35.2)		
III	83 (20.2)	45 (16.0)	38 (29.7)		
IV	51 (12.4)	40 (14.2)	11 (8.5)		
Cancer types				1.115†	0.291
Small cell carcinoma	73 (17.8)	54 (19.1)	19 (14.8)		
Non-small cell carcinoma	337 (82.2)	228 (80.9)	109 (85.2)		
BMI	20.88 ± 1.78	20.43 ± 1.54	21.90 ± 2.98	1.445*	0.384
Hypertension	128 (31.2)	84 (29.8)	44 (34.4)	0.863†	0.353
Diabetes	144 (35.1)	102 (36.2)	42 (32.8)	0.435†	0.509
Coronary heart disease	64 (15.6)	37 (13.1)	27 (21.2)	4.249†	0.039
Heart rate, beats/min	91.76 ± 20.34	91.43 ± 21.54	92.34 ± 17.92	1.432*	0.758
KPS	80.23 ± 12.44	82.34 ± 13.54	76.34 ± 8.342	0.552*	0.817
Smoking history	167 (40.7)	110 (39.0)	57 (44.5)	1.113†	0.292
LSpO2 (%)	78.32 ± 10.23	87.32 ± 15.64	69.43 ± 6.31	1.954*	0.009
T90%, min	56.34 ± 3.41	23.43 ± 1.65	91.23 ± 4.43	1.943*	0.001
TS90%, %	9.32 ± 2.01	1.32 ± 1.03	22.41 ± 2.89	3.215*	0.001
ODI4	0.45 ± 0.19	0.23 ± 0.08	1.98 ± 0.28	1.344*	0.001

Data were shown as mean ± standard deviation, n (%).

**t-test.*

†x2 value.

AHI, apnea hypopnea index; BMI, body mass index; LSpO2 (%), lowest arterial oxygen saturation; T90%, oxygen below 90% of the time; TS90%, the percentage of the total recorded time spend below 90% oxygen saturation; ODI4, oxygen desaturation index.

TNM stage, types, BMI, LSpO2 (%) and ODI4 were related to OS. All of the potentially important biomarkers identified in univariate analysis were further included in the multivariate analysis. Based on 90 OSA with lung cancer patients with complete information, age, AHI, TNM stage, types, BMI and ODI4 were significant predictors of OS.

Development of the Prediction Model

A nomogram is a graphic representation of the solution of an equation that provides a reasonable approximation of the probability of a particular outcome, nomogram was developed to predict for survival using the six independent covariates identified in the multivariate model, the mode explanatory covariables consisted of age, AHI, TNM stage, types, BMI and ODI4. A nomogram was constructed to predict 1-, 3-, and 5-year OS (**Figure 1**).

Validation of the Predictive Accuracy of Nomograms for OS

After internal verification, the C-index of the nomogram model for OS prediction was 0.802 (95% CI 0.767–0.885). The calibration curve illustrates how the predictions from the nomogram compare with actual outcomes for the 90 patients. The dashed line represents the performance of an ideal nomogram, in which predicted outcomes mostly match with the actual outcomes. The dots were calculated from sub-cohorts of our dataset and represent the performance of our nomogram based on the six biomarkers of Cox model. The calibration plot for the probability of OS at 1, 3, or 5 years after therapy showed an optimal agreement between the prediction by nomogram and actual observation (**Figure 2**).

ROC of the Predictive Accuracy of Nomograms for OS

The ROC curve analysis for the nomogram, area under curve (AUC) is used to evaluate the accuracy of the model, the higher the AUC value, the better the model effect. Results show 1-year survival (AUC = 0.827), 3-year survival (AUC = 0.867), 5-year survival (AUC = 0.801) in the development cohort and 3-year survival (AUC = 0.863) in the validation cohort were with good accuracy (13) (**Figure 3**).

TABLE 2 | Baseline clinical features of lung cancer patients with OSA [Mean ± SD/No (%)].

Characteristics	Total ($n = 128$)	Development cohort ($n = 90$)	Validation cohort ($n = 38$)	Statistics	*P*
Age, year	60.98 ± 2.45	60.53 ± 2.34	61 ± 1.98	1.453*	0.224
Sex				0.048†	0.827
Male	86 (67.2)	61 (67.8)	25 (65.8)		
Female	42 (32.8)	29 (32.2)	13 (34.2)		
AHI	9.87 ± 1.98	9.42 ± 1.53	10.32 ± 0.97	0.634*	0.543
TNM stage				2.460†	0.483
I	34 (26.6)	23 (25.6)	11 (28.9)		
II	45 (35.2)	31 (34.4)	14 (36.8)		
III	38 (29.7)	26 (28.9)	12 (31.6)		
IV	11 (8.5)	10 (11.1)	1 (2.7)		
Cancer types				0.547†	0.460
Small cell carcinoma	19 (14.8)	78 (86.7)	31 (82.6)		
Non-small cell carcinoma	109 (85.2)	12 (13.3)	7 (18.4)		
BMI	21.90 ± 2.98	22.74 ± 3.42	21.45 ± 2.54	1.425*	0.628
Hypertension	44 (34.4)	31 (34.5)	13 (34.2)	0.001†	0.979
Diabetes	42 (32.8)	30 (33.3)	12 (31.6)	0.037†	0.847
Coronary heart disease	27 (21.2)	20 (22.2)	7 (18.4)	0.232†	0.630
Heart rate, beats/min	92.34 ± 17.92	93.44 ± 16.43	91.43 ± 13.54	0.425*	0.087
KPS	76.34 ± 8.342	74.55 ± 9.43	79.54 ± 6.74	1.445*	0.154
Smoking history	57 (44.5)	42 (46.7)	15 (39.5)	0.559†	0.454
LSpO2 (%)	69.43 ± 6.31	70.87 ± 7.43	68.43 ± 5.73	1.434*	0.563
T90%,min	91.23 ± 4.43	87.54 ± 3.43	93.23 ± 5.43	2.543*	0.623
TS90%,%	22.41 ± 2.89	21.75 ± 2.54	23.21 ± 3.54	1.240*	0.154
ODI4	1.98 ± 0.28	1.72 ± 0.23	2.01 ± 0.35	0.643*	0.634

Data were shown as mean ± standard deviation, n (%).
**t-test.*
†x2 value.

TABLE 3 | Univariate and multivariate Cox hazards analysis between clinical features and OS ($n = 90$).

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age (≥60 vs. <60 岁)	4.523	1.432–7.546	0.008	2.543	1.053–5.324	0.021
Sex (male vs. female)	2.435	0.234–3.253	0.454			
AHI (≥15 vs. <15)	5.434	2.432–7.545	0.032	3.245	1.323–5.435	0.006
TNM stage (≥3 vs. <3)	8.655	4.345–9.553	0.027	2.431	1.634–4.523	0.005
Cancer types (small cell carcinoma vs. non- small cell carcinoma)	1.321	1.023–4.328	0.008	1.043	1.002–2.431	0.038
BMI (≥24 vs. <24)	2.341	1.453–4.523	0.012	1.532	1.332–3.454	0.007
Hypertension (yes vs. no)	2.412	0.453–4.545	0.673			
Diabetes (yes vs. no)	1.167	0.446–1.438	0.098			
Coronary heart disease (yes vs. no)	1.432	0.314–1.634	0.342			
Heart rate (<90 vs. ≥90 beats/min)	1.342	0.754–2.525	0.234			
KPS (<90 vs. ≥90)	1.554	0.186–2.345	0.423			
Smoking history (yes vs. no)	1.543	0.423–2.253	0.564			
LSpO2% (60 vs. <60%)	1.234	1.134–4.323	0.006	1.543	0.156–3.234	0.078
T90% (≥60 vs. <60 min)	2.421	0.543–2.232	0.743			
TS90% (≥80 vs. <80%)	1.432	0.453–1.354	0.355			
ODI4 (≥15 vs. <15)	1.543	1.023–4.323	0.046	1.554	1.043–2.456	0.031

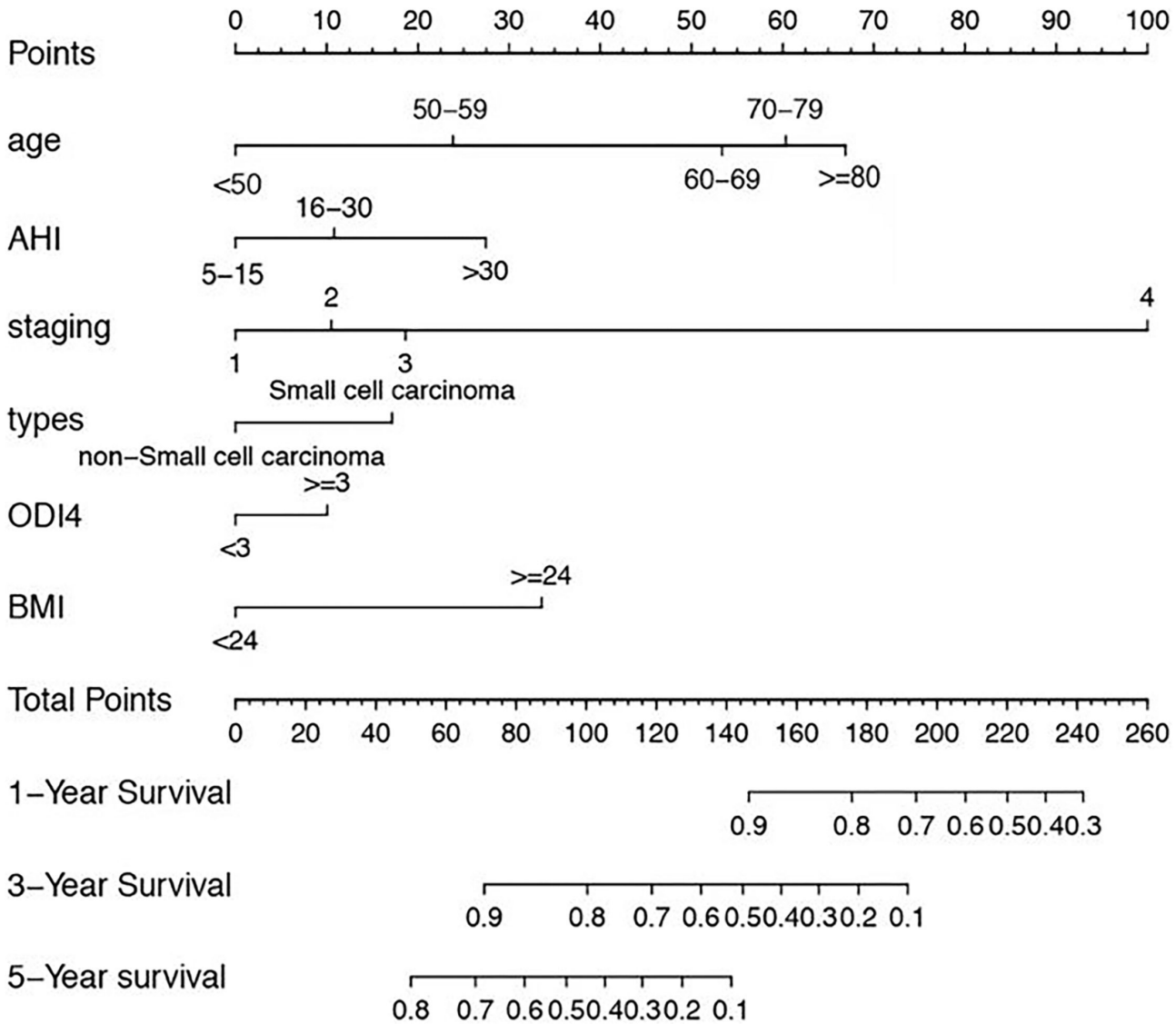

FIGURE 1 | Nomogram, including Age, AHI, TNM stage, types, BMI and ODI4 for 1, 3, and 5 years overall survival (OS) in lung cancer patients with OSA. The nomogram is valued to obtain the probability of 1, 3, and 5 years survival by adding up the points identified on the points scale for each variable.

Clinical Application of Prognostic Nomogram

Decision curve analysis (DCA) is used to evaluate the predictive effect of nomogram on OS, it is very important for clinical decision-making to accurately judge the impact of clinical features and related indicators on the prognosis of lung cancer patients with OSA (14). Factors not related to prognosis were represented by black line, factors related to prognosis were represented by gray line, the model of nomogram represented by the blue line. Results show net benefit can be obtained when make decisions by nomogram (**Figure 4**).

Using this prediction model to calculate the total score, the median of the total score of all patients was 137, total score ≥137 belong to high-risk group, total score <137 belong to low-risk group. Kaplan-Meier was used to analyze OS survival in low-risk group and high-risk group, results show there was statistically significant difference in high risk group and low risk group ($P < 0.05$), the model has good accuracy and practicability (**Figure 5**).

DISCUSSION

Prognostic models can facilitate discussion between physicians and patients, the models help to identify high-risk of OSA patients individualized treatments and clinical trials can be developed and may provide insight into the biology of disease. Nomograms have been developed to predict various clinical end points for patients with all kinds of malignancies.

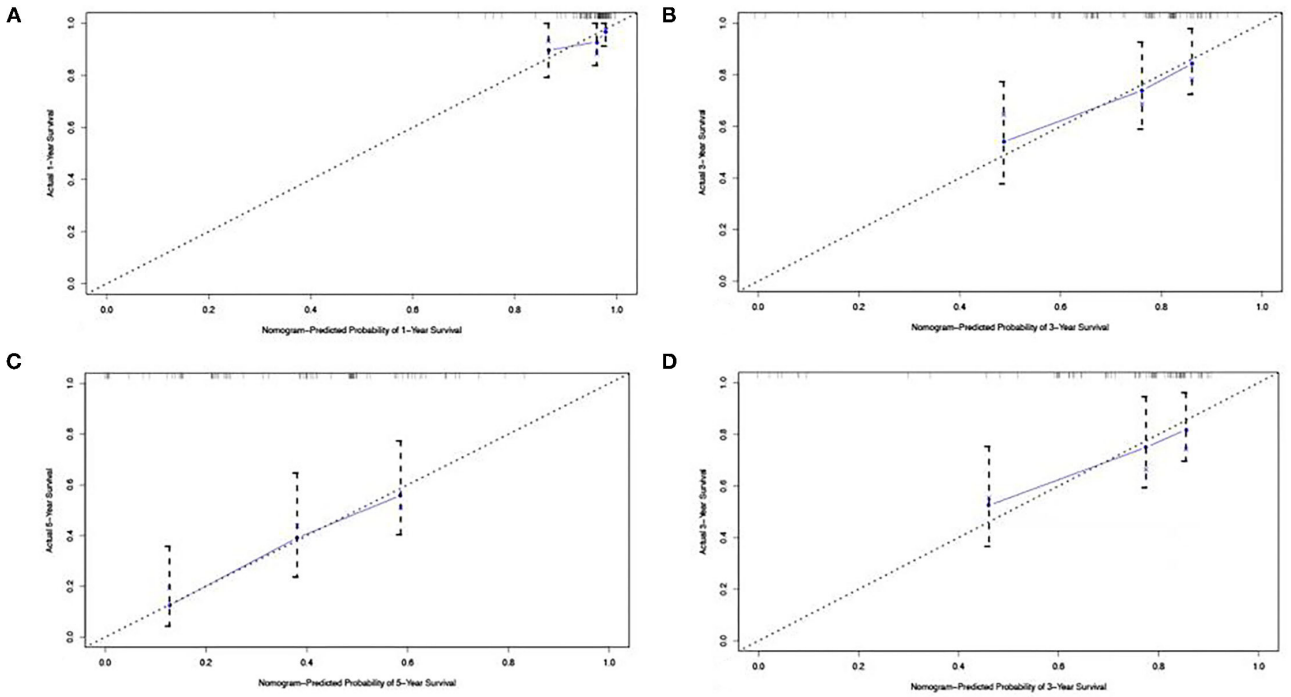

FIGURE 2 | The calibration curve for predicting patient survival at **(A)** 1 year, **(B)** 3 years, and **(C)** 5 years in the development cohort and at **(D)** 3 years in the validation cohort. Nomogram-predicted probability of overall survival is plotted on the *x*-axis; actual overall survival is plotted on the *y*-axis.

In recent years, multi-national cohort studies found that OSA increases the mortality of cancer, among which lung cancer was the most common malignant tumor (15, 16), Dreher et al. proposed that the incidence of OSA in new diagnosed lung cancer was 49%, the incidence of moderate/severe OSA was 17% (17), Perez-Warnisher et al. proposed that the incidence of OSA in lung cancer patients was 77.5%, in which moderate/severe OSA accounted for 41.1% (16), which consistent with the results of this study. Li et al. found that the OS of lung cancer patients with severe OSA was lower than that of patients with mild OSA, suggesting that the occurrence and severity of OSA are risk factors to promote cancer development (18). The univariate and multivariate logistic analysis indicated that age, AHI, TNM stage, cancer types, BMI and ODI4 were risk factors for overall survival. Studies confirmed that age is an important factor in the occurrence of lung cancer and as an independent risk factor for survival and prognosis of lung cancer patients (19). The continuous increase of obstructive sleep apnea with age challenges the current theory that mortality due to obstructive sleep apnea and cardiovascular co-morbidities affect obstructive sleep apnea prevalence at an advanced age (20). Body fat effect obstructive sleep apnea syndrome severity in different age groups, the neck and waist circumferences showed a statistically significant correlation with apnea-hypopnea index in both the full sample and in the $\geq$40 and <60 years age group, these variables did not show any significant correlation with the other two age groups (<40 and $\geq$60 years) (21). We found that age is an independent risk factor for lung cancer patients with OSA, and the nomogram score increases fastest in the age range of 50–60 years. The elderly patients with lung cancer complicated with OSA should be closely monitored to prevent the occurrence of disease-related complications.

Apnea hypopnea index (AHI) was the gold standard for the diagnosis of OSA. AHI refers to the average number of apnea and hypoventilation per hour during sleep. AHI also a standard for grading the severity of OSA. The results suggest that the higher AHI, the lower the survival rate of lung cancer patients with OSA and the hypoxia microenvironment promotes the growth of lung tumors. This conclusion has been confirmed by relevant studies. Stimulating the intermittent hypoxia in patients with OSAS induce pulmonary metastasis of melanoma (22), other evidence also suggests that hypoxic microenvironment contributing the development of non-small cell lung cancer (23). *In vitro* studies further proved that intermittent hypoxia lung cancer cells are more resistant and more prone to metastasis (24), indicating that lung cancer and OSAS promote each other, leading to disease progression and reduced survival.

Li et al. reported that tumor staging is related to the severity of OSA, jointly effect the prognosis of lung cancer patients with OSA (18). This study explored the effect of TNM stage to the prognosis, results show TNM stage was an independent risk factor for the prognosis of lung cancer patients with OSA. In addition, the nomogram score of patients with TNM stage IV increased significantly. TNM stage was not simple linear relationship with OS and prognosis, we should pay attention to the progress of the disease of patients with

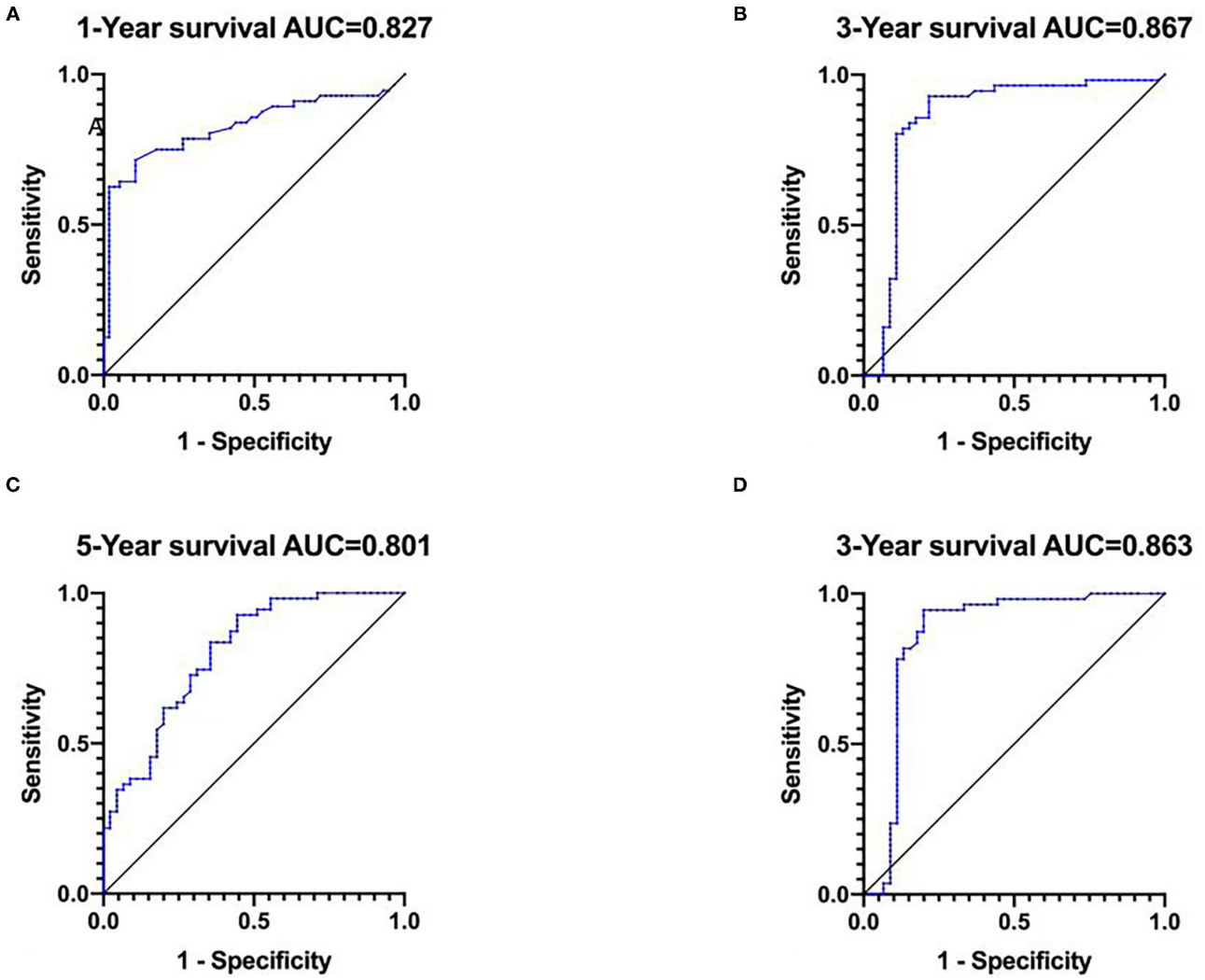

FIGURE 3 | The ROC curve for predicting patient survival at **(A)** 1 year, **(B)** 3 years, and **(C)** 5 years in the development cohort and at **(D)** 3 years in the validation cohort.

advanced lung cancer, actively treatment intervention to slow down the progress of the disease and improve the quality of life. According to histological classification, lung cancer can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), non-small cell lung cancer accounts for 80% of lung cancer. After multi-disciplinary comprehensive treatments in recent years, the 5-year survival rate has been greatly improved. However, only 20–30% of patients were in the early stage when diagnosed, so most of them fail to carry out standardized treatment in time and delayed the best treatment period (25). This study analyzed the prognosis of lung cancer patients with OSA, results show the prognosis of patients with small cell lung cancer was poor and the survival time was significantly reduced, although small cell lung cancer had a good response to treatment, it was often too late to make radical resection.

Obesity is one of the most important risk factors for OSA. The results of this study show BMI is an independent prognostic factor for lung cancer patients with OSA. Obesity not only aggravates the severity of OSA, but also reduces the OS of lung cancer patients with OSA. Obese patients with lung cancer and OSA are at high risk of death. Obesity is related to the increase of throat fat, tongue fat and volume (26, 27). Obesity patients always bear severe upper airway stenosis. Abdominal and thoracic fat weaken the longitudinal tracheal traction and pharyngeal wall tension, decrease chest wall compliance, decrease lung capacity, aggravate the severity of OSA. The increased of BMI is accompanied by an increase of the incidence of respiratory events and more severe nocturnal hypoxemia (28), indicating that the higher the degree of obesity, the higher the severity of OSA (29). However, some studies suggest that BMI effects the prognosis of lung cancer by influencing all aspects of physical

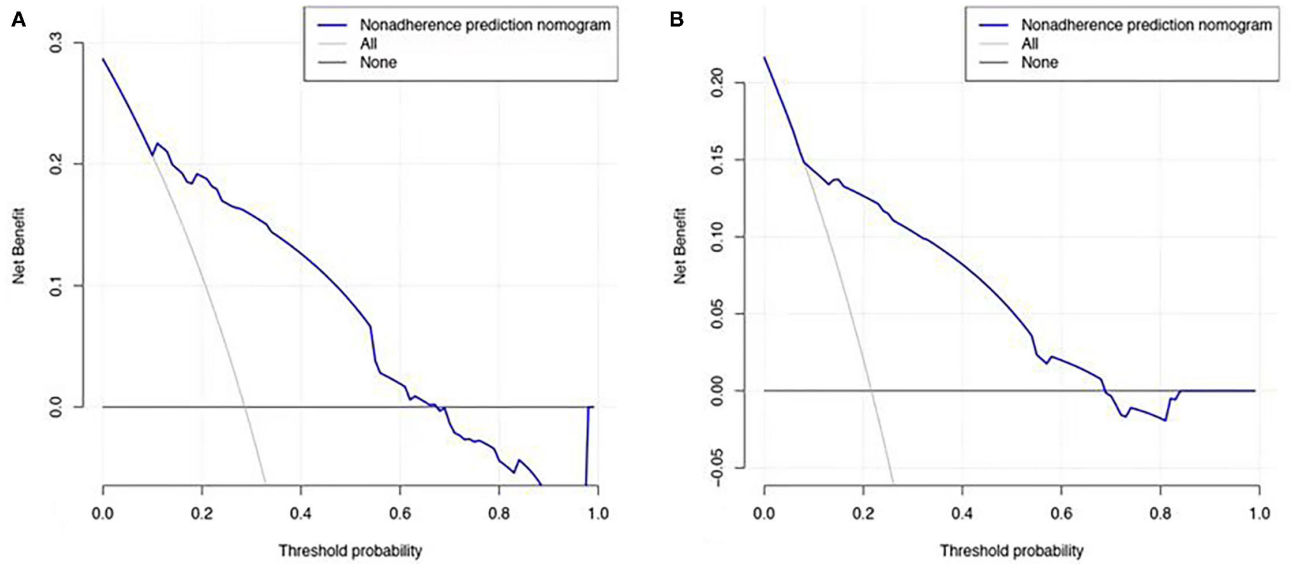

FIGURE 4 | Decision curve analysis for overall survival. **(A)** In the development cohort. **(B)** In the validation cohort. The Black line: no effect of relevant independent factors. Gray line: effect of relevant independent factors. The Blue dashed line: the model of nomogram.

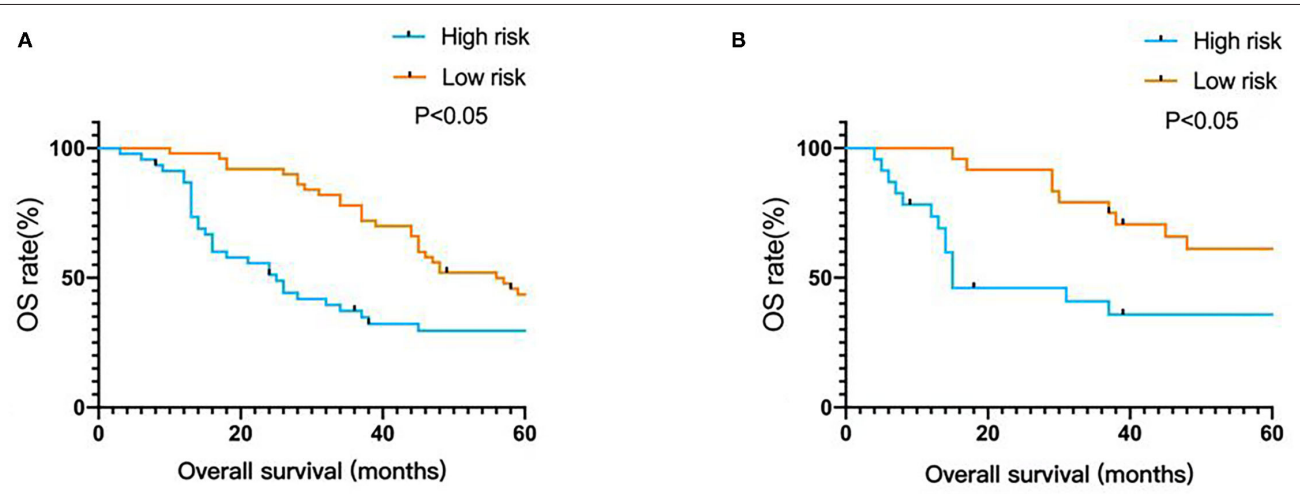

FIGURE 5 | Kaplan-Meier survival curves of nomogram. **(A)** In the development cohort. **(B)** In the validation cohort.

fitness of the body (30). Others studies suggest that high BMI is closely related to the better OS of lung cancer patients (31). But smoking is also an important confounding factor of lung cancer, so the influence of BMI on lung cancer needs further explored.

Results of Wisconsin Cohort research show severe sleep disordered breathing increases nearly five times death risk of cancer (32). Lung cancer patients prone to combined with intermittent hypoxia, apnea and daytime sleepiness (6). This study show ODI4 was an independent risk factor for lung cancer patients with OSA. Hypoxia environment plays an important role in the development of lung cancer. On the one hand, adequate oxygenation plays an important role in maintaining the normal function of cells, tissues and organs. Hypoxia is prevalent in tumor tissues, even in the absence of severe respiratory diseases. Hypoxia is the result of high proliferation rate of cancer cells, when the speed of neovascularization is slower than that of tumor growth, the amount of oxygen for metabolism can't be provided. On the other hand, lung cancer patients prone to sleep disorders. In addition to the persistent hypoxia of tumor tissue, vascular compression also promotes intermittent hypoxia and any factors causing intermittent hypoxia and apnea can aggravate OSA.

CONCLUSION

This research has some limitations. The number of samples included is limited, and the follow-up time is long, so

incomplete clinical information can't be avoided. It is still necessary to carry out external verification with large sample and multi center.

In summary, age, AHI, TNM stage, cancer types, BMI and ODI4 are clinical factors affecting the prognosis of lung cancer patients with OSA. The nomogram established in this study can be used to predict the prognosis of lung cancer patients with OSA and provide help for patients to formulate individualized treatment strategies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Renmin Hospital of Wuhan University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to data analysis and drafting or revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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REFERENCES

1. Zhao GQ, Li YR, Wang XY, Ding X, Wang CY, Xu W, et al. [Differential evaluation of diagnostic criteria for pediatric obstructive sleep apnea hypopnea syndrome]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* (2018) 32:12–17, 22. doi: 10.13201/j.issn.1001-1781.2018.01.003
2. Molero-Ramirez H, Tamae Kakazu M, Baroody F, Bhattacharjee R. Polysomnography parameters assessing gas exchange best predict postoperative respiratory complications following adenotonsillectomy in children with severe OSA. *J Clin Sleep Med.* (2019) 15:1251–9. doi: 10.5664/jcsm.7914
3. Spicuzza L, Campisi R, Crimi C, Frasca E, Crimi N. Prevalence and determinants of co-morbidities in patients with obstructive apnea and chronic obstructive pulmonary disease. *Eur J Intern Med.* (2019) 69:e15–6. doi: 10.1016/j.ejim.2019.08.020
4. Huang HY, Lin SW, Chuang LP, Wang CL, Sun MH, Li HY, et al. Severe OSA associated with higher risk of mortality in stage III and IV lung cancer. *J Clin Sleep Med.* (2020) 16:1091–8. doi: 10.5664/jcsm.8432
5. Justeau G, Gerves-Pinquie C, Le Vaillant M, Trzepizur W, Meslier N, Goupil F, et al. Association between nocturnal hypoxemia and cancer incidence in patients investigated for OSA: data from a large multicenter french cohort. *Chest.* (2020) 158:2610–20. doi: 10.1016/j.chest.2020.06.055
6. Liu W, Luo M, Fang YY, Wei S, Zhou L, Liu K. Relationship between occurrence and progression of lung cancer and nocturnal intermittent hypoxia, apnea and daytime sleepiness. *Curr Med Sci.* (2019) 39:568–75. doi: 10.1007/s11596-019-2075-6
7. International Bladder Cancer Nomogram C, Bochner BH, Kattan MW, Vora KC. Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. *J Clin Oncol.* (2006) 24:3967–72. doi: 10.1200/JCO.2005.05.3884
8. Karakiewicz PI, Briganti A, Chun FK, Trinh QD, Perrotte P, Ficarra V, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol.* (2007) 25:1316–22. doi: 10.1200/JCO.2006.06.1218
9. Wierda WG, O'Brien S, Wang X, Faderl S, Ferrajoli A, Do KA, et al. Prognostic nomogram and index for overall survival in previously untreated patients with chronic lymphocytic leukemia. *Blood.* (2007) 109:4679–85. doi: 10.1182/blood-2005-12-051458
10. Karakontaki FV, Panselinas ES, Polychronopoulos VS, Tzioufas AG. Targeted therapies in interstitial lung disease secondary to systemic autoimmune rheumatic disease. Current status and future development. *Autoimmun Rev.* (2021) 20:102742. doi: 10.1016/j.autrev.2020.102742
11. Zhao B, Ma W. Dexamethasone and number of days alive without life support in adults with COVID-19 and severe hypoxemia. *JAMA.* (2022) 327:682. doi: 10.1001/jama.2021.24525
12. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res.* (2004) 10:7252–9. doi: 10.1158/1078-0432.CCR-04-0713
13. Walker SP. The ROC curve redefined - optimizing sensitivity (and specificity) to the lived reality of cancer. *N Engl J Med.* (2019) 380:1594–5. doi: 10.1056/NEJMp1814951
14. Baker SG. Decision curves and relative utility curves. *Med Decis Making.* (2019) 39:489–90. doi: 10.1177/0272989X19850762
15. Martinez-Garcia MA, Martorell-Calatayud A, Nagore E, Valero I, Selma MJ, Chiner E, et al. Association between sleep disordered breathing and aggressiveness markers of malignant cutaneous melanoma. *Eur Respir J.* (2014) 43:1661–8. doi: 10.1183/09031936.00115413
16. Perez-Warnisher MT, Cabezas E, Troncoso MF, Gomez T, Melchor R, Pinillos EJ, et al. Sleep disordered breathing and nocturnal hypoxemia are very prevalent in a lung cancer screening population and may condition lung cancer screening findings: results of the prospective Sleep Apnea In Lung Cancer Screening (SAILS) study. *Sleep Med.* (2019) 54:181–6. doi: 10.1016/j.sleep.2018.10.020
17. Dreher M, Kruger S, Schulze-Olden S, Keszei A, Storre JH, Woehrle H, et al. Sleep-disordered breathing in patients with newly diagnosed lung cancer. *BMC Pulm Med.* (2018) 18:72. doi: 10.1186/s12890-018-0645-1
18. Li L, Lu J, Xue W, Wang L, Zhai Y, Fan Z, et al. Target of obstructive sleep apnea syndrome merge lung cancer: based on big data platform. *Oncotarget.* (2017) 8:21567–78. doi: 10.18632/oncotarget.15372
19. Choi WI, Choi J, Kim MA, Lee G, Jeong J, Lee CW. Higher age puts lung cancer patients at risk for not receiving anti-cancer treatment. *Cancer Res Treat.* (2019) 51:1241–8. doi: 10.4143/crt.2018.513
20. Fietze I, Laharnar N, Obst A, Ewert R, Felix SB, Garcia C, et al. Prevalence and association analysis of obstructive sleep apnea with gender and age differences - Results of SHIP-Trend. *J Sleep Res.* (2019) 28:e12770. doi: 10.1111/jsr.12770
21. Borges Pde T, Silva BB, Moita Neto JM, Borges NE, Li LM. Cephalometric and anthropometric data of obstructive apnea in different age groups. *Braz J Otorhinolaryngol.* (2015) 81:79–84. doi: 10.1016/j.bjorl.2014.06.001
22. Almendros I, Wang Y, Becker L, Lennon FE, Zheng J, Coats BR, et al. Intermittent hypoxia-induced changes in tumor-associated macrophages and tumor malignancy in a mouse model of sleep apnea. *Am J Respir Crit Care Med.* (2014) 189:593–601. doi: 10.1164/rccm.201310-1830OC
23. Giovannetti E, Wang Q, Avan A, Funel N, Lagerweij T, Lee JH, et al. Role of CYB5A in pancreatic cancer prognosis and autophagy modulation. *J Natl Cancer Inst.* (2014) 106:djt346. doi: 10.1093/jnci/djt346
24. Liu Y, Song X, Wang X, Wei L, Liu X, Yuan S, et al. Effect of chronic intermittent hypoxia on biological behavior and hypoxia-associated gene expression in lung cancer cells. *J Cell Biochem.* (2010) 111:554–63. doi: 10.1002/jcb.22739

25. Yang L, Wang S, Zhou Y, Lai S, Xiao G, Gazdar A, et al. Evaluation of the 7(th) and 8(th) editions of the AJCC/UICC TNM staging systems for lung cancer in a large North American cohort. *Oncotarget.* (2017) 8:66784–95. doi: 10.18632/oncotarget.18158
26. Isono S. Obesity and obstructive sleep apnoea: mechanisms for increased collapsibility of the passive pharyngeal airway. *Respirology.* (2012) 17:32–42. doi: 10.1111/j.1440-1843.2011.02093.x
27. Pahkala R, Seppa J, Ikonen A, Smirnov G, Tuomilehto H. The impact of pharyngeal fat tissue on the pathogenesis of obstructive sleep apnea. *Sleep Breath.* (2014) 18:275–82. doi: 10.1007/s11325-013-0878-4
28. Aihara K, Oga T, Harada Y, Chihara Y, Handa T, Tanizawa K, et al. Analysis of anatomical and functional determinants of obstructive sleep apnea. *Sleep Breath.* (2012) 16:473–81. doi: 10.1007/s11325-011-0528-7
29. Jeong JI, Gu S, Cho J, Hong SD, Kim SJ, Dhong HJ, et al. Impact of gender and sleep position on relationships between anthropometric parameters and obstructive sleep apnea syndrome. *Sleep Breath.* (2017) 21:535–41. doi: 10.1007/s11325-016-1413-1
30. Oldenburg CS, Boll D, Nicolaije KA, Vos MC, Pijnenborg JM, Coebergh JW, et al. The relationship of body mass index with quality of life among endometrial cancer survivors: a study from the population-based PROFILES registry. *Gynecol Oncol.* (2013) 129:216–21. doi: 10.1016/j.ygyno.2012.12.041
31. Sepesi B, Gold KA, Correa AM, Heymach JV, Vaporciyan AA, Roszik J, et al. The influence of body mass index on overall survival following surgical resection of non-small cell lung cancer. *J Thorac Oncol.* (2017) 12:1280–7. doi: 10.1016/j.jtho.2017.05.010
32. Shimoda LA, Semenza GL. HIF and the lung: role of hypoxia-inducible factors in pulmonary development and disease. *Am J Respir Crit Care Med.* (2011) 183:152–6. doi: 10.1164/rccm.201009-1393PP

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Associations of Depression, Anxiety, and Life Events With the Risk of Obstructive Sleep Apnea Evaluated by Berlin Questionnaire

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Background: Psychological problems are prevalent in the general population, and their impacts on sleep health deserve more attention. This study was to examine the associations of OSA risk with depression, anxiety, and life events in a Chinese population.

Methods: A total of 10,287 subjects were selected from the Guangzhou Heart Study. Berlin Questionnaire (BQ) was used to ascertain the OSA. The Center for Epidemiologic Studies Depression Scale (CES-D) and Zung's self-rating anxiety scale (SAS) were used to define depression and anxiety. A self-designed questionnaire was used to assess life events. Odds ratio (OR) with 95% confidence interval (95% CI) was calculated by using the logistic regression model.

Results: There were 1,366 subjects (13.28%) classified into the OSA group. After adjusting for potential confounders, subjects with anxiety (OR: 2.60, 95% CI: 1.63–4.04) and depression (OR: 1.91, 95% CI: 1.19–2.97) were more likely to have OSA. Subjects suffering from both anxiety and depression were associated with a 3.52-fold (95% CI: 1.88–6.31) risk of OSA. Every 1-unit increment of CES-D score and SAS index score was associated with 13% (95% CI: 1.11–1.15) and 4% (95% CI: 1.03–1.06) increased risk of OSA. Neither positive life events nor adverse life events were associated with OSA.

Conclusions: The results indicate that depression and anxiety, especially co-occurrence of both greatly, were associated with an increased risk of OSA. Neither adverse life events nor positive life events were associated with any risk of OSA. Screening for interventions to prevent and manage OSA should pay more attention to depression and anxiety.

Keywords: depression, anxiety, obstructive sleep apnea, adverse life events, positive life events

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BACKGROUND

Obstructive sleep apnea (OSA), a relatively common sleep disorder in both general and specific disease-related populations (1), is characterized by recurrent episodes of a partial or complete collapse of the upper airway during sleep (2), with consequent oxygen desaturation, frequent arousals, and sleep fragmentation (3). The prevalence of OSA ranged from 9 to 38% in Europe and America (1) and was around 7% in Asia (4) and 24.2% in China (5). Approximately one billion adults aged 30–69 years worldwide are suffering from OSA and about 425 million required medical treatment (5). Moreover, OSA can further result in severe cardiovascular diseases and cognitive impairment (6–9).

Many factors including aging, male, obesity, snoring, and craniofacial and upper airway abnormalities were found to be associated with OSA occurrence (10, 11). Increasing literature is highlighting the critical effects of social and psychological problems on OSA-related sleep disorders (6, 12–14). According to Rezaeitalab et al. (15), anxiety and depression are the two most common comorbidities of sleep disorders and respiratory diseases. A meta-analysis found that the prevalence of OSA was 25.7% among patients with serious mental illness (16). Studies have found that anxiety and depression could disrupt sleep rhythm, and chronic disturbance of normal sleep could aggregate sleep apnea (13, 17–19). Depression and anxiety may occur simultaneously; it is found that about 85% of depressive patients have significant anxiety, and 90% of patients with anxiety disorder have depression (20). However, there lack of studies to examine the independent and joint effects of anxiety and depression on the occurrence of OSA.

Adverse life events, one of the major sources of social stress, were found to be related to the onset of a wide range of psychiatric disorders, such as depression, anxiety, and substance use (21). Some common adverse life events include divorce or separation, widowed, bereavement, serious illness of family members, serious natural disaster, unemployment, violence, and bankruptcy (21). Adverse life events are very common in the general population with most adults (60.7% of men and 51.2% of women) reporting having experienced at least one event in their lifetime (22). Tripathi et al. (23) found that early stressful life events might initiate and aggravate tissue inflammation, leading to deregulation in the hypothalamo-pituitary axis and an increase in serum levels of cortisol and C-reactive protein, and in turn finally result in the development of OSA. Nevertheless, the association between OSA risk and life events is unclear.

Therefore, this study aimed to investigate the associations of depression, anxiety, and life events with OSA occurrence.

Abbreviations: OSA, obstructive sleep apnea; BQ, Berlin Questionnaire; CES-D, The Center for Epidemiologic Studies Depression Scale; SAS, Zung's self-rating anxiety scale; OR, Odds ratio; CI, confidence interval; BMI, body mass index; GC, glucocorticoid; CRP, C-reactive protein; LTPA, leisure-time physical activity; DAG, directed acyclic graph.

MATERIALS AND METHODS

Setting and Subjects

Subjects in this cross-sectional study were selected from the baseline survey of an ongoing prospective longitudinal study-the Guangzhou Heart Study. A detailed description of the cohort has been presented in our previous reports (24, 25). In brief, a total of 12,013 permanent residents aged ≥35 years accomplished the baseline survey during the year 2015-2017. In this study, 1,726 participants were excluded for the age of more than 74 years (1,043 participants), incomplete OSA-related information (5 participants), or suffering from a chronic obstructive pulmonary disease (678 participants). Finally, a total of 10,287 subjects were included in the following analysis. The flow chart for the selection process of subjects can be seen in **Figure 1**. This study was approved by the Ethical Committee of Guangdong Provincial People's Hospital and by the Ethical Review Committee for Biomedical Research, School of Public Health, Sun Yat-sen University. The study was performed in line with the Declaration of Helsinki and all participants provided informed consent.

OSA Ascertainment

The risk of OSA was assessed with Berlin Questionnaire (BQ) (26). The 10-item questions comprise three categories: frequency and intensity of snoring (category 1, items 1–5), frequency of daytime sleepiness or fatigue (category 2, items 6–9), body mass index (BMI), and hypertension (category 3, item 10). The first and second categories were assessed as positive if persistent symptoms (>3 to 4 times/week) were reported, while category 3 was positive if there was a history of hypertension or a BMI of higher than 30 kg/m^2. If two or more categories were positive, the participant was considered at high risk of OSA and classified into the OSA group, otherwise at low risk of OSA and classified into the non-OSA group (27).

Depression, Anxiety, and Life Events Assessment

Depression and anxiety were measured using the Center for Epidemiologic Studies Depression Scale (CES-D) (28) and Zung's self-rating anxiety scale (SAS) (29), both of which have been demonstrated to have credible internal consistency and adequate test-retest repeatability in the Chinese population (29, 30). The CES-D scale contains 20 items. Each participant was asked to answer the frequency of feelings or behaviors for each item over the past week. Ratings were based on a 4-point scale from 0 (rarely or none of the time) to 3 (most or all the time); the items of 4, 8, 12, and 16 are reverse-scored; the scores for all items are added to get the total score, that is the CES-D score (28). The CES-D score ranges from 0 to 60 and a participant with the score of ≥16 was defined as having depression and otherwise having no depression (28, 31).

The SAS is a 20-item scale, adopting a 4-point scale ranging from 1 (none, or a little of the time) to 4 (most, or all the time). Fifteen items presented adverse experiences, and 5 items presented positive experiences with reverse scoring. Each participant was asked to select the frequency of each item and the

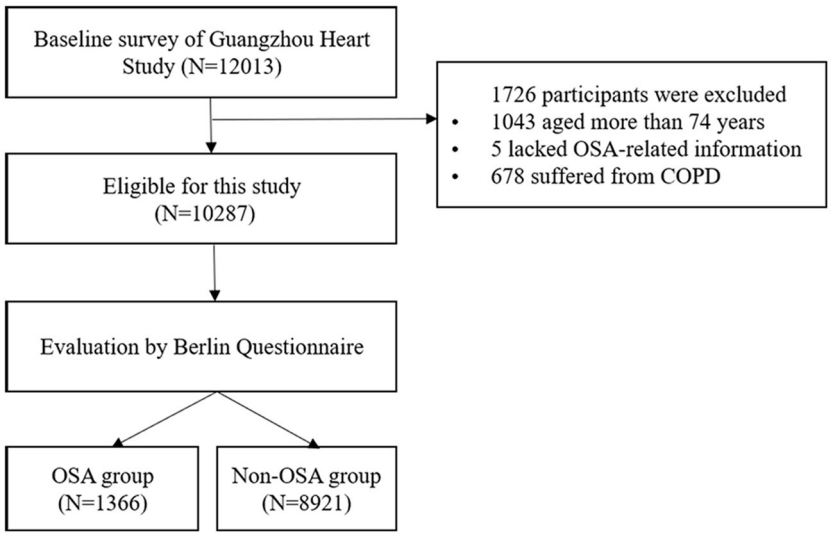

FIGURE 1 | Flow chart for the selection process of subjects.

total score was calculated by adding the score of each item. The raw total score ranged from 20 to 80, and then the raw total score was converted to an index score by dividing the sum of the raw score by 80 and multiplying by 100 (29). Therefore, the SAS index score ranged from 25 to 100 and a participant with the SAS index score of ≥45 was judged as having anxiety, otherwise as having no anxiety (29, 32).

Considering that depression and anxiety often coexist (33) and the depression and anxiety comorbidity may lead to higher severity of illness (34), we categorized all participants into three groups (Neither, One, Both) according to the status of the combination of depression and anxiety. Participants in the Neither group means they had neither depression nor anxiety; participants in the One group means they had either depression or anxiety; participants in the Both group means they had both depression and anxiety. Neither group was taken as the reference group for further analysis. In addition, the CES-D score and SAS index score were converted from continuous variables into categorical variables based on cut-off points of tertiles of scores.

Life event was defined as a social experience or change with a specific onset and course that has a psychological impact on a person (21). A self-designed 10-item structured questionnaire was used to collect the information of the ten life events commonly occurring in daily life (**Supplementary Figure 1**). The questionnaire was examined twice with 2 month-intervals among 180 local adults and found to have moderate to good reliability and reproducibility (unpublished). This questionnaire contained eight items of adverse life events and two items of positive life events. Eight adverse life events included divorce or separation, widowed, bereavement, serious illness of family members, serious natural disaster, unemployment or lay-off, suffering from violence, and bankruptcy or large property loss; two positive life events included winning the lottery or a windfall, and joyful events. Each participant was asked to answer whether he or she had experienced a certain life event during the past year; if the response was "yes," it meant that he or she had experienced the corresponding event, otherwise not. For the adverse life events, a point of 0 was assigned to each item if the response was "no" and a point of 1 was assigned if the response was "yes;" for the positive life events, a point of 0 was assigned to each item if the response was "no" and a point of 1 was assigned if the response was "yes." Then, we calculated the total scores of adverse life events and positive life events, respectively; if the total score of adverse life events or positive life events of a participant was non-zero, this participant was deemed to have experienced an adverse or positive life event, otherwise not experienced. Some studies have investigated the overall effect of both adverse and positive life events (35, 36), we also calculated the life event score for each participant by summing each score of all life events, and divided the participants into three groups with zero as the cut-point: <0 (means that the number of positive life events exposure exceeds the number of adverse life event exposure), 0 (means that the number of positive life events exposure equals to the number of adverse life event exposure, or means that the participant dose not expose to any life events), >0 (means that the number of adverse life events exposure exceeds the number of positive life event exposure).

Potential Confounding Factors

A self-administered questionnaire was used to collect demographic and lifestyle information, including age (years), sex (male, female), education (primary school or lower, junior high school, senior high school, and college or above), and marital status (married and others), smoking (non-smoker, ex-smoker, and current smoker), alcohol drinking (never, occasion and frequent), fruit intake (≥once/day, <once/day), vegetable intake (≥once/day, <once/day) and leisure-time physical activity (LTPA). The total volume of leisure-time

TABLE 1 | Baseline characteristics of the participants by OSA.

Characteristic	Non-OSA group (*N* = 8,921)	OSA group (*N* = 1,366)	*P*-value
Age (years), mean (S.D.)	56.02 (10.01)	57.89 (9.17)	<0.001[a]
Leisure-time physical activity, MET-h/week, median (IQR)	35.70 (17.90, 59.20)	33.60 (12.43, 57.10)	<0.001[d]
Body mass index, kg/m^2, mean (S.D.)	23.61 (3.24)	26.74 (3.97)	<0.001[a]
Waist-hip ratio, mean (S.D.)	0.88 (0.07)	0.92 (0.07)	<0.001[a]
Age, *N* (%)			<0.001[b]
35–54	3,922 (43.96)	501 (36.68)	
55–74	4,999 (56.04)	865 (63.32)	
Sex, *N* (%)			<0.001[b]
Male	2,797 (31.35)	712 (52.12)	
Female	6,124 (68.65)	654 (48.87)	
Education, *N* (%)			0.003[b]
Primary school or less	3,185 (35.70)	489 (35.80)	
Junior high school	2,259 (25.32)	342 (25.04)	
Senior high school	2,261 (25.35)	392 (28.70)	
Junior college or higher	1,216 (13.63)	143 (10.46)	
Marital status, *N* (%)			<0.001[b]
Married	7,801 (87.45)	1,251 (91.58)	
Others	1,120 (12.55)	115 (8.42)	
Smoke, *N* (%)			<0.001[c]
Non-smoker	7,218 (80.91)	945 (69.18)	
Ex-smoker	396 (4.44)	127 (9.30)	
Current-smoker	1,307 (14.65)	294 (21.52)	
Alcohol drinking, *N* (%)			<0.001[c]
Never	7,043 (78.95)	962 (70.43)	
Occasion	1,394 (15.63)	265 (19.40)	
Frequent	484 (5.42)	139 (10.17)	
Fruit intake, *N* (%)			<0.001[b]
≥Once/day	5,778 (64.77)	799 (58.49)	
<Once/day	3,143 (35.23)	567 (41.51)	
Vegetable intake, N (%)			0.310[b]
≥Once/day	8,608 (96.49)	1,310 (95.90)	
<Once/day	313 (3.51)	56 (4.10)	
Hypertension, *N* (%)			<0.001[b]
No	7,024 (78.74)	240 (17.57)	
Yes	1,897 (21.26)	1,126 (82.43)	
Cardiovascular disease, *N* (%)			<0.001[b]
No	442 (4.95)	112 (8.20)	
Yes	8,479 (95.05)	1,254 (91.80)	
Dyslipidemia, *N* (%)			<0.001[b]
No	2,755 (30.88)	338 (24.74)	
Yes	6,166 (69.12)	1,028 (75.26)	
Depression, *N* (%)			0.138[b]
No	8,975 (98.59)	1,339 (98.02)	
Yes	126 (1.41)	27 (1.98)	
Anxiety, *N* (%)			0.018[b]
No	8,807 (98.72)	1,337 (97.87)	
Yes	114 (1.28)	29 (2.12)	
Combination of depression and anxiety			0.017[c]
Neither	8,733 (97.89)	1,328 (97.22)	
One	136 (1.52)	20 (1.46)	
Both	52 (0.58)	18 (1.32)	
Adverse life event, *N* (%)			0.857[b]
No	8,061 (90.36)	1,237 (90.56)	
Yes	860 (9.64)	129 (9.44)	
Positive life event, *N* (%)			0.047[b]
No	8,264 (92.64)	1,265 (91.07)	
Yes	657 (7.36)	124 (8.93)	

[a] *P-value for t-test.*
[b] *P-value for chi-square test.*
[c] *P-value for Cochran-Armitage trend test.*
[d] *P-value for Wilcox rank sum test.*

physical activity was the sum of the volume of each type of leisure-time physical activity, which was obtained by multiplying the intensity of the physical activity by its duration and by its frequency. The physician-diagnosed disease of hypertension (yes, no), dyslipidemia (yes, no), cardiovascular disease (yes, no) was required to report. Cardiovascular disease included any myocardial infarction, stroke, valvular heart disease, heart failure, and atrial fibrillation. Physical measurements, including height, weight, waist circumference, hip circumference, and blood pressure, were performed in line with standard instruments and protocols. Body mass index was calculated as weight divided by height squared (kg/m^2). The waist-hip ratio was calculated by dividing waist circumference (cm) by hip circumference (cm).

Statistical Analyses

Shapiro-Wilk test was used to examine the normality; then the chi-squared test, *t*-test, and Wilcoxon rank-sum test were used to examine the distribution of categorical and continuous variables between the OSA group and the non-OSA group. Cochran-Armitage trend test was used for the distribution of a combination of depression and anxiety. We established three models: model 1 was not adjusted for any variable; model 2 was adjusted for age, sex, education, marital status, waist-hip ratio, leisure-time physical activity, smoking, alcohol drinking, fruit intake, vegetables intake, and dyslipidemia; model 3 was adjusted for body mass index as well as the covariables adjusted in the model 2. All confounders were selected based on the directed acyclic graph (DAG) model of OSA and the minimal sufficient adjustment sets for estimating the direct effect of anxiety, depression, life events on OSA were adopted (**Supplementary Figure 2**). Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) were estimated by using logistic regression. Given the depressive and anxiety symptoms often co-occurred, we estimated the association of combined exposure of depression and anxiety with OSA risk. To examine the stability and robustness of the results, we did

TABLE 2 | Association of depression, anxiety, and life events with OSA risk.

	N[a]		Effect estimates		
	Non-OSA group	OSA group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]	Adjusted OR (95% CI)[c]
Depression					
No	8,975	1,339	1.00	1.00	1.00
Yes	126	27	1.41 (0.91, 2.11)	1.60 (1.02, 2.44)	1.91 (1.19, 2.97)
Anxiety					
No	8,807	1,337	1.00	1.00	1.00
Yes	114	29	1.68 (1.09, 2.49)	2.11 (1.35, 3.20)	2.60 (1.63, 4.04)
Combination of depression and anxiety					
Neither	8,733	1,328	1.00	1.00	1.00
One	136	20	0.97 (0.59, 1.51)	1.18 (0.71, 1.87)	1.35 (0.80, 2.19)
Both	52	18	2.28 (1.29, 3.83)	2.70 (1.49, 4.70)	3.52 (1.88, 6.31)
P for trend			0.017	0.018	<0.001
Adverse life event					
No	8,061	1,237	1.00	1.00	1.00
Yes	860	129	0.98 (0.80, 1.18)	1.06 (0.87, 1.30)	1.08 (0.87, 1.33)
Positive life event					
No	8,264	1,244	1.00	1.00	1.00
Yes	657	122	1.23 (0.99, 1.50)	1.27 (1.03, 1.56)	1.24 (0.99, 1.54)
Life event score					
<0	589	104	1.00	1.00	1.00
0	7,529	1,147	0.86 (0.70, 1.08)	0.83 (0.66, 1.04)	0.84 (0.67, 1.07)
>0	803	115	0.81 (0.61, 1.08)	0.85 (0.63, 1.14)	0.89 (0.65, 1.21)
P for trend			0.165	<0.001	<0.001
Every 1-unit increment			0.92 (0.80, 1.04)	0.95 (0.82, 1.09)	0.96 (0.83, 1.11)

[a]*N represents sample size for the non-OSA group or for the OSA group; OSA represents obstructive sleep apnea.*
[b]*Adjustment for age, sex, education, marital status, waist-hip ratio, leisure-time physical activity, smoking, alcohol drinking, fruit intake, vegetables intake, and dyslipidemia.*
[c]*Additional adjustment for body mass index.*

the sensitivity analysis by excluding participants aged 60 years or above and excluding those with cardiovascular disease. In addition, overweight and obesity are related to anxiety and depression, so we conducted a sensitivity analysis by using the OSA subitems [snoring (category 1), daytime sleepiness (category 2), obesity (category 3, defined as BMI more than 30 kg/m^2), and hypertension (category 3)] as the outcomes to eliminate the potential bias. Statistical analysis was conducted by using R (version 3.6.3). All tests were two-tailed and a *P*-value of < 0.05 was considered statistically significant.

RESULTS

A total of 10,287 participants were included in this study, of which 8,921 (86.72%) were classified into the non-OSA group and 1,366 (13.28%) into the OSA group (**Table 1**). There were 153 participants having depression, 143 having anxiety, and 70 having both depression and anxiety. In comparison with the non-OSA group, the OSA group has a higher proportion of patients with anxiety and positive life events ($P < 0.05$). There was no significant difference in the occurrence of depression and adverse life events between the non-OSA group and the OSA group ($P > 0.05$).

The means of age, BMI and waist-hip ratio were all larger in the OSA group than those in the non-OSA group (all $P < 0.05$), whereas, the mean of the volume of leisure-time physical activity was higher in the non-OSA group ($P < 0.05$). Besides, more participants in the non-OSA group than in the OSA group were non-smoker, non-drinker, ate fruits at least once per day, ate vegetables at least once per day, and did not have hypertension, dyslipidemia, or cardiovascular disease (all $P < 0.05$).

Participants suffering from anxiety (OR: 2.60, 95% CI: 1.63–4.04) and depression (OR: 1.91, 95% CI: 1.19–2.97) were associated with an increased risk of OSA after considering potential confounders (**Table 2**). In comparison to participants with neither depression nor anxiety, those who only suffered from depression or only suffered from anxiety were associated with 1.35-fold (95% CI: 0.80–2.19) risk of OSA, those suffering from both depression and anxiety were associated with 3.52-fold (95% CI: 1.88–6.31) risk of OSA; a significant exposure-response trend was also observed ($P < 0.001$). Neither adverse life events nor positive life events were associated with any risk of OSA. The life event score was not associated with the risk of OSA, even every 1-unit increment of life event score did not reach a significant result.

The risk of OSA increased with the increment of the CES-D score and SAS index score (**Table 3**). Every 1-unit increment of

TABLE 3 | Association of CES-D score and SAS index score with OSA risk.

	N[a]		Effect estimates		
	Non-OSA group	OSA group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]	Adjusted OR (95% CI)[c]
CES-D score					
Tertile 1	3,694	565	1.00	1.00	1.00
Tertile 2	2,471	361	0.96 (0.83, 1.10)	1.06 (0.91, 1.22)	1.15 (0.99, 1.34)
Tertile 3	2,756	440	1.04 (0.91, 1.19)	1.15 (1.00, 1.32)	1.27 (1.10, 1.47)
P for trend			0.579	<0.001	<0.001
Every 1-unit increment			1.13 (1.11, 1.14)	1.13 (1.11, 1.15)	1.13 (1.11, 1.15)
SAS index score					
Tertile 1	3,591	513	1.00	1.00	1.00
Tertile 2	2,595	402	1.08 (0.94, 1.25)	1.16 (1.01, 1.34)	1.19 (1.02, 1.38)
Tertile 3	2,735	451	1.15 (1.01, 1.32)	1.30 (1.12, 1.49)	1.40 (1.21, 1.62)
P for trend			0.038	<0.001	<0.001
Every 1-unit increment			1.02 (1.01, 1.03)	1.03 (1.02, 1.05)	1.04 (1.03, 1.06)

[a]*N represents sample size for the non-OSA group or for the OSA group; OSA represents obstructive sleep apnea; CES-D score represents the Center for Epidemiologic Studies Depression Scale score; SAS index score represents index score from Zung's self-rating anxiety scale.*
[b]*Adjustment for age, sex, education, marital status, waist-hip ratio, leisure-time physical activity, smoking, alcohol drinking, fruit intake, vegetables intake, and dyslipidemia.*
[c]*Additional adjustment for body mass index.*

CES-D score was associated with a 13% increased risk of OSA (OR: 1.13, 95% CI: 1.11–1.15) and every 1-unit increment of SAS index score was associated with a 4% increased risk of OSA (OR: 1.04, 95% CI: 1.03–1.06) after adjustment for confounders; when comparing with the lowest tertile of the score, the highest tertile of the CES-D score and SAS index score were associated with 27% (95% CI: 1.10–1.47, $P_{-\text{trend}} < 0.001$) and 40% (95% CI: 1.21–1.62, $P_{-\text{trend}} < 0.001$) increased risk of OSA after considering potential confounders.

In sensitivity analysis, repeated analyses were conducted after excluding the subjects aged 60 years or above and similar consistent results were obtained (**Supplementary Tables 1**, **2**). We also did the analysis after excluding participants with cardiovascular disease, and similar results were obtained except for depression (**Supplementary Table 3**); however, when comparing the highest with lowest tertiles, CES-D score was associated with increased OSA risk and every 1-unit increment of the CES-D score was associated with 1.12-fold (95% CI: 1.10–1.14) risk of OSA after adjusting for potential confounders (**Supplementary Table 4**). In the sensitivity analyses by using OSA subitems as outcomes, depression, anxiety, adverse life events, and positive life events were all not associated with obesity and hypertension. However, depression and anxiety, especially their coexistence, were associated with an increased risk of snoring and daytime sleepiness; exposure to adverse life events was associated with a 34% increased risk of daytime sleepiness (**Supplementary Tables 5**–**8**).

DISCUSSION

The results from this study manifest that the presence of anxiety and depression was associated with an increased risk of OSA and the coexistence of depression and anxiety had a more significant adverse effect on OSA risk. Neither adverse life event nor positive life event was associated with OSA risk.

In this study, participants with anxiety were 2.60 times more likely to suffer from OSA than those without anxiety after adjustment for all potential confounders. This was consistent with the results from a lifestyle intervention that the persistence of anxiety was independently associated with elevated levels of sleep-disordered breathing (37). Moreover, we also observed that every 1-unit increment of SAS index score was associated with a 4% increased risk of OSA, indicating that the impact of anxious mood accumulation on OSA may be progressive. The possible mechanism may be due to that anxiety could influence several brain regions, including ventral medial prefrontal, cingulate, parietal, and insular cortices, and the uncus of the hippocampal formation, extending to the amygdala (38). These regions oversaw the regulation of respiratory control, fear emotion, cognition, sensory and motor action (38). Besides, anxiety-like behavior can cause stress, which in turn can raise the level of cortisol and then act on glucocorticoid (GC) receptors (39, 40). GC-induced neurotoxicity can damage the hippocampus, amygdala, and prefrontal cortex accompanying repeated episodes of apnea and anxiety (41). After a single GC exposure, hippocampal dendrites showed reversible damage, and repeated exposure may elicit injury. The hippocampal loss was also reported to be correlated with the severity of OSA (42). Both animal and human researches corroborated that physiological, psychological, and metabolic consequences of increased sympathetic nerve tone associated with anxiety and inflammatory mediators can contribute to the pathogenesis of OSA (39, 43). The Lifelines study with 54,326 participants has demonstrated that anxiety disorders were associated with higher serum C-reactive protein (CRP) levels after adjusting for all covariates (43). Persistent anxiety disrupted autonomic nervous system functions and provoked low-grade inflammation,

and pronounced pro-inflammatory states have also been directly linked to both anxiety and OSA (37).

Depression was observed to improve the risk of OSA in this study, which was consistent with results from a population-based longitudinal study among Taiwanese (18). Subjects might suffer from age-related diseases with aging, and the latter was reported to have a relationship with OSA (44–47). In this study, we yielded similar results that depression was associated with an increased risk of OSA after excluding subjects aged 60 years or more. The association of OSA risk with depression did not reach statistical significance after excluding participants with cardiovascular disease. This may be due to that most of the subjects with cardiovascular diseases aged more than 60 years old and only a few subjects left after excluding subjects with cardiovascular diseases. However, our study found that every 1-unit increment of CES-D score was associated with a 13% increased risk of OSA, indicating the even very mild symptom of depression could increase the risk of adverse health consequences. The possible effects of depression on OSA might be due to that depression can lead to notably difficulties falling asleep, frequent awakenings during the night and early morning awakenings, a shortened rapid eye movement latency as well as non-refreshing sleep (48). In addition, depression and anxiety could increase the risk of snoring and daytime sleepiness, which was consistent with previous studies (49–51). A population-based 10-year follow-up study found that anxiety and depression were the most important factors for predicting incidents of excessive daytime sleepiness (49). Gould et al. found that affective anxiety symptoms and depressive symptoms have independent associations with sleep disturbance (50). A Chinese cohort study of 0.5 million adults demonstrated the significant positive association between depression and daytime napping, as well as daytime dysfunction and snoring (51).

We found that the impact of both depression and anxiety exposure on OSA risk was much more significant than that of the single exposure. Although depression and anxiety have essentially been seen as distinct conditions, the two disorders were not mutually exclusive and often coexist to varying degrees in the same patient possibly due to the overlapped risk factors (33). In this study, nearly half of depressed participants suffered from anxiety simultaneously. Patients who have depression and anxiety comorbidity tend to have higher severity of illness and significantly greater impairment in work functioning, psychosocial functioning, and quality of life than patients not suffering from comorbidity (34).

Positive life event exposure was not observed to be related to the OSA risk, which was inconsistent with reports by Tripathi et al. (23). Studies have found that adverse life events could induce acute or chronic stress, which might lead to deregulation in the hypothalamo-pituitary axis and eventually accelerated the occurrence of OSA by increasing serum levels of cortisol and CRP (23). Vahtera et al. (52) found that exposure to adverse life events was strongly associated with sleep disturbances. However, no association between adverse life events and OSA risk was found in this study. This might be due to the limited number of adverse life events collected in our study, which might not well reflect the whole impact of multiple dimensional life events on OSA. However, the sensitivity analysis showed that exposure to adverse life events was associated with a 34% increased risk of daytime sleepiness, which indicated that adverse life events might impair nighttime sleep and leading to daytime sleepiness.

Given the significant discrepancy in life experience and physical functioning between middle-aged and elderly adults (53, 54), we excluded older adults aged more than 60 years for sensitivity analysis and obtained consistent results. Older people experienced retirement, relocation to more appropriate housing, and others; their lifestyles might be changed accordingly (54). Studies have demonstrated that exposure to adverse life events could have an especially erosive effect on older adults than younger and middle-aged adults (53). In addition, Geriatric syndrome can develop as the elderly age (55), and obstructive sleep apnea of geriatric patients was generally associated with sarcopenia, poor sleep quality, cognitive dysfunction, and nocturia different from the classic syndrome of obstructive sleep apnea of middle-age (56). Moreover, there are also many common risk factors between OSA and chronic diseases such as cardiovascular disease, the sensitivity analysis which excluded older adults aged more than 60 years or excluded subjects with cardiovascular disease could rule out potential bias caused by aging and other comorbidities. Our four sensitivity analyses implied that depression and anxiety were associated with the increased risk of snoring and daytime sleepiness but not obesity or hypertension. The effect of depression and anxiety on OSA was not mediated or confounded by obesity, which improved the reliability of this study greatly.

This study has several strengths. First, we used international standardized questionnaires to ascertain OSA, depression, and anxiety, which help to minimize information bias and benefit the comparisons with counterpart studies. Second, selection bias was minimized by using the multi-stage sampling method, which could to some degree make sure that participants in this study had good representativeness. Third, we adjusted as many as covariates to control the confounders using the multivariate model. Fourth, we performed several sensitivity analyses to examine the stability of our results, and the consistent results indicate the robustness of our results.

The limitations of this study are as follows. First, the prevalence of depression (1.49%) and anxiety (1.39%) in this study was lower than those in other studies which used the same instruments to assess depression and anxiety (16). Because of social stigma and the diverse nature of psychotic symptoms in China (57), the prevalence of depression and anxiety as obtained by a face-to-face interview in community surveys might be underestimated. Nevertheless, we found that OSA risk increased with the increment of the CES-D score and the SAS index score, indicating that the risk caused by depression and anxiety on OSA was credible to a large degree. Second, the diagnosis of OSA was based on Berlin Questionnaire, which was mostly used as a clinical screening test and epidemiological tool; we could not classify the severity of OSA due to the lack of polysomnography. Third, causal inference can not be

made due to the restriction of cross-sectional analysis, so it is essential to be alert to reverse causality. However, our results were comparable to other studies (18, 23, 33, 37), which indicating that to some degree our results were credible. In the coming future, we will solve these problems with a prospective longitudinal design and more precise measurements of exposure and outcome.

CONCLUSIONS

The results indicate that depression and anxiety, especially co-occurrence of both greatly, were associated with an increased risk of OSA. Neither adverse life events nor positive life events were associated with any risk of OSA. Screening for interventions to prevent and manage OSA should pay more attention to depression and anxiety.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be available from the corresponding author upon request. A proposal with description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests if someone requests data sharing.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of Guangdong Provincial People's Hospital and the Ethical Review Committee for Biomedical Research, School of Public Health, Sun Yat-sen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XL and HD conceived and designed the study. XD, MZ, JH, LL, and HL collected the data. XD analyzed the data. XD, MZ, and JH drafted the manuscript. LL, HL, WZ, JL, WC, HD, and XL reviewed and edited the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep Apnea in the general population: a systematic review. *Sleep Med Rev.* (2017) 34:70–81. doi: 10.1016/j.smrv.2016.07.002
2. Punjabi NM. The epidemiology of adult obstructive sleep Apnea. *Proc Am Thorac Soc.* (2008) 5:136–43. doi: 10.1513/pats.200709-155MG
3. Sunwoo JS, Hwangbo Y, Kim WJ, Chu MK, Yun CH, Yang KI. Prevalence, sleep characteristics, and comorbidities in a population at high risk for obstructive sleep apnea: a nationwide questionnaire study in South Korea. *PLoS ONE.* (2018) 13:e0193549. doi: 10.1371/journal.pone.0193549
4. Mirrakhimov AE, Sooronbaev T, Mirrakhimov EM. Prevalence of obstructive sleep apnea in Asian adults: a systematic review of the literature. *BMC Pulm Med.* (2013) 13:10. doi: 10.1186/1471-2466-13-10
5. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep Apnoea: a literature-based analysis. *Lancet Respir Med.* (2019) 7:687–98. doi: 10.1016/S2213-2600(19)30198-5
6. Garbarino S, Bardwell WA, Guglielmi O, Chiorri C, Bonanni E, Magnavita N. Association of anxiety and depression in obstructive sleep Apnea patients: a systematic review and meta-analysis. *Behav Sleep Med.* (2020) 18:35–57. doi: 10.1080/15402002.2018.1545649
7. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep Apnea in adults. *Jama.* (2004) 291:2013–6. doi: 10.1001/jama.291.16.2013
8. Gao C, Guo J, Gong T-T, Lv J-L, Li X-Y, Liu F-H, et al. Sleep duration/quality with health outcomes: an umbrella review of meta-analyses of prospective studies. *Front Med.* (2022) 8:813943. doi: 10.3389/fmed.2021.813943
9. Steardo L, de Filippis R, Carbone EA, Segura-Garcia C, Verkhratsky A, De Fazio P. Sleep disturbance in bipolar disorder: neuroglia and circadian rhythms. *Front Psychiatry.* (2019) 10:501. doi: 10.3389/fpsyt.2019.00501
10. Xu Z, Wu Y, Tai J, Feng G, Ge W, Zheng L, et al. Risk factors of obstructive sleep Apnea syndrome in children. *J Otolaryngol Head Neck Surg.* (2020) 49:11. doi: 10.1186/s40463-020-0404-1
11. Zhou X, Lu Q, Li S, Pu Z, Gao F, Zhou B. Risk factors associated with the severity of obstructive sleep Apnea syndrome among adults. *Sci Rep.* (2020) 10:13508. doi: 10.1038/s41598-020-70286-6
12. BaHammam AS, Kendzerska T, Gupta R, Ramasubramanian C, Neubauer DN, Narasimhan M, et al. Comorbid depression in obstructive sleep Apnea: an under-recognized association. *Sleep Breath.* (2016) 20:447–56. doi: 10.1007/s11325-015-1223-x
13. Andrews JG, Oei TP. The roles of depression and anxiety in the understanding and treatment of obstructive sleep Apnea syndrome. *Clin Psychol Rev.* (2004) 24:1031–49. doi: 10.1016/j.cpr.2004.08.002
14. Okada I, Miyata S, Iwamoto K, Fujishiro H, Noda A, Ozaki N. Prevalence of obstructive sleep Apnea as assessed by polysomnography

in psychiatric patients with sleep-related problems. *Sleep Breath.* (2022). doi: 10.1007/s11325-022-02566-6. [Epub ahead of print].
15. Rezaeitalab F, Moharrari F, Saberi S, Asadpour H, Rezaeetalab F. The correlation of anxiety and depression with obstructive sleep Apnea syndrome. *J Res Med Sci.* (2014) 19:205–10.
16. Stubbs B, Vancampfort D, Veronese N, Solmi M, Gaughran F, Manu P, et al. The prevalence and predictors of obstructive sleep apnea in major depressive disorder, bipolar disorder and schizophrenia: a systematic review and meta-analysis. *J Affect Disord.* (2016) 197:259–67. doi: 10.1016/j.jad.2016.02.060
17. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med.* (2013) 11:200. doi: 10.1186/1741-7015-11-200
18. Pan M-L, Tsao H-M, Hsu C-C, Wu K-M, Hsu T-S, Wu Y-T, et al. Bidirectional association between obstructive sleep apnea and depression: a population-based longitudinal study. *Medicine.* (2016) 95:e4833-e. doi: 10.1097/MD.0000000000004833
19. Weiner CL, Meredith Elkins R, Pincus D, Comer J. Anxiety sensitivity and sleep-related problems in anxious youth. *J Anxiety Disord.* (2015) 32:66–72. doi: 10.1016/j.janxdis.2015.03.009
20. Tiller JWG. Depression and anxiety. *Med J Aust.* (2013) 199:S28–31. doi: 10.5694/mja12.10628
21. Olaya Guzmán B, Essau CA. Life events. In: Goldstein S, Naglieri JA, editors. Encyclopedia of Child Behavior and Development. Boston, MA: Springer (2011) 885–7. doi: 10.1007/978-0-387-79061-9_1656
22. Karatzias T, Yan E, Jowett S. Adverse life events and health: a population study in Hong Kong. *J Psychosom Res.* (2015) 78:173–7. doi: 10.1016/j.jpsychores.2014.11.024
23. Tripathi A, Bagchi S, Singh J, Pandey P, Tripathi S, Gupta NK. Lifestyle and occupational stress: a potential risk factor for obstructive sleep apnea in nonobese male subjects. *J Prosthodont.* (2018) 27:716–21. doi: 10.1111/jopr.12627
24. Deng H, Guo P, Zheng M, Huang J, Xue Y, Zhan X, et al. Epidemiological characteristics of atrial fibrillation in Southern China: results from the Guangzhou heart study. *Sci Rep.* (2018) 8:17829. doi: 10.1038/s41598-018-35928-w
25. Duan X, Zheng M, He S, Lao L, Huang J, Zhao W, et al. Association between physical activity and risk of obstructive sleep apnea. *Sleep Breath.* (2021) 25:1925-34. doi: 10.1007/s11325-021-02318-y
26. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* (1999) 131:485–91. doi: 10.7326/0003-4819-131-7-199910050-00002
27. Tan A, Yin JD, Tan LW, van Dam RM, Cheung YY, Lee CH. Using the Berlin questionnaire to predict obstructive sleep apnea in the general population. *J Clin Sleep Med.* (2017) 13:427–32. doi: 10.5664/jcsm.6496
28. Radloff LS. The Ces-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas.* (1977) 1:385–401. doi: 10.1177/014662167700100306
29. Zung WW. A rating instrument for anxiety disorders. *Psychosomatics.* (1971) 12:371–9. doi: 10.1016/S0033-3182(71)71479-0
30. Stahl D, Sum CF, Lum SS, Liow PH, Chan YH, Verma S, et al. Screening for depressive symptoms: validation of the center for epidemiologic studies depression scale (Ces-D) in a multiethnic group of patients with diabetes in Singapore. *Diabetes Care.* (2008) 31:1118–9. doi: 10.2337/dc07-2019
31. Moon JR, Huh J, Song J, Kang IS, Park SW, Chang SA, et al. The center for epidemiologic studies depression scale is an adequate screening instrument for depression and anxiety disorder in adults with congential heart disease. *Health Qual Life Outcomes.* (2017) 15:176. doi: 10.1186/s12955-017-0747-0
32. Dunstan DA, Scott N, Todd AK. Screening for anxiety and depression: reassessing the utility of the zung scales. *BMC Psychiatry.* (2017) 17:329. doi: 10.1186/s12888-017-1489-6
33. Gorman JM. Comorbid depression and anxiety spectrum disorders. *Depress Anxiety.* (1996) 4:160–8. doi: 10.1002/(SICI)1520-6394(1996)4:4<160::AID-DA2>3.0.CO;2-J
34. Hirschfeld RMA. The comorbidity of major depression and anxiety disorders: recognition and management in primary care. *Prim Care Companion J Clin Psychiatry.* (2001) 3:244–54. doi: 10.4088/PCC.v03n0609
35. Kornerup H, Osler M, Boysen G, Barefoot J, Schnohr P, Prescott E. Major life events increase the risk of stroke but not of myocardial infarction: results from the Copenhagen city heart study. *Eur J Cardiovasc Prev Rehabil.* (2010) 17:113–8. doi: 10.1097/HJR.0b013e3283359c18
36. Salleh MR. Life event, stress and illness. *Malays J Med Sci.* (2008) 15:9–18.
37. Lehto SM, Sahlman J, Soini EJ, Gylling H, Vanninen E, Seppä J, et al. The association between anxiety and the degree of illness in mild obstructive sleep apnoea. *Clin Respir J.* (2013) 7:197–203. doi: 10.1111/j.1752-699X.2012.00304.x
38. Macey KE, Macey PM, Woo MA, Henderson LA, Frysinger RC, Harper RK, et al. Inspiratory loading elicits aberrant FMRI signal changes in obstructive sleep apnea. *Respir Physiol Neurobiol.* (2006) 151:44–60. doi: 10.1016/j.resp.2005.05.024
39. Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci.* (1990) 10:2897–902. doi: 10.1523/JNEUROSCI.10-09-02897.1990
40. Kumar R, Macey PM, Cross RL, Woo MA, Yan-Go FL, Harper RM. Neural alterations associated with anxiety symptoms in obstructive sleep apnea syndrome. *Depress Anxiety.* (2009) 26:480–91. doi: 10.1002/da.20531
41. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry.* (2003) 54:338–52. doi: 10.1016/S0006-3223(03)00347-0
42. Owen JE, BenediktsdÓttir B, Gislason T, Robinson SR. Neuropathological investigation of cell layer thickness and myelination in the hippocampus of people with obstructive sleep apnea. *Sleep.* (2019) 42:1–13. doi: 10.1093/sleep/zsy199
43. Naudé PJW, Roest AM, Stein DJ, de Jonge P, Doornbos B. Anxiety disorders and crp in a population cohort study with 54,326 participants: the lifelines study. *World J Biol Psychiatry.* (2018) 19:461–70. doi: 10.1080/15622975.2018.1433325
44. Baril AA, Carrier J, Lafreniere A, Warby S, Poirier J, Osorio RS, et al. Biomarkers of dementia in obstructive sleep apnea. *Sleep Med Rev.* (2018) 42:139–48. doi: 10.1016/j.smrv.2018.08.001
45. Khan AM, Ashizawa S, Hlebowicz V, Appel DW. Anemia of aging and obstructive sleep apnea. *Sleep Breath.* (2011) 15:29–34. doi: 10.1007/s11325-010-0326-7
46. Park S-Y, Nam H-W. Aging and obstructive sleep apnea syndrome. *J Korean Sleep Res Soc.* (2011) 8:1–3. doi: 10.13078/jksrs.11001
47. You H, Teng M, Gao CX, Yang B, Hu S, Wang T, et al. Construction of a nomogram for predicting survival in elderly patients with lung adenocarcinoma: a retrospective cohort study. *Front Med.* (2021) 8:680679. doi: 10.3389/fmed.2021.680679
48. Schröder CM, O'Hara R. Depression and obstructive sleep apnea (Osa). *Ann Gen Psychiatry.* (2005) 4:13. doi: 10.1186/1744-859X-4-13
49. Theorell-Haglöw J, Åkerstedt T, Schwarz J, Lindberg E. Predictors for development of excessive daytime sleepiness in women: a population-based 10-year follow-up. *Sleep.* (2015) 38:1995–2003. doi: 10.5665/sleep.5258
50. Gould CE, Spira AP, Liou-Johnson V, Cassidy-Eagle E, Kawai M, Mashal N, et al. Association of anxiety symptom clusters with sleep quality and daytime sleepiness. *J Gerontol Series B Psychol Sci Soc Sci.* (2018) 73:413–20. doi: 10.1093/geronb/gbx020
51. Liu Y, Peng T, Zhang S, Tang K. The relationship between depression, daytime napping, daytime dysfunction, and snoring in 05 million Chinese populations: exploring the effects of socio-economic status and age. *BMC Public Health.* (2018) 18:759. doi: 10.1186/s12889-018-5629-9
52. Vahtera J, Kivimäki M, Hublin C, Korkeila K, Suominen S, Paunio T, et al. Liability to anxiety and severe life events as predictors of new-onset sleep disturbances. *Sleep.* (2007) 30:1537–46. doi: 10.1093/sleep/30.11.1537
53. Cairney J, Krause N. Negative life events and age-related decline in mastery: are older adults more vulnerable to the control-eroding effect of stress? *J Gerontol Series B.* (2008) 63:S162–70. doi: 10.1093/geronb/63.3.S162
54. World Health Organization. *Aging and Health*. (2018). Available online at: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (accessed October 4, 2021).
55. World Health O. *Integrated Care for Older People: Guidelines on Community-Level Interventions to Manage Declines in Intrinsic Capacity*. Geneva: World Health Organization (2017).
56. Morley JE, Sanford A, Bourey R. Sleep apnea: a geriatric syndrome. *J Am Med Dir Assoc.* (2017) 18:899–904. doi: 10.1016/j.jamda.2017.08.020

57. Huang Y, Wang Y, Wang H, Liu Z, Yu X, Yan J, et al. Prevalence of mental disorders in China: a cross-sectional epidemiological study. *Lancet Psychiatry*. (2019) 6:211–24. doi: 10.1016/S2215-0366(18)30511-X

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A New Berlin Questionnaire Simplified by Machine Learning Techniques in a Population of Italian Healthcare Workers to Highlight the Suspicion of Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) syndrome is a condition characterized by the presence of repeated complete or partial collapse of the upper airways during sleep associated with episodes of intermittent hypoxia, leading to fragmentation of sleep, sympathetic nervous system activation, and oxidative stress. To date, one of the major aims of research is to find out a simplified non-invasive screening system for this still underdiagnosed disease. The Berlin questionnaire (BQ) is the most widely used questionnaire for OSA and is a beneficial screening tool devised to select subjects with a high likelihood of having OSA. We administered the original ten-question Berlin questionnaire, enriched with a set of questions purposely prepared by our team and completing the socio-demographic, clinical, and anamnestic picture, to a sample of Italian professional nurses in order to investigate the possible impact of OSA disease on healthcare systems. According to the Berlin questionnaire, respondents were categorized as high-risk and low-risk of having OSA. For both risk groups, baseline characteristics, work information, clinical factors, and symptoms were assessed. Anthropometric data, work information, health status, and symptoms were significantly different between OSA high-risk and low-risk groups. Through supervised feature selection and Machine Learning, we also reduced the original BQ to a very limited set of items which seem capable of reproducing the outcome of the full BQ: this reduced group of questions may be useful to determine the risk of sleep apnea in screening cases where questionnaire compilation time must be kept as short as possible.

Keywords: obstructive sleep apnea (OSA), Berlin questionnaire (BQ), risk factors, machine learning, simplified berlin questionnaire, screening test

INTRODUCTION

Obstructive Sleep Apnea (OSA) is a syndrome characterized by partial or complete obstruction of the upper airways during sleep. This phenomenon, in turn, causes numerous and repetitive arousal from sleep to restore airways, leading to disrupted sleep, daytime hypersomnolence, and sympathetic activation. The obstruction of the airways may also lead to blood oxygen desaturation (1) during sleep, and cardiovascular lesions (2). OSA is associated with numerous conditions including stroke, hypertension and death (3, 4). These comorbidities are particularly evident in obese patients, and varying in severity according to gender and age.

The prevalence of OSA is highly different in the general population, ranging from 9 to 38%, with older age, male gender, and obesity as known risk factors (1, 5, 6). In advanced age groups, prevalence can even increase to 84% (1).

According to a worldwide epidemiological prevalence study (5) there are an estimated 936 million OSAS patients aged 30–69 years with mild-moderate OSA and 425 million patients aged 30–69 years with severe OSA who need Continuous Positive Airway Pressure (CPAP) treatment. In Italy, one study estimated the prevalence of moderate-to-severe OSA in 27% of the general population, with an overall prevalence of mild and moderate-to-severe OSA of more than 24 million people in the ages 15–74 years (54% adult population), while from a practical perspective, Italian NHS physicians diagnosed only 460,000 moderate-to-severe patients (4% of estimated prevalence) and 230,000 patients were treated (2% of estimated prevalence), highlighting a substantial gap between diagnosis and treatment. Considering that each patient is diagnosed many years after the onset of the disease, the direct and indirect healthcare costs determine a significant burden for the National Health System (NHS), which affects every single citizen. Prevention and early diagnosis are the only ways to achieve cost containment and improved quality of life.

Although studies have considerably increased in recent years, to date OSA is still a highly underdiagnosed disease. The gold standard for OSA diagnosis is nocturnal polysomnography (PSG) in the sleep laboratory. However, since this is not well workable for large numbers of patients, the Home Sleep Test (HST) is also an accepted validated ambulatory diagnostic method. Among non-invasive screening tools for OSA diagnosis in the general population, the Berlin questionnaire (BQ) (7) is the most widely used to define patients at risk for OSA. It was employed for the first time in the US: it contains ten questions related to risk factors and symptoms of OSA with the purpose of selecting high-risk OSA patients that may undergo polysomnography and increase the number of diagnosed patients.

The main purpose of this study was to find possible risk factors that are best correlated with being at high risk for OSA—according to the BQ—in professional nurses in order to investigate the possible impact of OSA on healthcare systems by considering one of the most important categories in health and assistance fields. We also assessed the capabilities of a reduced BQ of predicting a high-risk OSA group according to the result of the standard BQ. For this purpose, we used techniques related to supervised feature selection and Machine Learning.

METHODS

Design

From May 2020 to September 2021 a cross sectional, multicenter study was conducted among professional nurses. Four hundred and five Italian subjects agreed to participate in the study. No eligible criteria were applied to the volunteers. The survey was conducted by means of an anonymous electronic questionnaire distributed on a voluntary basis. All subjects were asked to answer the BQ (7) and an additional set of 38 questions including items about baseline socio-demographic characteristics, work information, clinical status, and symptoms category. In particular, socio-demographic characteristics included gender, age, BMI, smoking, and neck circumference. For work information, we intended years of work experience, working hours, work shift, work shift regularity. For health status, we assessed the presence of arrhythmias, sleep disturbances, hypo/hyperthyroidism, anxiety, hypertension, transient ischemic attack or stroke, diabetes mellitus, chronic obstructive pulmonary disease (COPD), asthma, anxiety, depression, frequent confusion or agitation, craniofacial morphological alterations, alcohol and drug abuse. Symptoms category included difficulty staying awake during an activity, difficulty concentrating, difficulty in expressing oneself, use of stimulants, interference with work, interference with social relationships, slow reactions and difficulty keeping attention up, difficulty in paying attention to several tasks at once, striving not to make mistakes, and need to doze off.

The Berlin Questionnaire

The BQ (7) is the most widely used non-invasive screening tool for OSA diagnosis devised to identify subjects with a high likelihood of having OSA based on the frequency, loudness, disturbance and breathing interruptions of nocturnal snoring, on daytime sleepiness, and on the presence of high blood pressure/obesity. The BQ consists of three categories of questions related to the risk of having sleep apneas. Patients can be classified into high-risk or low-risk based on their responses to the individual items and their overall scores in the symptom categories. Category 1 contains five items and incorporates questions about snoring; Category 2 contains three items investigating daytime somnolence; Category 3 contains one item assessing hypertension and information about the Body Mass Index (BMI). Scores from the first two categories were positive if the responses indicated frequent symptoms, such as more than 3–4 times per week, whereas the score from the third category was positive if there was a history of hypertension or a BMI > 30 Kg/m^2 (7). The overall score was determined from the response to the three categories. Patients were scored as being at OSA high-risk when they had a positive score on two or more categories, else they were considered as being at low-risk (7).

Statistical Analysis

The answers of all respondents to the BQ were analyzed using descriptive statistics. To identify items associated with being at high-risk of OSA, baseline characteristics, working information, health status, and symptoms category were separately studied in the two OSA risk groups. Continuous variables were summarized by mean and standard deviation (SD) and categorical variables by frequencies and percentages. Kruskal Wallis test and Mann-Whitney U-test were used for assessing difference between high vs. low risk of having OSA. Contingency tables were also analyzed, and chi-square and Fisher's exact tests were carried out to ascertain the presence of relations between the two OSA risk groups. A p-value < 0.05 was considered statistically significant. BQ scoring and statistical analyses were conducted for all qualitative and quantitative variables using Matlab software.

Predictive Value

Calculating group statistics is important to establish the statistical relevance of variables in a diagnostic problem so that risk factors or relationships with comorbidities can be assessed. Nonetheless, it is well known (8–10) that relevance is not a synonym for discriminant power, the latter being most useful in classification and prediction: significant variables in a statistical model do not guarantee prediction performance, and non-significant attributes might reveal predictive. For this reason, we decided to also study both Berlin and our questionnaires from the point of view of their prediction capabilities, by techniques related to supervised feature selection and Machine Learning.

It must be noted that prediction in this case is not related to actual OSA diagnosis, because the only data on which we worked is the response to the questionnaires: therefore, the target variable was simply the high risk of being affected by OSA according to the result of the BQ. As the latter is not a perfect test and can give FP and FN (11, 12), our conclusions are valid within the same limits.

XGBoost (13) in python was chosen as the classifier model. A relevant reason was that the responses to the questionnaires unfortunately had a certain number of missing answers and out-of-the-box XGBoost deals quite satisfactorily with missing data thanks to the algorithm called "sparsity-aware split finding": therefore no explicit imputation mechanism (14) had to be implemented. Moreover, XGBoost is fast and reliable, as also witnessed by frequent wins on Kaggle competitions with this classifier[1].

After converting the ordered response scales to numeric, the following analysis were performed. First, the Fisher score (15) was calculated on each variable. This index measures the ratio between the inter-class distance and the total intra-class variance, $F = (\bar{x}_1 - \bar{x}_2)^2 / \left(\sigma_1^2 + \sigma_2^2\right)$ where $\bar{x}_j$ and σ_j^2 are the mean and the variance of a variable for class j. F is a parameter clearly related to the discrimination power of each attribute. Similarly, the area under the ROC (Receiver Operating Characteristics) curve (AUROC) for each variable was computed, directly measuring its predictive power. The Fisher score and the AUCROC have similar meaning but they are independent, so they complement each other. However, though these two figures of merit are important because they assess the discriminant power of each feature individually, nonetheless they only partially characterize the dataset, as they neglect the combination of features, which means evaluating two or more features together: it often happens that the scores for single features is low but their combination is strongly discriminant, so some mechanism of feature group scoring assessment is necessary. For this purpose, we employed the backward Sequential Feature Selector (bSSF) from scikit-learn[2], with XGBoost as the scorer, to build a plot of AUROC vs. the cardinality of the optimal subset of features, from which we could infer interesting conclusions on the prediction power of feature combinations. We finally performed some *ad-hoc* calculations on particular subsets of features, which we considered interesting.

The feature selection procedure based on bSSF was built as follows. We started from the whole dataset of feature vectors containing n attributes. The dataset was randomly split into two parts, one for feature selection ($P1$) and the other for quality assessment ($P2$) of each subset of selected features. Proportions between selection and quality assessment datasets were arbitrarily set to 70 and 30% of the whole dataset, respectively.

At the m-th step (m going from 0 to n – 2), feature selection by bSSF, from $n - m$ to $n - m - 1$ features, was applied on the $P1$ dataset, followed by prediction quality measurement on the selected features. Therefore, each iteration took as its input the dataset containing the "best" features, as selected by the preceding iteration. At each iteration (with fixed m), instead of performing feature selection just once, we preferred to study the robustness of the selected subset of features, by applying bSSF a given number of times (typically 100), each time recording which feature was considered as the least important (downvoted). As the $P1$ vectors were shuffled before bSSF application, we had a certain variability on the selected features and, at the end of this internal loop, we removed the feature that had been downvoted more often.

At this point, with a robust subset of features, we calculated the AUROC (arbitrarily with 50 iterations) on the quality assessment dataset $P2$ and assigned the average AUROC (with an uncertainty calculated as the standard deviation) to the feature set.

The loop on m then continued, until there was just one feature in the dataset.

The results of this process were:

- A graph showing AUROC as a function of the number of selected features.
- A list of features, ordered by importance (considering that the least predictive variables, in a multivariate framework, were discarded first).

The whole procedure was repeated many times, each time modifying the initial split between $P1$ and $P2$, so that the influence of random splitting might be judged.

Ethical Considerations

The ethical aspects of the study were set out in the questionnaire presentation, which was designed in accordance with the

[1]https://github.com/dmlc/xgboost/tree/master/demo#machine-learning-challenge-winning-solutions

[2]https://scikit-learn.org/

principles of the Italian data protection authority (DPA). It was emphasized that participation was voluntary and that the participant could refuse participation in the protocol whenever he or she wished. Those who were interested in participating were given an informed consent form, which recalled the voluntary nature of participation, as well as the confidentiality and anonymous nature of the information.

RESULTS

Sample Demographics

Out of 405 people to whom the BQ was administered, the response rate was 95% ($n = 387$). Women were 292 (75% of respondents) and 184 (47.5%) were over 40 years old. The median BMI was 25.4 Kg/m^2 (range 18–46 Kg/m^2).

Berlin Questionnaire Score and Metrics

The BQ was evaluated for all respondents and data were collected (**Table 1**). According to the questionnaire, the subjects were stratified into low vs. high OSA risk groups by means of a score calculation. Among all subjects, 76 (20%) were categorized as high likelihood of having OSA. **Table 2** shows the BQ answer counts subdivided between low and high Berlin score subjects.

Respondents were also asked if they had already been diagnosed for OSA through a gold standard test (e.g., polysomnography). Among the subjects identified as high-risk, 24% ($n = 18$, 5% of the complete sample) had already been diagnosed with OSA whereas 76% ($n = 58$, 15% of the sample) had not undergone any diagnostic test. Among the subjects categorized as low-risk for OSA, 1% ($n = 2$), had received a diagnosis of OSA (false negatives) whereas 99% had not been tested.

As reported in the literature (16), the dominant symptom of OSA is snoring with a prevalence of 75–90%. Accordingly, in our sample the high-risk OSA group had a significantly larger proportion of respondents reporting frequent snoring (95%) compared to the low-risk group (21%). Nocturnal snoring also increased in frequency and loudness in high-risk OSA cases compared with low-risk, and this difference was statistically significant ($p < 0.001$ for both). Specifically, 28% of the high-risk group report snoring very loudly compared with 3% of the low-risk group. The percentage of those who snore every night also increases from 10 to 63% in the high-risk group.

Nocturnal symptoms may also include apnea and dyspnea generally observed by bed partners and this was confirmed by the bothersome snoring percentage that passed from 22% in the low-risk to 80% in the high-risk group. These differences were statistically significant ($p < 0.001$).

The high-risk group also reported more breathing interruptions than the low-risk subjects ($p < 0.001$).

Fatigue, somnolence at awakening and during daytime are also symptoms significantly present in the high-risk group compared to the low risk group ($p = 0.0018$ and 0.0029, respectively). The percentage of those who reported falling asleep while driving a vehicle was also higher in the high-risk group (24%) than for the low-risk subjects (9%), with a statistically significant difference ($p < 0.001$).

This significance is also present in the frequency of episodes ($p < 0.001$).

High blood pressure was also reported in half of the high risk subjects (51%) compared with 5% of the low risk ones, and this difference was statistically significant.

Socio-demographic characteristics, work information, clinical factors, and symptoms category were compared between the two OSA risk groups. The results are summarized in **Table 3**.

Predictive Value of the Berlin Questionnaire Variables

Fisher Indices and AUROC for Single Variables

The ten variables from the BQ plus BMI were considered. The most discriminant variables were the four related to snoring (B1 to B4 in **Table 1**) with B1 being the most important in absolute (AUROC = 0.88, $F = 1.9$) and snoring loudness B2 being the least predictive. As to the two variables with relatively objective measurement, i.e., having high blood pressure, B10, and the body mass index (computed from the subject physical data), the former had high predictivity (AUROC = 0.74, $F = 0.80$) while the latter showed lower discriminant power (AUROC = 0.64, $F = 0.03$). This result was quite surprising if compared with the one reported in (18) where BMI is found to be quite a strong predictor.

Sequential Feature Selection

The typical relationship between the number of features and AUROC we obtained by the bSSF procedure is shown in **Figure 1**. Repeating the run with different random splits of $P1$ vs. $P2$ partitioning did not appreciably change the result, with AUROC for sets ≥ 3 features always attaining values near 1. Reaching so high AUROC with the full set of variables, of course, has no particular meaning because the target variable (high risk of OSA) is obtained from the BQ variables (the answers to the questions), so there exists a well-established *a priori* relationship between the variables and the target, which the classifier finds. On the other hand, what is surprising is the fact that a subset of three variables is capable of predictive power comparable to the whole questionnaire.

The subset of three variables was reasonably robust and did not depend too much on the particular dataset split; after about 60 runs, the subset was found to contain the variables computed from B10 (selected at every run), B1 (present in 73% of the "best" feature subsets), B6 (presence in 38%), B7 (37%), B3 (25%), B4 (2%). We remark that hypertension B10 is always among the most useful features [which was already known from the single-variable calculations; this result confirms what was found in (18)]. Considering now the remaining five features, three concern snoring (B1, the most voted after B10; then B3 and B4) while two concern feeling tired in daytime, either at wake-up or along the day (B6 and B7), with similar presence in the subsets. By calculating the (normalized) co-occurrence matrix of these five

TABLE 1 | The Berlin questionnaire evaluated for all respondents.

		N	%
B1	**Do you snore?**		
	No	166	43
	Do not know	66	17
	Yes	155	40
B2	**If you answered "yes"**		
	Slightly louder than breathing	249	64
	As loud as talking	13	3
	Louder than talking	23	6
	Very loud—it can be heard from adjacent rooms	29	7
	Missing	73	20
B3	**How often do you snore?**		
	Never or almost never	174	45
	1–2 times a month	51	13
	1–2 times a week	50	13
	3–4 times a week	33	9
	Every day	79	20
B4	**Has your snoring ever bothered other people?**		
	No	181	47
	Do not know	77	20
	Yes	129	33
B5	**Has anyone noticed that you stop breathing during your sleep?**		
	Never or almost never	340	88
	1–2 times a month	13	3
	1–2 times a week	14	4
	3–4 times a week	11	3
	Every day	9	2
B6	**How often do you feel tired or fatigued after your sleep?**		
	Never or almost never	125	32
	1–2 times a month	82	21
	1–2 times a week	77	20
	3–4 times a week	39	10
	Every day	64	17
B7	**During your waking time, do you feel tired, fatigued or not up to par?**		
	Never or almost never	84	22
	1–2 times a month	88	23
	1–2 times a week	99	25
	3–4 times a week	50	13
	Every day	66	17
B8	**Have you ever nodded off or fallen asleep while driving a vehicle?**		
	No	342	88
	Do not know	0	0
	Yes	45	12
B9	**How often does this occur?**		
	Never or almost never	249	64
	1–2 times a month	22	6
	1–2 times a week	10	2
	3–4 times a week	3	1
	Every day	3	1
	Missing	100	26
B10	**Do you have high blood pressure?**		
	No	317	82
	Do not know	15	4
	Yes	55	14

TABLE 2 | Berlin questionnaire items between low and high Berlin score (low vs. high OSA risk groups).

		Low score ($n = 311$) *N* (%)	High score ($n = 76$) *N* (%)	*p*-value
B1	**Do you snore?**			<0.001***
	No	164 (53%)	2 (3%)	
	Yes	64 (21%)	72 (95%)	
	Do not know	83 (27%)	2 (3%)	
B2	**If you answered "yes"**			<0.001***
	Slightly louder than breathing	213 (68%)	35 (46%)	
	As loud as talking	5 (2%)	8 (11%)	
	Louder than talking	11 (4%)	12 (16%)	
	Very loud—it can be heard from adjacent rooms	8 (3%)	21 (28%)	
	missing	74 (24%)	0	
B3	**How often do you snore?**			<0.001***
	Never or almost never	173 (56%)	1 (1%)	
	1–2 times a month	46 (15%)	5 (7%)	
	1–2 times a week	41 (13%)	9 (12%)	
	3–4 times a week	20 (6%)	13 (17%)	
	Every day	31 (10%)	48 (63%)	
B4	**Has your snoring ever bothered other people?**			<0.001***
	No	172 (55%)	9 (12%)	
	Yes	68 (22%)	61 (80%)	
	Do not know	71 (23%)	6 (8%)	
B5	**Has anyone noticed that you stop breathing during your sleep?**			<0.001***
	Never or almost never	299 (96%)	41 (54%)	
	1–2 times a month	3 (1%)	10 (13%)	
	1–2 times a week	3 (1%)	11 (14%)	
	3–4 times a week	3 (1%)	8 (11%)	
	Every day	3 (1%)	6 (8%)	
B6	**How often do you feel tired or fatigued after your sleep?**			0.0018**
	Never or almost never	117 (38%)	8 (11%)	
	1–2 times a month	73 (23%)	9 (12%)	
	1–2 times a week	68 (22%)	9 (12%)	
	3–4 times a week	23 (7%)	16 (21%)	
	Every day	30 (10%)	34 (45%)	
B7	**During your waking time, do you feel tired, fatigued or not up to par?**			0.0029**
	Never or almost never	76 (24%)	8 (11%)	
	1–2 times a month	82 (26%)	6 (8%)	
	1–2 times a week	88 (28%)	11 (14%)	
	3–4 times a week	33 (11%)	17 (22%)	
	Every day	32 (10%)	34 (45%)	
B8	**Have you ever nodded off or fallen asleep while driving a vehicle?**			<0.001***
	No	284 (91%)	58 (76%)	
	Yes	27 (9%)	18 (24%)	
B9	**How often does this occur?**			<0.001***
	Never or almost never	212 (68%)	37 (49%)	
	1–2 times a month	15 (5%)	7 (9%)	
	1–2 times a week	5 (2%)	5 (7%)	
	3–4 times a week	1 (0%)	2 (3%)	
	Every day	0	3 (4%)	
	missing	78 (25%)	22 (29%)	
B10	**Do you have high blood pressure?**			<0.001***
	No	284 (91%)	33 (43%)	
	Yes	16 (5%)	39 (51%)	
	Do not know	11 (4%)	4 (5%)	

$^{**}p < 0.01$; $^{***}p < 0.001$.

A p-value < 0.05 was considered statistically significant.

TABLE 3 | Baseline characteristics of nurses between low and high Berlin scores (low vs. high OSA risk groups).

Items	Low score ($n = 311$) *N* (%)	High score ($n = 76$) *N* (%)	*p*-value
Anamnesis factors			
Q1 Gender			<0.001***
Female	247 (79%)	46 (61%)	
Male	64 (21%)	30 (39%)	
Q2 Age (Y)			0.0011**
21–30	103 (33%)	12 (16%)	
31–40	75 (24%)	13 (17%)	
41–50	68 (22%)	32 (42%)	
51–60	62 (20%)	16 (21%)	
>61	3 (1%)	3 (4%)	
Q3 BMI group (Kg/m^2)			<0.001***
Underweight < 18.5	6 (2%)	2 (3%)	
Normal weight 18.5–24.9	179 (58%)	25 (33%)	
Overweight 25–29.9	73 (23%)	27 (36%)	
Obese ≥ 30	53 (17%)	22 (29%)	
Q4 Smoking			0.946
Yes	81 (26%)	23 (30%)	
No	190 (61%)	39 (51%)	
Ex-smoker	40 (135)	14 (18%)	
Q5 Neck circumference (cm)			0.834
<43 men/41 women	135 (43%)	29 (38%)	
≥43 men/41 women	18 (6%)	11 (14%)	
Unknown	158 (51%)	36 (47%)	
Working information			
Q6 Profession			0.039*
Nurse	282 (91%)	63 (83%)	
Coordinator	22 (7%)	5 (7%)	
Executive	1 (0%)	6 (8%)	
Other	6 (2%)	2 (3%)	
Q7 Instruction level			0.049*
Regional Diploma	61 (20%)	24 (32%)	
University Diploma	20 (6%)	7 (9%)	
Bachelor's degree	167 (54%)	31 (41%)	
Master degree	34 (11%)	8 (11%)	
Post-graduate	29 (9%)	6 (8%)	
Q8 Work experience (Y):			0.0072**
1–5	118 (38%)	12 (16%)	
6–10	32 (10%)	15 (20%)	
11-15	29 (9%)	2 (0%)	
16–20	30 (8%)	13 (17%)	
21–25	27 (12%)	15 (20%)	
26–30	37 (10%)	8 (10%)	
>31	38 (12%)	11 (14%)	
Q9 Working hours			0.325
Full-time	284 (91%)	72 (95%)	
Part-time	27 (9%)	4 (5%)	
Q10 Work shift			0.758
Daily shift only	129 (41%)	33 (43%)	
24 h shift	182 (57%)	43 (57%)	
Q11 Work shift regularity			0.277
Yes	193 (62%)	42 (55%)	
No	118 (38%)	34 (45%)	

(Continued)

TABLE 3 | Continued

Items	Low score ($n = 311$) *N* (%)	High score ($n = 76$) *N* (%)	*p*-value
Clinical factors			
Q12 Previous OSA diagnosis			<0.001***
Yes	2 (1%)	18 (24%)	
No	309 (99%)	58 (76%)	
Q13 Hypo/hyperthyroidism			<0.001***
No	265 (85%)	60 (79%)	
Yes	46 (15%)	16 (21%)	
Q14 Arrhythmias			<0.001***
No	272 (87%)	48 (63%)	
Yes	39 (13%)	28 (37%)	
Q15 Transient ischemic attack or stroke			0.0013**
No	310 (100%)	71 (93%)	
Yes	1 (0%)	5 (7%)	
Q16 Diabetes mellitus			<0.001***
No	305 (98%)	65 (86%)	
Yes	6 (2%)	11 (14%)	
Q17 Presence of cerebrovascular diseases			0.022*
No	309 (99%)	73 (96%)	
Yes	2 (1%)	3 (4%)	
Q18 Anxiety			0.0014**
No	207 (66%)	35 (46%)	
Yes	104 (33%)	41 (54%)	
Q19 Sleep disorders			<0.001***
No	239 (77%)	38 (50%)	
Yes	72 (23%)	36 (50%)	
Q20 Chronic obstructive pulmonary disease (COPD)			<0.001***
No	310 (100%)	70 (92%)	
Yes	1 (0%)	6 (8%)	
Q21 Asthma			0.0018**
No	291 (94%)	58 (76%)	
Yes	30 (6%)	18 (24%)	
Q22 Frequent confusion or agitation			0.022*
No	303 (97%)	68 (89%)	
Yes	8 (3%)	8 (11%)	
Q23 Alcohol abuse			0.022**
No	308 (99%)	71 (93%)	
Yes	3 (1%)	5 (7%)	
Q24 Drug abuse			0.0061*
No	307 (99%)	71 (93%)	
Yes	4 (1%)	5 (7%)	
Q25 Depression			0.0082*
No	280 (90%)	60 (79%)	
Yes	31 (10%)	16 (21%)	
Q26 Craniofacial morphological alterations			0.66
No	305 (98%)	74 (97%)	
Yes	6 (17)	2 (3%)	
Symptoms category			
Q27 Have you ever fallen asleep during an activity (e.g., during work)?			<0.001***
Never	284 (91%)	58 (76%)	
About once a week	20 (6%)	8 (11%)	
Two or three times a week	3 (1%)	5 (7%)	

(Continued)

TABLE 3 | Continued

Items	Low score ($n = 311$) *N* (%)	High score ($n = 76$) *N* (%)	*p*-value
Almost every day	3 (1%)	3 (4%)	
Several times a day	1 (0%)	2 (3%)	
Q28 Did you have difficulty concentrating during an assignment?			<0.001***
Never	152 (49%)	22 (29%)	
About once a week	117 (38%)	22 (29%)	
Two or three times a week	33 (11%)	14 (18%)	
Almost every day	7 (2%)	11 (14%)	
Several times a day	2 (1%)	7 (9%)	
Q29 Did you have to force yourself to express yourself clearly?			0.012**
Never	195 (63%)	36 (47%)	
About once a week	89 (29%)	16 (21%)	
Two or three times a week	16 (5%)	15 (20%)	
Almost every day	8 (3%)	6 (8%)	
Several times a day	3 (1%)	3 (3%)	
Q30 Have you had to use stimulants (coffee, tea, ginseng, etc.) to stay active?			0.0052**
Never	132 (42%)	21 (28%)	
About once a week	62 (20%)	12 (16%)	
Two or three times a week	29 (9%)	13 (17%)	
Almost every day	69 (22%)	−28%	
Several times a day	19 (6%)	9 (12%)	
Q31 Have the problems reported in the previous questions interfered with your ability to work?			<0.001***
I have not had these problems	138 (44%)	30 (39%)	
Never	112 (36%)	15 (20%)	
About once a week	48 (15%)	15 (20%)	
Two or three times a week	8 (3%)	12 (16%)	
Almost every day	4 (1%)	3 (4%)	
Several times a day	1 (0%)	1 (1%)	
Q32 Have the problems reported in the previous questions interfered with your social relationships?			<0.001***
I have not had these problems	133 (43%)	15 (20%)	
Never	104 (33%)	27 (36%)	
About once a week	58 (19%)	17 (22%)	
Two or three times a week	9 (3%)	11 (14%)	
Almost every day	6 (2%)	5 (7%)	
Several times a day	1 (0%)	1 (1%)	
Q33 Have your reactions in everyday situations been slow?			<0.001***
Never	189 (61%)	34 (45%)	
About once a week	92 (30%)	17 (22%)	
Two or three times a week	22 (7%)	15 (20%)	
Almost every day	4 (1%)	7 (9%)	
Several times a day	4 (1%)	3 (4%)	
Q34 Did you have to try harder than usual to keep track of what you were doing?			<0.001***
Never	169 (54%)	26 (34%)	
About once a week	106 (34%)	23 (30%)	
Two or three times a week	19 (6%)	14 (18%)	
Almost every day	14 (5%)	7 (9%)	
Several times a day	3 (1%)	6 (8%)	
Q35 Did you have difficulty paying attention for a long time on a task?			<0.001***
Never	180 (58%)	26 (34%)	
About once a week	105 (34%)	25 (33%)	
Two or three times a week	17 (5%)	13 (17%)	
Almost every day	6 (2%)	10 (13%)	

(Continued)

TABLE 3 | Continued

Items	Low score ($n = 311$) *N* (%)	High score ($n = 76$) *N* (%)	*p*-value
Several times a day	17 (5%)	2 (3%)	
Q36 Have you had difficulty paying attention to multiple tasks at once (e.g., listening to a radio program while driving a car)?			0.0033**
Never	208 (67%)	41 (54%)	
About once a week	82 (26%)	15 (20%)	
Two or three times a week	9 (3%)	10 (13%)	
Almost every day	12 (4%)	8 (11%)	
Several times a day	0	2 (3%)	
Q37 Did you have to work hard to pay attention and not make mistakes?			<0.001***
Never	165 (53%)	26 (34%)	
About once a week	115 (37%)	25 (33%)	
Two or three times a week	16 (5%)	12 (16%)	
Almost every day	11 (4%)	11 (14%)	
Several times a day	4 (1%)	2 (3%)	
Q38 Did you feel the need to doze off during the course of the day?			<0.001***
Never	79 (25%)	5 (7%)	
About once a week	99 (32%)	23 (30%)	
Two or three times a week	69 (22%)	18 (24%)	
Almost every day	61 (20%)	27 (36%)	
Several times a day	3 (%)	3 (4%)	

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
Anamnesis factors, work information, clinical status, and symptoms category were assessed. A p-value < 0.05 was considered statistically significant.

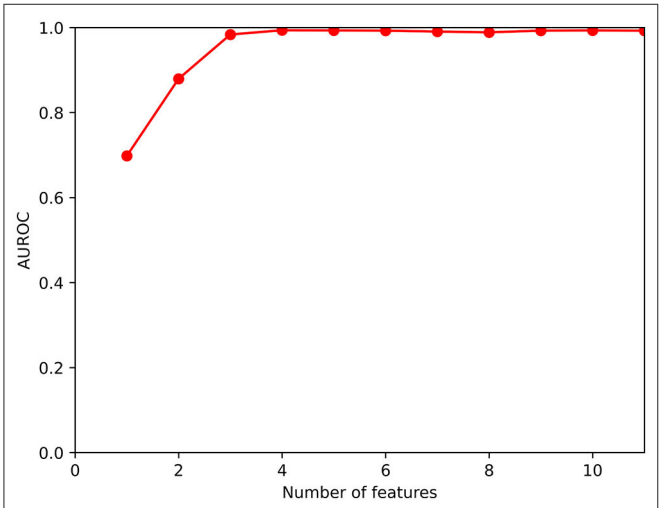

FIGURE 1 | Functional dependence of AUROC on the cardinality of the set of selected features.

TABLE 4 | Simplified Berlin questionnaire.

B1	"Do you snore?"	No/do not know/yes
B6	"How often do you feel tired or fatigued after your sleep?"	Never or almost never 1–2 times a month 1–2 times a week 3–4 times a week Every day
or		
B7	"During your waking time, do you feel tired, fatigued or not up to par?"	Never or almost never 1–2 times a month 1–2 times a week 3–4 times a week Every day
B10	"Do you have high blood pressure?"	No Do not know Yes

variables in the "best" feature subsets:

$$COM = \begin{array}{c} \\ B1 \\ B6 \\ B7 \\ B3 \\ B4 \end{array} \begin{pmatrix} 0.183 & 0.100 & 0.083 & 0 & 0 \\ 0.100 & 0.158 & 0 & 0.054 & 0.004 \\ 0.083 & 0 & 0.092 & 0.008 & 0 \\ 0 & 0.054 & 0.008 & 0.062 & 0 \\ 0 & 0.004 & 0 & 0 & 0.004 \end{pmatrix}$$

It is evident that B1 is always accompanied by B6 or B7, so two natural choices for three-variate subsets of features could be {B1, B6, B10}, immediately followed by {B1, B7, B10}. After selecting these "best" sets of variables, good practice would require verifying the conclusions on an independent test dataset. Being this impossible at this time for lack of data, their predictive values was recalculated on the whole available dataset, with 5-fold cross validation. AUROC were 0.98 for both.

Predictive Value for the Proprietary Questionnaire Variables

The proprietary questionnaire was also examined from the Machine Learning point of view, with a similar approach but very different results. The target variable was, as in the preceding analysis, the BQ output in terms of high vs. low risk of OSA. Global AUROC was not too high, with values about 0.80, which witnesses the relationship between the questions and the pathology, but also the scarce usefulness of the proprietary questionnaire in a ML context, at least with the data we possess. No variable derived from the questionnaire items revealed to be strikingly discriminant *per se*. Moreover, the partially stochastic nature of the feature selection process (due to the different random choices of the selection and quality assessment sets, respectively, *P*1 and *P*2) , leaded to quite different AUROC vs. number of features functional dependences at each run (in which AUROC slowly decreased from 80 to 60% with the progressive depletion of the feature set).

DISCUSSION

Of 387 screened patients who completed the BQ, about 20% ($n = 76$) fell within the high-risk group. Socio-demographic characteristics, work information, clinical factors, and symptoms category were compared between the two groups and are reported in **Table 2**.

Socio-Demographic Baseline Characteristics

Age is a well-established risk factor for OSA (19, 20). The increase in the prevalence of OSA with age could be explained in part by the increase in comorbidities, menopause, hypertension, BMI, but also by the decrease of tongue and palate muscle functions and activities that occurs in older adults (21, 22). Regarding the age of the sample, in the high-risk group 67% ($n = 51$) was ≥41 years old compared to 41% ($n = 133$) in the low-risk group. We have to consider that our cohort is predominantly composed of young subjects, more than half being <40 years old and only <2% of subjects being more than 60 years old. In our cohort, age was also found to be a risk factor significantly associated with high risk of OSA ($p < 0.0001$).

With respect to gender, epidemiological studies reported a prevalence ranging from 13 to 31% in men and 4 to 21% in women (17, 23–27). It is difficult to confirm this prevalence in our analysis, considering that our sample is predominantly female (76%). Despite this, we found a statistically significant difference between low-risk and high-risk groups with respect to gender ($p = 0.0011$). In particular, the percentage of men increases from 21% at low-risk to 39% at high-risk. In contrast, the percentage of women at low-risk is 79% and decreases in high-risk subjects (61%).

Obesity is the most severe known risk factor for OSA. Generally, almost 60% of patients with OSA are obese (28). The risk of OSA increases progressively with BMI and also with neck circumferences (29). In our analysis, the mean of BMI was significantly higher in the high-risk group than in the low-risk group ($p < 0.001$). Regarding neck circumferences, half of subjects did not know their neck circumferences. However, neck circumferences were higher than the chosen cut-off in the high-risk group (14%) compared to the low-risk group (6%).

No association was found with smoking and OSA in our sample and this reflects what is found in the literature (30). However, inhalation of cigarette smoke increases oxidative stress and systemic inflammation, which are typically present in OSA (30). Thus, the concomitant presence of OSA in smoker could worsen disease progression.

Work Information

Regarding work information, only the number of years of work experience seems to be associated with a high risk of OSA. However, rather than being a risk factor *per se*, this variable could be significant just because it is correlated with increasing age, an important risk factor previously discussed. Distribution of working time (full time/part time), work shift (day shift only or 24 h shift) and work shift regularity (yes/no) were not found to be associated with a high risk of OSA. Interestingly, professional categories and instruction level appear to be determinants between the two groups (0.039 and 0.049, respectively).

Health Status

Among all the clinical factors investigated, only the presence of craniofacial morphological alterations was not found to be a risk factor associated with an elevated risk of OSA, contrary to what reported in the literature (31). However, we must consider that only 8 subjects declared to have these alterations, which makes the sample less significant. Sleep disorders, instead, were obviously statistically significant between the two groups ($p < 0.001$), demonstrating the reliability of the sample.

Hypertension was already known to be associated with OSA (32, 33). Normally, 50% of hypertensive patients have OSA and this percentage rises to 85% in patients with hypertension who have at least another OSA symptom (34, 35). Subjects with OSA have an 1.8-times increased risk of resistant hypertension compared to non-OSA individuals (36). Our sample confirmed these data since 51% of high-risk persons were hypertensive compared with 5% found in low-risk subjects.

Arrhythmias and transient ischemic attack or stroke were found to be associated to high OSA risk score ($p < 0.001$ and $p = 0.0013$, respectively). This is in line with the literature, which attests that prevalence of OSA is estimated to be between two and three times higher in patients with cardiovascular diseases (37).

The percentage of OSA patients who suffer from type 2 diabetes was about 30% ($n = 118$). The link between diabetes and OSA seems bidirectional but has not been fully evaluated yet. In our cohort, 14% of the high-risk group shows presence of diabetes mellitus, compared to 2% of patients found in the low-risk group. This is statistically significant and the association between diabetes mellitus and being at high-risk is also significant ($p < 0.001$).

OSA and asthma are closely related. Numerous studies have consistently reported higher OSA burden among subjects with asthma (38, 39) and in relation to asthma severity (38, 40). In our

sample, the percentage of individuals with asthma in the low-risk group was 6% rising to 24% in high-risk group. Asthma was also found to be a strong risk factor for OSA ($p = 0.0018$).

Chronic obstructive pulmonary disease (COPD) is also highly associated with OSA. COPD is one of the most prevalent respiratory diseases worldwide. There exists what is called COPD-OSA overlap syndrome that represents a distinct clinical diagnosis, where clinical outcomes are even worse than in each disease alone (41). Based on this evidence, we found a significant difference between the low and high-risk groups ($p < 0.001$).

Recent systematic reviews and meta-analyses reported that OSA is linked to depression (42) and anxiety (43). Other longitudinal studies suggested that patients with OSA are about twice as likely to be depressed than those without OSA (44, 45). In our sample, the rate of depression increased from 10% in the low-risk group to 21% in the high-risk OSA group, while the rate of anxiety increased from 33 to 54%. We also found a strong correlation between being at high-risk of OSA and having both depression and anxiety ($p = 0.0014$ and $p = 0.0082$, respectively).

Frequent confusion and agitation resulted also to be an important risk factor ($p = 0.0022$) in our cohort. In particular, 11% of the high-risk subjects show presence of confusion and agitation, compared to 3% of those found in the low-risk group. This phenomenon could be related to anxious behavior, but several efforts should be done for understanding this association.

Excessive alcohol consumption and drug abuse were also assessed between low vs. high score. Results from the literature revealed that alcohol consumption is associated with 25% increased risk of OSA (46). To the best of our knowledge, no data was shown for drug abuse. We found that 7% of the high-risk group declared alcohol and drug abuse, compared to 1% of patients found in the low-risk group. Alcohol and drug abuse were also found to be two independent risk factors for the high-risk group ($p = 0.0022$ and $p = 0.0061$, respectively).

Symptoms Category

Daytime OSA symptoms consist of unexplained fatigue and excessive sleepiness. Patients also report repetitive problems with concentration and memory as well as depressive symptoms (47) and impairment of cognitive functions (48). Moreover, a study of men and women aged 60 years and older showed memory impairment related to OSA and hypertension (49). All of these evidences are in line with our findings: difficulty staying awake during an activity, difficulty concentrating, difficulty in expressing oneself, use of stimulants, interference with work, interference with social relationships, slow reactions and difficulty keeping attention up, difficulty in paying attention to several tasks at once, striving not to make mistakes, and need to doze off, are all significantly strong risk factors related to high-risk of having OSA. These symptoms fully describe the OSA patient during his/her daily activity, including working and social activities.

Predictive Value of Questionnaire Items

As concerns the predictive value of the variables acquired by the BQ, our conclusion was that a reduced set of questions, i.e., a reduced set of selected features, composed only of **Table 4**, is sufficient to obtain an output close to that of the BQ, by using a trained XGBoost classifier.

This reduced questionnaire shows some similarity with the one proposed in Arunsurat et al. (18) with the important difference that (as already remarked) BMI is not preserved in the reduced set. The discrepancy might partly come from the different group considered, i.e., the high percentage of young and prevalently female respondents in our sample compared to the all-male healthcare workers investigated in Arunsurat et al. (18).

From the Results section, it is also evident that the proprietary questionnaire is interesting from the point of view of risk factor assessment, but the ML approach gave no hint on the possibility of replacing/integrating the original Berlin test with (parts of) it. In order to clarify this possibility, a dataset with ground truth coming from PSG or HST is needed along with the questionnaire itself.

Limits

The results of our study must be considered taking into account some limitations that concern the sample size, the lack of the actual disease diagnosis for most subjects, the absence of disease follow-up and long-term effect investigation for the subjects who declared to suffer from OSA and, finally, the possible reluctance of the respondents to faithfully declare their health status since they are professional nurses. Moreover, our survey group does not fully represent the general population, because of the high percentage of young and prevalently female respondents. Finally, we are also aware that the study might give different conclusions in different ethnic groups, depending on language, habits, lifestyles or physical conformation.

Conclusions

In conclusion, there are numerous risk factors associated with a high-risk of having OSA in a population of nurses. Given the high percentage of people who are still underdiagnosed for OSA and the lack of knowledge about this disease, our study contributes to highlight an alarming result that may be just the tip of the iceberg. This study could be helpful to expand awareness about it, especially among professional nurses, who are one of the most important categories in health and our care. It could also allow more professionals to investigate suspected patients who could undergo overnight polysomnography, as well as to explore possible alternative screening tests and cures for the treatment of this still too hidden disease.

Further efforts should be done to increase the number of diagnoses but also, more importantly, to refer these subjects for screening. On this regard, our simplified test might also allow a better administration of the questionnaire facilitating the orientation of the subject at risk toward the diagnostic pathway. We plan indeed a prospective clinical trial that can use the simplified Berlin test together with our proprietary questions on the general population, with the aim

of possibly creating a richer questionnaire with better sensitivity and specificity.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GDN, LC, RL, and LDB contributed to conception and design of the study. LC, GDN, AC, ME, and MC organized the database. LC, GDN, and EV performed the statistical analysis. LC and GDN wrote the first draft of the manuscript. LC, GDN, MA, DT, and LDB wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REFERENCES

1. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev.* (2017) 34:70–81. doi: 10.1016/j.smrv.2016.07.002
2. Practice guidelines for the perioperative management of patients with obstructive sleep apnea. *Anesthesiology*. (2006) 104:1081–93. doi: 10.1097/00000542-200605000-00026
3. Marin JM, Carrizo SJ, Vicente E, Agusti AG. 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) 365:1046–53. doi: 10.1016/S0140-6736(05)71141-7
4. Dyken ME, Im KB. Obstructive sleep apnea and stroke. *Chest*. (2009) 136:1668–77. doi: 10.1378/chest.08-1512
5. Benjafield A V, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med.* (2019) 7:687–98. doi: 10.1016/S2213-2600(19)30198-5
6. Fietze I, Laharnar N, Obst A, Ewert R, Felix SB, Garcia C, et al. Prevalence and association analysis of obstructive sleep apnea with gender and age differences - results of SHIP-Trend. *J Sleep Res.* (2019) 28:e12770. doi: 10.1111/jsr.12770
7. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* (1999) 131:485. doi: 10.7326/0003-4819-131-7-199910050-00002
8. Lo A, Chernoff H, Zheng T, Lo S-H. Why significant variables aren't automatically good predictors. *Proc Natl Acad Sci.* (2015) 112:13892–7. doi: 10.1073/pnas.1518285112
9. Bzdok D, Engemann D, Thirion B. Inference and prediction diverge in biomedicine. *Patterns.* (2020) 1:100119. doi: 10.1016/j.patter.2020.100119
10. Varga T V., Niss K, Estampador AC, Collin CB, Moseley PL. Association is not prediction: a landscape of confused reporting in diabetes – a systematic review. *Diabetes Res Clin Pract.* (2020) 170:108497. doi: 10.1016/j.diabres.2020.108497
11. Tan A, Yin JDC, Tan LWL, van Dam RM, Cheung YY, Lee C-H. Using the Berlin Questionnaire to predict obstructive sleep apnea in the general population. *J Clin Sleep Med.* (2017) 13:427–32. doi: 10.5664/jcsm.6496
12. Bernhardt L, Brady EM, Freeman SC, Polmann H, Réus JC, Flores-Mir C, et al. Diagnostic accuracy of screening questionnaires for obstructive sleep apnoea in adults in different clinical cohorts: a systematic review and meta-analysis. *Sleep Breath.* (2021) 18:1–26. doi: 10.1007/s11325-021-02450-9
13. Chen T, Guestrin C. XGBoost. In: *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*. New York, NY: ACM. (2016). p. 785–94.
14. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Med Res Methodol.* (2017) 17:162. doi: 10.1186/s12874-017-0442-1
15. Duda RO, Hart PE, Stork DG. *Pattern Classification*. Hoboken, NJ: John Wiley & Sons (2001).
16. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med.* (2015) 3:310–8. doi: 10.1016/S2213-2600(15)00043-0
17. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* (2013) 177:1006–14. doi: 10.1093/aje/kws342
18. Arunsurat I, Luengyosluechakul S, Prateephoungrat K, Siripaupradist P, Khemtong S, Jamcharoensup K, et al. Simplified Berlin Questionnaire for screening of high risk for obstructive sleep apnea among Thai male healthcare workers. *J UOEH.* (2016) 38:199–206. doi: 10.7888/juoeh.38.199
19. Braley TJ, Dunietz GL, Chervin RD, Lisabeth LD, Skolarus LE, Burke JF. Recognition and diagnosis of obstructive sleep apnea in older Americans. *J Am Geriatr Soc.* (2018) 66:1296–302. doi: 10.1111/jgs.15372
20. Zamarrón C, Gude F, Otero Y, Alvarez JM, Golpe A, Rodriguez JR. Prevalence of sleep disordered breathing and sleep apnea in 50- to 70-year-old individuals. *Respiration.* (1999) 66:317–22. doi: 10.1159/000029401
21. Eikermann M, Jordan AS, Chamberlin NL, Gautam S, Wellman A, Lo Y-L, et al. The influence of aging on pharyngeal collapsibility during sleep. *Chest.* (2007) 131:1702–9. doi: 10.1378/chest.06-2653
22. Worsnop C, Kay A, Kim Y, Trinder J, Pierce R. Effect of age on sleep onset-related changes in respiratory pump and upper airway muscle function. *J Appl Physiol.* (2000) 88:1831–9. doi: 10.1152/jappl.2000.88.5.1831
23. Appleton SL, Gill TK, Lang CJ, Taylor AW, McEvoy RD, Stocks NP, et al. Prevalence and comorbidity of sleep conditions in Australian adults: 2016 Sleep Health Foundation national survey. *Sleep Heal.* (2018) 4:13–9. doi: 10.1016/j.sleh.2017.10.006
24. Hiestand DM, Britz P, Goldman M, Phillips B. Prevalence of symptoms and risk of sleep apnea in the US population. *Chest.* (2006) 130:780–6. doi: 10.1378/chest.130.3.780
25. Huang T, Lin BM, Markt SC, Stampfer MJ, Laden F, Hu FB, et al. Sex differences in the associations of obstructive sleep apnoea with epidemiological factors. *Eur Respir J.* (2018) 51:1702421. doi: 10.1183/13993003.02421-2017
26. Sunwoo J-S, Hwangbo Y, Kim W-J, Chu MK, Yun C-H, Yang KI. Prevalence, sleep characteristics, and comorbidities in a population at high risk for obstructive sleep apnea: a nationwide questionnaire study in South Korea. *PLoS ONE.* (2018) 13:e0193549. doi: 10.1371/journal.pone.0193549
27. Matsumoto T, Murase K, Tabara Y, Minami T, Kanai O, Takeyama H, et al. Sleep disordered breathing and metabolic comorbidities across sex and menopausal status in East Asians: the Nagahama Study. *Eur Respir J.* (2020) 56:1902251. doi: 10.1183/13993003.02251-2019
28. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LRA. Obstructive sleep apnea syndrome in the Sao-Paulo epidemiologic sleep study. *Sleep Med.* (2010) 11:441–6. doi: 10.1016/j.sleep.2009.10.005

29. Young T. Risk factors for obstructive sleep apnea in adults. *JAMA*. (2004) 291:2013. doi: 10.1001/jama.291.16.2013
30. Lin YN, Zhou LN, Zhang XJ, Li QY, Wang Q, Xu HJ. Combined effect of obstructive sleep apnea and chronic smoking on cognitive impairment. *Sleep Breath.* (2016) 20:51–9. doi: 10.1007/s11325-015-1183-1
31. Brevi BC, Toma L, Magri AS, Sesenna E. Use of the mandibular distraction technique to treat obstructive sleep apnea syndrome. *J Oral Maxillofac Surg.* (2011) 69:566–71. doi: 10.1016/j.joms.2010.09.007
32. Kario K. Obstructive sleep apnea syndrome and hypertension: mechanism of the linkage and 24-h blood pressure control. *Hypertens Res.* (2009) 32:537–41. doi: 10.1038/hr.2009.73
33. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertens.* (2003) 42:1206–52. doi: 10.1161/01.HYP.0000107251.49515.c2
34. Börgel J, Springer S, Ghafoor J, Arndt D, Duchna H-W, Barthel A, et al. Unrecognized secondary causes of hypertension in patients with hypertensive urgency/emergency: prevalence and co-prevalence. *Clin Res Cardiol.* (2010) 99:499–506 doi: 10.1007/s00392-010-0148-4
35. Gonçalves SC, Martinez D, Gus M, de Abreu-Silva EO, Bertoluci C, Dutra I, et al. Obstructive sleep apnea and resistant hypertension. *Chest.* (2007) 132:1858–62. doi: 10.1378/chest.07-1170
36. Hou H, Zhao Y, Yu W, Dong H, Xue X, Ding J, et al. Association of obstructive sleep apnea with hypertension: a systematic review and meta-analysis. *J Glob Health.* (2018) 8:010405. doi: 10.7189/jogh.08.010405
37. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med.* (2000) 342:1378–84. doi: 10.1056/NEJM200005113421901
38. Julien JY, Martin JG, Ernst P, Olivenstein R, Hamid Q, Lemière C, et al. Prevalence of obstructive sleep apnea–hypopnea in severe versus moderate asthma. *J Allergy Clin Immunol.* (2009) 124:371–6. doi: 10.1016/j.jaci.2009.05.016
39. Yigla M, Tov N, Solomonov A, Rubin AE, Harlev D. Difficult-to-control asthma and obstructive sleep apnea. *J Asthma.* (2003) 40:865–71. doi: 10.1081/JAS-120023577
40. Teodorescu M, Broytman O, Curran-Everett D, Sorkness RL, Crisafi G, Bleecker ER, et al. Obstructive sleep apnea risk, asthma burden, and lower airway inflammation in adults in the severe asthma research program (SARP) II. *J Allergy Clin Immunol Pract.* (2015) 3:566–75.e1. doi: 10.1016/j.jaip.2015.04.002
41. D'Cruz RF, Murphy PB, Kaltsakas G. Sleep disordered breathing and chronic obstructive pulmonary disease: a narrative review on classification, pathophysiology and clinical outcomes. *J Thorac Dis.* (2020) 12:S202–16. doi: 10.21037/jtd-cus-2020-006
42. Edwards C, Almeida OP, Ford AH. Obstructive sleep apnea and depression: a systematic review and meta-analysis. *Maturitas.* (2020) 142:45–54. doi: 10.1016/j.maturitas.2020.06.002
43. Aftab Z, Anthony AT, Rahmat S, Sangle P, Khan S. An updated review on the relationship of depressive symptoms in obstructive sleep apnea and continuous positive airway pressure. *Cureus.* (2021) 13:e15907. doi: 10.7759/cureus.15907
44. Chen Y-H, Keller JK, Kang J-H, Hsieh H-J, Lin H-C. Obstructive sleep apnea and the subsequent risk of depressive disorder: a population-based follow-up study. *J Clin Sleep Med.* (2013) 9:417–23. doi: 10.5664/jcsm.2652
45. Peppard PE, Szklo-Coxe M, Hla KM, Young T. Longitudinal association of sleep-related breathing disorder and depression. *Arch Intern Med.* (2006) 166:1709–15. doi: 10.1001/archinte.166.16.1709
46. Roure N, Gomez S, Mediano O, Duran J, Peña M de la, Capote F, et al. Daytime sleepiness and polysomnography in obstructive sleep apnea patients. *Sleep Med.* (2008) 9:727–31. doi: 10.1016/j.sleep.2008.02.006
47. Sforza E, Saint Martin M, Barthélémy JC, Roche F. Mood disorders in healthy elderly with obstructive sleep apnea: a gender effect. *Sleep Med.* (2016) 19:57–62. doi: 10.1016/j.sleep.2015.11.007
48. Saint Martin M, Sforza E, Roche F, Barthélémy JC, Thomas-Anterion C. Sleep breathing disorders and cognitive function in the elderly: an 8-year follow-up study. The Proof-Synapse Cohort. *Sleep.* (2015) 38:179–87. doi: 10.5665/sleep.4392
49. Kato K, Noda A, Yasuma F, Matsubara Y, Miyata S, Iwamoto K, et al. Effects of sleep-disordered breathing and hypertension on cognitive function in elderly adults. *Clin Exp Hypertens.* (2020) 42:250–6. doi: 10.1080/10641963.2019.1632338

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Validation Study of Airgo, an Innovative Device to Screen Sleep Respiratory Disorders

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Background: Obstructive sleep apnea affects a consistent percentage of the population, and only a minority of patients have been diagnosed and treated because of a discrepancy between resources available for diagnosis and the epidemiology of a disorder possibly affecting nearly one billion people in the world.

Aim: We conducted a study to compare a standard home respiratory monitoring system (Nox T3) with a novel device (Airgo^{TM}) consisting of an elastic band and a small recorder, light, comfortable for the patient, and low-cost complete with automatic analysis of the data that produces a screening report indicating the type and severity of sleep respiratory disorder.

Patients and Results: We examined 120 patients, reduced to 118 for technical problems. The mean (*SD*) age of the patients is 55.7 ± 13 years, their BMI is 27.8 ± 4.3 kg/m^2, and their AHI is 22 ± 22 events/h. Patients belong to all the different severity rates of OSA, with a percentage of them classified as free of respiratory disorders. The Airgo^{TM} showed excellent agreement with the results of the gold standard, reporting high levels of sensitivity, specificity, positive and negative predicted value, and accuracy.

Conclusion: Airgo^{TM} is a reliable tool to screen patients with suspected sleep respiratory disorders, well tolerated by the patient based on totally automatic analysis and reporting system, leading to more efficient use of doctor's and clinician's time and resources and extending the opportunity to diagnose more possible candidates for treatment.

Keywords: respiratory pattern detection, respiratory sleep disorders, screening, sleep apnea, wearable devices and sensors

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INTRODUCTION

Sleep respiratory disorders are a common problem in the general population (1). Obstructive sleep apnea (OSA), a recurrent collapse of the upper airways occurring during sleep, leads to sleep fragmentation and intermittent oxyhemoglobin desaturations, which are significant risk factors for cardiovascular, cerebrovascular, and metabolic disorders (2). Since the disorder occurs only during sleep, patients are usually unaware of their condition and have to rely on symptoms that are

not related to upper airway function or to the respiratory system (i.e., nocturia, daytime fatigue, somnolence) or on somebody who witnesses the respiratory events during sleep and suggests seeking medical advice. A proper diagnosis is often delayed until after severe consequences have occurred (3).

Guidelines on the diagnosis of OSA (4) require an overnight study with polysomnography, a complex and expensive supervised monitoring of several vital functions, or at least a polygraphy, including a more limited set of sensors easy to apply at home. Considering the epidemiology of OSA (1), this is a considerable bottleneck in the management of patients since the estimate of people affected worldwide is close to one billion (5). Screening tools have been proposed based on a more limited set of sensors (i.e., oximetry) or questionnaires combining symptoms and clinical signs to identify subjects at risk. Excessive daytime somnolence is a landmark symptom easily measured with self-administered scales (Epworth sleepiness scale, Stanford sleepiness scale) (6), but it occurs only in one out of five patients with OSA (1). Similarly, oximetry is unreliable in detecting moderate OSA in patients with short events and good baseline SpO_2 values (7).

Common disorders like cardiac arrhythmias, mainly atrial fibrillation, or diabetes, stroke, chronic heart failure, and drug-resistant hypertension show a high OSA prevalence (up to 80% in paroxysmal atrial fibrillation) (8). In these patients, screening strategies currently available do not detect patients with OSA since they do not report daytime symptoms, and the employment of current diagnostic procedures extensively is an unreliable strategy considering epidemiology and the need for a timely diagnosis (9, 10).

A simple to use, reliable, and cost-effective screening device to rule-in or rule-out the occurrence of OSA would be a significant step forward in the management of the disease. The aim of the present study is to assess the performance of Airgo^{TM}, an innovative system of respiratory monitoring, as a screening tool for respiratory sleep disorders.

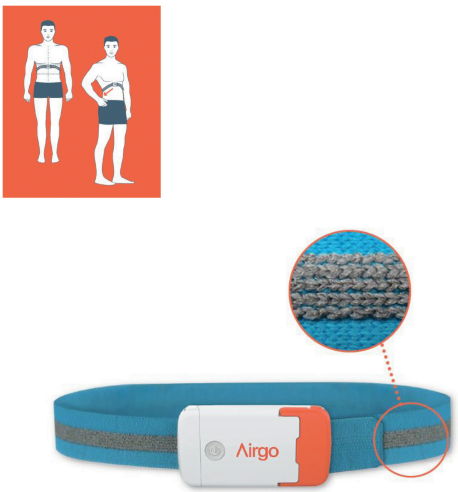


FIGURE 1 | The wearable device consists of an elastic band incorporating a silver-coated electrically conductive yarn (see detail), coupled with a microprocessor embedded in an ABS shell. The figure shows the proper placement position.

MATERIALS AND METHODS

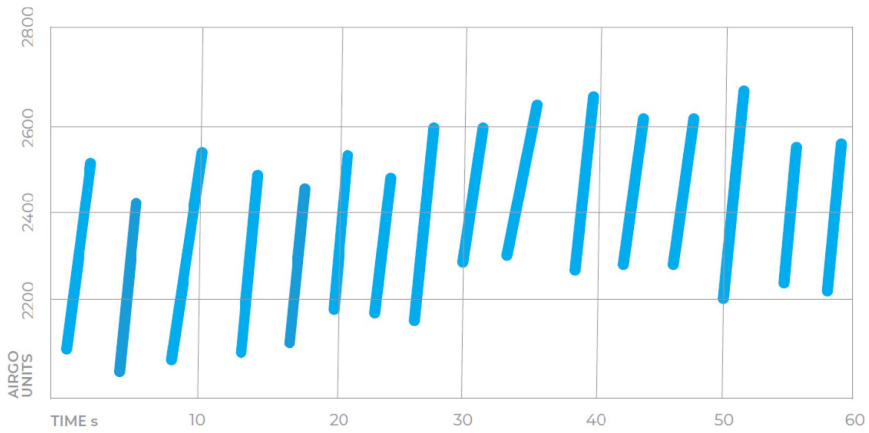
Study Design

The study is a single center, prospective comparison of a new device to assess sleep respiratory disorders vs. standard cardiorespiratory monitoring. Consecutive patients presenting at the sleep lab of Salvatore Maugeri IRCCS Veruno Medical Center were enrolled irrespective of the type of referred symptoms. Age under 18 years, pregnancy and inability to sign informed consent were the exclusion criteria. The study was approved by the "Salvatore Maugeri Foundation" ethics committee (2300 CE) and all the patients signed informed consent.

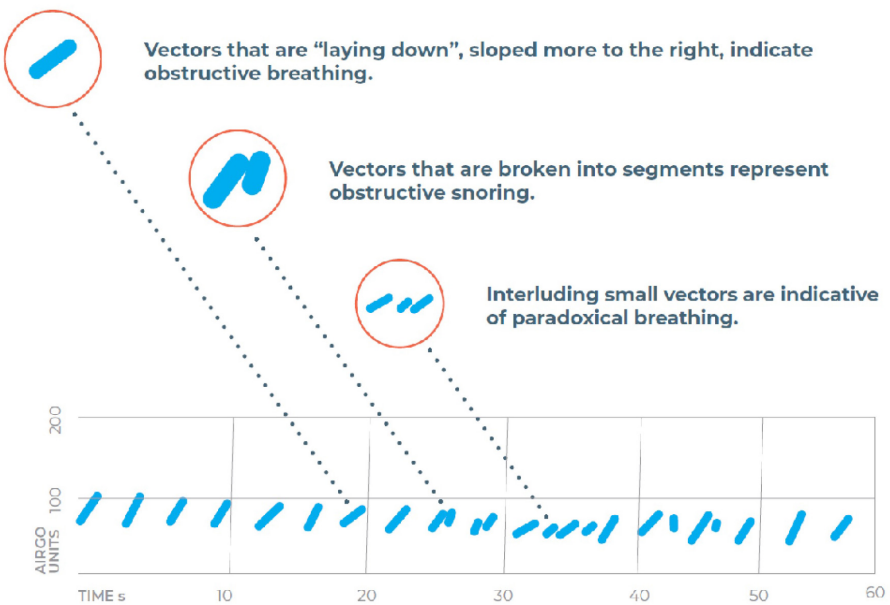
Devices

Airgo^{TM} (Myair Inc., Boston, MA, United States; Myairgo Italy Srl, Milan, Italy) is a wearable device consisting of an elastic band incorporating a silver-coated electrically conductive yarn, coupled with a microprocessor embedded in an ABS shell (**Figure 1**). The band is positioned at the level of the floating ribs and monitors continuously the changes in the volume of the thoracic cage by tracking the variation in electrical resistance of the silver-coated yarn as the circumference varies. The procedure of signal reconstruction and respiratory pattern assessment has been reported extensively previously (11). Briefly, the device samples data at a frequency of 10 Hz and identifies for each breathing cycle a minimum and a maximum. The patented algorithm produces a vector connecting these two points, which allows the computation of tidal volume and respiratory rate. Vectors are a very informative signal since their baseline points correspond to the functional residual capacity of every breath, their lengths allow the calculation of tidal volumes in arbitrary units and the slopes of the vectors or their fragmentation are indicative of the coordination between thorax and abdomen. Every time an upper airway obstruction occurs, there is a paradoxical movement (partial or complete according to the degree of obstruction) of the thoracic cage, which changes the slope and the shape of the vectors as shown in **Figure 2**. The changes in minute ventilation are calculated dynamically by comparing the window of the last 10 s (MV10) with the mean of the previous 60 s (MV60) and respiratory events are detected when MV10 crosses the threshold of MV60. The breath by breath assessment facilitates the construction of respiratory instability curves (RICs), a very informative visualization of respiratory patterns during sleep since they do not focus on respiratory events *per se*, but on the variability of respiratory amplitude, which becomes apparent when comparing the deciles of MV reduction. The trend of RICs is thus informative on the occurrence of respiratory events as well as respiratory instability, which could be of non-respiratory origin (e.g., periodic leg movements, insomnia) (**Figure 3**).

The device includes three accelerometers to assess body position. This is particularly useful for correlating the occurrence



The figure shows 1 minute of normal spontaneous breathing at the rate of 16 breaths per minute. **The vertical vector, naturally chaotic, correctly represents a free flow through the thoracic volume.**



Airgo™ Vectair® documents respiratory instability events: vertical vector slope decrease visualizes obstructed breathing and FRC decrease is reported by the vector baseline moving downward. The vectors that are broken into segments represent the respiratory instability events due to obstructive snoring.

FIGURE 2 | The algorithm of Airgo™ transforms every breath into a vector with a specific length (corresponding to tidal volume), a baseline (corresponding to the punctual functional residual capacity) and a shape here described as proportional to upper airway patency.

and severity of respiratory events with body position. Although actigraphy has specific rules which cannot be fulfilled by a device positioned on the thorax, the signal is processed to describe both the position and activity of the patient, which easily identifies when the patient wakes up and gives information useful to discriminate wakefulness during the recording.

Nox T3 (Nox Medical, Reykjavík Iceland) has been used as the gold standard in a setting fulfilling the recommendations for

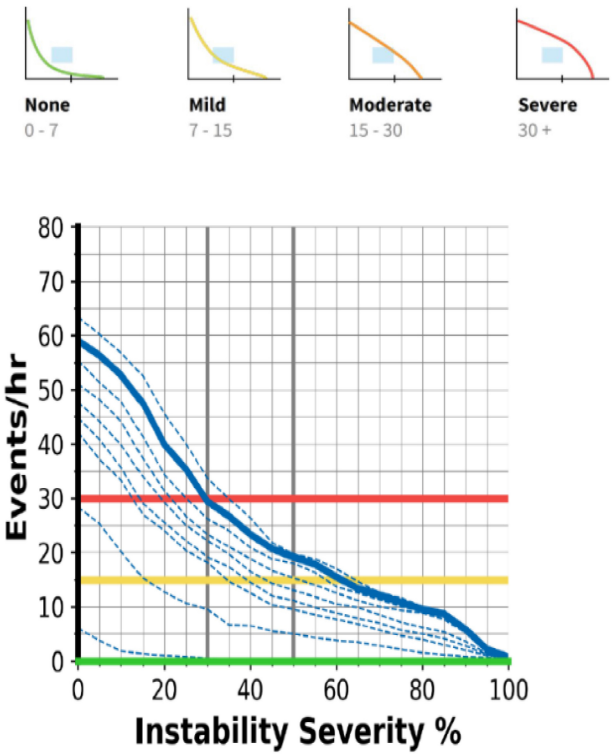


FIGURE 3 | The respiratory instability curves (RIC) discriminate the occurrence, severity, and type of sleep respiratory disorder according to the interception of the target area. See text for details.

home cardiorespiratory sleep studies, including nasal cannula, thoracic and abdominal inductive plethysmographic bands, pulse oximetry, microphone for snoring, body position sensor, and leg movement sensors.

Patients came to the lab in the afternoon and were instructed on how to wear the sensors of Nox T3 at home. Airgo^{TM} was positioned by the sleep technician, and the patient was instructed to leave it as placed. A telephone line with the hospital was available in case of problems. Synchronization of the two devices was set with an iPhone used to manage the starting procedures of the Airgo^{TM}, and the same time was set on the PC at the initialization of Nox T3.

Event Detection

Data from cardiorespiratory monitoring were manually scored in accordance with the AASM 2012 recommendations for adults (12). Apnea has been defined as the cessation of airflow for at least 10 s; hypopnea is the reduction of airflow signal of at least 30% with an oxyhemoglobin desaturation of 3% or more.

Airgo^{TM} does not record oxyhemoglobin saturation and relies on a complex algorithm to detect the changes in tidal volume and minute ventilation. Central apnea is easily detected by the absence of the vectorized signal. Obstructive events are detected by a reduction in minute ventilation and a change in the morphology of the vectors caused by paradoxical movements of the thoracic cage. Since the desaturation criterion cannot be applied to validate hypopneas, small changes in ventilation could lead to false-positive detections. Considering that the aim of the study is to assess the reliability of Airgo^{TM} as a screening tool for respiratory sleep disorders, a graphic interpretation of the RICs automatically generated by the program has been developed to describe the pattern and severity of the events detected (**Figure 4**). Patients are allocated to one of the following groups: no respiratory events; mild-to-moderate sleep apnea (AHI 5–30 at the Nox study); severe sleep apnea (AHI 30 or more at the Nox study); positional sleep apnea (pOSA); respiratory pattern instability. The latter group is a miscellanea of sleep disturbances of non-respiratory origin (i.e., myoclonus, insomnia), or occurring only in specific sleep stages (i.e., REM-related OSA), which cause a quick change in the trend of the RIC deciles.

Statistical Analysis

Quantitative variables are expressed as the mean ± *SD*. Qualitative variables are expressed as the number of patients and percentage. Positive predictive value, negative predictive value, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and accuracy have been calculated for every category of disease detected by Airgo^{TM} compared with Nox results, with 95% confidence intervals for every category.

RESULTS

One hundred twenty patients (23 F) agreed to participate in the study. The mean *(SD)* age of the patients is 55.7 ± 13 years, their BMI is 27.8 ± 4.3 kg/m^2, and their AHI is 22 ± 22 events/h. Two patients were excluded from the analysis, one who inadvertently switched off the Airgo^{TM} before the beginning of recording, other for the loss of the oximetry sensor of the Nox T3 for more than 70% of the night, and refusing to repeat the study. **Table 1** reports anthropometric data for the different groups. We recruited consecutive patients presenting to our sleep center, so the woman:man ratio was 1:5, a common bias of sleep centers case series compared to the prevalence of the disorder in the global population. Airgo^{TM} classified properly 27 severe OSA pts, 16 postural OSA (pOSA), 16/19 non-OSA pts (3 FP), 35/40 mild-to-moderate OSA (3 scored severe and 2 FN), and 14/16 pts (2 FN) with irregular breathing of non-OSA origin (**Table 2**). The diagnostic accuracy evaluation is shown in **Table 3** reporting data on the whole population studied and in **Table 4** reporting data on patients with OSA or normal breathing, excluding patients with irregular breathing of non-OSA origin to focus on the performance of the device in the OSA group. In **Table 5** the time spent on the single steps of the recording procedure has been compared for the two systems.

DISCUSSION

Our study shows that Airgo^{TM} can be used to screen for sleep respiratory disorders with an easy-to-use, non-invasive device and without the need for manual analysis. The trend of RICs is

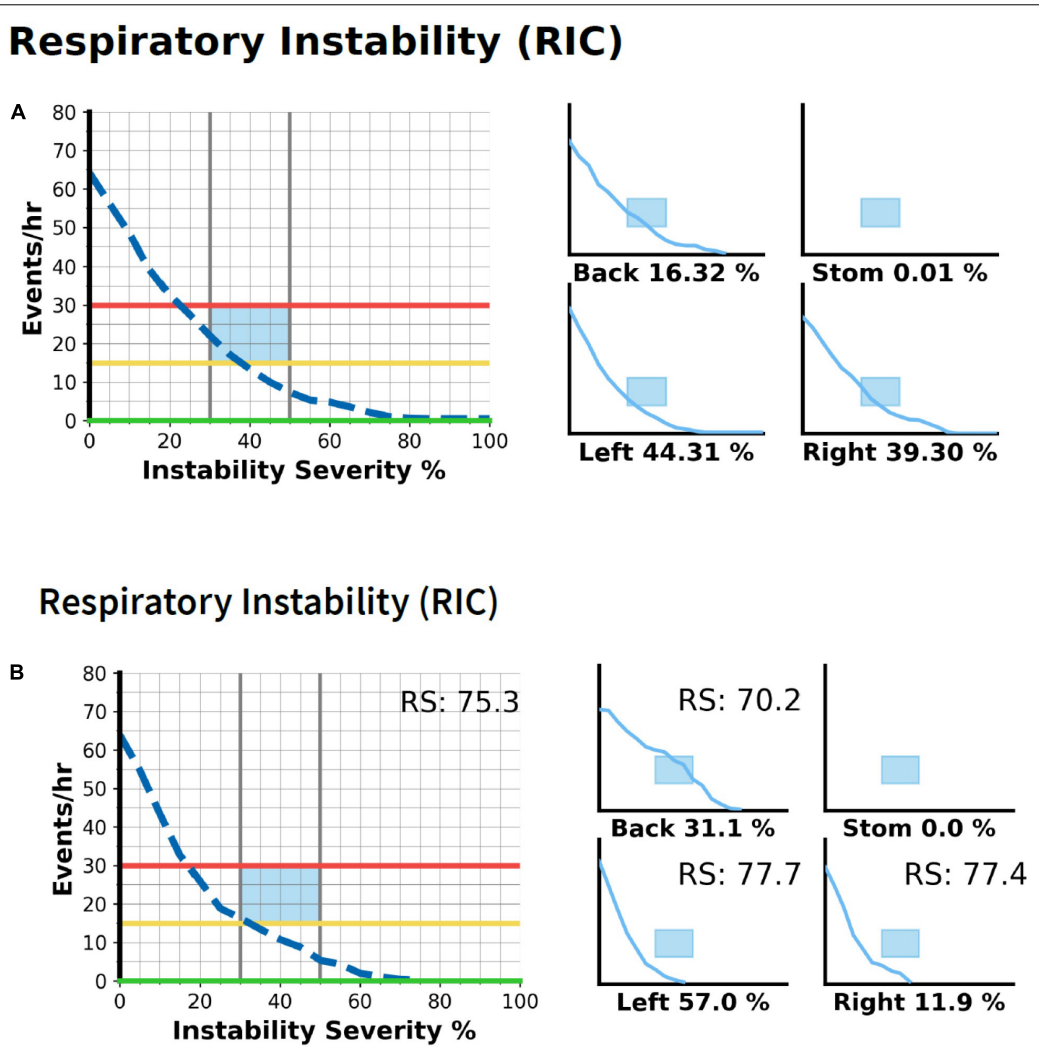


FIGURE 4 | The postural OSA is detected by comparing RICs in different body positions. On the left is the whole night RIC graph, on the right data are split by body position, with the percentage of time spent in every position reported. **(A)** The patient is classified as mild-to-moderate OSA and events occur irrespective of body position. **(B)** The patient would be classified as mild OSA considering the graph of the whole night, instead, he has severe sleep apnea in the supine position and almost no events in the lateral position.

TABLE 1 | Anthropometric data and results of sleep studies in the different groups of patients (mean ± *SD*).

	Normal	Mild-to-moderate OSA	Severe OSA	Positional OSA	Non-OSA disease
Nr	19	40	27	16	16
Age	49.8 ± 14.14	56.7 ± 10.3	59.5 ± 14.4	56.2 ± 11.1	56.1 ± 10.2
Height (cm)	171.3 ± 9.7	171.8 ± 9.9	172.8 ± 6.5	173.2 ± 9.9	170.4 ± 9.2
Weight (Kg)	76.9 ± 12.9	81.5 ± 14.7	89.5 ± 13.7	78.4 ± 13.6	79.4 ± 13.7
BMI (Kg/m^2)	26.2 ± 3.6	27.6 ± 4.1	30.0 ± 4.6*	26.1 ± 4.0	27.3 ± 4.0
AHI	2.5 ± 1.4	15.2 ± 6.3	57.2 ± 15.2	14.2 ± 8.9	13.1 ± 9.1

*$P < 0.05$.

an informative and innovative modality to rule in and rule out the occurrence of respiratory sleep disorders and immediately identifies the more severe OSA patients (i.e., AHI > 30 events per hour), those who have respiratory events only or mostly in the supine position (p-OSA) and patients with complex respiratory disorders who will probably benefit from formal polysomnography to define a proper diagnosis.

In our case series, 27 patients (23% of the sample), all males, had severe obstructive sleep apnea. Airgo^{TM} was identified correctly in 100% of the cases. This could be very useful in clinical

TABLE 2 | Comparison of diagnosis obtained with Airgo™ vs. Nox T3 (confusion matrix).

Airgo™	Nox T3				
	Normal	**Mild-to-moderate OSA**	**Severe OSA**	**Positional OSA**	**Non-OSA disease**
Normal	16	2	0	0	2
Mild-to-moderate OSA	3	35	0	0	0
Severe OSA	0	3	27	0	0
Positional OSA	0	0	0	16	0
Non-OSA disease	0	0	0	0	14

TABLE 3 | Evaluation of Airgo™ performance vs. Nox T3 in classifying OSA occurrence (n = 118).

	Value	**95% CI**
Prevalence (%)	70.3	62.1–78.5
Sensitivity (%)	97.6	94.8–1.0
Specificity (%)	91.4	86.3–96.5
Positive predictive value (%)	96.4	93.0–99.8
Negative predictive value (%)	94.1	89.8–98.3
Positive likelihood ratio	11.4	5.7–17.1
Negative likelihood ratio	0.03	−0.01–0.06
Accuracy (%)	95.8	92.2–99.4

CI, confidence interval.

TABLE 4 | Evaluation of Airgo™ performance vs. Nox T3 in classifying OSA severity (n = 102).

	Value	**95% CI**
Prevalence (%)	78.4	70.4–86.4
Sensitivity (%)	97.5	94.4–1.0
Specificity (%)	72.7	64.1–81.3
Positive predicted value (%)	92.8	87.8–97.8
Negative predicted value (%)	88.8	82.7–94.9
Positive likelihood ratio	3.6	−0.0–0.07
Negative likelihood ratio	0.03	−0.01–0.01
Accuracy (%)	92.1	86.9–97.3

CI, confidence interval.

TABLE 5 | Comparison of time spent on the standard procedures to record sleep studies and produce a final report.

	Airgo	**Nox T3**
Device preparation	5–10	15–20
Patient training to wear the device	3–12	15–30
Pre-scoring procedures	5–10	10
Scoring of events by experts	0	60–120
Report production	5	5
Cleaning	2	5–10
Total	20–39	110–195

Data are expressed in minutes.

practice in several settings. Severe OSA has three landmarks, namely, recurrent desaturations, which cause an increase in the production and release of inflammatory factors; increased ortosympathetic tone, which is caused by autonomic nervous system activation and the release of epinephrine; a mechanical stretch of the heart walls, which causes nocturia and eases the insurgence of arrhythmias; and eccentric ventricular hypertrophy (8). The combination of these three factors in populations already predisposed to cardiovascular disease poses an additional risk of events. In the DREAM study (13), consecutive patients with an indication of PM had a prevalence of moderate to severe OSA assessed with a PSG of 78%. In paroxysmal atrial fibrillation, OSA can occur in up to 80% of patients. Most of these subjects do not report the classic symptoms of OSA patients, particularly do not complain of excessive daytime sleepiness (EDS). In the Hypnolaus study (1), a large population-based, epidemiologic study conducted in Lausanne, Switzerland, only one out of five patients with OSA complained of EDS. Therefore, although EDS is often the symptom prompting the patient to look for medical advice, in comorbid populations, particularly in cardiovascular patients, many patients do not report its occurrence. In these subjects, there is a clear need for a device that objectively measures and identifies the disorder and can be applied to large populations. Standard diagnostic procedures based on home sleep studies are currently insufficient to deal with the number of patients affected by a treatable disease, such as drug-resistant hypertension or a non-dipping profile, drug-resistant diabetes, cardiac arrhythmias, and stroke. Airgo™ could be proposed as a possible tool since automatic analysis requires no operator time to immediately identify patients with severe OSA. Although this is just a screening and does not properly classify the degree of the global risk of the patient since no information on the depth of desaturations can be obtained, it could nonetheless reliably identify the most severe patients in a case series of consecutive patients at high-risk. This could be used to prioritize waiting lists for home sleep studies, predict appropriateness in using less complex devices than polysomnography, identify subjects at risk of primary intervention failure, such as ablation for atrial fibrillation, or identify subjects at increased anesthesiologic risk for surgery patients.

Respiratory data are correlated with the signal of the three accelerometers indicating the position, and a RIC analysis is available for every position. This is crucial to identify patients with pOSA (14), 16 in our case series, who have all been identified correctly. A prevalence of 13% of pOSA is close to figures of the literature. Considering that pOSA can be treated effectively with specific instruments (15), such as postural trainers or mandibular advancement devices, when waiting lists for standard diagnosis

cause a significant delay in the management, the treatment could be instituted immediately. The percentage of time spent in the different positions is reported under each RIC, and if less than 10% of time is spent in the supine position, the reliability is low and requires further validation. Night to night variability is common in pOSA and mean AHI can vary substantially, but the index in the supine position is quite constant and its severity is informative to the clinician on the opportunity to begin treatment.

A screening tool is particularly useful when it correctly identifies subjects who do not have the disease. In our case series, 16 patients had an AHI below 5, and Airgo^{TM} identified properly 14 patients. The other two patients were misclassified as having moderate OSA since they had an intermittent flow limitation mimicking hypopneas, but without 3% desaturation. As a consequence, they had fluctuations of ventilation greater than 30%, but the high basal saturation and the short length of events did not cause significant desaturations. The definition of hypopnea has been revised in the guidelines several times, and the last edition of AASM recommendations has privileged the link to a desaturation of at least 3% to validate the semi-quantitative assessment of ventilation provided by nasal cannula and respiratory bands (16). This approach has a limit compared to the polysomnographic definition of earlier editions, which included an arousal at the end of the event even without desaturation (16). An arousal increases the tidal volume since respiratory control shifts from sleep drive to wakefulness drive (17), which is set on a lower level of carbon dioxide. Airgo^{TM} relies only on changes in ventilation to detect respiratory events, so compared to home sleep studies, it can overestimate the severity of the disorder in some patients, particularly when wakefulness respiratory drive is more active and causes big breaths at airflow resumption.

Considering the aim of screening, the correct identification of 87% of patients without OSA is important to avoid worthless polygraphy/polysomnography, sparing resources, and shortening waiting lists. The false-positive patients (13% in our case series) have no harm since they will undergo a home sleep study that will show no respiratory events requiring treatment.

Mild-to-moderate OSA patients require a formal sleep study for a proper diagnosis. The correct identification of this group in the screening could be assigned a lower priority in waiting lists and identify patients at a lower risk of consequences from OSA. Again, the discrepancy in the hypopnea detection led us to overestimate the severity of 3/40 patients (7.5%) who were allocated to the severe group. Two further patients (5%) were scored as normal and were false negatives. They had an AHI at Nox T3 of 17.9 and 18.4 events per hour, respectively, and a basal SaO_2 of close to 92%, therefore near to the steep portion of the oxyhemoglobin dissociation curve. In this case, the definition of hypopnea will consider as significant any change in ventilation greater than 30%, as SpO_2 will sharply decrease and validate the event. In these two patients, Airgo^{TM} underestimated the severity of the disease.

Finally, a group of 16 patients had miscellaneous disorders that caused turbulence in respiratory rhythm but could not be considered OSA patients. The underlying disorders were myoclonus in 4 patients, insomnia in 6 patients, periodic breathing with central hypopneas in 2 patients, and REM-related OSA in 4 patients. Despite the heterogenous origin of the disorder, all patients had in common an instability of respiratory rhythm, caused by sighs in the myoclonus and insomnia, in periodic breathing linked to the crescendo-decrescendo pattern of ventilation, and in REM-related due to the occurrence in clusters not related to body position. All these disorders caused a sharp decrease of RICs in the target area, going from severe to normal-mild in three deciles, a trend which is not typical of the more repetitive pattern of OSA. Airgo^{TM} identified 14 out of 16 patients correctly (87.5%) and considered normal the other 2 patients (one myoclonus and one REM-related). The opportunity to discriminate amongst these patients can be considered specific to Airgo^{TM} and is potentially useful in clinical practice. The correct diagnosis requires a setting more sophisticated than usual home sleep polygraphy, with at least leg movement sensors for myoclonus, standard PSG for insomnia, and REM-related OSA (18). Using a standard home sleep monitor would be inconclusive, and again, this screening tool could help in sparing resources and avoiding useless polygraphies.

Considering the overall performance of the Airgo^{TM}, data on sensitivity and specificity are consistent with the opportunity to implement the use of the device as a screening tool for sleep respiratory disorders, particularly for OSA. The positive likelihood ratio is above 10 and the negative likelihood ratio is below 0.1, both suggesting reliability in ruling in and ruling out the disorder. The classification of severity in a few patients (3 normals and 2 mild OSAs) has been overestimated. This is caused by the above-mentioned difference in scoring hypopneas only when at least a 3% desaturation occurs compared to the modulation of tidal volume assessed by the algorithm of Airgo^{TM}. In the real world, this could mean a few more studies performed in the diagnostic path following the screening, but considering the data reported in **Table 5**, the net amount of time saved and the consequent possible increase in the number of patients diagnosed properly seem to balance these few patients who would have to undergo a polygraphy without need.

Limitations of the Study

This is a monocentric study on patients referred to a sleep center for symptoms, clinical signs, or witnessed apneas. It is possible that in a specific subgroup of patients or in the general population sensitivity and specificity could vary. The number of patients tested is large, but the results should be validated in bigger numbers. The percentage of females is low, 23 out of 120 patients recruited, a 19% rate which does not allow separate analysis of data to assess a possible difference in sensitivity gender-related. This is not surprising since patients of sleep centers are predominantly males and it is possible that the results of the present study cannot be representative of the female population. The results have not been compared with other screening tools (i.e., questionnaires) since the study focused on the use of the device *per se* and at least two groups of patients (pOSA and non-OSA patients) are not stratified by common questionnaires. Airgo^{TM} was positioned by sleep lab technicians and despite the simplicity of the procedure, it is possible that

in less experienced centers or when the patient himself has to wear the band more studies could fail. Considering that one of our patients had switched off the device before the beginning of the study, the Airgo™ was then modified to avoid this inconvenience. Pregnancy is a condition that changes respiratory mechanics and adds a second breathing organism. Considering the characteristics of the curve detected in the validation study (11) the device would probably be unreliable. Patients with recent thoracic or abdominal surgery are poor candidates due to the effect on ventilatory mechanics of the procedure and complete recovery should be awaited. Kyphoscoliosis and other thoracic abnormalities could reduce the reliability of Airgo™, but have not been specifically tested in the present study and none of the patients enrolled had thoracic abnormalities.

Perspectives

A promising application of the device is the possibility to perform monitoring over consecutive nights, up to 21 with a single battery. The memory of the device supports the storing of every single breath. The use of a single night study has been questioned, particularly in mild to moderate disease, posture-related OSA, and in patients with irregular sleep habits (i.e., shift workers, binge drinking on the weekend). In the prospect of personalized medicine and in the correct allocation of risk category, using the device for at least three nights could be more informative than a single-night traditional study (19). The assessment of treatment results alternative to CPAP could also benefit from this approach. Mandibular advancement devices and position trainers can change their effectiveness from night to night, a piece of information that standard sleep studies do not provide. Another group of patients who could benefit from this approach is those with OSA and insomnia, who are often disturbed by the number of sensors of usual polygraphy and who again have a high night-to-night variability. The opportunity to have a single band and more than one night of assessment could be much more informative than traditional techniques in a consistent number of patients, quantified in different studies as between 20 and 60% of the total number of OSA patients.

The use of Airgo™ as a screening tool is only a part of the rich, informative signal processing of the device. The visualization of vectors recorded overnight is far more informative, but goes beyond the aim of this study which excluded the operator's skill in interpreting the results and just applied the automatic analysis to obtain a low-cost, time-saving screening tool.

CONCLUSION

Airgo™ is a reliable tool to screen patients with respiratory sleep disorders. In OSA patients, it discriminates between severe OSA and positional OSA and is quite accurate in ruling out those who have no respiratory disturbances. Mild to moderate OSA is correctly identified as well in the large majority of the patients, but the difference in technology leads to some discrepancy in the hypopnea detection compared to standard polygraphy. A clinically useful additional information is the detection of patients who have irregularities of breathing patterns as a consequence of sleep fragmentation (i.e., insomnia, myoclonus), candidates for polysomnography for proper diagnosis, avoiding an inconclusive home sleep study, and contributing to optimize resources and the waiting list of the sleep lab.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by "Salvatore Maugeri Foundation" Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB and DK contributed to conception and design of the study. MG and FR organized the database. AB and CS scored the studies. AB, DK, and EM wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REFERENCES

1. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the hypnolaus study. *Lancet Respir Med.* (2015) 3:310–8. doi: 10.1016/S2213-2600(15)00043-0
2. Salman LA, Shulman R, Cohen JB. Obstructive sleep apnea, hypertension, and cardiovascular risk: epidemiology, pathophysiology, and management. *Curr Cardiol Rep.* (2020) 22:6. doi: 10.1007/s11886-020-1257-y
3. Rundo JV. Obstructive sleep apnea basics. *Cleve Clin J Med.* (2019) 86:2–9. doi: 10.3949/ccjm.86.s1.02
4. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. 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.
5. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med.* (2019) 7:687–98. doi: 10.1016/S2213-2600(19)30198-5
6. Bock J, Covassin N, Somers V. Excessive daytime sleepiness: an emerging marker of cardiovascular risk. *Heart.* (2022). 319596. doi: 10.1136/heartjnl-2021-319596
7. Fietze I, Dingli K, Diefenbach K, Douglas NJ, Glos M, Tallafuss M, et al. Night-to-night variation of the oxygen desaturation index in sleep apnoea

syndrome. *Eur Respir J.* (2004) 24:987–93. doi: 10.1183/09031936.04.00100203
8. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, et al. Obstructive sleep apnea and cardiovascular disease a scientific statement from the American heart association. *Circulation.* (2021) 144:e56–67.
9. Mittal S, Golombeck D, Pimienta J. Sleep apnoea and AF: where do we stand? Practical advice for clinicians. *Arrhythmia Electrophysiol Rev.* (2021) 10:140–6. doi: 10.15420/aer.2021.05
10. Ranjan R. Is it time to screen all patients for sleep apnea before atrial fibrillation ablation? *JACC: Clin Electrophysiol.* (2020) 6:1507–8. doi: 10.1016/j.jacep.2020.06.018
11. Antonelli A, Guilizzoni D, Angelucci A, Melloni G, Mazza F, Stanzi A, et al. Comparison between the airgoTM device and a metabolic cart during rest and exercise. *Sensors.* (2020) 20:1–19. doi: 10.3390/s20143943
12. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. *J Clin Sleep Med.* (2012) 8:597–619. doi: 10.5664/jcsm.2172
13. Defaye P, De La Cruz I, Martí-Almor J, Villuendas R, Bru P, Sénéchal J, et al. A pacemaker transthoracic impedance sensor with an advanced algorithm to identify severe sleep apnea: the DREAM European study. *Hear Rhythm.* (2014) 11:842–8. doi: 10.1016/j.hrthm.2014.02.011
14. Oksenberg A, Gadoth N, Töyräs J, Leppänen T. Prevalence and characteristics of positional obstructive sleep apnea (POSA) in patients with severe OSA. *Sleep Breath.* (2020) 24:551–9. doi: 10.1007/s11325-019-01897-1
15. Mok Y, Tan A, Hsu PP, Seow A, Chan YH, Wong HS, et al. Comparing treatment effects of a convenient vibratory positional device to CPAP in positional OSA: a crossover randomised controlled trial. *Thorax.* (2020) 75:331–7. doi: 10.1136/thoraxjnl-2019-213547
16. Collop N, Berry R. COUNTERPOINT: should hypopneas only be scored when accompanied by oxygen desaturation? *Chest.* (2021) 160:417–9. doi: 10.1016/j.chest.2020.08.2139
17. Horner RL, Rivera MP, Kozar LF, Phillipson EA. The ventilatory response to arousal from sleep is not fully explained by differences in CO2 levels between sleep and wakefulness. *J Physiol.* (2001) 534:881–90.
18. Ferri R, Fulda S, Allen RP, Zucconi M, Bruni O, Chokroverty S, et al. World association of sleep medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms developed by a joint task force from the international and the European restless legs syndrome study groups (IRLSSG and EURLSSG). *Sleep Med.* (2016) 26:86–95. doi: 10.1016/j.sleep.2016.10.010
19. Penzel T, Dietz-Terjung S, Woehrle H, Schöbel C. New paths in respiratory sleep medicine: consumer devices, e-health, and digital health measurements. *Sleep Med Clin.* (2021) 16:619–34. doi: 10.1016/j.jsmc.2021.08.006

Conflict of Interest: ICS Maugeri holds stocks of Myair Inc. DK, CEO of both Myair Inc. and its subsidiary Myairgo Italy Srl, has a clear conflict of interest in this study. DK is a major shareholder in Myair Inc. as well as the inventor and principal developer of the Airgo technology platform and the author of all related patents. DK has provided much of the know-how and developed many of the algorithms used to produce the Airgo Sleep Reports being tested in this clinical trial.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between sleep-disordered breathing and periodontal diseases: A systematic review protocol

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Background: Sleep-disordered breathing (SDB) is a chronic sleep-related breathing disorder, considered associated with increased risk of cardiovascular disorders, metabolic disorders, cognitive dysfunction and behavior changes. Periodontal diseases are chronic infectious diseases that are also believed to be associated with cardiovascular diseases, metabolic syndrome and cognitive dysfunction. Several studies have indicated that SDB may be associated with periodontal diseases through certain mechanisms such as inflammation response, oxidative stress and oral dryness. The aim of this systematic review is to explore the association between SDB and periodontal diseases in an integrated approach.

Materials and methods: This systematic review will include cohort studies, cross-sectional studies and case-control studies that are identified by electronic and manual searches. Electronic searches will be conducted in the following databases: PubMed, Embase, Scopus and Web of Science. Our search will cover articles published from inception of databases to March 2022 without restrictions in language and settings. Pre-determined eligibility criteria include: participants (participants without a history of respiratory diseases, history of periodontal treatment within the past 6 months and history of medication that is known to influence SDB or periodontal diseases); exposure (participants who have been diagnosed with SDB or at high-risk for SDB); comparison (participants without SDB); and outcome (periodontal parameters, such as probing depth, clinical attachment level, bleeding on probing, radiographic bone loss). Two authors will perform study screening and data extraction independently and in duplicate. All discrepancies will be solved by discussion. The methodological quality of included studies will be assessed using the Newcastle-Ottawa Scale.

Discussion: This systematic review will summarize the existing evidence on the association between SDB and periodontal diseases, a topic of controversy and clinical significance. Its findings can provide evidence for the development of relevant prevention and treatment strategies. The results will be disseminated through peer-reviewed journals.

Systematic review registration: www.crd.york.ac.uk/PROSPERO, identifier: CRD42022313024. Registered on March 28th 2022.

KEYWORDS

sleep-disordered breathing, obstructive sleep apnea, periodontal diseases, systematic review, protocol

Introduction

Sleep-disordered breathing (SDB) encompasses a spectrum of disorders, including primary snoring, obstructive sleep apnea (OSA) disorders, central sleep apnea (CSA) syndromes, sleep-related hypoventilation and sleep-related hypoxemia (1). Characterized by episodic sleep-related obstruction of the upper airway, OSA is the most common phenotype of SDB (2). Predisposing factors include obesity, tonsillar and adenoid hypertrophy, a short neck and retrognathia (2, 3). As a consequence of sleep apnea, sleep fragmentation results in excessive daytime sleepiness and poor concentration (4). SDB is associated with increased incidence of cardiovascular diseases, neurocognitive deficits and metabolic syndrome (5, 6). The prevalence of SDB ranges widely from 0.7 to 36.5%, depending on gender, age and ethnicity (7–9).

Periodontal diseases mainly include gingivitis and periodontitis, which are a series of chronic inflammatory diseases caused by bacteria in the dental plaque and products of host immune response (10, 11). In 2015–2016 prevalence of periodontitis in Mainland China population aged 35 years or older was almost 90%, and the rate of severe periodontitis was over 30% (12). The periodontal diseases are associated with systemic chronic diseases including diabetes mellitus, atherosclerosis, cardiovascular diseases and metabolic syndrome (13–16). Recently, studies have indicated that periodontal diseases may be associated with SDB (17, 18).

Some potential mechanisms underlying the association between SDB and periodontal diseases have been raised in the literature. Cyclical episodes of hypoxemia-reoxygenation injury in SDB patients can enhance levels of pro-inflammatory cytokines and oxygen free radicals, leading to oxidative stress and inflammation response (2). Likewise, in patients with periodontitis, the inflammatory cytokines have been shown to be elevated (19). The pro-inflammatory cytokines and oxidative stress are responsible for the destruction of periodontal tissue (20). Evidence indicated that inflammation biomarkers related to both conditions include interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-α (TNF-α), high-sensitivity C-reactive protein (hs-CRP) and others (21). Consequently, the pro-inflammatory immune response may result in a bidirectional link between the two conditions. Another potential mechanism is oral dryness due to mouth breathing. Dry mouth symptoms caused by prolonged oral breathing are common in patients with SDB (22), which leads to greater bacterial colonization and accumulation, as well as increased risk of periodontal diseases (23, 24).

Several studies have reported a significant association between SDB and periodontitis (17, 25, 26). An observational study found that the risk of periodontitis in patients at high risk of OSA was approximately double that at low risk of OSA (27). In addition, a population-based study indicated a lower proportion of OSA in periodontal patients who had undergone either periodontal flap surgery or gingivectomy (28). Conversely, some researchers demonstrated a conflicting conclusion that there was no association between OSA and the prevalence of moderate/severe periodontitis (29). To our knowledge, there is no published systematic review on the relationship between SDB and periodontal diseases. Al-Jewair et al. (30), Lembo et al. (31) and Khodadadi et al. (32) investigated the relationship between OSA and periodontal diseases, but those reviews focused on OSA rather than all sleep-related breathing disorders. Hence, the results of this systematic review will be more comprehensive and detailed.

Materials and methods

Protocol and registration

This protocol was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist. The checklist is displayed in Supplementary file 1. The present systematic review is registered in the PROSPERO database (CRD42022313024).

Research question

This systematic review summarizes the existing evidence regarding the relationship between SDB and periodontal diseases. The aim is to investigate whether there is an association between various types of SDB and periodontal diseases.

Criteria for considering studies for this review

Types of studies

We will include observational studies using a cohort, case-control, or cross-sectional design that report the correlation between various types of SDB and periodontal diseases. Book chapters, opinion pieces, abstracts, review articles, case report, case series and randomized controlled trials will be excluded.

Types of participants

We will include observational studies of participants with and without SDB, diagnosed either objectively with overnight polysomnography (PSG) or subjectively using self-reported questionnaires. SDB is classified into the following categories: OSA, CSA, sleep-related hypoventilation, sleep-related hypoxemia and snoring (1). The apnea-hypopnea index (AHI) is defined as the number of apneas and hypopneas per hour during sleep. The American Academy of Sleep Medicine defines apnea and hypopnea as varying degrees of reduction in respiratory airflow, and these events at least have a span of 10 s (33). OSA is indicated when the PSG results suggest AHI $\geq$5/h in adult patients or AHI $\geq$1/h in pediatric patients. CSA is defined as AHI $\geq$5/h in adult or AHI $\geq$1/h in children, with $\geq$50% of these apneas /hypopneas being due to central respiratory events (34, 35). Sleep-related hypoventilation is characterized by an elevated level of $PaCO_2$ to a value $\geq$45 mmHg while asleep or by abnormally increased $PaCO_2$ levels compared to those while awake (36). Sleep-related hypoxemia is defined as an arterial oxygen saturation of $\leq$88% for more than 5 min during sleep (1). Snoring is the acoustic phenomena during sleep reported by the affected patient or bed partner. It is an isolated diagnosis without hints for OSA (37). The self-reported questionnaires used to assess risk of SDB include Berlin Questionnaire (BQ), Epworth's Sleepiness Scale (ESS), Pediatric Sleep Questionnaire (PSQ), Stanford Sleepiness Scale, the snoring, tiredness, observed apnea, high BP, BMI, age, neck circumference, and male gender (STOP-Bang) questionnaire, and Apnea Risk Evaluation System (ARES). We will exclude studies in which over 30% participants had a history of respiratory diseases, history of periodontal treatment within the past 6 months or history of medication that is known to influence SDB or periodontal diseases.

Types of outcome measures

The selection of periodontal parameters was based on the 2018 Consensus Report of Classification of Periodontal and Peri-implant Diseases and Conditions (38).

Primary outcome

- Probing depth (PD)

Secondary outcomes

- Clinical attachment level (CAL)
- Bleeding on probing (BOP)
- Radiographic bone loss (RBL)
- Oral hygiene indices (OHI)
- Plaque index (PI)
- Gingival index (GI)
- Gingival recession (GR)
- Inflammation biomarkers (e.g., IL-1, IL-6, TNF-α, hs-CRP).

Search strategy

We will conduct both electronic searches and manual searches to identify articles related to our research question. Electronic searches without any language and geographic setting restrictions will be conducted in the following four databases: PubMed, Embase, Scopus, and Web of Science (from inception to March 2022). Search strategies combining medical subject headings (MeSH) and free texts will be used according to specifications of each database. Search strategy for PubMed is shown in Table 1 and details for other three databases is depicted in Supplementary file 2. We will also conduct a supplementary manual search by checking the reference lists of key relevant studies and review articles for additional studies that are missed in electronic searches.

Data collection and analysis

Study selection

Records retrieved from each database will be imported into Endnote X9 and duplicates will be identified and removed. Two authors will independently check the titles and abstracts of retrieved records and exclude articles that clearly do not meet the inclusion criteria. Then we will examine full texts of the remaining articles independently and in duplicate to identify studies that meet the eligibility criteria. Any discrepancy regarding the eligibility of articles will be resolved by discussion among authors. The study selection process will be presented with a flow chart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (39).

TABLE 1 Example search strategy for PubMed.

Search concept	
Sleep-disordered breathing	Periodontal diseases
#1 Sleep Apnea Syndromes [Mesh Terms]	**#5** Dentistry [Mesh Terms]
#2 Mouth breathing [Mesh Terms]	**#6** Periodontal Diseases [Mesh Terms]
#3 (sleep apnea* OR sleep disordered breathing OR sleep-related breathing disorder* OR sleep breathing disorder* OR snoring OR snore OR SDB OR OSA OR OSAS OR OSAHS) [Title/Abstract]	**#7** Gingival Diseases [Mesh Terms]
	#8 (periodontal disease* OR periodontitis OR gingival disease* OR gingivitis OR periodontal index OR gingival index OR plaque index OR alveolar bone loss OR clinical attachment loss OR periodontal pocket depth* OR tooth mobility OR tooth loss* OR gingival recession* OR dental plaque*) [Title/Abstract]
#4 #1 OR #2 OR #3	**#9** #5 OR #6 OR #7 OR #8

Overall search = #4 AND #9. The * symbol indicates the variable truncation.

Data extraction and management

Two authors will use a piloted data extraction form to collect data from each included study independently and in duplicate. We will resolve discrepancies through discussion and consult a third reviewer if necessary to reach a consensus. If full-texts of included studies lack required information or data, we will contact the corresponding authors and request them to provide. If multiple publications exist for the same study, we will use data from the article that report the latest follow-up or contain the most information. We will record the following data:

- Study characteristics (author; title; publication year; geographical setting; study design; sample size);
- Participant characteristics (number; age; sex; inclusion and exclusion criteria; SDB diagnostic criteria; periodontal parameters);
- Outcome characteristics (primary and secondary outcomes collected; duration of follow-up);
- Other characteristics (funding sources; conflicts of interest).

Assessment of risk of bias in included studies

We will use Newcastle-Ottawa Quality Assessment Scale (NOS) (40) to assess the methodological quality of included cohort and case-control studies, and an adapted form of NOS (41) to assess cross-sectional studies. NOS uses a semi quantitative "star system" with a maximum score of 9 to judge studies from three perspectives: selection of study groups, comparability of groups, and ascertainment of outcomes. We will classify the overall risk of bias for each included study as low risk of bias if the NOS score is equal to or >6 and high risk of bias if the score is <6 (42, 43). Two authors will independently assess the included studies and any disagreement will be resolved by discussion with two other experts.

Measures of association

For dichotomous outcomes, we will use odd ratios (OR) with 95% confidence intervals (CI) to express estimates of effect. For continuous results measured using the same scale, we will summarize the data with mean difference (MD) and standard deviations (SD). For continuous results measured using different scales or units, we will use standardized mean difference (SMD).

Assessment of heterogeneity

Before combining studies in meta-analysis, we will assess clinical heterogeneity by examining the diversity of participants, exposures and outcomes to ensure that the included studies are sufficiently homogeneous to estimate summary effects. We will evaluate statistical heterogeneity with a chi-square test, using P-value < 0.1 as indicator of statistically significant heterogeneity. The I square (I^2) statistic will be used to quantify heterogeneity with low values indicating little heterogeneity and high values indicating high heterogeneity:

- 0–40%: low heterogeneity;
- 30–60%: moderate heterogeneity;
- 50–90%: considerable heterogeneity;
- 75–100%: high heterogeneity (44).

Assessment of reporting biases

A funnel plot and the Egger's test will be used to assess publication bias of studies if more than 10 studies are included in a meta-analysis (45). If asymmetry is found, we will investigate the possible causes.

Data synthesis

When two or more studies provide comparable data, we will perform a meta-analysis to explore the association between SDB and periodontal diseases. Meta-analyses will be performed using the generic inverse variance method with Review Manager 5.3. Where meta-analyses are not possible, we will use a narrative approach to present data on outcome of interest.

Subgroup analyses and investigation of heterogeneity

If the included studies can provide adequate data, we will perform subgroup analyses according to the following characteristics:

- Study design (cohort study, case-control study, cross-sectional study);
- Age of participants (children vs. adults);
- Type of SDB (snoring, obstructive sleep apnea disorders, central sleep apnea syndromes, sleep-related hypoventilation, sleep-related hypoxemia).

Sensitivity analyses

Sensitivity analyses will be carried out to evaluate the robustness of meta-analysis results. We will repeat the analysis with the adjustment of excluding studies with high risk of bias.

Discussion

Over the past few years, several studies have investigated the bi-directional relationship between SDB and periodontal diseases, suggesting that the two conditions share some common risk factors (17, 25–27). SDB and periodontal diseases are both associated with some systematic diseases, including cardiovascular diseases, metabolic disorders and cognitive dysfunction (5, 10, 46). Some potential mechanisms have been introduced in the direction of the association between the two diseases. Oxidative stress, inflammation response and oral dryness maybe the bridges between them (20–22, 24). However, other studies have found that SDB was not related to periodontal diseases (29, 47). With increasing complexity of the question, it is necessary to synthesize and update available evidence.

We will conduct this systematic review based on PRISMA guidelines and assess the methodological quality of included studies according to NOS. Strict inclusion and exclusion criteria will be considered, and both electronic and manual searches will be performed to obtain comprehensive data. However, potential limitations of this systematic review are worth noting. Inconsistent sample characteristics and diagnostic methods may result in substantial heterogeneity. If possible, we will perform subgroup analyses to investigate heterogeneity.

In summary, this systematic review will integrate the existing evidence regarding the association between SDB and periodontal diseases, which are important components of population health. Our search strategy has no restriction on age, language or race, which may lead us to find more comprehensive and detailed evidence of the association between SDB and periodontal diseases. Our findings will help to motivate clinicians and policy makers to consider the importance of the association between these two diseases, and will promote prevention and treatment strategies for both diseases. By integrating existing evidence, we may uncover gaps in research of this field, thereby provide guidance for future research.

Author contributions

DC, ZM, and FH conceived the idea. DC, ZM, TZ, XY, HH, and FH designed methodology. DC, ZM, and XY developed search strategies. DC and ZM drafted the original manuscript. TZ, HH, FH, and WD revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.960245/full#supplementary-material

References

1. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest.* (2014) 146:1387–94. doi: 10.1378/chest.14-0970

2. Cowie MR. Sleep apnea: state of the art. *Trends Cardiovasc Med.* (2017) 27:280–9. doi: 10.1016/j.tcm.2016.12.005

3. Veasey SC, Rosen IM. Obstructive sleep apnea in adults. *N Engl J Med.* (2019) 380:1442–9. doi: 10.1056/NEJMcp1816152

4. Kuzniar TJ, Kasibowska-Kuzniar K. Sleep-disordered breathing. *Dis Month.* (2011) 57:394–402. doi: 10.1016/j.disamonth.2011.06.002

5. Farrell PC, Richards G. Recognition and treatment of sleep-disordered breathing: an important component of chronic disease management. *J Transl Med.* (2017) 15:114. doi: 10.1186/s12967-017-1211-y

6. Scalzitti NJ, Sarber KM. Diagnosis and perioperative management in pediatric sleep-disordered breathing. *Paediatric Anaesth.* (2018) 28:940–6. doi: 10.1111/pan.13506

7. Yamagishi K, Ohira T, Nakano H, Bielinski SJ, Sakurai S, Imano H, et al. Cross-cultural comparison of the sleep-disordered breathing prevalence among Americans and Japanese. *Eur Resp J.* (2010) 36:379–84. doi: 10.1183/09031936.00118609

8. Khokhrina A, Andreeva E, Degryse JM. The prevalence of sleep-disordered breathing in Northwest Russia: the ARKHsleep study. *Chron Respir Dis.* (2020) 17:1479973120928103. doi: 10.1177/1479973120928103

9. Bixler EO, Vgontzas AN, Lin H-M, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample prevalence and risk factors. *Sleep*. (2009) 32:731–6. doi: 10.1093/sleep/32.6.731

10. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. *Nat Rev Dis Primers.* (2017) 3:17038. doi: 10.1038/nrdp.2017.38

11. Khan SA, Kong EF, Meiller TF, Jabra-Rizk MA. Periodontal diseases: bug induced, host promoted. *PLoS Pathog.* (2015) 11:e1004952. doi: 10.1371/journal.ppat.1004952

12. Jiao J, Jing W, Si Y, Feng X, Tai B, Hu D, et al. The prevalence and severity of periodontal disease in Mainland China: data from the fourth national oral health survey (2015-2016). *J Clin Periodontol.* (2021) 48:168–79. doi: 10.1111/jcpe.13396

13. Taylor JJ, Preshaw PM, Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. *J Periodontol.* (2013) 84(Suppl. 4):S113–34. doi: 10.1902/jop.2013.134005

14. Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, et al. Periodontitis and cardiovascular diseases: consensus report. *J Clin Periodontol.* (2020) 47:268–88. doi: 10.1111/jcpe.13189

15. Jepsen S, Suvan J, Deschner J. The association of periodontal diseases with metabolic syndrome and obesity. *Periodontol 2000.* (2020) 83:125–53. doi: 10.1111/prd.12326

16. Beck JD, Slade G, Offenbacher S. Oral disease, cardiovascular disease and systemic inflammation. *Periodontology*. (2000) 23:110–20. doi: 10.1034/j.1600-0757.2000.2230111.x

17. Sanders AE, Essick GK, Beck JD, Cai J, Beaver S, Finlayson TL, et al. Periodontitis and sleep disordered breathing in the hispanic community health study/study of latinos. *Sleep*. (2015) 38:1195–203. doi: 10.5665/sleep.4890

18. Grillo C, La Mantia I, Zappala G, Cocuzza S, Ciprandi G, Andaloro C. Oral health in children with sleep-disordered breathing: a cross-sectional study [Article]. *Acta Biomed*. (2019) 90:52–9. doi: 10.23750/abm.v90i7-S.8661

19. Cardoso EM, Reis C, Manzanares-Cespedes MC. Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases. *Postgraduate Med.* (2018) 130:98–104. doi: 10.1080/00325481.2018.1396876

20. Sczepanik FSC, Grossi ML, Casati M, Goldberg M, Glogauer M, Fine N, et al. Periodontitis is an inflammatory disease of oxidative stress: we should treat it that way. *Periodontol 2000.* (2020) 84:45–68. doi: 10.1111/prd.12342

21. Liu X, Ma Y, Ouyang R, Zeng Z, Zhan Z, Lu H, et al. The relationship between inflammation and neurocognitive dysfunction in obstructive sleep apnea syndrome. *J Neuroinflammation.* (2020) 17:229. doi: 10.1186/s12974-020-01905-2

22. Zhang C, Shen Y, Liping F, Ma J, Wang GF. The role of dry mouth in screening sleep apnea. *Postgrad Med J.* (2021) 97:294–8. doi: 10.1136/postgradmedj-2020-137619

23. Lamster IB, Asadourian L, Del Carmen T, Friedman PK. The aging mouth differentiating normal aging from disease. *Periodontology 2000.* (2016) 72:96–107. doi: 10.1111/prd.12131

24. Mizutani S, Ekuni D, Tomofuji T, Azuma T, Kataoka K, Yamane M, et al. Relationship between xerostomia and gingival condition in young adults. *J Periodontal Res.* (2015) 50:74–9. doi: 10.1111/jre.12183

25. Gamsiz-Isik H, Kiyan E, Bingol Z, Baser U, Ademoglu E, Yalcin F. Does obstructive sleep apnea increase the risk for periodontal disease? A case-control study. *J Periodontol.* (2017) 88:443–9. doi: 10.1902/jop.2016.160365

26. Chen Y, Metz JE, Gao H, Gao X. Association between obstructive sleep apnea and periodontitis in Chinese male adults: a cross-sectional study. *J Prosthetic Dent.* (2021) S0022-3913(21)00594-1. doi: 10.1016/j.prosdent.2021.11.001. [Epub ahead of print].

27. Al Habashneh R, Khassawneh B, Khader YS, Abu-Jamous Y, Kowolik MJ. Association between obstructive sleep apnea and periodontitis among male adults attending a primary healthcare facility in jordan. *Oral Health Prev Dent.* (2016) 14:157–64. doi: 10.3290/j.ohpd.a35002

28. Keller JJ, Wu CS, Chen YH, Lin HC. Association between obstructive sleep apnoea and chronic periodontitis: a population-based study [Article]. *J Clin Periodontol.* (2013) 40:111–7. doi: 10.1111/jcpe.12036

29. Loke W, Girvan T, Ingmundson P, Verrett R, Schoolfield J, Mealey BL. Investigating the association between obstructive sleep apnea and periodontitis. *J Periodontol.* (2015) 86:232–43. doi: 10.1902/jop.2014.140229

30. Al-Jewair TS, Al-Jasser R, Almas K. Periodontitis and obstructive sleep apnea's bidirectional relationship: a systematic review and meta-analysis. *Sleep Breath.* (2015) 19:1111–20. doi: 10.1007/s11325-015-1160-8

31. Lembo D, Caroccia F, Lopes C, Moscagiuri F, Sinjari B, D'Attilio M. Obstructive sleep apnea and periodontal disease: a systematic review. *Medicina.* (2021) 57:640. doi: 10.3390/medicina57060640

32. Khodadadi N, Khodadadi M, Zamani M. Is periodontitis associated with obstructive sleep apnea? A systematic review and meta-analysis. *J Clin Exp Dent.* (2022) 14:e359–65. doi: 10.4317/jced.59478

33. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American academy of sleep medicine task force. *Sleep*. (1999) 22:667–89. doi: 10.1093/sleep/22.5.667

34. Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. *Eur Resp J.* (2017) 49:1600959. doi: 10.1183/13993003.00959-2016

35. Berry RB, Quan SF, Abreu AR. *The AASM Manual for Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.6*. Darien, IL: American Academy of Sleep Medicine (2020).

36. Casey KR, Cantillo KO, Brown LK. Sleep-related hypoventilation/hypoxemic syndromes. *Chest.* (2007) 131:1936–48. doi: 10.1378/chest.06-2334

37. Stuck BA, Hofauer B. The diagnosis and treatment of snoring in adults. *Deutsches Arzteblatt Int.* (2019) 116:817–24. doi: 10.3238/arztebl.2019.0817

38. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. *J Periodontol.* (2018) 89(Suppl. 1):S173–82. doi: 10.1002/JPER.17-0721

39. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* (2009) 339:b2535. doi: 10.1136/bmj.b2535

40. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z

41. Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC Public Health.* (2013) 13:154. doi: 10.1186/1471-2458-13-154

42. Araújo MM, Martins CC, Costa LC, Cota LO, Faria RL, Cunha FA, et al. Association between depression and periodontitis: a systematic review and meta-analysis. *J Clin Periodontol.* (2016) 43:216–28. doi: 10.1111/jcpe.12510

43. Zheng DX, Kang XN, Wang YX, Huang YN, Pang CF, Chen YX, et al. Periodontal disease and emotional disorders: a meta-analysis. *J Clin Periodontol.* (2021) 48:180–204. doi: 10.1111/jcpe.13395

44. Higgins JPTJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021)*. London: The Cochrane Collaboration (2021).

45. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629

46. Calvin AD, Albuquerque FN, Lopez-Jimenez F, Somers VK. Obstructive sleep apnea, inflammation, and the metabolic syndrome. *Metab Syndr Relat Disord.* (2009) 7:271–8. doi: 10.1089/met.2008.0093

47. Sales-Peres SH, Groppo FC, Rojas LV, de CS-PM, Sales-Peres A. Periodontal status in morbidly obese patients with and without obstructive sleep apnea syndrome risk: a cross-sectional study. *J Periodontol.* (2016) 87:772–82. doi: 10.1902/jop.2016.150587

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