frontiers | Research Topics

Recent advances in obstructive sleep apnoea (OSA)

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Published in
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-8325-6375-5
DOI 10.3389/978-2-8325-6375-5

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Recent advances in obstructive sleep apnoea (OSA)

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Citation

Zhou, L., Liu, H., Lombardi, C., Gouveris, H., eds. (2025). *Recent advances in obstructive sleep apnoea (OSA)*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-6375-5

Table of contents

frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 09 May 2025
DOI 10.3389/fmed.2025.1609695

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 10 April 2025
ACCEPTED 25 April 2025
PUBLISHED 09 May 2025

CITATION
Zhou L, Wang L, Zheng P, Zhu X, Zi G, Chen L, Cai X, Liu H and Liu W (2025) Editorial: Recent advances in obstructive sleep apnoea (OSA). *Front. Med.* 12:1609695. doi: 10.3389/fmed.2025.1609695

Editorial: Recent advances in obstructive sleep apnoea (OSA)

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KEYWORDS

obstructive sleep apnea, bioinformatics, multidisciplinary approach, translational research, cardiovascular-metabolic comorbidity

Editorial on the Research Topic
Recent advances in obstructive sleep apnoea (OSA)

Introduction

Obstructive sleep apnea (OSA), a chronic respiratory disorder characterized by recurrent upper airway collapse during sleep, has emerged as a global health challenge, affecting nearly one billion individuals worldwide. Its prevalence exceeds 50% in certain high-risk populations, underscoring its status as a silent epidemic (1). Beyond its direct respiratory consequences, OSA is intricately linked to a 2–3-fold increased risk of cardiovascular and metabolic diseases, including hypertension, coronary heart disease, diabetes, and cognitive impairment (2). Despite its profound public health burden, therapeutic options remain limited, with continuous positive airway pressure (CPAP) therapy recognized as the gold standard; however, adherence rates are suboptimal (3). The absence of definitive pharmacological interventions and reliable biomarkers further complicates clinical management. This Research Topic, "*Recent Advances in Obstructive Sleep Apnea (OSA)*," was conceived to address these gaps by fostering interdisciplinary dialogue, highlighting novel methodologies, and translating mechanistic insights into actionable clinical strategies. The 10 articles featured in this Research Topic reflect the diversity and depth of contemporary OSA research. They encompass pathophysiology, genetic and epidemiological associations, biomarker discovery, and therapeutic innovations, collectively advancing our understanding of OSA as a systemic disorder with far-reaching implications. Below, we synthesize these contributions within three thematic frameworks: (1) OSA as a multisystem disease, (2) bioinformatics and genetic insights, and (3) therapeutic advancements and challenges.

OSA as a Multisystem Disease: Unraveling Complex Associations recurring theme across this Research Topic is the recognition of obstructive sleep apnea (OSA) as a systemic condition intertwined with a variety of comorbidities. Liu P. et al. explore the bidirectional relationship between OSA and polycystic ovary syndrome (PCOS), positing shared hormonal and inflammatory pathways. Their work highlights insulin

resistance and hyperandrogenism as potential mediators, suggesting that OSA screening should be prioritized in cohorts with PCOS. Similarly, Zhao et al. employ Mendelian randomization (MR) to disentangle the causal links between hypothyroidism and OSA. Their findings reveal a bidirectional association, implicating thyroid hormone dysregulation in upper airway collapsibility and intermittent hypoxia (IH)-induced thyroid dysfunction. These studies underscore the necessity for holistic management of OSA within the context of endocrine disorders. The systemic impact of OSA extends to musculoskeletal and oncological domains. Research synthesizes evidence linking OSA to osteoarthritis (OA), proposing chronic inflammation and oxidative stress as shared mechanisms (Weng et al.). Meanwhile, Yao et al. combine cohort studies and MR to demonstrate a robust association between OSA and lung cancer risk. Their analysis suggests that IH-driven hypoxia-inducible factor (HIF) activation and immune dysregulation may fuel carcinogenesis, a hypothesis warranting longitudinal validation. Cardiovascular complications, a hallmark of OSA, are revisited by Chen et al. Research who elucidate the role of cardiac autonomic dysfunction and structural remodeling in OSA-related arrhythmias (Chen et al.). Their work emphasizes the need for early autonomic profiling to stratify arrhythmia risk in patients with OSA. Collectively, these articles reinforce OSA's role as a multisystem disruptor, urging clinicians to adopt a proactive, comorbidity-aware approach.

Bioinformatics and Genetic Insights: Decoding OSA's Complexity The integration of bioinformatics and genetic methodologies has revolutionized research on obstructive sleep apnea (OSA), enabling high-throughput discovery of biomarkers and mechanistic pathways. Xie et al. introduce the Intermittent Hypoxia Index, a novel metric for quantifying the severity of intermittent hypoxia. By correlating IHI with markers of endothelial dysfunction and oxidative stress, they provide a framework for personalized risk assessment. This aligns with the findings of Liu, Yang et al., who review pharmacological targets derived from transcriptomic and proteomic analyses, including hypoxia-inducible factor (HIF) inhibitors and anti-inflammatory agents. Genetic epidemiology takes center stage in the work of Zhao et al. and Yao et al., Both leveraging Mendelian randomization (MR) to infer causality-a method that minimizes confounding biases inherent to observational studies. These contributions exemplify how genetic tools can disentangle the etiological web of OSA, identifying modifiable risk factors and therapeutic targets. Research explores the regulatory role of estrogen in the pathogenesis of OSA, integrating gene expression data from animal models and clinical cohorts (Zhou et al.). The authors propose estrogen replacement therapy as a potential intervention for postmenopausal women with OSA, bridging bench-to-bedside innovation. Such findings underscore the transformative potential of bioinformatics in guiding precision medicine.

Therapeutic Advancements and Challenges: Toward Personalized Management Despite the efficacy of Continuous Positive Airway Pressure (CPAP) therapy, its limitations necessitate the exploration of alternative strategies. Seifen et al. investigate periodic limb movements (PLMs) in obstructive sleep apnea (OSA) patients without comorbidities, revealing a subset of patients who experience PLM-driven sleep fragmentation that is resistant to CPAP treatment. Their work advocates for the use of polysomnographic phenotyping to tailor therapeutic interventions. The critical appraisal of pharmacological innovation is presented by Liu, Xu et al., who catalog emerging drug candidates that target pathways induced by intermittent hypoxia (IH). Promising agents identified include leptin analogs and antioxidants; however, clinical trial data remain sparse. Their findings advocate for multidisciplinary care models that integrate expertise from respiratory, endocrine, and nutritional disciplines.

This Research Topic underscores the complexity of OSA while charting a path toward translational solutions. Key takeaways include: 1. OSA serves as a gateway to systemic disease, necessitating focused screening and management of comorbidities. 2. Bioinformatics and genetic tools are indispensable for unraveling the heterogeneity of OSA and identifying relevant biomarkers. 3. Multidisciplinary therapies—combining CPAP, pharmacological agents, and lifestyle interventions—hold promise for mitigating metabolic and cardiovascular sequelae. However, challenges persist. The lack of large-scale omics datasets from diverse populations limits the generalizability of biomarkers. Furthermore, the bidirectional causality between OSA and its comorbidities necessitates longitudinal studies to clarify temporal relationships.

Conclusion

The articles in this Research Topic exemplify the vibrancy of Obstructive Sleep Apnea (OSA) research, effectively bridging mechanistic discovery and clinical innovation. As guest editors, we express our sincere gratitude to the authors, reviewers, and readers for their invaluable contributions to this evolving field. By fostering collaboration across genetics, bioinformatics, and clinical medicine, we are progressing toward transforming OSA from a widespread burden into a manageable condition.

Author contributions

LZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. PZ: Conceptualization, Investigation, Methodology, Writing – review & editing. XZ: Conceptualization, Investigation, Methodology, Software, Writing – review & editing. GZ: Conceptualization, Investigation, Writing – review & editing. LC: Conceptualization, Investigation, Writing – review & editing. XC: Conceptualization, Investigation, Software, Writing – review & editing. HL: Writing – original draft, Writing – review & editing, Data curation. WL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration,

Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National Natural Science Foundation of China (82270104), Scientific and Technological Innovation 2030 (2023ZD0506700, 2024ZD0541700), Health Commission of Hubei Province Scientific Research Project (WJ2023Z010), Hubei Provincial Natural Science Foundation (2024AFB050, 2025AFB057), the Postdoctor Project of Hubei Province under Grant Number (2024HBBHCXB025), the Natural Science Foundation of Wuhan (2024040801020345), and Tongji Hospital Fund Cultivation project (2024B10, 2024B26).

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

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 01 March 2024
DOI 10.3389/fmed.2024.1359461

OPEN ACCESS

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RECEIVED 21 December 2023
ACCEPTED 22 February 2024
PUBLISHED 01 March 2024

CITATION
Liu J, Yang X, Li G and Liu P (2024) Pharmacological interventions for the treatment of obstructive sleep apnea syndrome.
Front. Med. 11:1359461.
doi: 10.3389/fmed.2024.1359461

Pharmacological interventions for the treatment of obstructive sleep apnea syndrome

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Obstructive Sleep Apnea Syndrome (OSAS) affects 13–33% of males and 6–9% of females globally and poses significant treatment challenges, including poor adherence to Continuous Positive Airway Pressure (CPAP) and residual excessive sleepiness (RES). This review aims to elucidate the emerging interest in pharmacological treatments for OSAS, focusing on recent advancements in this area. A thorough analysis of extensive clinical trials involving various drugs, including selective dopamine reuptake inhibitors, selective norepinephrine inhibitors, combined antimuscarinic agents, and orexin agonists, was conducted. These trials focused on ameliorating respiratory metrics and enhancing sleep quality in individuals affected by OSAS. The studied pharmacological agents showed potential in improving primary outcomes, notably the apnea-hypopnea index (AHI) and the Epworth sleepiness scale (ESS). These improvements suggest enhanced sleep quality and symptom management in OSAS patients. With a deeper understanding of OSAS, pharmacological interventions are emerging as a promising direction for its effective management. This review provides a comprehensive overview of the current state of drug research in OSAS, highlighting the potential of these treatments in addressing the disorder's complex challenges.

KEYWORDS

OSAS, pharmacological treatments, respiratory disorder, ESS, CPAP

1 Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is a prevalent sleep disorder affecting approximately 9–38% of adults worldwide. It is more common in males (13–33%) than females (6–19%), with a higher prevalence among older adults. Excessive daytime sleepiness seems to have a greater impact on younger adults than the elderly. Genetic factors also contribute to the development of OSAS, emphasizing its importance as a global public health issue (1–3).

The hallmark of OSAS revolves around upper airway obstructions or dysfunctions, leading to symptoms such as intermittent hypoxemia, oxidative stress, sleep fragmentation, and excessive daytime sleepiness (4, 5). Patients with moderate to severe OSAS often encounter an array of health concerns, including cognitive impairments, and psychological ailments (4, 6–8). More alarmingly, untreated OSAS is associated with severe health issues like cardiovascular diseases, diabetes, and hyperlipidemia. Such comorbidities often worsen

the prognosis for OSAS patients, affecting their quality of life and treatment adherence (5, 9–11).

Continuous positive airway pressure (CPAP) is recognized as the primary therapeutic intervention for patients with moderate to severe OSAS and is judiciously prescribed for select mild cases. While CPAP has been demonstrated to substantially mitigate symptoms such as hypoxemia, fatigue, depression, and anxiety, and diminish the associated cardiovascular mortality risk, its implementation does present certain challenges (12). However, the long-term adherence to CPAP remains suboptimal. This, coupled with the chronic nature of OSAS treatment, results in many unsuccessful treatment endeavors. Other alternatives like mandibular advancement devices and surgical interventions, though beneficial to some extent, are constrained by their cost and uncertain outcomes (13). Other non-surgical methods, such as positional therapy and transcutaneous electrical stimulation, are yet to be validated in extensive clinical trials. A profound understanding of OSAS and the exploration of new treatment modalities is crucial. This study aims to delve deeper into the pathophysiological mechanisms of OSAS, hoping to pave the way for the development of novel, safe, and effective pharmaceuticals.

2 Pathophysiological mechanisms and risk factors of OSAS

2.1 Introduction to OSAS etiology

Recent research on OSAS has enhanced our understanding that its etiology may be associated with impaired function of the upper airway dilator muscles during sleep, constricted airway passages, and reduced respiratory stability (14). This understanding opens avenues for tailored treatments based on individual patient phenotypes.

2.2 Inducing factors

These insights guide ongoing and forthcoming research toward developing targeted treatments tailored to diverse patient phenotypes. OSAS is a chronic disorder, originating from various anatomical abnormalities. This review concisely summarizes its pathophysiological underpinnings, encompassing both the initiating factors and risk components (4, 14). Several inducing factors contribute to OSAS, such as reduced surface tension, upper airway luminal narrowing, diminished lung volume, unstable respiratory control, dysfunctional upper airway muscles, and a low arousal threshold. Generally, pharyngeal collapse, primarily due to anatomical alterations in the upper airway, is considered a predominant etiological factor (15).

2.3 The role of high loop gain

The term "high loop gain," a feedback control system in the human body, reflects the balance between ventilation and its disturbances, and its role in OSAS is associated with upper airway muscle activity and carbon dioxide concentration (14, 16).

2.4 Arousal threshold

The arousal threshold plays a pivotal role in the pathogenesis of OSAS. Some studies have indicated that arousals can be triggered once inhalation reaches a certain intensity (17) which subsequently impacts respiratory stability. Frequent arousals can lead to blood oxygen disturbances, resulting in fragmented sleep patterns that prevent patients from entering deeper stages of sleep, thereby exacerbating their OSAS (18–21).

2.5 Upper airway muscle dysfunction

This dysfunction is central to OSAS development. While effective in countering inhalation-induced negative pressure when awake, during sleep, these muscles' activity diminishes, predisposing the pharynx to collapse and result in respiratory obstruction (22). The genioglossus muscle, a principal part of the pharyngeal dilator muscles, exhibits varied activity across different sleep stages; it's more active during inhalation than exhalation. Therefore, the loss of reflexes between central input neurons and upper airway muscles might contribute to the onset of OSAS (22–25). Additionally, neurogenic damage or excessive muscle fatigue leading to reduced genioglossus muscle function, or pharyngeal sensory impairments, can cause airway collapse (26–28).

2.6 Specific risk factors

Some factors, such as a low arousal threshold, reduced lung volume, or unstable respiration, might seem normal but can still lead to OSAS (29). Smoking, which relaxes the respiratory muscles causes upper airway obstruction (30, 31). Aging, characterized by a reduction in pulmonary elastic recoil, can lead to airway collapse. Alcohol intake impacts not just sleep quality but also significantly elevates the risk for OSAS. Studies have demonstrated that elevated alcohol consumption raises the risk of sleep apnea by 25% (relative risk 1.25, with a 95% confidence interval of 1.13–1.38, $p < 0.0001$) (32). This link between high alcohol intake and increased sleep apnea risk underscores the importance of reducing alcohol consumption as a potential therapeutic and preventive approach to this condition. Additionally, gender and body composition play a role: males inherently have longer airways than females, increasing their susceptibility to passive airway collapse, while obesity may result in fat deposition within the tongue, potentially compromising the function of the genioglossus muscle and impacting lung volume. Furthermore, conditions such as menopause and adenotonsillar hypertrophy (4) are also recognized as potential risk factors for OSAS (33–35).

2.7 The PALM model

Eckert et al. proposed a comprehensive model in 2013 to elucidate the pathophysiological mechanisms underlying OSAS.

This model incorporates Pharyngeal critical pressure (P), a Low arousal threshold (A), a High loop gain (L), and the Muscle responsiveness of the upper airway (M). The prominence of the PALM-2 phenotype allows for tailored treatment strategies aligned with the distinct pathophysiological characteristics of individual patients (36).

2.8 Identifying subtypes of OSAS

Obstructive Sleep Apnea Syndrome is characterized by significant health risks and symptom variability, making its management complex. Subtype analysis has been key in identifying OSA subgroups like "excessively sleepy" and "disturbed sleep," which differ in cardiovascular risk and treatment efficacy (37). Labarca et al. (38) highlight that patients with the "excessively sleepy" subtype face a higher cardiovascular mortality risk after 5 years, emphasizing the need for customized treatment approaches (38). Specifically, the "excessively sleepy" group may require more intensive treatments to lower cardiovascular risk, while those with "disturbed sleep" could benefit from cognitive behavioral therapy focused on specific symptoms.

3 Diagnosis

3.1 Polysomnography (PSG) in OSAS diagnosis

Polysomnography is the gold standard for diagnosing OSAS. It involves the monitoring of a multitude of physiological parameters to evaluate the patient's condition: Electroencephalography of bilateral frontal, central, and occipital lobes to assess cerebral electrical activity. Surface chin and leg electromyogram to evaluate the genioglossus muscle beneath the chin, crucial for identifying rapid eye movement sleep. Left and right eye electrooculograms to monitor eye movements. Nasal pressure sensors to measure variations in nasal airflow. Pulse oximetry for measuring hemoglobin saturation levels. Monitoring the intensity and frequency of snoring and utilizing respiratory inductive plethysmography belts, among others.

3.2 Home sleep apnea testing (HSAT)

In cases where patients lack severe comorbidities—like stroke, central sleep disorders, or a history of prolonged opioid use—Home Sleep Apnea Testing can be an alternative. The test should span over more than one night, as multiple nights' records can enhance diagnostic accuracy and prognostic value. HSAT offers better patient compliance and cost-effectiveness compared to PSG. However, it falls short in sensitivity relative to PSG. Hence, if HSAT doesn't confirm the diagnosis, PSG remains the preferred choice. Future advancements should focus on refining HSAT and improving its associated technology (39).

4 Pharmacological interventions in OSAS treatment

Exploring the pathophysiological complexities of OSAS paves the way for pinpointing appropriate therapeutic agents for alleviating symptoms. A range of medications, rigorously tested in clinical trials, has emerged as notably effective. Among them are drugs modulating neurotransmitters, especially impacting dopamine (DA) and norepinephrine (NA) receptor levels. This category includes selective dopamine reuptake inhibitors, norepinephrine inhibitors, combined adrenergic-anticholinergic agents, and orexin agonists. Several drugs, including modafinil, pitolisant, and solriamfetol, enhance alertness in patients, helping to alleviate daytime drowsiness and cognitive lapses. At the same time, medications such as atomoxetine, oxybutynin, reboxetine, and oxybutynin target specific muscles in the upper respiratory tract, such as the genioglossus, elevator, and tensor palatine muscles, to mitigate sleep-related breathing problems. In essence, our deepening grasp of pathophysiology informs these therapeutic directions. The effectiveness of these drugs in trials underscores the merit of this strategy, hinting at even more refined OSAS interventions on the horizon (40, 41). The relevant studies on pharmacological treatments for OSAS are summarized in **Table 1**.

4.1 Modafinil and armodafinil: wake-promoting agents

Modafinil was originally developed for the treatment of narcolepsy. Its pharmacological actions have been partially elucidated, suggesting that its efficacy might be achieved through a combination of actions on norepinephrine α1, dopamine, and orexin receptors. Animal studies have further implied its association with α1B adrenergic receptors or in conjunction with cAMP response element-binding protein and mitogen-activated protein kinase promoting binding with D1 receptors in mouse wakefulness regions (42, 43). Furthermore, in rodent studies, MOD increased dopamine levels in the brain and decreased GABA release, leading to the continuous activation of brain regions associated with alertness (44, 45). Distinctively, MOD's neuron activation is more localized in certain brain regions compared to traditional stimulants like amphetamines (46).

Interestingly, MOD is also considered a catecholamine reuptake inhibitor. Animal investigations further suggest that it can affect dopamine and norepinephrine transporters in the brains of adult monkeys, elevating the levels of DA and NA, and thereby aiding in maintaining an alert state (47). In 2004, the US FDA approved MOD as an effective treatment for OSAS, particularly beneficial for patients who still exhibit excessive daytime sleepiness (EDS) after CPAP treatment. The recommended initial dose should not exceed 200 mg (48–50). Numerous randomized controlled trials (RCT) have attested to MOD's superior efficacy in treating OSA (51–60). An RCT conducted by Julia et al. revealed that treatment with 200 mg of modafinil for over 2 weeks significantly improved symptoms of EDS in patients with mild to moderate OSAS (52). The Epworth Sleepiness Scale (ESS) scores decreased by 3.6 points. Interestingly, the therapeutic effects were comparable,

TABLE 1 Summary of pharmacological treatments for OSAS.

Drug name	References	Research design	Study duration	Treatment measure		Outcome
				Treatment group (N)	Control group (N)	
Modafinil	(49)	RCT	2 weeks	200 mg/day (16)	Placebo (15)	Modafinil reduced daytime sleepiness in men with mild to moderate OSA
Modaifinil	(52)	OCT	12 months	200–400 mg/day (266)		Modafinil boosts alertness and functioning, leading to better quality of life with long-term tolerability
Modaifinil	(54)	RCT	12 weeks	200 mg/day (104) 400 mg/day (101)	Placebo (104)	Modafinil improves clinical metrics and performance with good tolerability
Modaifinil	(55)	OCT	12 weeks	200–400 mg/day (58)	Placebo (67)	Modaifinil reduced daytime sleepiness and improved sleep function and quality of life
Modafinil	(56)	RCT	4 weeks	200–400 mg/day (77)	Placebo (80)	Modafinil reduced daytime sleepiness and enhanced psychomotor vigilance
Armodafinil	(58)	RCT	2 weeks	150 mg/day (35)	Placebo (34)	Armodafinil improved driving safety and quality of life for patients awaiting CPAP therapy
Armodafinil	(50)	RCT	12 weeks	200 mg/day (125)	Placebo (124)	Armodafinil improved ESS and CGI-C scores, with MWT slightly higher
Armodafinil	(53)	RCT	12 weeks	150 mg/day (131) 250 mg/day (131)	Placebo (130)	Armodafinil mitigates the effects of excessive sleepiness on daily life
Pitolisant	(63)	RCT	12 weeks	20 mg/days (200)	Placebo (68)	In patients not using CPAP, Pitolisant enhanced daytime alertness and overall clinical status
Pitolisant	(65)	RCT	12 weeks	20 mg/day (183)	Placebo (61)	Pitolisant notably reduced sleepiness symptoms and improved patients' condition severity
Solriamfetol	(73)	RCT	12 weeks	37.5–300 mg/day (355)	Placebo (119)	Solriamfetol enhanced patients' alertness with favorable results
Solriamfetol	(72)	RCT	6 weeks	75–300 mg/day (62)	Placebo (62)	Solriamfetol enhanced alertness and reduced subjective sleepiness
Solriamfetol	(75)	RCT	2 weeks	150–300 mg/day (17)	Placebo (17)	Solriamfetol enhanced driving performance in those with EDS
Solriamfetol	(80)	RCT	12 weeks	37.5–300 mg/day (355)	Placebo (119)	Armodafinil enhanced driving performance and life quality in OSA patients awaiting CPAP treatment
Solriamfetol	(78)	RCT	12 weeks	37.5–300 mg/day (345)	Placebo (114)	Solriamfetol reduced daytime sleepiness
Reb-Oxy	(89)	RCT	2 weeks	Reb 4 mg-Oxy 5 mg/day (9)	Placebo (9)	Reb-Oxyreduced daytime sleepiness
AD109	(92)	RCT	3 night	Low-dose (37.5 + 2.5 mg, 32) high dose (75+2.5 mg, 25)	Placebo (28) Placebo (15)	AD109 boosted sleep quality in mild to moderate patients
Ato-Oxy	(95)	RCT	3 night	Ato 80 mg–Oxy 5 mg (32)	Placebo (20)	Ato-Oxy enhanced sleep quality in mild to moderate patients
Ato-Oxy	(96)	RCT	1 month	Ato 80 mg (15) Oxy 15 mg (10)	Placebo (10)	Ato-Oxy improved sleep with high tolerability

RCT, randomized controlled trial; OCT, openly clinical-trials; OSA, obstructive sleep Apnea; ES, excessive sleepiness; CGI-C, clinical global impression of change; CPAP, continuous positive airway pressure; Reb, reboxetine; AD109, armodafinil dimesylate; Ato, atomoxetine; Oxy, oxybutynin.

if not superior, to standard CPAP treatment. Moreover, patients expressed a preference for pharmacological intervention over CPAP. Similarly, a cross-over RCT by David and colleagues demonstrated that modafinil (400 mg for 3 weeks) ameliorated electroencephalographic activities during periods when CPAP treatment was halted (51). The study also noted enhancements in cognitive and neurobehavioral functions. A 1-year open-label study echoed the safety and efficacy outcomes observed in shorter trials, highlighting improvements in the patient's quality of life (55).

Armodafinil, recognized as the R-enantiomer of modafinil, operates via a similar mechanism. Several RCTs have documented its beneficial effects (61). A meta-analysis by Julia and Liora incorporated 10 studies with 1466 patients (48). Their findings solidified the therapeutic value of modafinil and armodafinil. Compared to placebo, the ESS scores of patients improved by 2.2 points, and the Maintenance of Wakefulness Test (MWT) duration increased by 3 min. Clinically, symptom improvement was 1.6 times higher than that of placebo. However, some research indicates that armodafinil doesn't alter frontal cortex MRI readings, suggesting that patients might still experience persistent hypersomnia (62).

Regarding side effects, modafinil's most common adverse reaction is headaches, which are experienced by over 35% of users. Other mild side effects, such as nausea, diarrhea, altered taste sensations, anxiety, and insomnia, have been reported but are less prevalent. Notably, headaches remain the predominant complaint among patients (47).

4.2 Pitolisant: a selective H3 receptor antagonist

Pitolisant stands as a selective H3 receptor antagonist or inverse agonist. By uniquely binding to the H3 receptors, it fosters a heightened release of histamine, thereby promoting wakefulness in patients. Current studies suggest its applicability in treating conditions like narcolepsy, Parkinson's disease, and daytime hypersomnia in patients with OSAS (63). Furthermore, pitolisant augments the levels of other monoaminergic neurotransmitters, such as NA, acetylcholine, and DA, offering additional symptomatic relief (64). The drug exhibits a plasma half-life between 10 and 12 h. It is predominantly absorbed in the gastrointestinal tract, metabolized in the liver, and excreted via the kidneys. As such, caution is advised for patients with renal insufficiency (50, 65). Dauvilliers et al. (66) conducted a study with 268 patients, of whom 75% were male. The average age of the participants was 52, and their baseline characteristics included an AHI index of 49/h and a baseline ESS score of 15.7. This study aimed to evaluate the efficacy and safety profile of Pitolisant in OSAS patients. The outcomes indicated a significant reduction in the ESS score compared to a placebo group, with no noted withdrawal symptoms post-discontinuation. Moreover, several double-blind RCTs revealed Pitolisant's ability to alleviate fatigue and ameliorate the severity of the disorder (67, 68).

A meta-analysis involving 678 patients, including 166 with narcolepsy and 512 with OSAS, indicated that Pitolisant exhibited a significantly greater therapeutic efficacy in OSAS patients compared to those with narcolepsy. This suggests that pitolisant may be more suitable for the treatment of OSAS (69). Common adverse reactions post-pitolisant administration include headaches, nausea, insomnia, and anxiety. Notably, the drug may induce a QT interval prolongation, warranting avoidance of concurrent administration with Class 1A and 3 antiarrhythmic drugs. The use of Pitolisant is contraindicated for individuals with severe hepatic or renal impairments (50).

4.3 Solriamfetol: a selective dopamine and norepinephrine reuptake inhibitor

In 2019, both the European Medicines Agency and the U.S. FDA endorsed the approval of Solriamfetol (Sunosi) for the treatment of narcolepsy and OSAS in adults. Sunosi functions as a selective reuptake inhibitor for dopamine and norepinephrine within the cells, targeting their transporters to suppress reuptake (70, 71). These neurotransmitters play pivotal roles in sleep modulation and excessive daytime sleepiness (72). For patients with OSAS, the recommended initial dosage is 37.5 mg/day. Depending on its efficacy and tolerability, the dosage may be adjusted up to a maximum recommended daily dose of 150 mg (71). However, several clinical trials have tested doses as high as 300 mg without significant adverse reactions (73–76). A meta-analysis conducted by Subedi et al. revealed no significant difference in outcomes, including mean differences in MWT and ESS scores and relative risk values for adverse events, between the 150 and 300 mg dosages (77). Significantly, it also highlighted a rising discontinuation rate with increasing dosages. When compared to other wakefulness-promoting drugs such as modafinil, pitolisant, and sodium oxybate, solriamfetol showed superior improvements in both MWT and ESS scores. The adverse event relative risk was lower than modafinil and sodium oxybate but higher than pitolisant.

Research led by Vinckenbosch explored the effects of solriamfetol on the road-driving behavior of OSA patients. Utilizing the standard deviation of lateral position as the primary measure, Solriamfetol notably improved both driving performance and alertness compared to a placebo (78). Badran's study also highlighted its positive influence on cognitive deficits and anxiety behaviors induced by chronic intermittent hypoxia in mouse models (79). Both short-term (12 weeks) and long-term (up to 52 weeks) trials showcased robust efficacy in ameliorating daytime activities and work efficiency in OSA patients with excessive daytime sleepiness, as assessed by MWT and ESS scores (80–83).

Adverse reactions associated with solriamfetol most commonly included headaches, nausea, and anxiety. These reactions peaked in the first week post-administration and mostly resolved within a week. While the incidence of severe side effects was comparable to the placebo group, doses exceeding the recommended 150 mg posed an increased risk of side effects (84, 85). Modafinil, pitolisant, and solriamfetol are medications that play a key role in the treatment of OSAS. Their mechanism of action for managing OSAS is depicted in **Figure 1A**. These drugs work by targeting specific pathways and receptors involved in sleep regulation, promoting wakefulness, and reducing excessive daytime sleepiness.

4.4 Reboxetine combined with oxybutynin: a potential dual-therapy for OSAS

In the pathophysiology of OSAS, there is a simultaneous interplay between pharyngeal changes and alterations in the control of upper airway muscles during sleep. It is estimated that over 30% of patients experience a reduction in the activity of the upper airway dilator muscles as a result of the narrowing of the airway (86, 87). However, to date, no drug has been approved

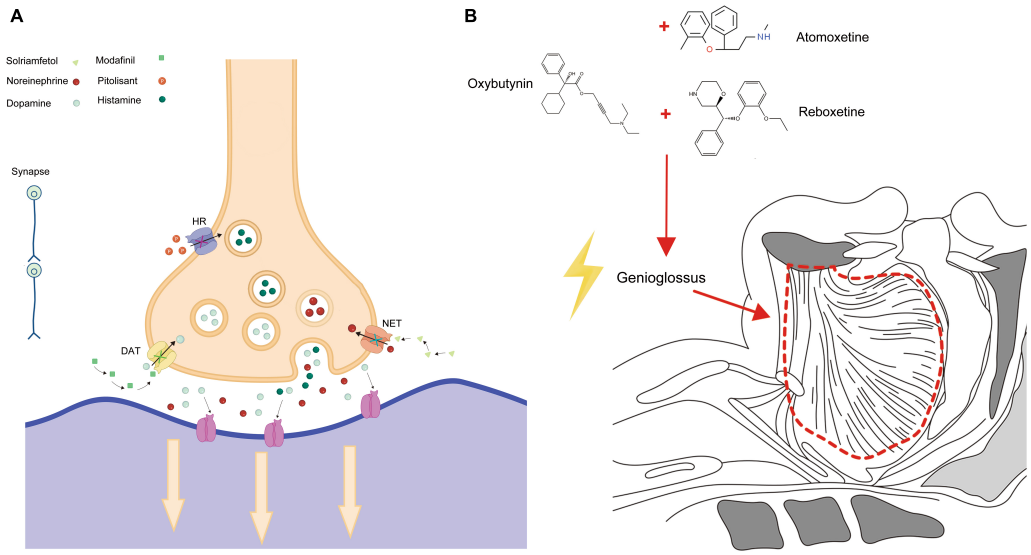

FIGURE 1
Pharmacological action in OSAS treatment. **(A)** Depicts the specific action mechanisms of Modafinil, Pitolisant, and Solriamfetol in treating OSAS. **(B)** Illustrates the broader pharmacological pathways and interactions of these medications.

to treat OSAS by enhancing the activity of the upper airway muscle. Nevertheless, animal studies have demonstrated that enhancing genioglossus muscle activity during both wakefulness and sleep can alleviate symptoms of OSAS (88). Research indicates that both noradrenergic and antimuscarinic agents modulate the genioglossus muscle during both non-REM and REM sleep (89).

Reboxetine, a noradrenaline reuptake inhibitor, enhances the activity of the central neurotransmitter, offering promise as a new-generation antidepressant to improve patient mood. A study by Lim et al. (90) found that when combined with oxybutynin, an antimuscarinic agent, reboxetine can modulate genioglossus muscle activity during sleep, improve airway function, and alleviate OSAS symptoms (91). This improvement is attributed to the increase in loop gain and a reduction in the ventilatory response during wakefulness (90). This drug combination significantly improves nocturnal hypoxemia in severe OSAS patients and reduces the AHI index to <15 events/hour, with a remarkable 59% reduction in AHI for 81% of patients within a week. Although many trials have shown that standalone drug treatments aren't significantly effective, this drug combination has demonstrated marked efficacy, reducing the severity of OSAS. However, this combined therapy is accompanied by certain adverse reactions, including insomnia, dry mouth, constipation, and excessive sweating. Currently, its mid-term effects and optimal dosages remain uncertain, necessitating further randomized controlled trials. These trials should encompass longer treatment durations, varying dosages, and larger sample sizes.

4.5 Combined therapy of atomoxetine and oxybutynin

Atomoxetine, a selective noradrenaline reuptake inhibitor, is predominantly employed in the clinical treatment of attention-deficit hyperactivity disorder (92). In OSAS patients, its therapeutic mechanism aligns with the above-mentioned rationale. Moreover, *in vitro* experiments have demonstrated that Atomoxetine can inhibit G-protein-coupled inwardly rectifying potassium channels. These channels play a pivotal role in reducing the excitability of hypoglossal motor neurons, thereby diminishing pharyngeal muscle tone during sleep and influencing sleep patterns (88, 93).

Oxybutynin, traditionally utilized for treating urinary disorders such as overactive bladder and urinary urgency, acts as an antimuscarinic agent. It exerts a potent muscle-relaxant effect on smooth muscles. Furthermore, antimuscarinics obstruct the inhibitory effect of acetylcholine on upper airway muscle tone during REM sleep (89).

Consequently, therapeutic interventions targeting the upper airway muscle group can effectively mitigate symptoms in patients with mild to moderate anatomical deficiencies (94–96). Montemurro found that concurrent evening administration of Atomoxetine and Oxybutynin could significantly reduce or even eliminate the severity of symptoms in patients. The fixed-dose combination, known as AD036 (comprising 80 mg Atomoxetine and 5 mg Oxybutynin), is still under development (96). However, preliminary trials, especially in patients with moderate OSAS, have indicated promising therapeutic outcomes. Another formulation, AD109 at higher doses (75/2.5 mg), has shown analogous efficacy (94, 97). Moreover, further studies have emphasized that the therapeutic potency of the Atomoxetine-Oxybutynin combination surpasses that of other antimuscarinic drugs by a considerable margin (98). As for side effects, patients may experience nausea, dry mouth, fatigue, and reduced appetite, but these typically subside within 2 weeks of medication commencement. No severe adverse reactions have been reported so far, possibly due to the short treatment duration.

At present, most studies on the Atomoxetine-Oxybutynin combination span just one night, with a relatively small sample size. Only one research endeavor has exceeded a month in duration (99). Given that OSAS is an irreversible chronic condition, it's imperative

to conduct more extensive evaluations to gauge long-term efficacy and safety (94). Oxybutynin, Atomoxetine, and Reboxetine are three medications that have been found to have an impact on OSAS. The action mechanisms by which these drugs exert their effects on OSAS are primarily depicted in **Figure 1B**. This figure serves as a visual representation of the intricate processes and pathways involved in how Oxybutynin, Atomoxetine, and Reboxetine interact with the condition, ultimately leading to potential therapeutic benefits for individuals suffering from OSAS.

4.6 Pharmacological advancements in OSAS treatment

Modafinil, armodafinil, pitolisant, and solriamfetol are currently authorized for managing a range of sleep disorders, as evidenced by their formal approval status. In contrast, reboxetine, oxybutynin, and atomoxetine are under investigation, with ongoing research and clinical trials assessing their effectiveness in the treatment of OSA, pending formal endorsement for this particular indication. Orexin neurons are primarily located in the hypothalamus and can be classified into two types: Type A and Type B. These neurons are associated with sleep-wake cycles, cardiopulmonary function, and autonomic regulation (100). Animal studies have demonstrated that the long-term effects of sleep fragmentation and intermittent hypoxia can lead to axonal lesions in orexin neurons, resulting in irreversible damage and subsequent impairment of the brain's sleep-wake state (101, 102). Hence, targeting orexin in the brain holds significant potential for the development of novel therapeutic drugs.

Danavorexton is a selective agonist for the orexin-B receptor, which can help sustain and promote wakefulness. It has been shown to improve sleep quality in patients with narcolepsy and OSAS, reducing the residual EDS these patients experience (103–105). Another drug, Daridorexant, an antagonist for both orexin receptors, has been observed to improve the AHI and nighttime blood oxygen saturation in patients with mild to moderate conditions (106, 107).

Furthermore, medications like acetazolamide (108), non-benzodiazepines (109), and intranasal corticosteroids (110) have shown promise in clinical trials. While no significant adverse reactions were reported, their long-term efficacy and safety still require further investigation. A novel treatment approach involving the combined use of atomoxetine and fesoterodine has also shown an overall improvement in the severity of OSAS in patients (111). In summary, based on the pathological mechanisms of OSAS, the development and application of corresponding drugs are anticipated to become a primary choice for enhancing the quality of life of patients.

5 Conclusion

Based on the information presented, OSAS, as a chronic disease, affects multiple organ systems. In severe cases, it can lead to cognitive impairments and an increased risk of cardiovascular diseases (112, 113). As a supplement to CPAP therapy, pharmacological interventions have been employed to address the persistent excessive sleepiness in those diagnosed with OSAS (114). The use of modafinil and armodafinil has been shown to significantly improve symptoms of excessive daytime sleepiness, boost focus and vigilance, and improve overall clinical conditions as assessed by the CGI-C (Clinical Global Impressions–Improvement Scale). However, there has been no confirmed improvement in life quality or other cognitive areas such as memory and executive functions (115). CPAP is currently the primary treatment and effectively alleviates most of the patient's symptoms, the long-term compliance associated with its use remains a challenge (116). Therefore, the development of new drugs, especially targeting pathological mechanisms such as noradrenaline and orexin in the brain, and upper airway muscle tone, is of paramount importance and may emerge as an alternative to CPAP in the future.

However, most drug trials are of short duration, which limits their primary therapeutic application. Key metrics, such as reducing the AHI value, improving EDS symptoms, and increasing oxygen levels, require long-term studies for OSAS severity. As our understanding of the disease mechanism deepens, future treatments might be tailored based on individual OSAS phenotypes. Whether it's monotherapy or combined drug therapy, these advancements represent a step in a more promising direction for patients.

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

JL: Conceptualization, Formal Analysis, Writing – original draft. XY: Investigation, Resources, Writing – original draft. GL: Funding acquisition, Project administration, Writing – review and editing. PL: Data curation, Project administration, Supervision, Writing – review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the Natural Science Foundation of Hubei Province, China (No. 2023AFD074).

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

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frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 07 March 2024
DOI 10.3389/fmed.2024.1354489

OPEN ACCESS

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RECEIVED 12 December 2023
ACCEPTED 22 February 2024
PUBLISHED 07 March 2024

CITATION
Liu J, Xu J, Guan S and Wang W (2024) Effects of different treatments on metabolic syndrome in patients with obstructive sleep apnea: a meta-analysis.
Front. Med. 11:1354489.
doi: 10.3389/fmed.2024.1354489

Effects of different treatments on metabolic syndrome in patients with obstructive sleep apnea: a meta-analysis

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Background: Obstructive sleep apnea (OSA) and metabolic syndrome (MetS) often coexist, and the causal relationship between them is not yet clear; treatments for OSA include continuous positive airway pressure (CPAP), mandibular advancement device (MAD), surgery, and lifestyle intervention and so on. However, the effects of different treatments on metabolic syndrome in OSA patients are still under debate.

Objectives: Review the effects of different treatments on metabolic syndrome in OSA patients by meta-analysis.

Methods: we searched articles in PubMed, Embase, Cochrane Library, CNKI, CBM, and Wanfang data from database construction to Feb. 2024.RevMan5.4 and Stata software were used to conduct a meta-analysis of 22 articles.

Results: A total of 22 articles were finally included. The results showed that CPAP treatment could reduce the prevalence of metabolic syndrome in OSA patients in randomized controlled trials (RCTs) (RR = 0.82 [95% CI, 0.75 to 0.90]; $p < 0.01$) and single-arm studies (RR = 0.73 [95% CI, 0.63 to 0.84]; $p < 0.01$). As for metabolic syndrome components, CPAP treatment reduces blood pressure, fasting glucose (FG), triglycerides (TG), and waist circumference (WC) but can't affect high-density lipoprotein cholesterol (HDL-C) levels. Lifestyle intervention could significantly reduce the prevalence of metabolic syndrome in OSA patients (RR = 0.60 [95% CI, 0.48 to 0.74]; $p < 0.01$) and can lower blood pressure, fasting glucose, and waist circumference but can't affect the lipid metabolism of OSA patients. Upper airway surgery can only reduce TG levels in OSA patients (MD = −0.74 [95% CI, −1.35 to −0.13]; $p = 0.02$) and does not affect other components of metabolic syndrome. There is currently no report on the impact of upper airway surgery on the prevalence of metabolic syndrome. No study has reported the effect of MAD on metabolic syndrome in OSA patients.

Conclusion: We confirmed that both CPAP and lifestyle intervention can reduce the prevalence of MetS in OSA patients. CPAP treatment can lower blood pressure, fasting glucose, waist circumference, and triglyceride levels in OSA

patients. Lifestyle intervention can lower blood pressure, fasting glucose, and waist circumference in OSA patients. Upper airway surgery can only reduce TG levels in OSA patients.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42022326857.

KEYWORDS

obstructive sleep apnea, metabolic syndrome, continuous positive airway pressure, exercise, diet, surgery, meta-analysis

1 Introduction

Obstructive sleep apnea is a common disease characterized by repetitive airway collapse during sleep, which can lead to decreased blood oxygen saturation, causing chronic intermittent hypoxia (CIH) and sleep fragmentation. The main symptoms include snoring, sleep apnea, and daytime sleepiness (1). MetS is a common comorbidity of OSA; the main diagnostic criteria include abdomen obesity, hypertension, hyperglycemia, and dyslipidemia (2). A growing number of studies have shown that OSA is associated with an increased risk of MetS (3, 4). As the leading cause of metabolic disorders, CIH can promote sympathetic nerve activation, thus increasing blood pressure (5). CIH increases triglycerides and phospholipid synthesis, inhibits liver cholesterol uptake, and reduces triglycerides clearance, thus contributing to hyperlipidemia (6–8). As for glucose metabolism, CIH induces insulin resistance by causing β cell dysfunction and adipose tissue inflammation (9–11). Among adults aged 30 to 70, approximately 13% of men and 6% of women have moderate to severe OSA (12). Studies have shown that the prevalence of MetS in the Chinese population over 15 years old is 24.5% (13). It is estimated that 50–60% of obese people with MetS have OSA. Many previous studies have shown that both the prevalence of OSA in patients with MetS and the prevalence of MetS in OSA patients were at a high level (between 60 and 70%) (14–16), and both OSA and MetS were associated with an increased risk of cardiovascular disease.

The overlap in health outcomes in individuals with MetS and OSA makes it difficult to disentangle cause and effect and whether OSA treatments, such as CPAP, MAD, upper airway surgery, and weight loss, can improve these outcomes (17). As the first-line treatment for moderate and severe patients with OSA (18), CPAP treatment can effectively reduce the collapse of the upper airway, alleviate hypoxia, and improve clinical symptoms, including snoring and excessive daytime sleepiness (9). The randomized controlled trials conducted by Giampa et al. (19, 20) showed a significant decrease in the incidence of MetS in OSA patients after CPAP treatment compared to the control group. However, other studies have reached the opposite conclusion, suggesting that CPAP did not change the prevalence of MetS (21, 22). Among the various components of MetS, previous studies have only reached a consensus on reducing blood pressure after CPAP treatment (23). There were many controversies regarding its impact on other components of MetS, such as fasting glucose, blood lipids, and obesity. Upper respiratory surgery is a standard treatment for OSA. It is suitable for OSA patients who cannot tolerate CPAP or have apparent upper respiratory tract structural abnormalities. Traditional surgical methods include Uvulopalatopharyngoplasty (UPPP) and related soft tissue procedures, maxillomandibular advancement, tracheostomy (rarely used), and hypoglossal nerve stimulation. Upper airway surgery can reduce the apnea and hypopnea index of OSA patients, thereby improving their quality of life. Surgical intervention is an irreplaceable way to improve OSA for patients with severe OSA who are complicated with anatomical abnormalities (24). Surgery undoubtedly can improve the condition of OSA, but its improvement of metabolic disorders complicated with OSA was controversial in previous studies. The study of Warner et al. (25) proved that upper airway surgery can reduce blood pressure and fasting glucose levels in OSA patients but can't affect the reduction of blood lipids. However, some studies have suggested that upper airway surgery can significantly reduce triglyceride levels in OSA patients (26), while previous studies have failed to report the impact of surgery on the prevalence of MetS. Lifestyle intervention for OSA patients includes a low-calorie diet and exercise training. Lifestyle intervention can improve the severity of OSA, improve the co-existing metabolic disorders in patients, and reduce the risk of obesity, hypertension, and diabetes (27–29). Lifestyle intervention is recommended for obese OSA patients of any severity. It can be used as a primary treatment and combined with other therapies (18). MAD applies to patients with mild and moderate OSA. Some studies have shown that applying MAD can reduce patients' blood pressure but does not affect fasting glucose and blood lipids (30, 31). There is no study report on the effect of MAD on the prevalence of MetS in OSA patients. As for the impact of different MetS treatments on OSA patients, there is heterogeneity among the results of previous studies. In this study, we conducted a meta-analysis to investigate whether rational treatment of OSA improves the co-existing MetS in patients.

2 Methods

2.1 Search strategy

We systematically searched English articles using PubMed, Embase, and the Cochrane Library and searched the Chinese ones using CNKI, CBM, and Wanfang data. The keywords used for the search included "Metabolic Syndrome," "obstructive sleep apnea," "sleep-disordered breathing," "OSA," "OSAHS," and

corresponding Chinese words. The search time of studies was from the time of database construction to Feb.2024.2 Independent reviewers performed the study searching and screening process, and disagreements were resolved by discussion.

2.2 Inclusion and exclusion criteria

The inclusion criteria were: (1) published articles on OSA patients combined with MetS; (2) only adults (aged 18 years) were included; (3) CPAP, surgery, or lifestyle intervention was applied, and the duration of CPAP therapy was ≥2 weeks; and (4) Reported the number of patients with MetS or one of the following indicators before and after treatment: triglycerides, high-density lipoprotein cholesterol, blood pressure, fasting glucose, and waist circumference;

The following studies were excluded: (1) Reviews, abstracts, case reports, letters, and non-human studies. (2) Insufficient information provided.

2.3 Quality assessment

Two independent reviewers (J. N. Liu and J. H. Xu) evaluated the included studies using the quality assessment method, and disagreements were resolved via discussion. The Cochrane Collaboration for Systematic Reviews of Interventions was used to assess randomized controlled trials, the methodological index for non-randomized studies (MINORS) was used to evaluate non-randomized clinical trials, and the Newcastle-Ottawa Scale (NOS) was used to assess the quality of single-arm studies. Agreements between reviewers were resolved by discussion to reach a consensus.

2.4 Data extraction

We extracted data from 22 studies. These data were the first author, year of publication, study design, body mass index (BMI), AHI or RDI values of the participants, age, number of subjects, the duration of intervention, the number of patients with MetS, the levels of TG, HDL-C, SBP, DBP, fasting glucose and waist circumference, data from both the experimental groups and control groups in controlled trials, before and after treatment in single-arm studies. Our final analysis examined the differences in these values between them. Two independent reviewers performed this process.

2.5 Data synthesis

We used mean differences (MDs) and standard deviations for continuous data such as TG, HDL-C, SBP, DBP, fasting glucose, and waist circumference. RR was used to estimate the impact of different treatments on the prevalence of MetS. The associated CIs were calculated with p-values < 0.05, indicating significance. We also use funnel plots and Egger's test to assess publication bias. Heterogeneity was assessed using the Cochrane Q and chi-square tests with I-squared index tests. I-square $>0\%$ with p-values < 0.05 was considered high heterogeneity, using the random-effects model; otherwise, the fixed-effects model was used. Cochrane Collaboration's RevMan 5.4 and Stata software were used to analyze all data.

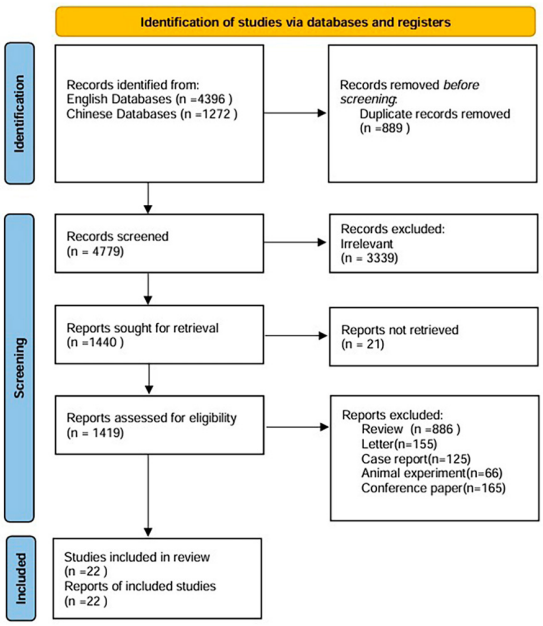

FIGURE 1
Flow diagram of the study selection process.

3 Results

A total of 5,668 studies were identified from different sources. Finally, data were taken from 22 articles, including 9 Chinese and 13 English articles. Figure 1 shows the process of the literature search. The characteristics of the studies are summarized in Table 1. According to the funnel plots and Egger's test outcome, the included studies had no significant publication bias.

3.1 Qualitative analysis

All included articles were published from 2007 to 2023. Of the 22 articles, 8 were RCTs, 2 were non-randomized controlled clinical trials, and the other 12 were single-arm studies. The mean age ranged between 35 and 70. The average Body Mass Index (BMI) ranged between 26.7 and 49.3 kg/m^2. The mean AHI ranged between 14 and 68.3/h. The duration of CPAP treatment and lifestyle intervention was 4 weeks to 12 months. The evaluation of surgical effectiveness is 6 or 12 months later.

3.2 Quality assessment

Newcastle-Ottawa Scale was used to evaluate the quality of single-arm studies. The eight single-arm studies' scores were six points or above, indicating high research quality. The MINORS scale was used to evaluate the study quality of non-randomized clinical trials. The scores of the two non-randomized clinical

TABLE 1 Characteristics of the enrolled studies in the meta-analysis.

References	Study design	Intervention	Population	AHI
Coughlin et al. (21)	RCT	CPAP	34	39.7 ± 13.8 (RDI)
Giampa et al. (20)	RCT	CPAP	100	58 ± 29
Sun et al. (19)	RCT	CPAP	128	CPAP: 48.9 ± 19.6 control: 46.8 ± 17.3
Hoyos (48)	RCT	CPAP	65	39.9 ± 17.7
Salord et al. (22)	RCT	CPAP	80	CPAP: 68.3 (43–88) control: 52.6 (37–78)
Xiao et al. (32)	RCT	CPAP	158	CPAP: 14 ± 12 control: 15 ± 10
Mota (49)	Single-arm study	CPAP	47	46.9+33.6
Oktay (50)	Single-arm study	CPAP	30	54.8 ± 22.9
Li et al. (6)	Single-arm study	CPAP	52	37.67 ± 17.95
Mineiro (51)	Single-arm study	CPAP	34	35.2 ± 18.8
Dorkova (52)	Single-arm study	CPAP	32	64.0 ± 20.8
Oyama (53)	Single-arm study	CPAP	32	56.2 ± 21.6
Xia (54)	Single-arm study	CPAP	112	–
Guo (55)	Single-arm study	CPAP	40	–
Desplan (56)	RCT	Exercise	20	Experimental 40.6 ± 19.4 control 39.8 ± 19.2
Cristiane (57)	Clinical trials	Low-calorie diet+exercise	24	Experimental 36 ± 5.1 control 36 ± 10.1
Edgar (58)	Clinical trials	Low-calorie diet+exercise	23	Experimental 31 ± 5 control 37 ± 7
Georgoulis et al. (27)	RCT	Low-calorie diet+exercise	180	MDG: 62 (37, 81) MLG: 60 (21,89) control: 52 (30, 84)
Peng (59)	Single-arm study	Surgery	45	55.1 ± 17.8
Hua (60)	Single-arm study	Surgery	23	51.9 ± 15.8
Zhu (61)	Single-arm study	Surgery	35	41.1 ± 6.2
Chen et al. (5)	Single-arm study	Surgery	26	37.65 ± 15.59
References	**BMI**	**Age**	**Duration of trials**	**Outcome**
Coughlin et al. (21)	36.1 ± 7.6	49 ± 8.3	1.5 months,3.9 ± 0.74 h/night	SBP, DBP, HDL-C, TG, FG, Mets
Giampa et al. (20)	33 ± 4	48 ± 9	6 months,5.5 ± 1.5 h/night	SBP, DBP, HDL-C, TG, FG, WC, Mets
Sun et al. (19)	CPAP 33.8 ± 4.7 control 31.8 ± 5.2	44 ± 9	5 months	SBP, DBP, HDL-C, TG, FG, WC, Mets
Hoyos (48)	31.3 ± 5.2	49 ± 12	3 months, CPAP 3.6 h/night,control 2.8 h/night	SBP, DBP, FG, WC, Mets
Salord et al. (22)	CPAP 45.7 ± 5 control 49.3 ± 6.6	CPAP 48.5 ± 8.6 control 44.6 ± 9.4	3 months,5.4 ± 1.6 h/night	SBP, DBP, HDL-C, TG, FG, WC, Mets
Xiao et al. (32)	CPAP 27.2 ± 2.19 control 27.1 ± 2.3	–	1 month	SBP, DBP, HDL-C, TG, FG
Mota (49)	33.4 +8.4	55.9 (10.7)	6 months	SBP, DBP, HDL-C, TG, FG, WC, Mets
Oktay (50)	32.9 ± 4	50.5 ± 7.7	12 months, >6 h/night	SBP, DBP, HDL-C, TG, FG, WC, Mets
Li et al. (6)	29.56 ± 2.36	–	3 months	SBP, DBP, HDL-C, TG, FG, WC, Mets
Mineiro (51)	31.2 ± 4.1	55.2 ± 7.9	4 months, ł 4 h/night	SBP, DBP, HDL-C, TG, FG, Mets
Dorkova (52)	35.1 ± 6.1	53.7 ± 9.6	2 months	SBP, DBP, HDL-C, TG, FG
Oyama (53)	26.7 ± 3.6	54 ± 9	3 months, ł 4 h/night	SBP, DBP, HDL-C, TG, FG, WC
Xia (54)	32.41 ± 4.53	–	2 months	SBP, DBP, HDL-C, TG, FG, WC
Guo (55)	–	–	3 months, 4-6 h/night	SBP, DBP, TG, FG, WC
Desplan (56)	Experimental 29.9 ± 3.4 control 31.3 ± 2.5	35–70	1 month	SBP, DBP, HDL-C, TG, FG, WC, Mets

(Continued)

TABLE 1 (Continued)

References	BMI	Age	Duration of trials	Outcome
Cristiane (57)	Experimental 32 ± 0.7 control 32 ± 1.3	Experimental 53 ± 1.7 control 42 ± 2.6	4 months	SBP, DBP, HDL-C, TG, FG, WC, Mets
Edgar (58)	32 ± 1	Experimental 52 ± 2 control 48 ± 3	4 months	SBP, DBP, HDL-C, TG, FG, WC, Mets
Georgoulis et al. (27)	MDG 34.8 ± 5.9 MLG 35.5 ± 5.6 control 35.8 ± 6.3	MDG 51 ± 9 MLG 47 ± 10 control 47 ± 11	12 months	SBP, DBP, HDL-C, TG, FG, WC, Mets
Peng (59)	28.1 ± 3.2	41.5 ± 8.7	12 months	HDL-C, TG, FG
Hua (60)	30.7 ± 3.2	40.3 ± 9.8	6 months	SBP, DBP, HDL-C, TG, FG, WC
Zhu (61)	31.1 ± 2.3	51.4 ± 7.3	6 months	SBP, DBP, HDL-C, TG, FG, WC
Chen et al. (5)	33.73 ± 4.28	–	6 months	SBP, DBP, HDL-C, TG, FG, WC

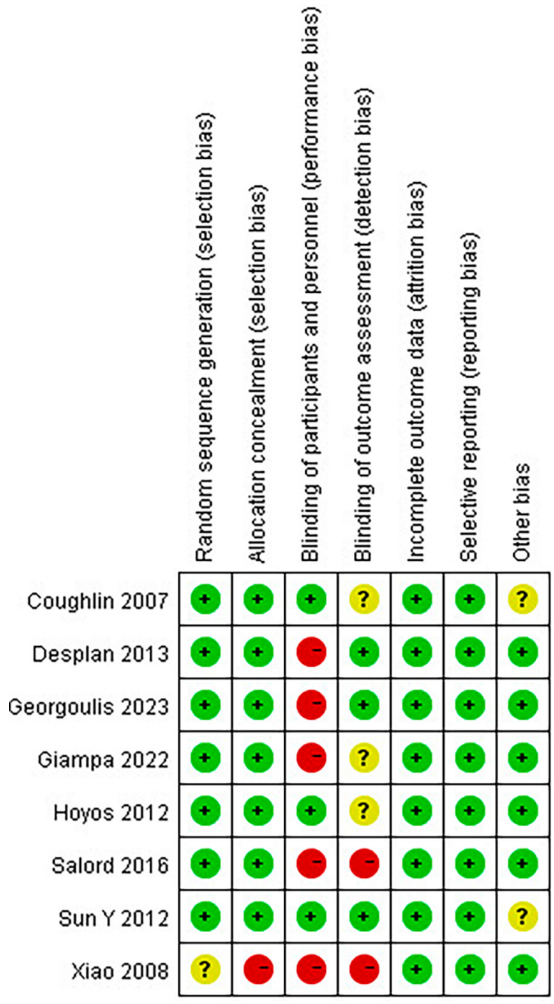

FIGURE 2
Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

trials included were 21 points, indicating high study quality. The results of the Cochrane Bias risk assessment of RCTs are shown in Figure 2.

3.3 Pooled analysis on MetS prevalence

3.3.1 Pooled analysis of the impact of CPAP on MetS prevalence

Nine studies have reported the number of patients diagnosed with MetS before and after CPAP treatment, five of which were randomized controlled trials. Pooled meta-analysis showed that compared with untreated patients, CPAP treatment could reduce the prevalence of MetS in OSA patients in both RCTs (RR = 0.82 [95% CI, 0.75 to 0.90]; $p < 0.01$) (Figure 3) and single-arm studies (RR = 0.73 [95% CI, 0.63 to 0.84]; $p < 0.01$) (Figure 4).

3.3.2 Pooled analysis of the impact of lifestyle intervention on MetS prevalence

Four clinical trials have reported the number of patients diagnosed with MetS before and after lifestyle intervention. Pooled meta-analysis showed that lifestyle intervention could significantly reduce the prevalence of MetS in OSA patients (RR = 0.60 [95% CI, 0.48 to 0.74]; $p < 0.01$) (Figure 5).

3.3.3 Pooled analysis of the impact of surgery and MAD on MetS prevalence

No study has reported the effect of surgery or MAD on MetS prevalence in OSA patients.

3.4 Pooled analysis of the changes in MetS components

3.4.1 Pooled analysis of the impact of CPAP on SBP

Continuous positive airway pressure reduced SBP in OSA patients. A total of 4 RCTs (MD = −5.91 [95% CI, −7.74 to −4.07]; $p < 0.01$) and 6 single-arm studies (MD = −12.72 [95% CI, −20.05 to −5.38]; $p < 0.01$) were included. The difference was statistically significant (Figure 6).

3.4.2 Pooled analysis of the impact of CPAP on DBP

Continuous positive airway pressure reduced DBP in OSA patients. A total of 4 RCTs (MD = −2.57 [95% CI, −6.05 to 0.91];

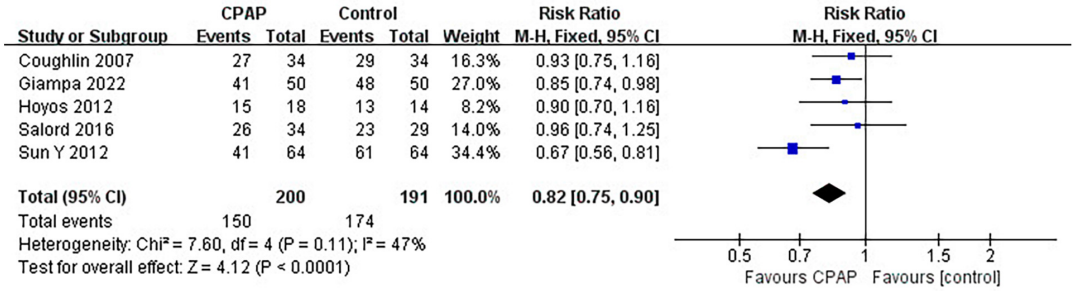

FIGURE 3
Impact of CPAP on Mets prevalence (RCTs).

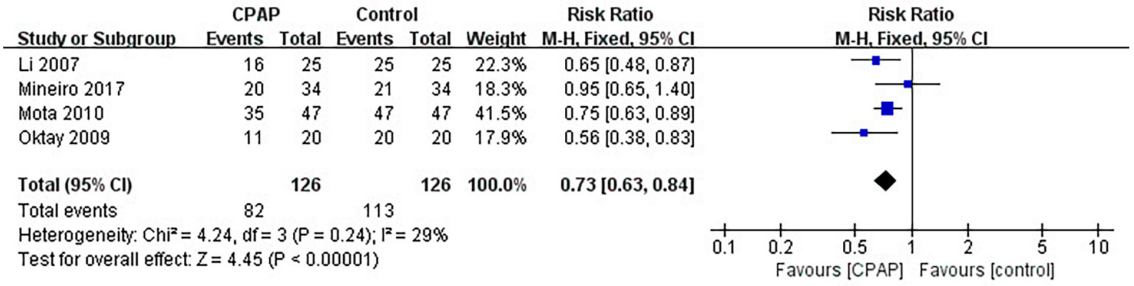

FIGURE 4
Impact of CPAP on Mets prevalence (single-arm studies).

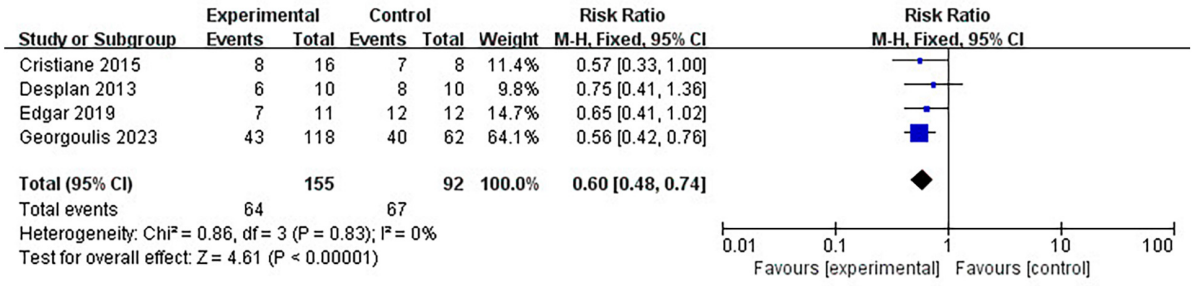

FIGURE 5
Impact of lifestyle intervention on Mets prevalence.

$p = 0.15$) and 6 single-arm studies (MD = −7.95 [95% CI, −11.89 to −4.01]; $p < 0.01$) were included. The difference in single-arm studies was statistically significant (Figure 7).

3.4.3 Pooled analysis of the impact of CPAP on FG

Continuous positive airway pressure reduced FG in OSA patients. A total of 4 RCTs (MD = −0.07 [95% CI, −0.10 to −0.03]; $p = 0.001$) and 6 single-arm studies (MD = −0.81 [95% CI, −1.43 to −0.19]; $p = 0.01$) were included. The difference was statistically significant (Figure 8).

3.4.4 Pooled analysis of the impact of CPAP on WC

Continuous positive airway pressure reduced WC in OSA patients. A total of 2 RCTs (MD = −1.16 [95% CI, −1.93 to −0.39], $p = 0.003$; $p = 0.001$) and 5 single-arm studies (MD = −4.75 [95% CI, −8.15 to −1.36], $p = 0.006$) were included. The difference was statistically significant (Figure 9).

3.4.5 Pooled analysis of the impact of CPAP on TG

Continuous positive airway pressure reduced TG in OSA patients. A total of 4 RCTs (MD = −0.15 [95% CI, −0.28 to −0.03], $p = 0.02$) and 6 single-arm studies (MD = −0.67 [95% CI, −1.31 to −0.03], $p = 0.04$) were included. The difference was statistically significant (Figure 10).

3.4.6 Pooled analysis of the impact of CPAP on HDL-C

Continuous positive airway pressure can't affect HDL-C levels in OSA patients. A total of 4 RCTs (MD = −0.17 [95% CI, −0.43 to

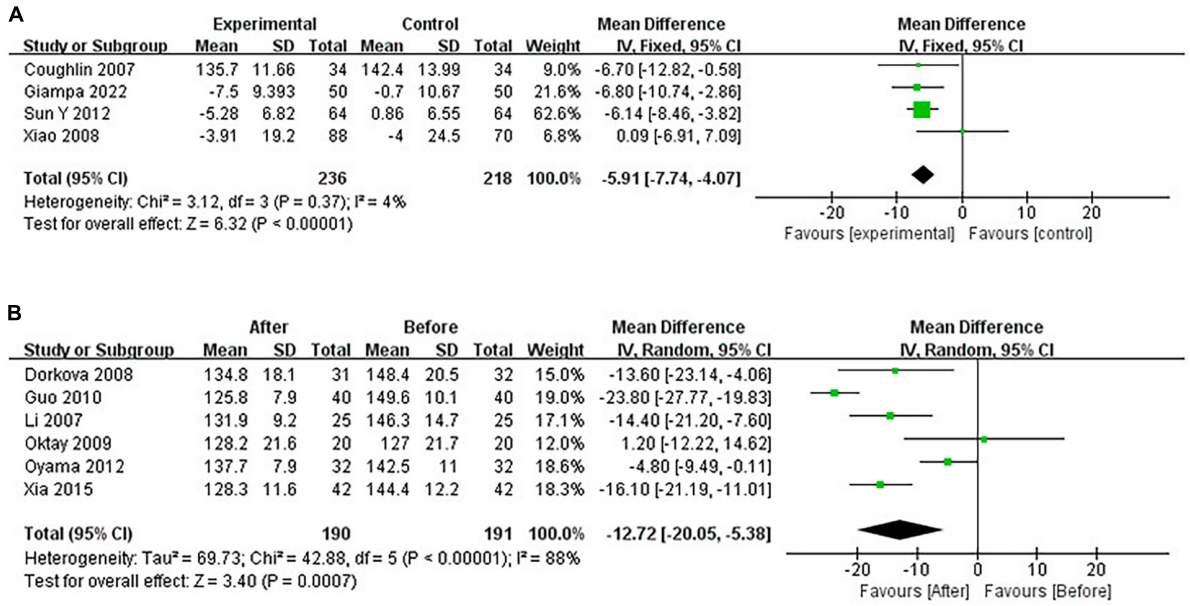

FIGURE 6
Change in SBP [**(A)**: RCTs; **(B)**: single-arm studies].

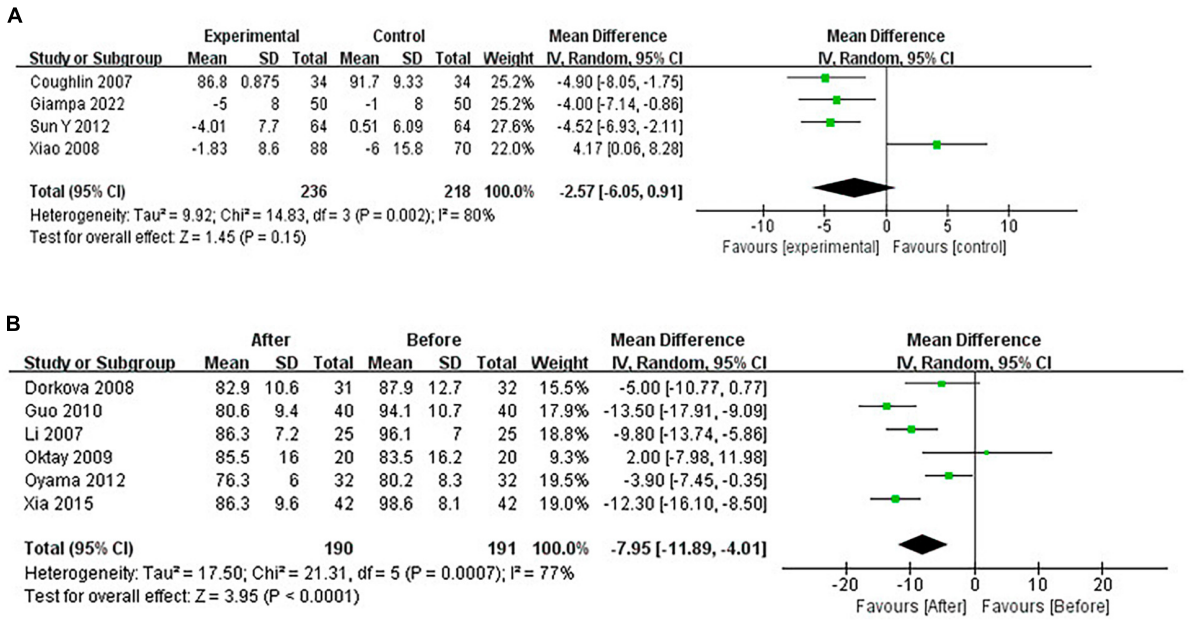

FIGURE 7
Change in DBP [**(A)**: RCTs; **(B)**: single-arm studies].

0.09], $p = 0.21$) and 5 single-arm studies (MD = 0.32 [95% CI, −0.02 to 0.67], $p = 0.07$) were included. The difference was not statistically significant (Figure 11).

3.4.7 Pooled analysis of the impact of lifestyle intervention on MetS components

Lifestyle intervention could lower blood pressure, fasting glucose, and waist circumference but can't affect the lipid metabolism of OSA patients (Table 2).

3.4.8 Pooled analysis of the impact of surgery on MetS components

Upper airway surgery can only reduce TG levels in OSA patients and does not affect other components of MetS (Table 3).

3.4.9 Heterogeneity and publication bias

Due to the heterogeneity of some included studies, this study conducted sensitivity analysis by successively excluding some studies. It was found that in the study on the effect of CPAP on

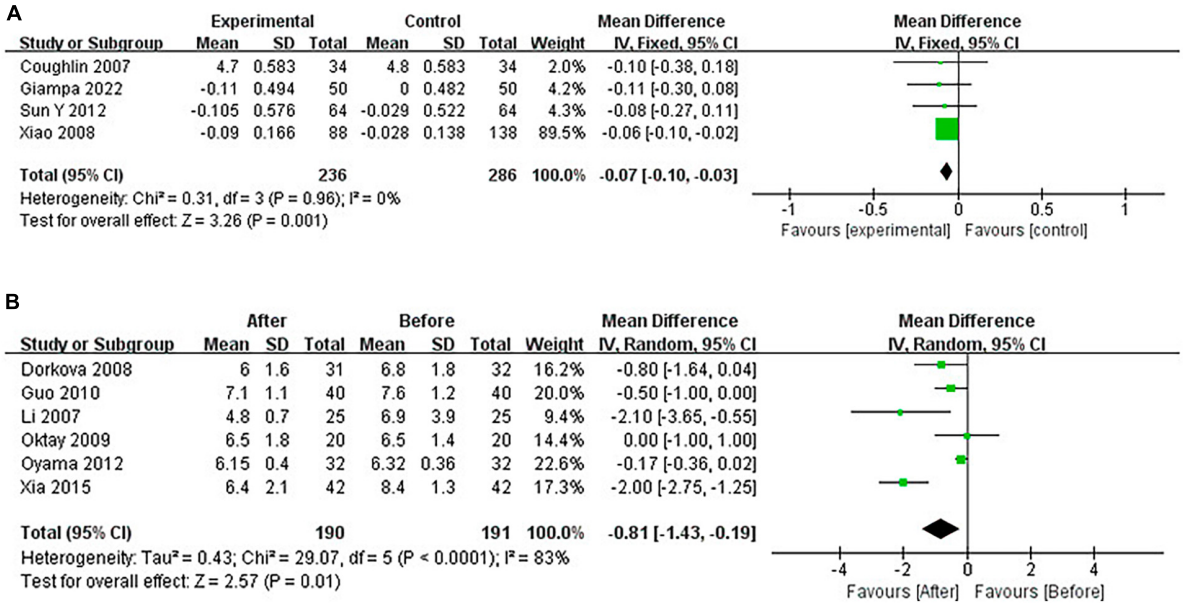

FIGURE 8
Change in FG [**(A)**: RCTs; **(B)**: single-arm studies].

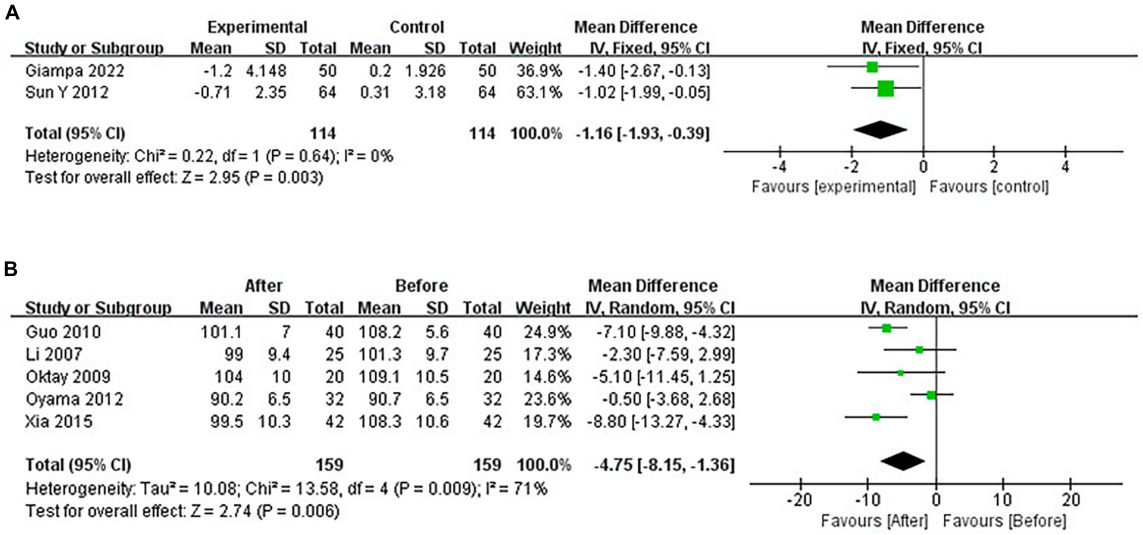

FIGURE 9
Change in WC [**(A)**: RCTs; **(B)**: single-arm studies].

DBP in OSA patients, after excluding the study of Xiao et al. (32), there is a significant change in the results (MD = −4.48 [95% CI, −6.11 to −2.85]; $p < 0.00001$) (Figure 12).

Funnel plots were used to evaluate publication bias; if the funnel plots showed apparent asymmetry, we used Egger's test for the quantitative evaluation. The results of Egger's test showed that the *P*-value of the test result of CPAP's effect on fasting blood glucose and triglyceride was <0.05, indicating the existence of publication bias. However, after trim and filling analysis, it was found that the publication bias had little impact on the study results. Publication bias was not present in the remaining outcomes. The funnel plots and Egger's test outcome are shown in Figure 13 and Table 4.

4 Discussion

Previous studies have shown that OSA can promote the occurrence of MetS (3, 4, 33). CIH and sleep fragmentation mainly characterize OSA. CIH promotes the activation of the sympathetic nerves, thereby increasing blood pressure; the increased level of circulating inflammatory products and reactive oxygen results in hyperglycemia and dyslipidemia (7, 9). OSA is more common in obese patients (34). Patients with OSA are 6–9 times more likely to have MetS than the general population (35–37). The existing research on the impact of different treatments for OSA on coexisting MetS in patients has inconsistent conclusions.

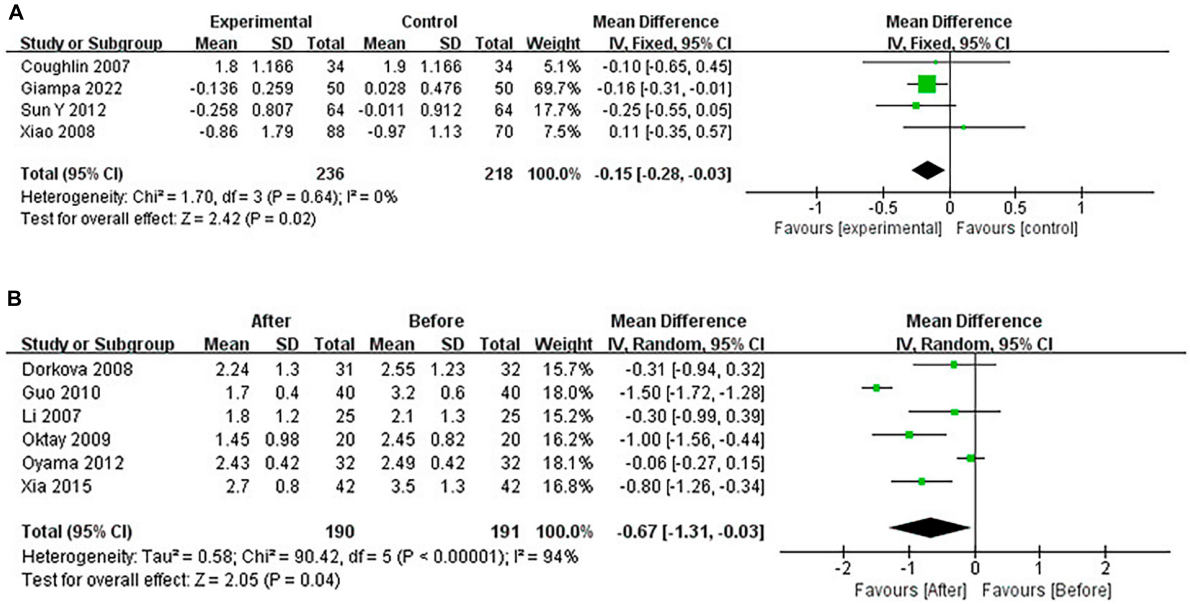

FIGURE 10
Change in TG [**(A)**: RCTs; **(B)**: single-arm studies].

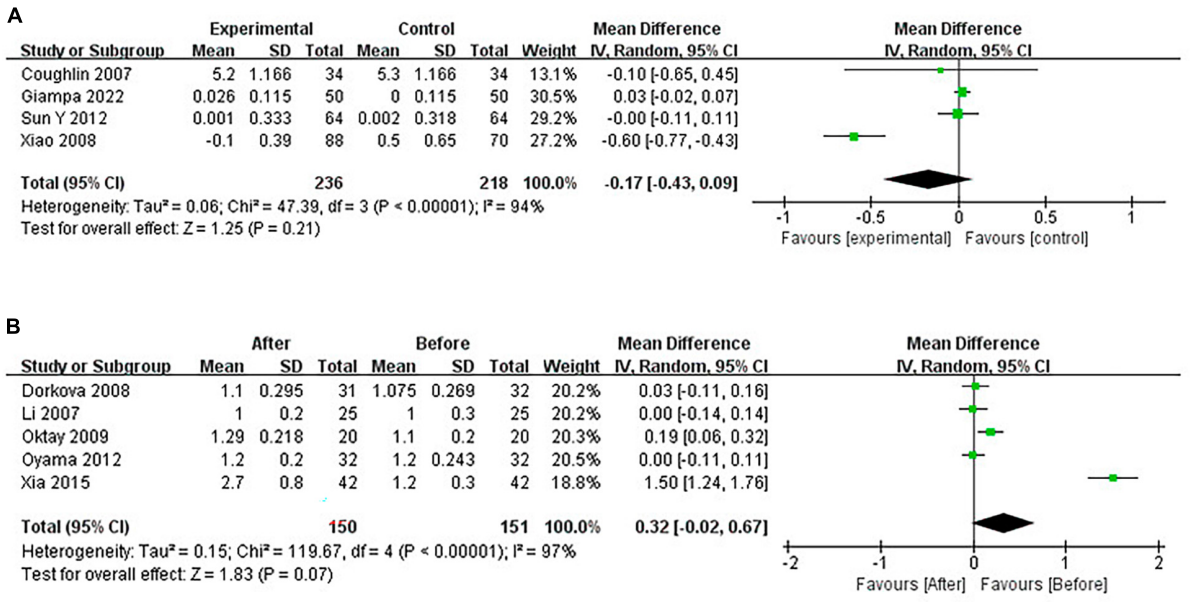

FIGURE 11
Change in HDL-C [**(A)**: RCTs; **(B)**: single-arm studies].

This study found through meta-analysis that CPAP and lifestyle intervention could reduce blood pressure, fasting glucose, and waist circumference in OSA patients, thereby reducing the prevalence of co-existing MetS. However, upper airway surgery can only reduce the triglycerides level of patients.

This meta-analysis confirmed that CPAP can reduce the prevalence of MetS, but the improvement of MetS with CPAP alone is limited (RCT: RR = 0.82; Single-arm studies: RR = 0.73). The formation of MetS is related to many factors, such as genetics, diet habits, exercise, and co-existing diseases, and OSA is only one of the many risk factors (38). In contrast, lifestyle interventions had a more dominant effect on MetS in OSA patients (RR = 0.60). Lifestyle intervention is an essential treatment for MetS (39), and the Mediterranean diet has been shown to reduce the risk of MetS and improve every component of it (40, 41). In various studies exploring lifestyle intervention, the prevalence of MetS was notably reduced in subjects receiving CPAP therapy simultaneously, suggesting that CPAP combined lifestyle intervention is essential in improving disease prognosis in OSA patients with MetS. There is an interaction between components

TABLE 2 Impact of lifestyle intervention on MetS components.

	MD [95% CI]	*P*-value	I^2; *P*-value	Studies
SBP	−13.92 [−19.80, −8.04]	<0.00001	74%; 0.05	2
DBP	−4.00 [−6.19, −1.81]	0.0003	0%; 1.00	2
FG	−0.63 [−0.75, −0.50]	<0.00001	0%; 0.37	2
TG	−0.26 [−0.56, 0.04]	0.08	69%; 0.07	2
HDL-C	0.01 [−0.07, 0.08]	0.83	57%; 0.13	2
WC	−6.65 [−7.99, −5.30]	<0.00001	46%; 0.17	2

TABLE 3 Impact of surgery on MetS components.

	MD [95% CI]	*P*-value	I^2; *P*-value	Studies
SBP	−4.86 [−11.32, 1.60]	0.14	82%; 0.004	3
DBP	−4.16 [−10.82, 2.49]	0.22	89%; 0.0002	3
FG	−2.18 [−4.60, 0.23]	0.08	97%; <0.00001	4
TG	−0.74 [−1.35, −0.13]	0.02	86%; <0.0001	4
HDL-C	−0.15 [−0.31, 0.00]	0.05	80%; 0.002	4
WC	−1.03 [−4.01, 1.94]	0.50	0%; 0.95	3

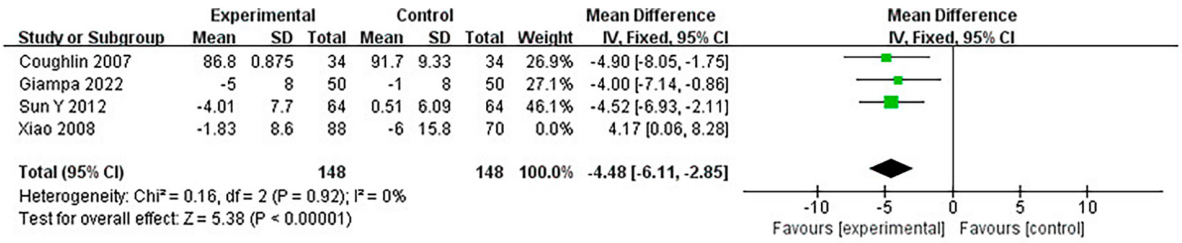

FIGURE 12
The outcome of sensitivity analysis.

of MetS, and weight loss can lead to changes in other components, such as blood lipid and fasting glucose (2). Therefore, lifestyle intervention is considered an essential and effective treatment for OSA (18). Our study showed that lifestyle intervention, including low-calorie diet and exercise, could reduce patients' blood pressure, fasting glucose, and waist circumference, and the impact on waist circumference was particularly significant. Lifestyle intervention can't affect lipid metabolism, which differs from previous studies (41, 42). This may be related to the short intervention time. The intervention time of the studies included in our report was only 4 months. Reducing blood lipid levels is a long-term process, so a short intervention may not seem to have a significant outcome. So far, no study has reported whether MAD and surgery can impact the prevalence of MetS in OSA patients.

Continuous positive airway pressure is the first-line treatment for patients with moderate to severe OSA. CPAP can effectively reduce CIH caused by airway collapse (37), but the therapeutic effect of CPAP depends on compliance. CPAP can reduce sympathetic nerve activation and vascular damage caused by intermittent hypoxia, thereby reducing blood pressure (42). Studies have proved that CPAP can significantly improve the condition of patients with refractory hypertension and can play an essential clinical role in the management of hypertension in these patients (23). Similarly, our study confirmed that CPAP can reduce blood pressure in OSA patients with MetS. There is much debate about the effects of CPAP on blood lipids in patients. Our study demonstrated a decrease in triglycerides after CPAP treatment. The formation of dyslipidemia in OSA patients with MetS is a long-term process influenced by many factors, of which OSA is only one. Triglycerides are more sensitive to reducing oxidative stress caused by OSA treatment (43), while HDL-C is mainly influenced by genetic factors and not easily changed by various intervention methods (44). When it comes to fasting glucose, we agree with previous studies. CPAP can reduce fasting glucose in OSA patients, regardless of whether they have MetS (45).

Surgery is the preferred treatment for patients who are intolerant to CPAP or have anatomic abnormalities in the upper airway. Intrapharyngeal surgery (soft tissue surgery) is widely used in treating OSA. Uvulopalatopharyngoplasty is the most effective method to solve oropharyngeal obstruction in OSA patients (18). Previous studies have confirmed the effectiveness of surgery in OSA patients (46). However, there is controversy in previous studies regarding the impact of surgery on MetS in OSA patients, and no RCTs have been published in relevant fields in the past. The studies included are all single-arm clinical trials. The meta-analysis showed that only TG was reduced after upper airway surgery. A liquid

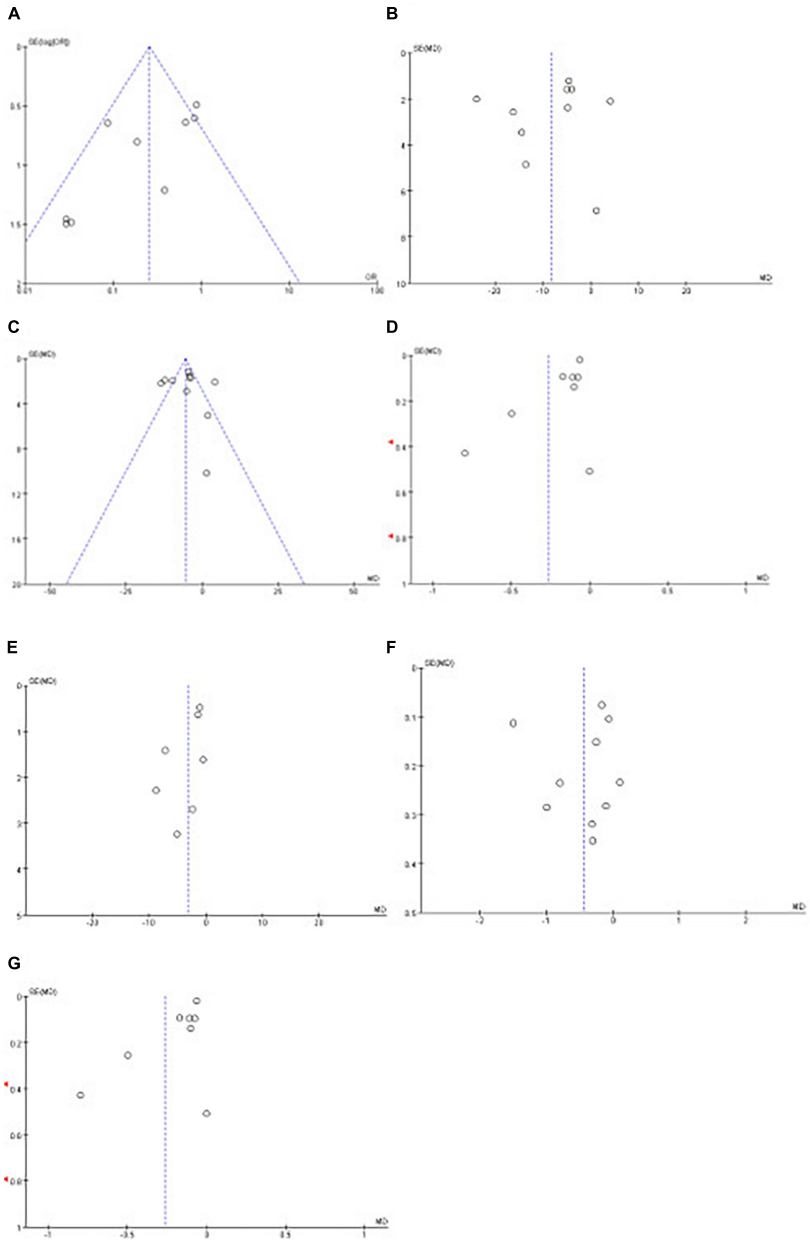

FIGURE 13
Funnel plots of the impact of CPAP. Funnel plots of the impact CPAP [**(A)**: MetS, **(B)**: SBP, **(C)**: DBP, **(D)**: FG, **(E)**: WC, **(F)**: TG, **(G)**: HDL-C].

TABLE 4 Egger's test of publication bias.

Outcome	*P*-value
SBP	0.865
DBP	0.509
FG	0.021
WC	0.12
TG	0.018
HDL-C	0.645

diet for some time after surgery can also reduce energy intake to some extent, thus lowering TG levels. Most of the included subjects were obese patients; after the surgery, the BMI of the patients all decreased to varying degrees, while TG levels were closely related to BMI decrease (47). All the above reasons could cause TG changes.

Our study had some limitations. First, only a few RCTs could be included, and the total number of samples was relatively small. Therefore, there were single-arm studies in our included studies. However, even so, existing studies have sufficiently confirmed the role of different treatments in reducing the incidence of MetS in OSA patients. This study analyzed RCTs and single-arm studies, respectively, and the conclusions were consistent. Secondly, in some of the studies, the duration of treatment was relatively short, which may not be sufficient to impact MetS, leading to significantly increased heterogeneity between studies. Therefore, future research requires RCTs with larger patient samples and longer follow-up times. Finally, although some studies have reported the effects of MAD on blood pressure, blood glucose, and blood lipids in

OSA patients (30), no study was conducted among patients with both OSA and MetS. Therefore, this study failed to conduct a comprehensive discussion on this aspect.

In conclusion, we confirmed that both CPAP treatment and lifestyle intervention could reduce the prevalence of MetS in OSA patients. CPAP can lower blood pressure, fasting glucose, waist circumference, and triglyceride levels. Lifestyle intervention can lower blood pressure, fasting glucose, and waist circumference in OSA patients. Upper airway surgery can only reduce TG levels in OSA patients. Research suggests that for patients with OSA combined with MetS, appropriate treatment should be selected promptly based on the condition to improve the patient's prognosis.

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.

Author contributions

JL: Data curation, Formal Analysis, Methodology, Resources, Software, Writing – original draft. JX: Investigation, Resources, Supervision, Validation, Writing – original draft. SG: Data curation, Investigation, Methodology, Visualization, Writing – original draft. WW: Conceptualization, Resources, Supervision, Writing – review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by the National Natural Science Foundation of China (82270107).

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.2024.1354489/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 02 April 2024
DOI 10.3389/fmed.2024.1346400

OPEN ACCESS

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RECEIVED 29 November 2023
ACCEPTED 20 March 2024
PUBLISHED 02 April 2024

CITATION
Chen H, Zhang Q, Hao Y, Zhang J, He Y and Hu K (2024) Cardiac autonomic dysfunction and structural remodeling: the potential mechanism to mediate the relationship between obstructive sleep apnea and cardiac arrhythmias.
Front. Med. 11:1346400.
doi: 10.3389/fmed.2024.1346400

Cardiac autonomic dysfunction and structural remodeling: the potential mechanism to mediate the relationship between obstructive sleep apnea and cardiac arrhythmias

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Background: Cardiac arrhythmias are very common in patients with obstructive sleep apnea (OSA), especially atrial fibrillation (AF) and nonsustained ventricular tachycardia (NVST). Cardiac autonomic dysfunction and structural remodeling caused by OSA provide the milieu for cardiac arrhythmia development. This study aimed to determine whether OSA is associated with various cardiac arrhythmias and investigate potential pathophysiologic pathways between them.

Methods: The analysis covered 600 patients with clinical suspicion of OSA hospitalized in Renmin Hospital of Wuhan University between January 2020 and May 2023. After undergoing sleep apnea monitor, all subjects received laboratory tests, Holter electrocardiography, and Echocardiography.

Results: Compared with those without OSA and adjusting for potential confounders, subjects with moderate OSA had three times the odds of AF (odds ratio [OR] 3.055; 95% confidence interval [CI], 1.002–9.316; $p = 0.048$). Subjects with severe OSA had three times the odds of AF (OR 3.881; 95% CI, 1.306–11.534; $p = 0.015$) and NSVT (OR 3.690; 95% CI, 0.809–16.036; $p = 0.046$). There were significant linear trends for the association between OSA severity with AF and NVST ($p < 0.05$). And this association was mediated by cardiac structural changes including left atrial diameter, left ventricular diastolic diameter, right atrial diameter and right ventricular diameter. In addition, the ratio of low-frequency and high-frequency individually mediated the association between severe OSA and NVST.

Conclusion: This study demonstrated that severe OSA was independently associated with AF and NSVT, and this association was mediated by autonomic nervous system changes and cardiac structural remodeling.

KEYWORDS

sleep disordered breathing, obstructive sleep apnea, cardiac arrhythmias, atrial fibrillation, non-sustained ventricular tachycardia, heart rate variability

Introduction

Sleep disordered breathing (SDB) mainly includes two types: central sleep apnea (CSA) and obstructive sleep apnea (OSA). OSA is a more common and increasingly recognized complex disorder. It is characterized by the occurrence of upper airway collapse, resulting in disruptive snoring, intermittent hypoxemia, sleep fragmentation, worsening sleep quality and excessive daytime sleepiness (1). According to estimates, the overall prevalence of OSA in the general population ranges from about 9–38% (2). Moreover, OSA is an independent risk factor for several diseases, such as hypertension (3, 4), diabetes (5), coronary artery disease (6), and cardiac arrhythmias (1, 7). Previous studies have demonstrated that OSA significantly increases the risk of several cardiac arrhythmias, including atrial fibrillation (AF), nonsustained ventricular tachycardia (NVST), and conduction delay arrhythmias (8–11).

However, few studies have analyzed the causes of arrhythmias in OSA in population studies. Several mechanisms, including cardiac autonomic dysfunction and structural remodeling caused by OSA, might explain these results (1, 3, 12). Our aim was to determine whether OSA is associated with various cardiac arrhythmias and investigate potential pathophysiologic pathways between them.

Methods

Study group

Figure 1 depicts a flowchart illustrating the study design and process. To ensure the validity of the assessment, the exclusion criteria were: age <18 years; ongoing OSA therapy; current use of anxiolytics, antidepressants, hypnotics, or antipsychotic drugs.

From January 2020 to May 2023, a total of 2,972 subjects were initially recruited. Among them, 147 subjects were excluded from formal enrollment due to age <18 years (n = 44), received OSA treatment (n = 50) or medication of anxiolytics, antidepressants, hypnotics, or antipsychotic drugs (n = 53). After undergoing overnight sleep apnea monitor, 600 subjects received laboratory tests, Echocardiography (ECHO) and Holter electrocardiography monitoring. Finally, this retrospective observational study included 600 subjects with clinical suspicion of OSA in Renmin Hospital of Wuhan University.

From the electronic medical records, we collected essential clinical information, including demographic and anthropometric data (such as sex, age, height, weight, systolic blood pressure, and diastolic blood pressure), as well as details related to cardiovascular risk factors (such as smoking, drinking, and diabetes) and cardiovascular diseases (such as hypertension, coronary heart disease, heart failure, and myocardial infarction).

All enrolled subjects signed written informed consent. The study has been approved by the ethics committee of Renmin Hospital of Wuhan University. All studies have been conducted according to the ethics guidelines laid down in the Helsinki Declaration.

Biochemical measurements

All subjects had undergone fasting blood tests including blood glucose, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglyceride (TG), total cholesterol (TC), brain natriuretic peptide (BNP), Creatinine (Cr), K, Na, CI, Ca, Activated Partial Prothrombin Time (APPT), Prothrombin Time (PT), Fibrinogen and D-Dimer.

Holter electrocardiography and heart rate variability analysis

HRV measurement was used to assess cardiac autonomic dysfunction. We analyzed the frequency and time domain of HRV by using Holter electrocardiography monitoring (BI9800, Biomedical Instruments Co., Ltd., Shenzhen, Guangdong, China). The time domain analysis includes parameters such as: standard deviation of normal-to-normal intervals (SDNN); standard deviation of 5 min average NN intervals (SDNN Index); standard deviation of 5 min average NN intervals (SDANN); root mean square successive difference (RMSSD); percentage of adjacent NN intervals (PNN50); and trigonometric index (11). The frequency analysis includes parameters such as: power in high frequency spectrum (HF; 0.15–0.4 Hz), power in low frequency spectrum (LF; 0.04–0.15 Hz), power in very low frequency spectrum (VLF; 0.003–0.04 Hz) and the ratio of the two values (LF/HF) (12).

RMSSD and HF predominantly represent cardiac parasympathetic nerve activity, whereas LF is associated with cardiac sympathetic nerve activity. Consequently, the LF/HF ratio serves as an indicator of the balance between sympathetic and parasympathetic functions, with elevated LF/HF values suggesting heightened sympathetic nerve excitability (11, 12).

Echocardiography

All subjects received transthoracic echocardiography with Color Doppler Echocardiography (ECHO) performed by an experienced ultrasound physician. The ascending aortic diameter (AAOD), main pulmonary artery diameter (MPAD), left atrial diameter (LAD), left ventricular diastolic diameter (LVDD), right atrial diameter (RAD), right ventricular diameter (RVD), left ventricular systolic diameter (LVSD) and left ventricular posterior wall thickness (LVPWD) were measured using standard M-mode ECHO. The aortic valve stroke volume (AVSV), mitral valve e peak velocity (MVE) and left ventricular ejection fraction (LVEF) values of each patient were obtained from the results of ECHO.

Sleep apnea parameters

Each subject was monitored for at least 7 h of sleep using a portable and non-contact sleep apnea monitor (Megasens Technology Co. Ltd., Hangzhou, China), including an ultra-wideband sleep apnea monitor (OrbSense, ZG-S01D) and blood oxygen saturation monitor (ZG-P11F). All of the subjects underwent 7 hours nighttime monitoring with this device in bed. No ingest caffeine, nap or engage and protracted or tedious exercises, and so on were informed during the study. The study recorded the following parameters: (1) Apnea-Hypopnea Index (AHI), which is the average number of apnea and hypopnea episodes per hour of sleep; (2) An apnea, which is a

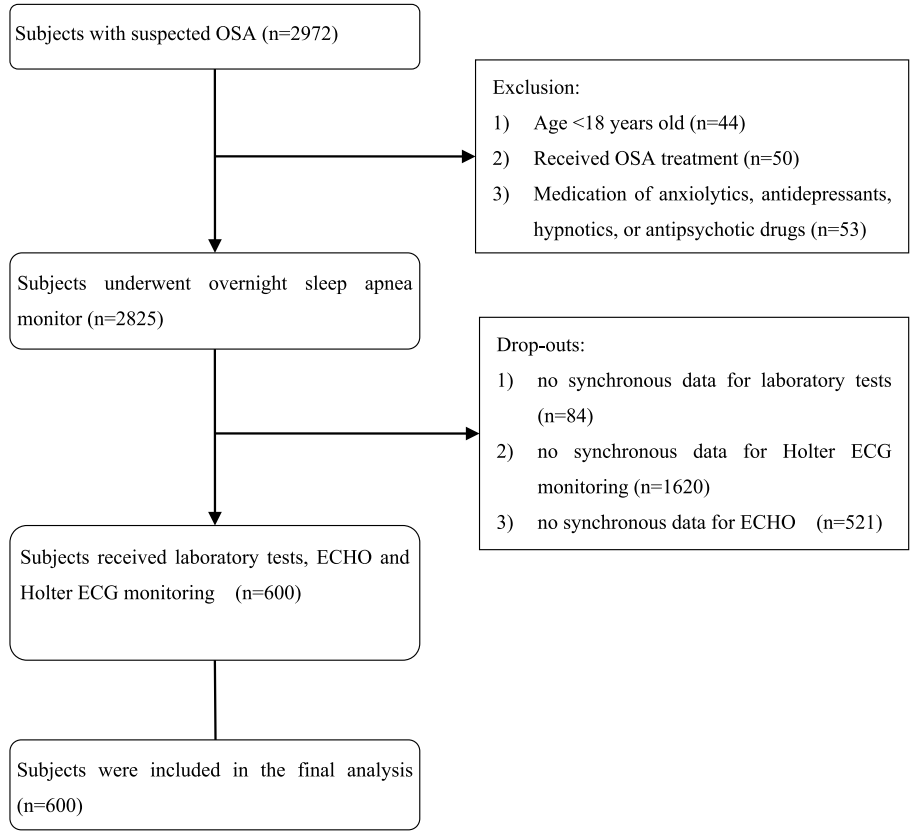

FIGURE 1
Flow diagram of this study. OSA, obstructive sleep apnea; ECG, electrocardiography; ECHO, echocardiography.

reduction in nasal airflow of at least ≥10 s 80%; (3) A hypopnea, which is a decrease in nasal airflow ≥30% and a decrease in oxygen saturation ≥4%; (4) the lowest and mean arterial oxygen saturation (LSaO2 and MSaO2), estimated by pulse oximetry during sleep [%], (5) Oxygen Desaturation Index (ODI), which is the number of average hourly decreases in oxygen saturation of ≥4%; and (6) the total sleep time with oxygen saturation below 90% (TST90) [%] (8–10). Subjects were categorized into four groups based on AHI by using common clinical cutoff points: none (AHI < 5), mild (5 ≤ AHI < 15), moderate (15 ≤ AHI < 30), and severe (AHI ≥ 30).

Statistical analysis

Based on the specific distribution and type of data, the results are presented as either mean ± standard deviation or number (percentage). Analysis of variance (ANOVA) was used for the normal distribution of data, and the Welch's test was used for non-normally distributed data. The chi-squared test was used to compare categorical data. The relationship between variables was tested by Pearson and Spearman correlations, and multiple linear regression analyses were performed to evaluate the associations between dependent and independent variables. Statistical analyses were performed using SPSS v26.0 (IBM Corp., Armonk, NY, United States) and R program (v4.0; R Foundation, Vienna, Austria). The significance level of $p < 0.05$ was considered statistically significant for the entire analysis.

Multivariate logistic regression analysis was conducted to test for the correlation between OSA severity with AF and NSVT. Multivariate linear regression analysis was utilized in determining associations between OSA severity and various measurements of HRV and ECHO. Age, sex, BMI, drinking, smoking, hypertension, diabetes and myocardial infarction were considered as covariates in the multivariable models. In this study, mediation analysis was utilized for test whether the correlations of severe OSA with AF and NVST were mediated by HRV and ECHO indicators.

Results

Baseline characteristics

From January 2020 to May 2023, after screening 2,972 subjects with clinical suspicion of OSA in Renmin Hospital of Wuhan University, 600 subjects fulfilled these inclusions and were included in this study (Figure 1).

Table 1 summarizes the baseline characteristics of the study population and the four subgroups based on OSA severity. Of 600 subjects, 522 (87.0%) were diagnosed with OSA, including 145 with mild, 157 with moderate, and 122 with severe OSA. As expected, OSA severity was found to be associated with BMI and male gender. The incidence of smoking, drinking, hypertension, diabetes mellitus and myocardial infarction tended to increase in subjects with more severe OSA. The distribution of coronary artery disease and heart failure did

TABLE 1 Characteristics of subjects with different OSA severity.

Variables	None OSA (n = 78)	Mild OSA (n = 145)	Moderate OSA (n = 157)	Severe OSA (n = 220)	p-value
Ages (years)	59.8 ± 14.3	61.9 ± 13.7	61.9 ± 12.4	60.9 ± 14.3	0.649
Gender (male, %)	52 (66.7%)	99 (68.3%)	110 (70.1%)	183 (83.2%)	0.001
BMI (kg/m^2)	24.8 ± 3.7	24.9 ± 4.2	25.4 ± 4.2	27.4 ± 5.4	<0.001
SBP (mmHg)	132.4 ± 22.5	135.5 ± 19.7	132.4 ± 23.9	134.2 ± 23.1	0.412
DBP (mmHg)	75.7 ± 14.6	80.6 ± 14.7	79.5 ± 14.8	80.1 ± 14.5	0.096
Smoking	24 (30.8%)	55 (37.9%)	66 (42.0%)	109 (49.5%)	0.018
Drinking	16 (20.5%)	48 (33.1%)	40 (25.5%)	77 (35.0%)	0.043
Comorbidities, n (%)					
Hypertension	47 (60.3%)	94 (64.8%)	99 (63.1%)	165 (75.0%)	0.024
Diabetes mellitus	10 (12.8%)	27 (18.6%)	37 (23.6%)	71 (32.3%)	0.001
Coronary heart disease	26 (33.3%)	51 (35.2%)	59 (37.6%)	79 (35.9%)	0.930
Heart failure	8 (10.3%)	19 (13.1%)	24 (15.3%)	44 (20.0%)	0.137
Myocardial infarction	2 (2.6%)	3 (2.1%)	5 (3.2%)	18 (8.2%)	0.019
ECHO indicators					
AAOD (mm)	32.5 ± 4.0	33.2 ± 3.8	33.2 ± 3.7	34.4 ± 3.8	<0.001
MPAD (mm)	21.5 ± 2.3	21.9 ± 2.8	21.8 ± 2.9	22.6 ± 3.4	0.019
LAD (mm)	35.1 ± 5.0	36.4 ± 6.0	36.2 ± 6.7	38.9 ± 7.1	<0.001
LVDD (mm)	45.3 ± 3.4	46.1 ± 4.9	46.3 ± 5.8	48.4 ± 7.2	0.001
RAD (mm)	34.7 ± 3.8	35.0 ± 5.5	35.5 ± 5.4	37.1 ± 5.9	<0.001
RVD (mm)	20.4 ± 2.0	21.1 ± 3.0	21.0 ± 2.9	21.8 ± 2.4	<0.001
LVSD (mm)	9.9 ± 1.4	10.1 ± 1.7	10.1 ± 1.8	10.3 ± 1.8	0.149
LVPWD (mm)	9.8 ± 1.3	9.9 ± 1.3	9.9 ± 1.6	10.5 ± 3.7	0.021
AVSV (cm/s)	133.6 ± 37.8	129.2 ± 27.0	128.1 ± 26.1	127.8 ± 26.0	0.633
MVE (cm/s)	71.7 ± 20.8	72.3 ± 23.2	73.5 ± 24.1	73.6 ± 21.5	0.764
LVEF (%)	58.6 ± 2.7	57.1 ± 7.8	56.9 ± 7.3	55.6 ± 8.8	0.024
Sleeping indicators					
AHI, events/h	2.7 ± 1.4	9.7 ± 2.8	21.9 ± 4.6	48.5 ± 12.6	<0.001
ODI, events/h	3.9 ± 3.4	11.8 ± 8.2	22.7 ± 11.8	41.3 ± 18.2	<0.001
MSaO2 (%)	96.0 ± 1.6	94.9 ± 1.5	93.5 ± 3.3	92.6 ± 3.0	<0.001
LSaO2 (%)	86.5 ± 6.2	80.9 ± 9.9	77.4 ± 9.5	70.4 ± 12.9	<0.001
TST90 (%)	0.6 ± 1.3	2.9 ± 3.7	10.6 ± 14.9	17.3 ± 15.6	<0.001
Biochemical indicators					
BNP (pg/mL)	268.9 ± 567.3	545.2 ± 1136.6	666.8 ± 1420.4	1043.9 ± 4014.6	0.002
TCH (mmol/L)	4.1 ± 1.1	4.2 ± 1.1	4.0 ± 0.9	4.1 ± 1.0	0.794
TG (mmol/L)	1.6 ± 1.1	1.7 ± 1.3	1.6 ± 0.9	1.7 ± 1.2	0.127
HDL (mmol/L)	1.1 ± 0.3	1.0 ± 0.3	1.1 ± 0.2	1.1 ± 0.3	0.112
LDL (mmol/L)	2.4 ± 1.0	2.4 ± 0.8	2.3 ± 0.8	2.4 ± 0.8	0.811
Cr (μmol/L)	70.3 ± 18.9	73.9 ± 20.1	77.2 ± 35.0	81.9 ± 37.5	0.015
K (mmol/L)	4.0 ± 0.4	3.9 ± 0.4	3.9 ± 0.3	4.0 ± 0.8	0.284
Na (mmol/L)	141.1 ± 2.2	140.7 ± 2.8	141.1 ± 2.8	141.0 ± 3.6	0.978
Cl (mmol/L)	106.6 ± 2.4	106.3 ± 3.4	106.6 ± 3.8	106.2 ± 3.0	0.227
Ca (mmol/L)	2.2 ± 0.1	2.2 ± 0.2	2.2 ± 0.1	2.2 ± 0.2	0.056
Glucose (mmol/L)	5.7 ± 3.1	5.6 ± 3.9	5.6 ± 2.3	6.1 ± 2.0	<0.001

(Continued)

TABLE 1 (Continued)

Variables	None OSA ($n = 78$)	Mild OSA ($n = 145$)	Moderate OSA ($n = 157$)	Severe OSA ($n = 220$)	p-value
PT (sec)	11.5 ± 3.3	11.6 ± 2.2	11.6 ± 2.2	11.5 ± 1.9	0.709
APPT (sec)	28.4 ± 3.1	27.5 ± 3.4	27.5 ± 3.9	27.6 ± 3.8	0.174
FIB (g/L)	3.2 ± 1.9	3.1 ± 1.1	3.0 ± 1.1	3.3 ± 1.3	0.154
D-Dimer (mg/L)	0.5 ± 0.6	1.0 ± 4.6	1.0 ± 2.9	0.7 ± 1.4	0.480

Data are shown as mean ± SD or as number of cases (percentage). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UCG, ultrasonic cardiogram with color doppler; AAOD, ascending aortic diameter; MPAD, main pulmonary artery diameter; LAD, left atrial diameter; LVDD, left ventricular diastolic diameter; RAD, right atrial diameter; RVD, right ventricular diameter; LVSD, left ventricular systolic diameter; LVPWD, left ventricular posterior wall thickness; AVSV, aortic valve stroke volume; MVE, mitral valve E peak velocity; LVEF, left ventricular ejection fraction; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; MSaO2, mean oxygen saturation; LSaO2, lowest oxygen saturation; TST90, total sleep time with oxygen saturation under 90%; BNP, brain natriuretic peptide; TCH, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Cr, creatinine; PT, prothrombin time; APPT, activated partial prothrombin time; FIB, fibrinogen.

not vary significantly among patients with and without sleep apnea. AAOD, MPAD, LAD, LVDD, RAD, RVD, BNP, Cr and fasting glucose were significantly higher in subjects with OSA than in those without OSA (all $p < 0.05$). In contrast, subjects with OSA had a significantly lower LVEF in comparison to those without OSA ($p < 0.05$). Table 1 also summarizes the sleep study parameters.

Holter electrocardiographic and HRV data

Table 2 summarizes the types of arrhythmias in subgroups based on OSA severity. The prevalence of AF and ventricular arrhythmias increased with the worsening OSA severity. There were no significant differences between groups regarding sinus arrhythmias and conduction delay arrhythmias. In addition, as shown in Table 3, considering the impact of AF on HRV, HRV parameters were compared among the different groups that excluded atrial fibrillation. The 24 h mean heart rate (HR), LF and LF/HF increased significantly as the worsened OSA severity. In contrast, SDNN, RMSSD and PNN50 decreased significantly as the worsened OSA severity.

Correlation analysis between OSA with AF and OSA with NSVT

Table 4 demonstrates that unadjusted and adjusted logistic regression examined the association between OSA with AF and NSVT. Compared with the group with none OSA, subjects with mild OSA had three times the unadjusted odds of AF (odds ratio [OR] 3.309; 95% confidence interval [CI], 1.097–9.977; $p = 0.034$). Subjects with moderate OSA had three times the unadjusted odds of AF (OR 3.338; 95% CI, 1.116–9.989; $p = 0.031$). Subjects with severe OSA had four times the unadjusted odds of AF (OR 4.624; 95% CI, 1.604–13.336; $p = 0.005$) and NSVT (OR 4.653; 95% CI, 1.073–20.169; $p = 0.040$). After further adjustments for age, gender, BMI, smoking, drinking, hypertension, diabetes mellitus and myocardial infarction, subjects with moderate OSA had three times the odds of AF (OR 3.055; 95% CI, 1.002–9.316; $p = 0.048$). Subjects with severe OSA had three times the odds of AF (OR 3.881; 95% CI, 1.306–11.534; $p = 0.015$) and NSVT (OR 3.690; 95% CI, 0.809–16.036; $p = 0.046$). In the unadjusted and adjusted model, there were significant linear trends for the association between OSA severity with AF and NVST (P for linear trends <0.05).

Correlation analysis between severe OSA with HRV and ECHO indicators

On the basis of Tables 1, 3, the correlations of severe OSA with significant indicators of HRV and ECHO indicators are shown in Table 5. After full adjustment for confounders, multivariate linear regression model showed that increased LAD, LVDD, RAD and RVD were independently associated with severe OSA ($\beta = 1.638$, $p = 0.004$; $\beta = 1.069$, $p = 0.032$; $\beta = 1.418$, $p = 0.003$; $\beta = 0.590$, $p = 0.012$, respectively) after full adjustment for confounders. Furthermore, after removing the influence of patients with AF, multivariate analysis demonstrated that severe OSA ($\beta = 151.424$, $p = 0.010$ and $\beta = 0.334$; $p = 0.036$, respectively) remained significantly associated with increases in LF and LF/HF.

Mediation analysis

Based on multivariate linear regression analysis, we examined whether severe OSA and AF and NVST were mediated by the significant HRV and ECHO indicators. Table 6 shows each step of the mediation analysis. These analyses, adjusted for potential confounders, yielded a mediation effect ratio that means how much the mediation effect accounts for the total effect of the independent variable on the dependent variable. In the mediation analysis between severe OSA and AF, the decomposition of the total effect showed that 93.1% of the total effect was mediated by the LAD, 16.1% of the total effect was mediated by the LVDD, 71.4% of the total effect was mediated by the RAD and 18.4% of the total effect was mediated by the RVD. And none of the controlled direct effect (effect directly associated with severe OSA) were significant (all $p > 0.05$). The relationship between severe OSA severity and AF depends almost entirely on LAD, LVDD, RAD and RVD (Figures 2A, B). In the mediation analysis between severe OSA and NSVT, the decomposition of the total effect showed that although the direct effect of severe OSA on NSVT remained significant (all $p < 0.05$), 19.9% of the total effect was mediated by the LAD, 9.7% of the total effect was mediated by the LVDD, 16.6% of the total effect was mediated by the RAD, and 10.6% of the total effect was mediated by the RVD (Figures 2C, D).

Considering the impact of AF on HRV, we also explored the associations mediated by LF and LF/HF between severe OSA and NSVT in patients who excluded atrial fibrillation. Compared with LF which indirect effect was not significant ($b = 0.000$; $p = 0.820$), the

TABLE 2 Frequency and type of arrhythmias in different OSA groups.

Variables	None OSA (n = 78)	Mild OSA (n = 145)	Moderate OSA (n = 157)	Severe OSA (n = 220)	p-value
Sinus arrhythmia					
Sinus tachycardia >100 bpm	9 (11.5%)	16 (11.0%)	13 (8.3%)	25 (11.4%)	0.770
Sinus bradycardia <50 bpm	4 (5.1%)	9 (6.2%)	15 (9.6%)	19 (8.6%)	0.539
Sinus pauses >2 s	6 (7.7%)	16 (11.0%)	18 (11.5%)	31 (14.1%)	0.481
Supraventricular arrhythmias					
Isolated PAC	60 (76.9%)	109 (75.2%)	123 (78.3%)	160 (72.7%)	0.504
Paired PAC	31 (39.7%)	58 (40.0%)	57 (36.3%)	87 (39.5%)	0.901
Atrial bigeminy	11 (14.1%)	24 (16.6%)	23 (14.6%)	30 (13.6%)	0.363
Atrial trigeminy	10 (12.8%)	19 (13.1%)	19 (12.1%)	30 (13.6%)	0.978
Atrial fibrillation	4 (5.1%)	22 (15.2%)	24 (15.3%)	44 (20.0%)	0.021
Supraventricular tachycardia	19 (24.4%)	24 (16.6%)	39 (24.8%)	45 (20.5%)	0.303
Ventricular arrhythmias					
Isolated PVC	38 (48.7%)	95 (65.5%)	97 (61.8%)	155 (70.5%)	0.006
Paired PVC	5 (6.4%)	24 (16.6%)	18 (11.5%)	54 (24.5%)	<0.001
Ventricular bigeminy	5 (6.4%)	14 (9.7%)	16 (10.2%)	42 (19.1%)	0.005
Ventricular trigeminy	6 (7.7%)	13 (9.0%)	18 (11.5%)	38 (17.3%)	0.045
Non-sustained VT	2 (2.6%)	5 (3.4%)	6 (3.8%)	24 (10.9%)	0.003
Conduction delay arrhythmias					
AVB type I–III	3 (3.8%)	2 (1.4%)	3 (1.9%)	7 (3.2%)	0.579

Data are shown as number of cases (percentage). VPB, ventricular premature beat; PAC, premature atrial complex; PVC, premature ventricular complexes; VT, ventricular tachycardia; AVB, atrioventricular block.

decomposition of the total effect indicated that 3.3% of the total effect was mediated by the LF/HF (Figure 2E).

Discussion

This study was the first to simultaneously focus on changes in the autonomic nervous system and cardiac structural remodeling in the connection between OSA and arrhythmia, and conveyed several new findings at the same time. First, severe OSA was an independent predictor of AF and NSVT and incident risk of the latter two diseases was augmented with the increase in OSA severity. Second, multiple HRV and ECHO indicators were significant factors associated with severe OSA after adjusting for potential confounders. Finally, we found that the association between severe OSA with AF and NVST was mediated by cardiac structural changes including LAD, LVDD, RAD and RVD. In addition, LF/HF individually mediated the association between severe OSA and NVST.

Many previous reports have shown the relationship between sleep disordered and cardiac arrhythmias in subjects with varying OSA severities, such as conduction delay arrhythmias (13), supraventricular arrhythmias, NVST (8, 14, 15) and AF (8, 16, 17). Both OSA and CSA were thought to predispose to cardiac arrhythmias, but complex ventricular ectopy was most strongly associated with OSA and hypoxia compared to CSA (10). A large multicenter study reported a significantly increased prevalence of AF (4.8% vs. 0.9%) and NSVT (5.3% vs. 1.2%) with severe OSA compared to those without OSA. Upon controlling for age, gender, BMI, and the presence of coronary artery disease, it was observed that those suffering from severe OSA were four times more likely to have AF and three times more likely to have NSVT (8). Another study showed a significant increase in the relative risk of AF and NVST during sleep shortly after respiratory disorders (11). Moreover, the rate of AF recurrence following cardioversion was found to be higher in untreated OSA patients (82%) compared to those with treated OSA (42%) and the control group without OSA (53%) (17). These results support the direct relationship between OSA with AF and NVST. However, it was not clear how this association arose and developed in patients with OSA.

There could be several mechanisms that potentially lead to an increased occurrence of AF and NSVT in patients diagnosed with OSA. On one hand, acute physiological changes resulting from airway collapse during sleep played an important role in arrhythmias caused by OSA. These alterations encompass hypoxemia, hypercapnia, changes in sympathetic and parasympathetic tension, and fluctuations in thoracic pressure (18). On the other hand, the chronic impacts of persistent and recurrent OSA were ultimately linked with cardiac structural remodeling (19, 20). In line with these mechanisms, multivariate linear regression analysis revealed that increased LAD, LVDD, RAD, RVD and LF/HF were associated with severe OSA in this study population. Moreover, our results demonstrated that the association between OSA with AF and NVST was mediated in part through autonomic nervous system changes and cardiac structural remodeling by mediation analysis.

Firstly, prior research has indicated that intermittent hypoxemia, coupled with hypercapnia via chemoreflexes, resulted in heightened

TABLE 3 Comparison of heart rate variability parameters between different OSA groups with atrial fibrillation removal.

Variables	None OSA (n = 74)	Mild OSA (n = 123)	Moderate OSA (n = 133)	Severe OSA (n = 176)	p-value
Mean HR (bmp)	72.5 ± 12.4	74.0 ± 10.9	73.5 ± 11.0	75.9 ± 12.3	0.009
Maximal HR (bmp)	114.2 ± 19.9	115.8 ± 19.7	111.6 ± 15.4	115.2 ± 19.5	0.350
Minimal HR (bmp)	52.6 ± 10.5	52.6 ± 9.2	53.0 ± 9.6	53.4 ± 10.6	0.684
Mean QTc (ms)	398.9 ± 33.1	397.6 ± 35.6	396.3 ± 31.6	406.4 ± 42.1	0.333
Maximal QTc (ms)	476.1 ± 58.3	470.4 ± 54.3	475.1 ± 58.5	483.5 ± 61.7	0.541
Time domain					
SDNN (ms)	122.2 ± 39.6	110.3 ± 33.9	111.4 ± 36.1	107.9 ± 33.2	0.042
SDANN (ms)	105.1 ± 39.7	99.8 ± 31.7	97.9 ± 34.3	93.4 ± 35.4	0.371
SDNN Index (ms)	50.7 ± 25.9	45.4 ± 17.9	46.9 ± 17.8	47.9 ± 19.3	0.343
RMSSD (ms)	35.9 ± 29.5	29.7 ± 21.5	29.0 ± 15.8	27.9 ± 15.2	0.042
PNN50 (%)	12.4 ± 13.5	7.6 ± 9.4	7.4 ± 8.5	7.5 ± 8.3	0.002
Trigonometric index (ms)	28.6 ± 10.1	25.5 ± 9.9	26.2 ± 10.8	25.3 ± 10.6	0.144
Frequency domain					
LF (ms^2)	287.8 ± 236.8	303.2 ± 256.5	349.2 ± 506.7	471.6 ± 770.8	0.034
HF (ms^2)	251.9 ± 240.8	287.0 ± 384.6	294.1 ± 521.6	354.6 ± 786.5	0.607
VLF (ms^2)	811.3 ± 376.2	819.3 ± 498.7	874.9 ± 513.2	1011.9 ± 610.3	0.120
LF/HF	1.6 ± 1.1	1.7 ± 1.4	1.8 ± 1.2	2.1 ± 1.9	0.031

Data are shown as mean ± SD. HR, heart rate estimated by pulse oximetry; QTc, corrected QT interval; SDNN, standard deviation of normal-to-normal intervals; SDANN, standard deviation of 5 min average NN intervals; RMSSD, root mean square successive difference; PNN50, percentage of adjacent NN intervals; LF, power in low frequency spectrum; HF, power in high frequency spectrum; VLF, power in very low frequency spectrum; LF/HF, ratio of low frequency and high frequency.

TABLE 4 Unadjusted and adjusted association between OSA (categorized by severity) and cardiac arrhythmias.

	OSA category	n (%)	Unadjusted adjusted			
			OR (95% CI)	p-value	OR (95% CI)	p-value
AF	None	4 (5.1%)	Reference	Reference	Reference	Reference
	Mild	22 (15.2%)	3.309 (1.097–9.977)	0.034	2.927 (0.954–8.979)	0.060
	Moderate	24 (15.3%)	3.338 (1.116–9.989)	0.031	3.055 (1.002–9.316)	0.048
	Severe	44 (20.0%)	4.624 (1.604–13.336)	0.005	3.881 (1.306–11.534)	0.015
	Linear Trend		/	0.004	/	0.024
NSVT	None	2 (2.6%)	Reference	Reference	Reference	Reference
	Mild	5 (3.4%)	1.357 (0.257–7.162)	0.719	1.360 (0.251–7.370)	0.722
	Moderate	6 (3.8%)	1.510 (0.298–7.659)	0.619	1.326 (0.255–6.897)	0.737
	Severe	24 (10.9%)	4.653 (1.073–20.169)	0.040	3.690 (0.809–16.036)	0.046
	Linear Trend		/	0.001	/	0.013

Adjusted for: age, gender, BMI, smoking, drinking, hypertension, diabetes mellitus, myocardial infarction. AF, atrial fibrillation; NVST, non-sustained ventricular tachycardia; CI, confidence interval; OR, odds ratios.

sympathetic activation and increased levels of catecholamines in patients with OSA, even during daytime normoxic wakefulness (21). HRV served as a valuable clinical indicator of autonomic balance. In another large-scale study of 4,152 participants to identify the impacts that OSA related to rapid eye movement (REM) exerts on cardiac autonomic dysfunction, measures of HRV revealed a transition to sympathetic predominance in OSA during REM sleep, manifesting as an increased LF/HF and LF (n.u) (22). Tachycardia, resulting from heightened sympathetic activation, led to the consumption of myocardial oxygen at the lowest blood oxygen saturation levels (18). This could potentially cause myocardial ischemia and impair cardiac contractility and diastolic relaxation. We found that increased LF/HF significantly mediated the association between severe OSA and NSVT, and this result was consistent with the previous conclusion.

Second, intrathoracic negative pressure fluctuations during inspiration against a collapsed upper airway in OSA stimulated cardiac mechanoreceptors and increased cardiac transmural pressure (a powerful stimulus to LV hypertrophy), which might mechanically stretch the myocardial walls, thereby promoting significant changes in myocardial excitability and structural remodeling of the myocardium

TABLE 5 Association of OSA (categorized by severity) with differential HRV indices and ECHO indicators.

Dependent variable	Independent variable: severe OSA (unadjusted)			Independent variable: severe OSA (adjusted)		
	β (95% CI)	p-value	R^2	β (95% CI)	p-value	R^2
HRV indicators*						
SDNN (ms)	−5.614 ([−12.443]–1.215)	0.107	0.004	−1.229 ([−8.556]–5.967)	0.725	0.018
RMSSD (ms)	−2.951 ([−6.770]–0.869)	0.130	0.003	−1.811 ([−5.878]–2.255)	0.382	0.029
PNN50 (%)	−1.138 ([−3.015]–0.739)	0.234	0.001	−0.867 ([−2.887]–1.152)	0.399	0.004
LF (ms^2)	153.666 (47.478–259.854)	0.005	0.016	151.424 (36.904–265.943)	0.010	0.012
LF/HF	0.439 (0.140–0.739)	0.004	0.016	0.334 (0.022–0.647)	0.036	0.076
ECHO indicators						
AAOD (mm)	1.287 (0.650–1.924)	<0.001	0.024	0.618 ([−0.015]–1.250)	0.055	0.143
MPAD (mm)	0.793 (0.290–1.297)	0.002	0.014	0.566 (0.039–1.093)	0.075	0.044
LAD (mm)	2.913 (1.822–4.004)	<0.001	0.043	1.638 (0.537–2.739)	0.004	0.133
LVDD (mm)	2.354 (1.356–3.351)	<0.001	0.034	1.069 (0.090–2.048)	0.032	0.170
RAD (mm)	1.968 (1.055–2.880)	<0.001	0.028	1.418 (0.479–2.357)	0.003	0.088
RVD (mm)	0.819 (0.374–1.264)	<0.001	0.020	0.590 (0.131–1.049)	0.012	0.072
LVPWD (mm)	0.548(0.129–0.968)	0.010	0.009	0.413 ([−0.030]–0.857)	0.068	0.018
LVEF (%)	−1.748 ([−3.021]-[−0.474])	0.007	0.011	−0.972 ([−2.300]–0.356)	0.151	0.047

Adjusted for: age, gender, BMI, smoking, drinking, hypertension, diabetes mellitus, myocardial infarction. *The study population excluded patients with atrial fibrillation. SDNN, standard deviation of normal-to-normal intervals; RMSSD, root mean square successive difference; PNN50, percentage of adjacent NN intervals; LF, power in low frequency spectrum; LF/HF, ratio of low frequency and high frequency; AAOD, ascending aortic diameter; MPAD, main pulmonary artery diameter; LAD, left atrial diameter; LVDD, left ventricular diastolic diameter; RAD, right atrial diameter; RVD, right ventricular diameter; LVPWD, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction; CI, confidence interval.

TABLE 6 Mediation analysis testing associations of severe OSA with AF and NVST mediated by significant ECHO and HRV indicators.

Model	a	p	b	p	c_n	p	c	p	Mediation effect ratio (%)
1	1.638	0.004	0.228	<0.001	0.073	0.803	0.401	0.043	93.1
2	1.069	0.032	0.060	0.002	0.317	0.206	0.401	0.043	16.1
3	1.418	0.003	0.202	<0.001	0.088	0.753	0.401	0.043	71.4
4	0.590	0.012	0.125	0.003	0.321	0.198	0.401	0.043	18.4
5	1.638	0.004	0.129	<0.001	0.854	0.032	1.061	0.005	19.9
6	1.069	0.032	0.096	0.001	0.855	0.027	1.061	0.005	9.7
7*	1.418	0.003	0.124	<0.001	0.827	0.034	1.061	0.005	16.6
8*	0.590	0.012	0.196	0.001	0.962	0.013	1.061	0.005	10.9
9	151.44	0.010	0.000	0.820	0.882	0.070	0.010	<0.001	NA
10	0.334	0.036	0.106	0.036	0.746	0.033	0.010	<0.001	3.3

Mediation analysis by multivariate linear regression analysis and multivariate logistic regression, testing associations of severe OSA with AF and NSVT mediated by mean HR, HRV and ECHO indices. All analyses were adjusted for age, gender, BMI, smoking, drinking, hypertension, diabetes mellitus and myocardial infarction. *The study population excluded patients with atrial fibrillation. Model 1–4, Y = AF, X = Severe OSA and M (Mediator) = ECHO indicators (LAD, LVDD, RAD or RVD). Model 2–8, Y = NSVT, X = Severe OSA and M (Mediator) = ECHO indicators (LAD, LVDD, RAD or RVD). Model 9–10, Y = NSVT, X = Severe OSA and M (Mediator) = HRV indicators (LF or LF/HF). Analysis of Y and X = c; Analysis of M and X = a; Analysis of Y and M (together with X) = b; Analysis of Y and X (together with M) = c_n; Mediation effect ratio = ab/c. NA, not available.

(1, 18, 23). In addition, these forces also lead to a leftward displacement of the interventricular septum during diastole, which hinders LV filling and subsequently decreases stroke volume (12, 24). This repetitive mechanism, occurring during each stage of apnea, might cause stretching of the cardiac wall and intrathoracic vessels. Consequently, it potentially results in both short-term electrical and

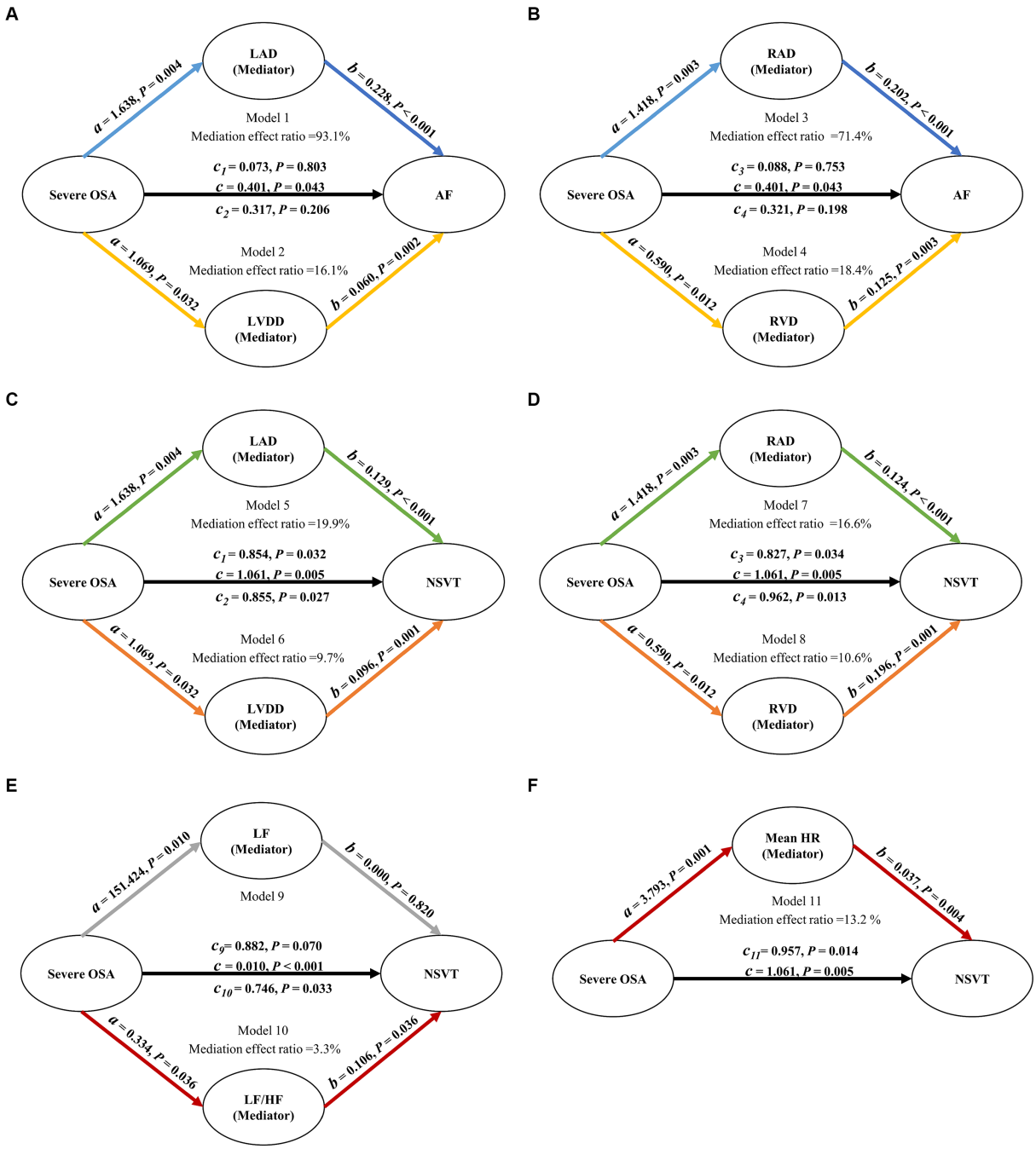

FIGURE 2
Path diagram of mediation analysis. **(A–D)** LAD, LVDD, RAD, and RVD mediated the relationship between severe OSA and AF. **(C,D)** LAD, LVDD, RAD, and RVD mediated the relationship between severe OSA and NSVT. **(E)** After removing the influence of patients with AF, LF/HF mediated the relationship between severe OSA and NSVT. All analyses were adjusted for age, gender, BMI, smoking, drinking, hypertension, diabetes mellitus and myocardial infarction. OSA, obstructive sleep apnea; LAD, left atrial diameter; LVDD, left ventricular diastolic diameter; RAD, right atrial diameter; RVD, right ventricular diameter; LF, power in low frequency spectrum; LF/HF, ratio of low-frequency and high-frequency; HR, mean heart rate; AF, atrial fibrillation; NSVT, nonsustained ventricular tachycardia.

long-term mechanical remodeling of the atrium and LV, thereby increasing the risk of the occurrence of atrial and ventricular dysrhythmias (12, 24). Chronic LA enlargement and diastolic dysfunction were observed in numerous animal models of chronic OSA (25, 26). Moreover, Neilan et al. (20) reported that patients with OSA had increased pulmonary artery pressure, RA size, LA size, and LV mass compared with those without OSA. Since it was well established that enlarged LAD was an independent risk factor for AF and NVST (14, 27), this fact might help to explain the increased risk of AF and NVST in patients with OSA.

However, the existing literature on conduction delay arrhythmias is limited and often contradictory. Some studies have reported a

prevalence of 13.3% in patients with OSA, compared to only 3% in healthy population (1). Conversely, another study found no significant differences in the occurrence of conduction delay arrhythmias between OSA patients and matched control groups (8). Our study results revealed no significant difference in conduction delay arrhythmia between subjects with OSA and those without. This observation may be attributed to variations in study design and the characteristics of the study population.

Finally, increased systemic inflammation, oxidative stress and vascular dysfunction caused by OSA may serve as intermediate pathways for triggering arrhythmias (3, 12). These pathophysiological changes may synergistically exacerbate the occurrence of arrhythmias in patients with OSA.

AF and NSVT were significant risk factors for cardiovascular death and sudden cardiac death in patients with OSA (23, 28). In multiple large prospective cohort trials, the incidence of fatal and non-fatal cardiovascular events was higher in patients with severely untreated OSA compared to patients without OSA. There is a correlation between OSA severity and the risk of cardiovascular disease, however, the effectiveness of CPAP significantly decreases the cardiovascular outcomes related to this disease (29–31). Meanwhile, CPAP could reduce the occurrence of ventricular arrhythmia and reduce the recurrence rate of AF after electrical cardioversion by other studies (17, 20, 32). International professional societies recommended that patients with severe OSA should receive CPAP therapy as early as possible (3). Consistent with this recommendation, we anticipate that prompt diagnosis and timely CPAP therapy will decrease the occurrence of AF and NSVT and potentially lower the frequency of cardiovascular disease mortality. Consequently, further investigations are needed to establish whether treatment of OSA during sleep may reduce the risk of cardiac arrhythmia; such studies include determining the optimal CPAP usage to reverse adverse cardiovascular and metabolic outcomes.

Meanwhile, Sinha et al. (33) reported that cardiac resynchronization therapy might lead to a reduction of CSA and to increased sleep quality in patients with heart failure and SDB. In addition, in another prospective study of 67 patients with mitral regurgitation, patients with mitral regurgitation and SDB who underwent MitraClip-placement showed a significant AHI improvement (34). Although the study sample is small and the specific mechanism still needs to be studied, this provides new ideas for the treatment of OSA.

The present study has the following limitations. First, due to the relatively small number of cases of NVST in each group, the OR confidence intervals for cardiac arrhythmias in patients with severe OSA were wide, despite adequate test reliability. Second, data on cardiac arrhythmias and OSA in the context of mortality are scarce and all additional information can help to create a more complete picture. Lastly, the study was the lack of follow-up of patients with diagnosed OSA-related cardiac arrhythmias who were eligible for CPAP therapy. Therefore, further work is needed to determine the prognostic significance of CPAP in NSVT and AF.

Conclusion

This study demonstrated that severe OSA was independently associated with AF and NSVT, and this association was mediated by autonomic nervous system changes and cardiac structural remodeling. Further research is required to clarify the exact mechanisms underlying the relationship of OSA with AF and NSVT, and to assess the effect of OSA therapy on the development, treatment, and prognosis of AF and NSVT.

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 humans were approved by ethics committee of Renmin Hospital of Wuhan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HC: Methodology, Writing – original draft. QZ: Methodology, Writing – original draft. YuH: Data curation, Writing – original draft. JZ: Software, Writing – original draft. YaH: Supervision, Visualization, Writing – original draft. KH: Funding acquisition, Resources, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research was supported by a grant from the National Natural Science Foundation of China (No. 82270101).

Acknowledgments

The authors thank all patients for their participation in this study. The authors would also like to thank all the researchers from the Department of Respiratory and Critical Care Medicine, Renmin Hospital of Wuhan University, for their assistance in data processing. No content generated by AI technologies has been presented as this work.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 26 April 2024
DOI 10.3389/fmed.2024.1378410

OPEN ACCESS

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RECEIVED 29 January 2024
ACCEPTED 15 April 2024
PUBLISHED 26 April 2024

CITATION
Seifen C, Herrmann M, Pordzik J, Matthias C and Gouveris H (2024) Periodic limb movements in patients with suspected obstructive sleep apnea without comorbid conditions.
Front. Med. 11:1378410.
doi: 10.3389/fmed.2024.1378410

Periodic limb movements in patients with suspected obstructive sleep apnea without comorbid conditions

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Background: Periodic limb movement disorder (PLMD) and obstructive sleep apnea (OSA) are overlapping clinical syndromes with common risk factors. However, current literature has failed to establish a clear pathophysiological link between them. Thus, little is known about periodic limb movements (PLM) in otherwise healthy patients with suspected OSA.

Methods: We performed a retrospective analysis of 112 patients (age: 44.5 ± 12.0 years, 14.3% female) with suspected OSA who underwent full night polysomnography for the first time. Patients with chronic diseases of any kind, recent infections, malignancies, or daily or regular use of any type of medication were excluded. Group comparisons were made based on the severity of OSA (using the apnea hypopnea index, AHI) or the periodic limb movement index (PLMI).

Results: Both, PLMI and the total number of periodic limb movements during sleep (PLMS), showed a significant increase in patients with severe OSA. In addition, AHI and apnea index (AI) were significantly higher in patients with PLMI >15/h, with a similar trend for hypopnea index (HI) ($p < 0.001$, $p < 0.001$, and $p > 0.05$, respectively). PLMI was significantly positive correlated with AHI, AI, and HI ($r = 0.392$, $p < 0.001$; $r = 0.361$, $p < 0.001$; and $r = 0.212$, $p < 0.05$, respectively). Patients with PLMI >15/h were significantly older ($p < 0.001$). There was no significant association between body mass index (BMI) and PLMI >15/h.

Conclusion: We found a significant association between the severity of OSA and PLM in our study population with suspected OSA but without other comorbidities. PLMI and PLMS were significantly increased in patients with severe OSA. Future prospective studies with larger collectives should verify the presented results and should include mechanistic aspects in their evaluation.

KEYWORDS

periodic limb movement, PLM, obstructive sleep apnea, OSA, PLMI, PLMS

1 Introduction

Periodic limb movements during sleep (PLMS) are an involuntary sleep-related phenomenon defined as periodic episodes of repetitive limb movements (1). More often than not the lower extremities are affected, with typical dorsiflexion of the toes and ankles and occasional flexion of the hips and knees. In contrast, the upper extremities are less commonly affected (2). Periodic

limb movements (PLM) are often described as "Babinski-like" response (3). Scoring criteria require the repetitive movements to last between 0.5 and 5 s (1, 4). To determine the frequency of PLMS occurrence, the periodic limb movement index (PLMI), calculated as the number of PLM per hour of sleep, is commonly used (4). Five PLM per hour of sleep used to be the diagnostic threshold for periodic limb movement disorder (PLMD) (5). However, several studies have shown that healthy individuals without sleep disorders may have more than ten PLM per hour of sleep (6). Therefore, the current guidelines have set the threshold for PLMI in adults at 15 events/h (h) for the diagnosis of PLMD (4). Moreover, the diagnosis of PLMD is a diagnosis of exclusion. Thus, underlying restless legs syndrome (RLS), narcolepsy, or REM sleep behavior disorder (RBD) should be excluded (7). A prevalence of PLMD in 4–11% of the general adult population has been advocated (8).

Community-based studies have highlighted the significance of age, male gender and RLS as independent risk factors for PLMD (9). In addition to RLS, the occurrence of PLMD has been associated with heart disease (10), musculoskeletal disease (10), narcolepsy with cataplexy (10), chronic kidney disease (11), magnesium deficiency (12), neuropsychiatric and neurodegenerative disorders (13), iron deficiency (10), and diabetes mellitus (14). However, the pathophysiological mechanisms underlying these associations are far from clear, particularly with respect to neuropsychiatric and neurodegenerative disorders. Similarly, the use of several psychotropic medications has been linked to PLMD, or PLMI >15/h, for example tricyclic anti-depressants (e.g., amitriptyline), or serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine and mirtazapine) (15). Lifestyle habits such as increased caffeine consumption, higher body mass index (BMI), and working nights or shifts have also been linked to an increased number of PLM (9, 10).

Although PLM are considered a potential sleep disruptor, their clinical significance is unclear (16). Retrospective studies suggest a high prevalence of comorbid PLM in patients with obstructive sleep apnea (OSA) (16). OSA is known as the most relevant form of sleep-disordered breathing, anatomically defined by partial to complete airway obstruction during sleep, even when respiratory effort is still present (17, 18). The relationship between OSA and PLM is complex, and a precise rationale is unclear. Recently, a large prospective multicenter randomized controlled trial found that guideline-directed therapy for OSA with continuous positive airway pressure (CPAP) had no effect on the severity or expression of PLM (16). These and other studies suggest that the periodicity of OSA and PLM are not caused by a common central generator (16, 19). Moreover, an increasing accumulation of comorbidities has been previously associated with an increased OSA severity, especially in older male subpopulations (20).

To this end, the purpose of this study was to investigate the extent to which PLM vary in otherwise healthy individuals with clinical suspicion of OSA. Through careful patient selection, we aimed to minimize important confounding factors that may independently influence PLM as well as OSA, such as concomitant acute or chronic diseases or daily medication use.

2 Methods

2.1 Design

In our accredited sleep laboratory, patients receive full-night polysomnography (PSG) for the diagnosis or treatment monitoring of sleep-related breathing disorders. A licensed technician ensures that each PSG is performed correctly, and a board-certified sleep physician accomplishes evaluation (including the assessment of periodic limb movements) according to the American Academy of Sleep Medicine standard guidelines (4).

Our institutional guidelines require an outpatient polygraphy (PG) with a home sleep-apnea testing device as the initial diagnostic approach for patients suspected of having a sleep-related breathing disorder. An additional PSG is performed to validate an accurate diagnosis, or to definitively exclude a sleep-related breathing disorder when results are inconclusive. Ultimately, PSG is performed to initiate the optimal therapeutic management of a sleep-related breathing disorder.

For this study, we screened our clinical database from January 1, 2020, to December 31, 2022, for all patients who underwent PSG for the first time. In an initial step, all patients with a technically qualitative PSG were included in the study, provided that a diagnosis of OSA was made or a clinically relevant sleep-related breathing disorder was ruled out. The diagnosis of any type of sleep-related breathing disorder other than OSA (e.g., periodic breathing or Cheyne-Stokes breathing) resulted in study exclusion.

Then, the medical records of these patients were searched to obtain information on age, BMI, and sex. Likewise, the medical records were screened for information on chronic diseases of any types (e.g., type 2 diabetes, arterial hypertension, pulmonary disease, cardiovascular disease, chronic mental disorders, or any others, e.g., RLS), recent infections, malignancies, and daily or regular (e.g., weekly, monthly) use of medications of any types. In this next step, only patients who were at least 18 years of age and did not have any recorded comorbidities, namely any chronic condition, recent infections, or malignancies, and were not taking medications of any types were further considered for study inclusion.

In all included patients, each PSG recording was analyzed for selected parameters (in alphabetical order):

- AHI: apnea hypopnea index: apneas and hypopneas/h;
- AI: apnea index: apneic events/h;
- ARI: arousal index: number of arousals/h of sleep;
- HI: hypopnea index: hypopnea events/h;
- ODI: oxygen desaturation index: average number of desaturation episodes (decrease in the mean oxygen saturation of ≥3%) per hour;
- PLMI: periodic limb movement index: total number of periodic limb movements per hour of sleep;
- PLMS: periodic limb movements during sleep (total number);
- T90: percentage of cumulative time with peripheral oxygen saturation below 90% in total sleep time; and
- TST: total sleep time in minutes.

For further analysis, groups were formed based on OSA severity on the one hand or the presence of a pathological PLMI on the other. Based on epidemiological studies, the PLMI cut-off has been set to >15/h in adults when a diagnosis of PLMD is considered (4). However, PLMS can be scored according to the criteria recommended by the (above mentioned) AASM or the criteria recommended by the World Association of Sleep Medicine (WASM) (4, 21). In general, limb movements are more frequent after respiratory events than before and during respiratory events, and more respiratory-related leg movements

(RRLM) may be scored based on WASM criteria than based on AASM criteria (22).

Grouping based on OSA severity (4):

- all male and female patients with an AHI of <5/h ("none");
- all male and female patients with an AHI of ≥5 to <15/h ("mild");
- all male and female patients with an AHI of 15 to 30/h ("moderate"); and
- all male and female patients with an AHI of >30/h ("severe").

Grouping based on PLMI (4):

- all male and female patients with an PLMI of <15/h ("PLMI <15/h"); and
- all male and female patients with an PLMI of >15/h ("PLMI >15/h").

For a better understanding of the patient selection and study design, see the flowchart in Figure 1.

2.2 Statistics

GraphPad Prism Version 5.01 (GraphPad Software, Boston, MA, United States) was used for statistical analysis and graphical representation. Normally distributed values were described with mean and standard deviation (SD). Non-normally distributed values were described with median and interquartile range (IQR). The Kolmogorov–Smirnov test was used to analyze whether the values originated from a Gaussian distribution. If the values were normally distributed, comparisons between three groups (e.g., "no/mild OSA" vs. "moderate OSA" vs. "severe OSA") were performed using one-way ANOVA with Tukey's *post hoc* test. If no Gaussian distribution was found, then the comparison between three groups was carried out using the Kruskal-Wallis test and the Dunn's *post hoc* test. The comparison between the two groups of PLMD-severity (e.g., "PLMI <15/h" vs. "PLMI >15/h") was performed with an unpaired *t*-test if the distribution of values was normal, or with a Mann–Whitney test if no Gaussian distribution could be assumed. The Chi-square test or Fisher's exact test were used to test whether the proportion of female patients differed significantly between the groups. To test the correlation, Spearman's correlation coefficient was calculated. We considered the results significant if the *p*-value was <0.05 (*), $p < 0.01$ (**) and $p < 0.001$ (***). Boxplots representing median and IQR were used in the figures.

2.3 Ethics

In this study, only health data that is routinely collected in the clinic was analyzed retrospectively. So-called "third parties" did not have access to the data. The ethics committee of the State Medical Association of Rhineland-Palatinate approved the protocol (2023-17,345).

3 Results

3.1 Study population characteristics

Between January 1, 2020, to December 31, 2022, $n = 602$ patients underwent full night PSG for the first time in our accredited sleep laboratory. After considering all inclusion and exclusion criteria, $n = 112$ patients were included in the present study, 96 (85.7%) male and 16 (14.3%) female. The mean age of the study population was 44.5 ± 12.0 years, and the median BMI was 28.0 (25.0–30.0) kg/m^2.

After categorizing the study population based on AHI, one patient was included in the "none" OSA group (AHI < 5/h), 35 patients were included in the "mild" OSA-severity group (AHI ≥ 5/h but <15/h), 42 patients were included in the "moderate" OSA-severity group (AHI 15–30/h) and 34 patients were included

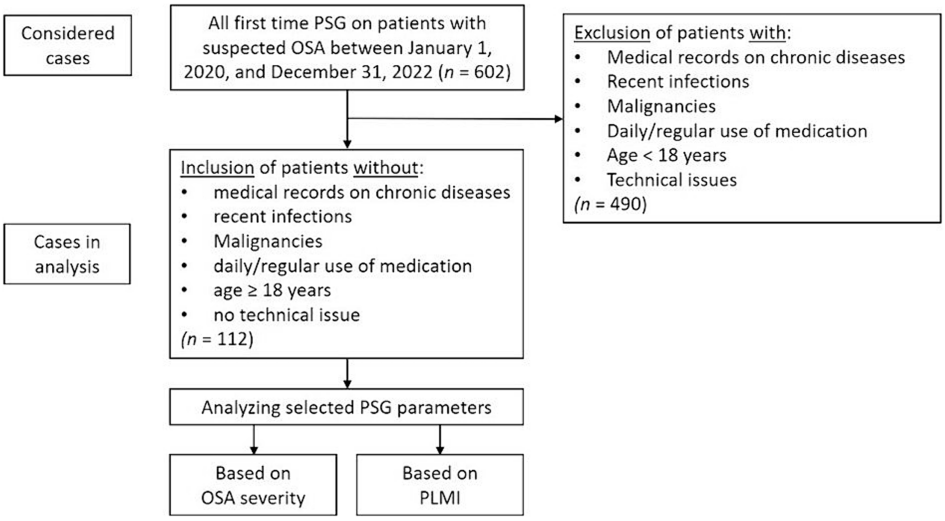

FIGURE 1
Flowchart for patient selection and study design. OSA, obstructive sleep apnea; PLMI, periodic limb movement index; PSG, polysomnography.

in the "severe" group (AHI > 30/h). To create more suitable group structures for the subsequent statistical analysis, the "none" and "mild" OSA-severity groups were combined into a new "none/mild" OSA-severity group. This measure was taken due to the only patient with an AHI of <5/h, which made a statistical analysis of such subgroup impracticable.

3.2 Association of periodic limb movements with obstructive sleep apnea

In a first step, the PLM (divided into PLMI and PLMS) were assessed according to the severity of OSA using the AHI. PLMI and PLMS showed a significant increase in patients with severe OSA, while both metrics did not differ significantly between patients with no or mild OSA and those with moderate OSA. T90 and ODI, both important metrics for the additional objective assessment of the severity of OSA, also increased significantly with AHI. Another finding was that a total of $n = 38$ patients (33.9% of the study population) had a PLMI >15/h. The proportion of female patients decreased with increasing severity of OSA, but without statistical significance. Detailed information about statistics and graphical representations of the PLMI and PLMS, as well as the epidemiological data and polysomnographic parameters of the study groups, can be found in Table 1 and Figure 2.

In a next step, different polysomnographic parameters were analyzed and compared based on the PLMI. AHI and AI were significantly elevated in group "PLMI >15/h." Accordingly, HI showed a clear tendency of higher values according to elevated PLMI but slightly without statistical significance. The proportion of female patients was lower in group "PLMI <15/h" compared to group "PLMI >15/h, but without statistical significance. The aforementioned and other polysomnographic parameters are detailed on Table 2 and shown in Figure 3.

3.3 Different correlations with the periodic limb movement index

Finally, correlation analyses were performed to ascertain possible factors associated with the existence and severity of PLMS. Spearman's correlation analysis identified a significant positive correlation between PLMI and age, AHI, AI, HI, ODI and T90 ($p < 0.05$, $p < 0.001$, $p < 0.001$, $p < 0.05$, $p < 0.001$ and $p < 0.05$, respectively). Contrarily, PLMI and BMI were not significantly correlated ($p > 0.05$). The correlation analyses are presented on Table 3. The example correlation between PLMI and AHI is shown in Figure 4.

4 Discussion

Studies addressing the impact of underlying OSA on PLM in patients with no comorbidities have been lacking. The present study therefore aimed to investigate the extent to which OSA and PLM are related or the severity of OSA influences PLM. For this purpose, in this study only (suspected) OSA patients without any other known comorbidities were included.

We provide evidence that PLM, divided into PLMI and PLMS, increased with OSA severity in OSA patients without any comorbid conditions. However, PLMI and PLMS did not differ significantly between patients with no or mild OSA and those with moderate OSA. In addition, AHI and AI were significantly higher in patients with PLMI >15/h, with a similar (although not reaching statistical significance) trend for HI. A significant positive correlation was found between PLMI and AHI, AI, and HI. In our study population, age was significantly higher in patients with a PLMI >15/h, whereas BMI tended to be similar in patients with relevant PLM and those without. In addition, the proportion of female patients was lower in the study subgroup with PLMI >15/h. The prevalence of patients with PLMI >15/h was 33.9% in our study, higher than the previously reported

TABLE 1 Comparison of periodic limb movements during sleep and periodic limb movement index among the three patient groups based on the severity of obstructive sleep apnea.

	None/mild	Moderate	Severe	Between group comparison (*p*-value)
Number of patients	36	42	34	
Number of female patients (%)	8 (22.2)	7 (16.7)	1 (2.9)	Not significant
Age in years (± SD)	41.5 ± 13.0	44.2 ± 12.8	47.8 ± 9.2	Not significant
BMI in kg/m² (IQR)	26.2 (24.0–28.0)	28.0 (25.6–30.0)	29.5 (27.0–33.3)	< 0.05 for none/mild vs. moderate, < 0.001 for none/mild vs. severe
AHI in n/h (± SD)	9.3 ± 3.1	22.6 ± 4.3	53.2 ± 19.2	< 0.001 for none/mild vs. moderate, < 0.001 for none/mild vs. severe, < 0.001 for moderate vs. severe
ODI in n/h (± SD)	8.2 ± 4.6	19.2 ± 6.5	50.1 ± 21.7	< 0.001 for none/mild vs. moderate, < 0.001 for none/mild vs. severe, < 0.001 for moderate vs. severe
T90 in % (IQR)	0.1 (0.0–0.4)	0.6 (0.1–1.5)	3.8 (1.1–13.4)	< 0.01 for none/mild vs. moderate, < 0.001 for none/mild vs. severe, < 0.001 for moderate vs. severe
PLMI in n/h (IQR)	2.8 (0.8–9.5)	4.3 (1.0–18.7)	16.3 (4.7–37.2)	< 0.001 for none/mild vs. severe, < 0.01 for moderate vs. severe
PLMS in *n* (IQR)	14.0 (5.0–59.0)	25.0 (6.5–117.8)	96.5 (31.5–185.0)	< 0.001 for none/mild vs. severe, < 0.01 for moderate vs. severe
TST in min (± SD)	361.2 ± 58.2	374.1 ± 51.0	378.0 ± 51.4	Not significant
ARI in n/h (± SD)	12.7 ± 7.0	15.1 ± 7.0	23.9 ± 12.7	< 0.001 for none/mild vs. severe, < 0.001 for moderate vs. severe

"None/mild"-all male and female patients with apnea hypopnea index (AHI) < 15/h; "moderate"-all male and female patients with AHI 15–30/h; "severe"-all male and female patients with AHI > 30/h. AHI, apnea hypopnea index; ARI, arousal index; BMI, body-mass index; IQR, interquartile range; ODI, oxygen desaturation index; PLMI, periodic limb movement index; PLMS, periodic limb movements during sleep; SD, standard deviation; T90, percentage of cumulative time with oxygen saturation below 90% in total sleep time; TST, total sleep time.

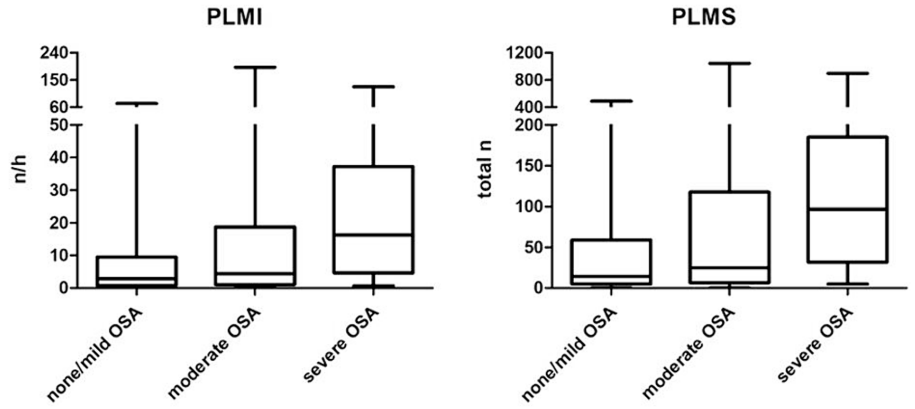

FIGURE 2
Periodic limb movements based on the severity of obstructive sleep apnea. OSA, obstructive sleep apnea; PLMI, periodic limb movement index; PLMS, periodic limb movements during sleep.

TABLE 2 Comparison of polysomnographic parameters between the two patient groups based on the periodic limb movement index.

	PLMI < 15/h	PLMI > 15/h	Between group comparison (*p*-value)
Number of patients	74	38	
Number of female patients (%)	12 (16.2)	4 (10.5)	Not significant
Age in years (± SD)	41.3 ± 11.8	50.6 ± 10.1	< 0.001
BMI in kg/m² (IQR)	27.5 (25.0–30.0)	28.0 (24.0–32.0)	Not significant
PLMI in n/h (IQR)	2.2 (0.8–5.3)	29.3 (19.4–40.4)	< 0.001
PLMS in *n* (IQR)	12.5 (5.0–35.0)	158.0 (129.8–281.5)	< 0.001
AHI in n/h (IQR)	18.8 (10.2–28.5)	29.1 (22.3–58.2)	< 0.001
AI in n/h (IQR)	3.7 (1.4–12.1)	11.4 (4.0–29.7)	< 0.001
HI in n/h (IQR)	11.5 (7.7–18.7)	16.5 (9.6–25.5)	Not significant
ODI in n/h (IQR)	15.5 (8.6–25.0)	26.3 (17.3–58.9)	< 0.001
T90 in % (IQR)	0.4 (0.0–2.1)	1.0 (0.3–13.1)	< 0.01
TST in min (± SD)	372.5 ± 49.4	368.4 ± 61.4	Not significant
ARI in n/h (IQR)	12.9 (8.5–18.9)	18.3 (13.0–29.1)	< 0.01

"PLMI < 15/h"-all male and female patients with periodic limb movement index < 15/h; "PLMI > 15/h"-all male and female patients with periodic limb movement index > 15/h. AHI, apnea hypopnea index; AI, apnea index; ARI, arousal index; BMI, body-mass index; IQR, interquartile range; HI, hypopnea index; ODI, oxygen desaturation index; PLMI, periodic limb movement index; PLMS, periodic limb movements during sleep; SD, standard deviation; T90, percentage of cumulative time with oxygen saturation below 90% in total sleep time; TST, total sleep time.

5–8% in adult community-based cohorts (23, 24). The higher prevalence of PLMI >15/h in our study could be the result of a selection bias, a higher proportion of male patients in this relatively small study population, or environmental factors such as measurement of PLM in a sleep laboratory. In addition, TST was comparable in patients with low and high PLMI, while ARI as a common sleep macrostructure metric was significantly higher in patients with a PLMI >15/h.

PLMD causes sleep fragmentation that may disturb underlying sleep rhythms and their intrinsic functions. Expected, patients affected by PLMD frequently complain about daytime sleepiness, poor concentration, or non-restorative sleep (25). Patients with OSA often report a similar constellation of symptoms. Although PLMD and OSA share overlapping symptoms, community-based studies have failed to detect a direct linkage between these conditions (9, 26). A possible explanation was provided previously in a study in which different periodicities of PLM and OSA before and after treatment with continuous positive airway pressure (CPAP) were found, suggesting that both conditions are not generated by a common central generator (19). Findings from another study that investigated coupling of electroencephalography and either chin- or leg-electromyography signals of PSG in OSA patients support the theory of a distinct central generator between OSA and PLMS (27).

However, another study showed PLM to increase in moderate to severe OSA after CPAP treatment, presumably due to "unmasking" underlying PLMD (28). The literature on the topic of correlation between PLM and severity of OSA, as depicted by the AHI, has been inconsistent. One study found a significant positive correlation between PLM and AHI (29). These findings are in line with the results of the present study. In contrast, another study found evidence for no significant correlation between PLM and AHI (16). It should be noted that the above studies (other than the present study) attempted to

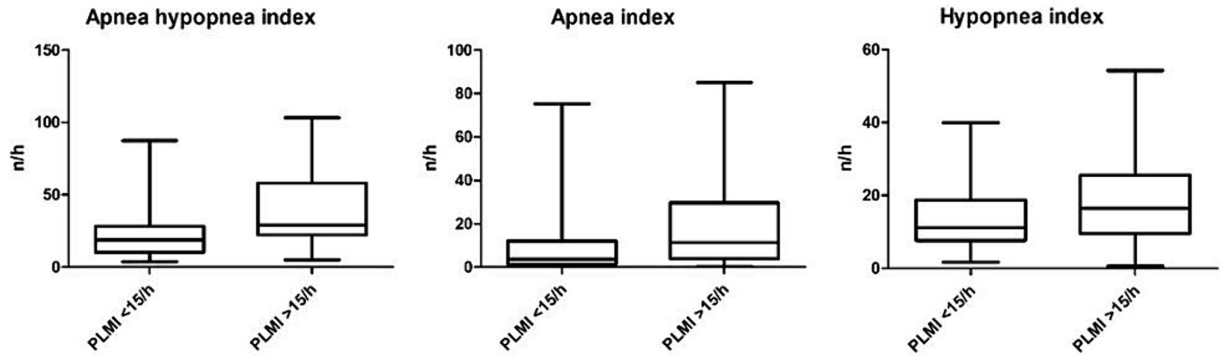

FIGURE 3
Apnea hypopnea index, apnea index, and hypopnea index based on the periodic limb movement index.

TABLE 3 Different correlations with the periodic limb movement index.

x	*y*	*r*	*p*-value
Age	PLMI	0.239	< 0.05
BMI	PLMI	0.035	> 0.05
AHI	PLMI	0.392	< 0.001
AI	PLMI	0.361	< 0.001
HI	PLMI	0.212	< 0.05
ODI	PLMI	0.397	< 0.001
T90	PLMI	0.223	< 0.05

AHI, apnea hypopnea index; AI, apnea index; BMI, body-mass index; HI, hypopnea index; ODI, oxygen desaturation index; PLMI, periodic limb movement index; T90, percentage of cumulative time with oxygen saturation below 90% in total sleep time.

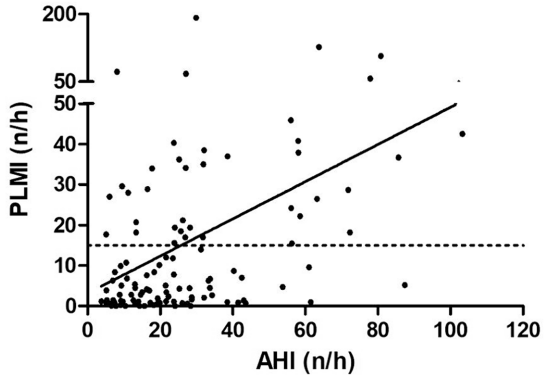

FIGURE 4
Correlation between apnea hypopnea index and periodic limb movement index. The dashed line shows the cut-off value at a periodic limb movement index of 15/h and the solid line shows the correlation. AHI, apnea hypopnea index; PLMI, periodic limb movement index.

minimize, but they did not exclude at last, confounding factors, such as possible influence of medications on PLM or severe comorbid conditions in their study populations.

Interestingly, in the HypnoLaus study, high PLMS was found mainly in middle-aged Europeans; in particular, the authors found age and male gender to be independent predictors of increased PLMS (9). This trend holds true for the results in the present study and is consistent with further previous studies (29). Conversely, increased BMI has been associated with an increased risk of PLMI >15/h (9). However, in the present study, BMI was approximately identical in the group with PLMI <15/h and the group with PLMI >15/h.

The major strength of our study is the strict selection of patients, as we extensively filtered the database of our sleep laboratory for those patients whose medical records excluded chronic diseases of any types, recent infections, malignancies, or daily or regular use of medications of any types. Through these measures, a possible impact of important confounders that have an influence on PLM could be kept to a minimum.

We acknowledge several limitations of the present study. One major limitation is that the results are based on observations in retrospective analyses. Because this study is observational, further randomized controlled and prospective trials are needed to validate the presented findings. Another important limitation is the lack of information on various lifestyle factors such as nicotine and alcohol consumption and night or shift work. In addition, other characteristics of the study population characteristics (e.g., head and neck circumference, Mallampati score, or body habitus other than BMI) were not included in the present study. These factors could have independently impact on the reported PLM. In addition, it cannot be ruled out that any condition (e.g., neurological, or psychiatric) was already present, although clinically unnoticed, at the time of data collection and were therefore not yet diagnosed at that time. This limitation may be better addressed in the future using a longitudinal study design. Also, the reported results refer to predominantly male study participants, especially in the group with severe OSA. We must acknowledge this gender bias as a major limitation that may have independently confounded the reported results. Regarding the female population and because of the retrospective data analysis, it was not possible to determine the premenopausal or postmenopausal status of the included female study participants. Ultimately, it should be considered that the PLM index is subject to high night-to-night variability (30–32), which could independently have limited the significance of these polysomnographic single-night measurements. In addition, the assessment of PLM is particularly challenging in patients with severe OSA, as limb movements associated with periodic

obstructive respiratory events (i.e., respiratory-related leg movements; RRLM) can "mimic" PLM (33).

The results of the present study cannot answer the question of a possible common central generator of OSA and PLM. However, the finding of increased PLMS in patients with clinically relevant OSA suggests that there may be a link between these two conditions: if not in the form of a periodicity, then perhaps in the form of mutual reinforcement.

Future prospective studies need to focus on the above limitations and examine them in larger study populations to validate the reported results. In addition, future studies should include additional biomarkers in their evaluation, e.g., as the intracellular storage protein ferritin (34–36).

5 Conclusion

Severe OSA is significantly associated with increased and likely clinically relevant PLM in OSA patients without comorbid conditions. A mechanistic link cannot be inferred from this observation and thus should be investigated in future studies. Additionally, prospective studies should verify the presented results.

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 humans were approved by Ethics committee of the State Medical Association of Rhineland-Palatinate. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

CS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. MH: Writing – review & editing. JP: Writing – review & editing. CM: Writing – review & editing. HG: Conceptualization, Formal analysis, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 28 June 2024
DOI 10.3389/fmed.2024.1429783

OPEN ACCESS

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RECEIVED 08 May 2024
ACCEPTED 19 June 2024
PUBLISHED 28 June 2024

CITATION
Liu P, Zhang Q, Ding H and Zou H (2024) Association of obstructive sleep apnea syndrome with polycystic ovary syndrome through bidirectional Mendelian randomization.
Front. Med. 11:1429783.
doi: 10.3389/fmed.2024.1429783

Association of obstructive sleep apnea syndrome with polycystic ovary syndrome through bidirectional Mendelian randomization

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Background: Observational studies have established a link between polycystic ovary syndrome (PCOS) and obstructive sleep apnea syndrome (OSAS), with obesity being a significant confounding factor that complicates the understanding of causality. This study seeks to clarify the causal relationship by utilizing bidirectional two-sample Mendelian randomization (MR) analysis.

Methods: A bidirectional MR strategy was implemented to investigate the potential causal relationship between PCOS and OSAS. Instrumental variables (IVs) for PCOS were sourced from a dataset comprising 3,609 cases and 229,788 controls. For OSAS, statistical data were obtained from a genome-wide association study (GWAS) involving 38,998 subjects, alongside a control group of 336,659 individuals. Our MR analysis utilized several methods, including inverse variance weighted (IVW), weighted mode, weighted median, simple mode, and MR-Egger, primarily focusing on the IVW technique. Sensitivity tests were conducted to ensure the robustness of our findings.

Results: Utilizing the IVW method, we identified a notable causal association from OSAS to PCOS, with an odds ratio (OR) of 1.463 and a 95% confidence interval (CI) of 1.086–1.971 ($p = 0.012$). In the opposite direction, PCOS also appeared to significantly affect OSAS development, indicated by an OR of 1.041 and a 95% CI of 1.012–1.072 ($p = 0.006$). The MR-Egger intercept test showed no evidence of directional pleiotropy, affirming the credibility of our causal findings ($p > 0.05$).

Conclusion: This study suggests a bidirectional causal relationship between PCOS and an increased risk of OSAS. These insights could guide future screening and prevention strategies for both conditions.

KEYWORDS

PCOS, OSAS, Mendelian randomization, causal inference, GWAS

1 Introduction

Polycystic ovary syndrome (PCOS) is a metabolic disorder affecting about 8–13% of women, marked by issues with ovulation, elevated androgen levels, and insulin resistance (1). This widespread endocrine disorder is marked by high androgen levels and menstrual disturbances, substantially increasing the risk of insulin resistance and metabolic syndrome. Factors like anovulation, hypothalamic dysfunctions, and menstrual irregularities can lead to diminished or absent progesterone in PCOS patients. The activity of estrogens, affected by their composition and metabolic traits in the body, is reduced in women with PCOS. Common manifestations of PCOS encompass hirsutism, obesity, acne, menstrual anomalies, and infertility (2, 3).

The worldwide occurrence of obstructive sleep apnea syndrome (OSAS) falls within a range of 9–38%, and it is progressively increasing due to the rising rates of obesity and the aging global population (4). Diagnosing OSAS involves identifying primary symptoms, including pronounced daytime fatigue, loud snoring, observed interruptions in breathing during sleep, and sleep analysis findings that reveal significant disruptions in breathing, specifically the apnea hypopnea index (AHI). In instances lacking overt symptoms, a diagnosis can still be established if the apnea-hypopnea index exceeds 15 episodes per hour (5, 6). Notably, the symptomatology in women with OSAS, characterized by difficulties in waking, insomnia, morning fatigue, headaches, depression, and anxiety, tends to be subtler and thus more frequently disregarded. This oversight contributes to a systemic underreporting of OSAS prevalence among females (7).

Mendelian randomization (MR) emerges as a crucial instrument in epidemiology, targeting the discovery of causal relationships between potential risk elements and health outcomes utilizing genetic variations as surrogates (8). Distinguished from traditional observational research, single nucleotide variations (SNPs) were identified via genome wide association studies (GWAS) functioning in the role of instrumental variables (IVs). This approach protects against confounding due to the random allocation of genetic variations at birth (9, 10). Our research endeavors to unravel the causative dynamics between PCOS and OSAS through bidirectional MR analysis.

2 Materials and methods

2.1 Study design

The two sample Mendelian randomization method was used to examine the potential causal link between PCOS and OSAS, as depicted in Figure 1. For accurate MR conclusions, adherence to three essential prerequisites is crucial: Assumption 1, the IVs must have a strong association with the exposure; Assumption 2, the genetic instruments should have no associations with potential confounding factors. Assumption 3, the impact of the genetic instruments on the outcome should be solely facilitated by the exposure.

2.2 Summary statistics from the GWAS for PCOS

The GWAS catalog provided the pooled data for analyzing PCOS, listed under the identifier ebi-a-GCST90044902 (11). This dataset was compiled by identifying PCOS diagnoses through ICD codes (ICD-8 256.90, ICD-9 256.4, and ICD-10 E28.2) within national health records, with the remainder of the female population serving as the control group. The study population, with European genetic backgrounds, comprised 3,609 cases of PCOS and 229,788 control subjects, with adjustments made for participant age to refine the study's accuracy.

2.3 GWAS summary statistics for OSAS

Genetic markers for the OSAS research were obtained from the FinnGen database (12). The identification of OSAS cases utilized the ICD-10 code G47.3, with the condition's diagnosis requiring clinical

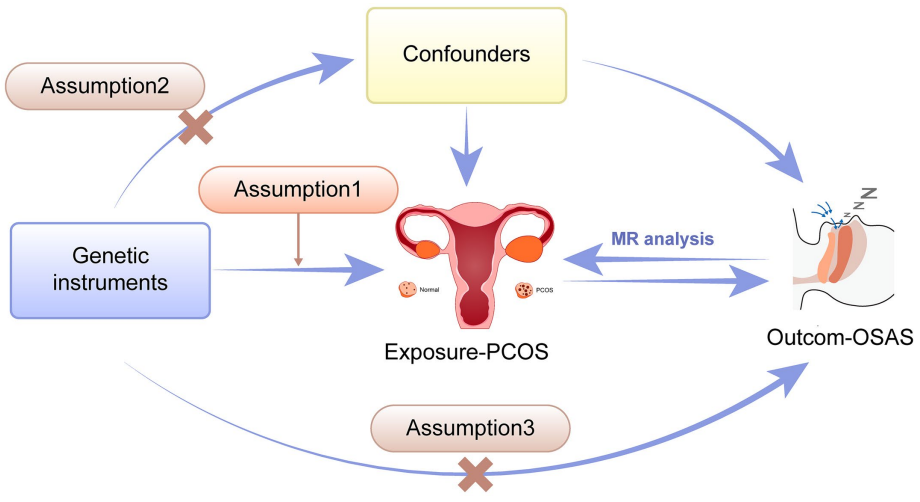

FIGURE 1
Schematic illustration showing the two-way Mendelian Randomization method employed to investigate the causal connection between PCOS and OSAS. PCOS, Polycystic ovary syndrome; OSAS, Obstructive sleep apnea syndrome.

evidence and an AHI of ≥5 events per hour. The dataset includes 38,998 subjects with OSAS and 336,659 controls, all of European ancestry, according to the database information.

2.4 SNP selection as IVs

In the segment focusing on OSAS, SNPs were chosen as instrumental variables (IVs) following a rigorous criterion of $p < 5 \times 10^{-8}$. Conversely, for analyzing PCOS as an exposure, a broader selection strategy was adopted for SNPs, applying the threshold of statistical significance for $p < 5 \times 10^{-6}$ to include a wider range of IVs. We meticulously excluded SNPs that violated the set linkage disequilibrium criterion ($r^2 < 0.001$ within a 10,000 kb span) (13). SNPs of the *F*-statistic ($Beta^2/SE^2$) below 10, indicating weak instrumental variables, were also removed from our study (14). Given the known confounding influence of obesity and BMI on both OSAS and PCOS, we diligently utilized the PhenoScanner to omit the instrumental variables linked to BMI and obesity, ensuring a more precise analysis of the results (15). PhenoScanner is a publicly accessible database and toolkit that enables users to query a wide range of public genetic datasets to explore associations between specific genotypes and phenotypes.

The concluding assessment pinpointed 13 SNPs as IVs for OSAS and 11 genetic variants for PCOS, employing a selective process that deliberately excluded certain SNPs to ensure only robust IVs were incorporated into the MR study. In summary, the approach rigorously filtered out palindromic SNPs and those showing genome-wide significant associations with the outcome, ensuring a robust selection of IVs.

2.5 Analysis of genetic correlations

We carried out a genetic correlation study to investigate the genetic links between OSAS and PCOS, employing Linkage Disequilibrium Score Regression (LDSC) as a key method to measure the genetic overlap and uncover possible common causal pathways between these conditions. To conduct this analysis, we utilized the LDSC software package (version 2.0.0). This tool is specifically designed for estimating heritability and genetic correlation from GWAS summary statistics, leveraging linkage disequilibrium information (16).

2.6 The methods for Mendelian randomization

This study utilized a suite of MR techniques, including IVW, weighted median, weighted mode, simple mode, and MR Egger, to examine the possible causative link connecting PCOS with OSAS (13, 17). The IVW approach was selected as the principal technique due to its enhanced statistical efficiency under the premise that all SNPs function as reliable instrumental factors (18). IVW exploits the genetic correlation between IVs, aggregating the accuracy of each estimate and thus prioritizing more accurate measures for dependable causal analysis. The additional methods provided support to IVW, each predicated on distinct assumptions about horizontal pleiotropy, aiming collectively to furnish thorough and solid MR findings under different scenarios (19).

2.7 Mendelian randomization assessment

Our analysis was conducted using the R programming environment (version 4.1.2) with the "TwoSampleMR" package. To examine the heterogeneity among instrumental variables, we applied Cochran's Q analysis as part of the IVW approach. Acknowledging the significance of pleiotropy, where genetic variants influence multiple traits, our study tackled horizontal pleiotropy and identified outliers using the method for residual sum and outlier analysis in Pleiotropy (MR-PRESSO) (20). For detecting directional pleiotropy among IVs, the MR-Egger intercept test was used, where an intercept differing from zero indicates directional pleiotropy (21). Moreover, we undertook a single exclusion method sensitivity analysis to identify any biases induced by specific SNPs, systematically removing each SNP to observe its effect on the findings (22), ensuring a thorough and unbiased assessment of the Mendelian randomization results.

3 Results

3.1 Genetic association between PCOS and OSAS

In the result of genetic association, we observed a modest genetic link between PCOS and OSAS, indicated by the genetic correlation of 0.03 and the *p* value of 0.77. This minimal genetic overlap suggested that the IVs employed in MR analysis were likely to be specific, enhancing the analysis by minimizing the influence of confounding factors and thereby making the causal inferences drawn from MR more trustworthy (Table 1).

3.2 Causal link between OSAS and PCOS through forward MR analysis

In the initial stage, we identified SNPs closely linked to OSAS across the genomic significance level, for a particular focus on those exhibiting no linkage disequilibrium. Following a meticulous process that involved the exclusion of SNPs with pleiotropic effects linked to obesity and BMI, we removed specific SNPs (rs10986730, rs11981973, and rs1228509). This rigorous curation ultimately led to the final selection of 13 SNPs, all of which demonstrated an *F*-Statistic surpassing 10, highlighting their robustness as IVs (Supplementary Table S1). In the application of the IVW methodology, our analysis identified an odds ratio (OR) of 1.463, with a 95% confidence interval (CI) extending from 1.086 to 1.971 and a significance level of $p = 0.012$. This indicates a probable causal association between PCOS and OSAS. Furthermore, employing the weighted median approach yielded an OR of 1.658, with a 95% CI ranging from 1.092 to 2.517, and a *p* value of 0.018, reinforcing the potential causal linkage. In contrast, the application of the MR Egger

TABLE 1 Genetic association between PCOS and OSAS derived from LDSC regression.

Trait 1	Trait 2	Rg (Se)	Pval
PCOS	OSAS	0.03 (0.11)	0.77

PCOS, Polycystic ovary syndrome; OSAS, Obstructive sleep apnea syndrome; Rg, Genetic correlation; Se, Standard error; Pval, *p* value.

method revealed an OR of 2.105, with a 95% CI from 0.715 to 6.201, and a *p* value of 0.204, while the simple mode approach produced an OR of 2.074, with a 95% CI of 1.009–4.261, and a *p* value of 0.070. Additionally, the weighted mode method indicated an OR of 1.762, with a 95% CI of 1.023 to 3.033, and a *p* value of 0.064, suggesting an ambiguous causal relationship between PCOS and OSAS (Figure 2A). The IVW method is notably advantageous in Mendelian randomization analyses for its capability to efficiently handle multiple SNPs as instrumental variables. This approach preserves the analytical rigor, even in the presence of minor correlations among SNPs. By calculating the average of the causal effect estimates from each SNP through inverse variance weighting, the IVW method significantly enhances the accuracy and reliability of causal determination (23, 24). Our analysis did not uncover significant heterogeneity, as indicated by the Cochran's *Q*-test, which presented a value of 9.823 with a *p* value of 0.631. Moreover, the MR Egger intercept test did not demonstrate any evidence of directional pleiotropy, with an intercept of −0.024 and a *p* value of 0.506 (Table 2). The findings were graphically depicted in scatterplots in Figure 2B. Additionally, the leave one out method scrutiny confirmed that none specific SNP disproportionately affected the estimated consequence of PCOS on OSAS risk (Figure 2C).

3.3 Causal connection between PCOS and OSAS through reverse MR analysis

In our reverse MR study, we investigated the potential of PCOS to cause OSAS, specifically by removing SNPs linked to obesity and increased BMI. After a thorough process that meticulously screened for SNPs with pleiotropic effects associated with obesity and BMI, two specific SNPs, namely rs804263 and rs71562896, were excluded. As a result of this refinement, IVs were narrowed down to a total of 11 specific SNPs (Supplementary Table S2), Utilizing the IVW methodology, our analysis substantiated a significant causal relationship

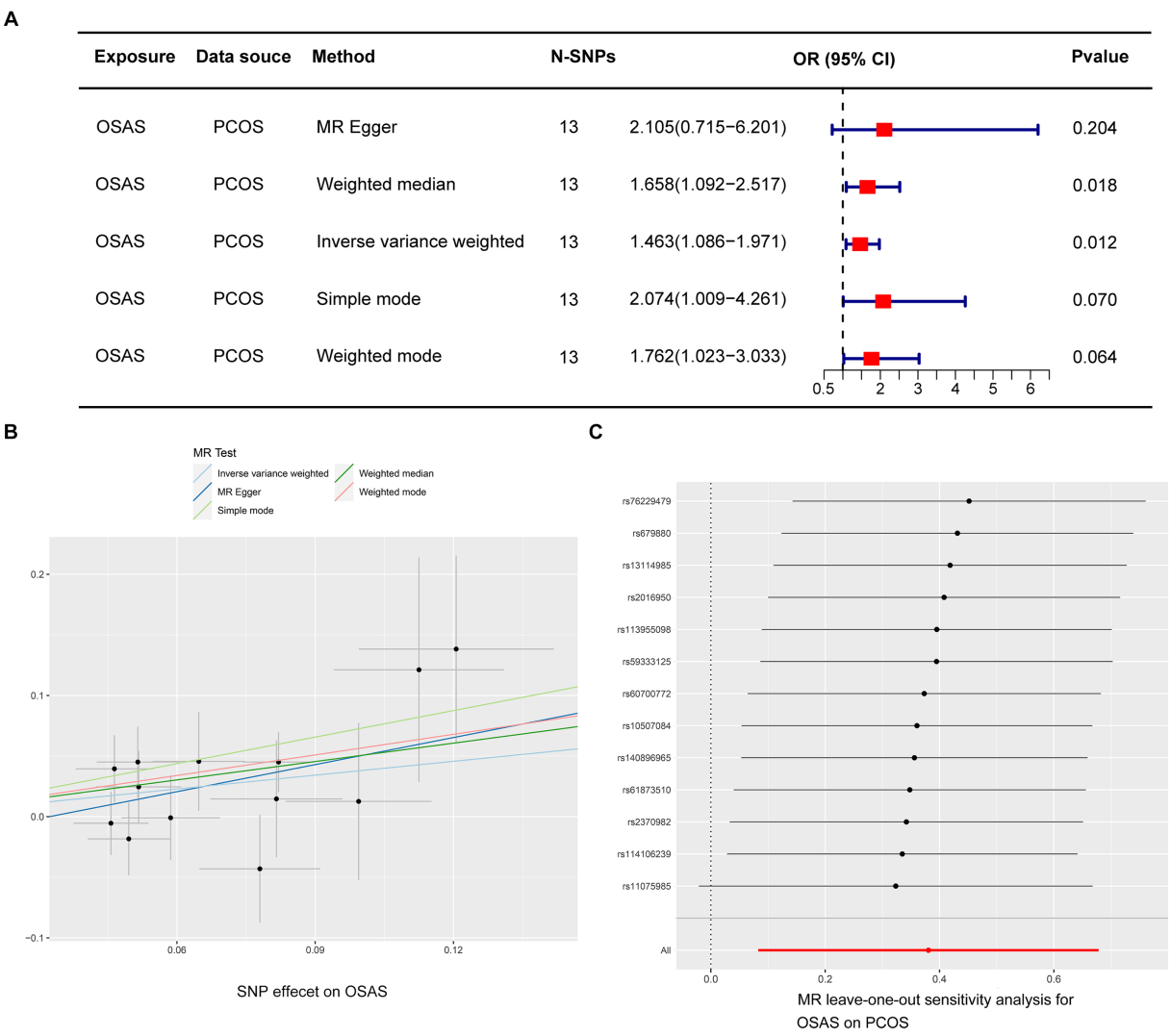

FIGURE 2
Depicts MR studies on the causal link with OSAS as the predictor and PCOS as the result. **(A)** Shows the causative influence of OSAS on PCOS. **(B)** A scatter diagram showing the analysis of individual SNPs to assess OSAS effect on the likelihood of PCOS. **(C)** A graph excluding one genetic variant shows the combined impact of SNPs on the link connecting OSAS with PCOS.

TABLE 2 PCOS and OSAS: heterogeneity and pleiotropy analysis.

Exposure	Outcome	Heterogeneity		MR-egger intercept	
		Cochrane's Q	Heterogeneity (pval)	Egger-intercept	Pleiotropy (pval)
OSAS	PCOS	9.823	0.631	−0.024	0.506
PCOS	OSAS	7.756	0.653	0.001	0.805

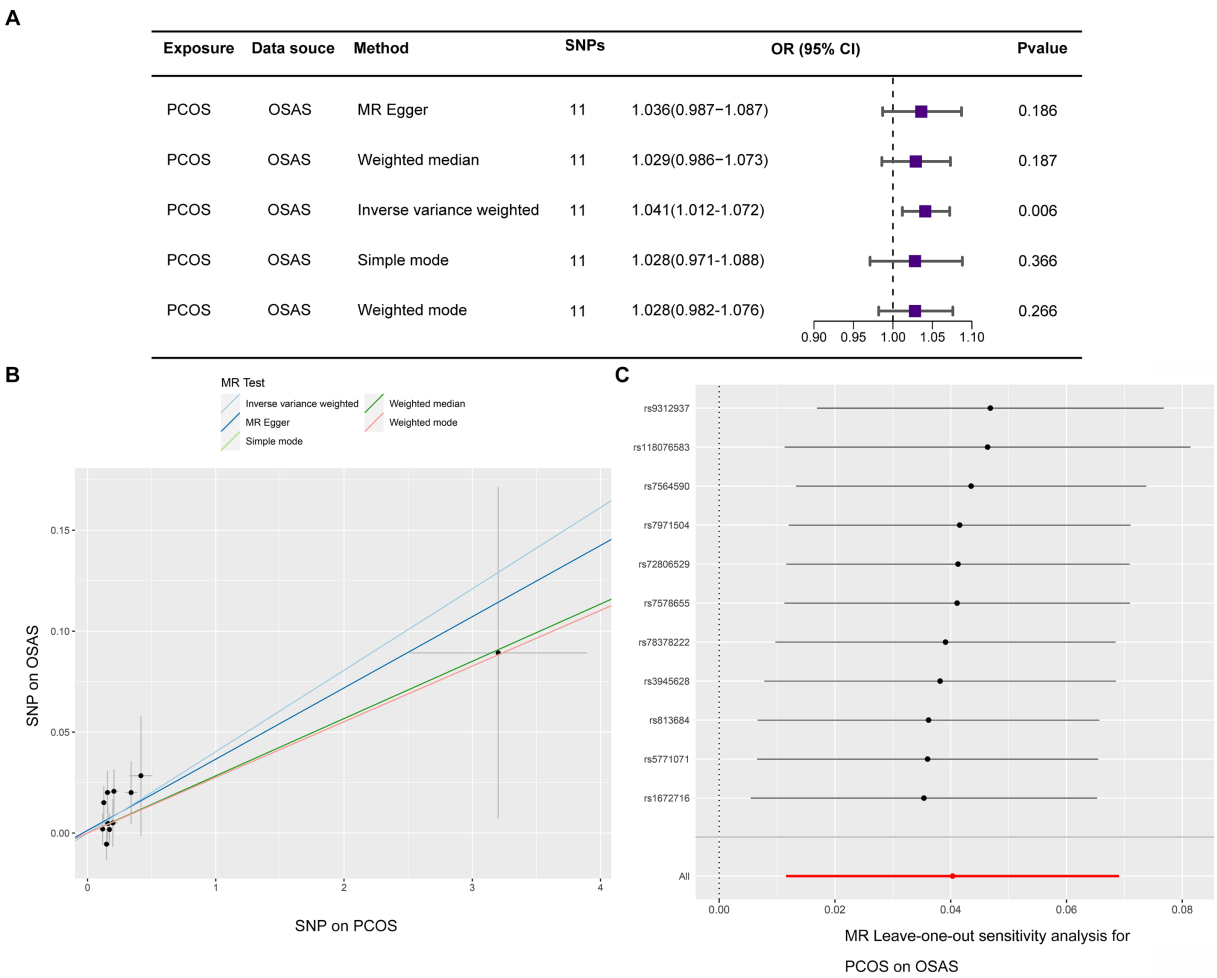

FIGURE 3
MR evaluations reveal causal relationships, with PCOS predicting OSAS the consequence. **(A)** Details the causative effect of PCOS on OSAS. **(B)** A scatter diagram examines the SNPs to understand how PCOS affects the onset OSAS. **(C)** A leave one out graph underscores the collective effects of SNPs and their impact link connecting PCOS and OSAS.

between PCOS and OSAS, evidenced by an OR of 1.041 within a 95% CI ranging between 1.012 and 1.072, achieving a *p* value of 0.006. The weighted mode analysis indicated an OR of 1.028 with a 95% CI between 0.982 and 1.076, resulting in a *p* value of 0.266; the MR Egger technique reported an OR of 1.036 with a 95% CI between 0.987 and 1.087, with a *p* value of 0.186; the simple mode method exhibited an OR of 1.028 with a 95% CI between 0.971 and 1.088, and a *p* value of 0.366; and the weighted median approach showed an OR of 1.029 with a 95% CI between 0.986 and 1.073, with a *p* value of 0.187.

The primary analysis using the IVW method, depicted in Figure 3A, established a causal link between PCOS and OSAS. Cochran's *Q*-test indicated homogeneity across studies with a *Q*-value of 7.756 and a *p* value of 0.653, suggesting no substantial differences. The MR-Egger intercept analysis presented an intercept of 0.001 with a *p* value of 0.805, indicating no evidence of directional pleiotropy, which implies minimal influence of pleiotropic effects on the results. The findings were graphically depicted in scatterplots in Figure 3B. Additionally, the leave one out method scrutiny confirmed that none specific SNP disproportionately affected the estimated consequence of PCOS on OSAS risk (Figure 3C).

4 Discussion

This is the inaugural investigation to deeply analyze the causative association between PCOS and OSAS by means of the utilization of

the two-sample Mendelian randomization approach. Concentrating on European ancestry subjects, it unveils the intricate dynamics between the two conditions. It provides crucial revelations about the interaction of PCOS and OSAS, underscoring their significant connection. As healthcare challenges continue to evolve, our research brings to light a new understanding of how OSAS and PCOS are interconnected, offering key insights that could lead to improved diagnostic accuracy and treatment options.

Our results affirm that PCOS notably boosts the risk of OSAS, establishing a direct connection that persists even after adjusting for obesity and BMI, consistent with prior research findings (25, 26). Obesity poses a substantial risk factor in the relationship between PCOS and OSAS, with controversy still existing over whether non-obese PCOS leads to OSAS. Obesity is also a frequent coexisting condition among women suffering from PCOS, not only increasing the metabolic burden on the body but also serving as one of the main mechanisms of the syndrome's pathogenesis (27). The accumulation of fat tissue around the upper airway increases its collapsibility, while upper-body obesity can decrease lung volume and negatively impact respiratory regulation (28). Studies reveal a link between PCOS and an increased likelihood of OSAS, especially pronounced among obese women. Nevertheless, this risk significantly diminishes in non-obese women with PCOS. The research found a 44.4% prevalence of OSAS in obese women with PCOS vs. a 5.5% prevalence in an obese control group with similar BMI levels ($p = 0.008$), indicating that obesity plays a crucial part in the interplay between PCOS and OSAS (29). However, other randomized controlled trials (RCTs) have suggested that patients with PCOS who are not overweight also have a high probability of developing OSAS. Tasali et al. documented a frequency of OSAS among women with PCOS at 56%, considerably greater than the 19% in the non-PCOS control group, a risk that remained even after controlling for BMI, age, and ethnicity (30). A substantial population-based cohort investigation from the United Kingdom demonstrated that the likelihood of developing OSAS was higher in women with PCOS regardless of being of normal weight, overweight, or obese, compared to age, BMI, and geographically matched non-PCOS control women (31). This is consistent with our Mendelian randomization analysis results, indicating a correlation between PCOS and OSAS, even in non-obese women, with obesity exacerbating this correlation.

Our findings indicate that OSAS may play a role in the onset of PCOS, emerging as a potential risk factor for PCOS beyond the effects of obesity and elevated BMI. Research has established a connection between PCOS and a state of mild chronic inflammation, where a complex interplay of hyperinsulinemia, hyperandrogenism, and inflammation perpetuates the disorder's pathophysiology in a vicious cycle (32). In individuals with OSAS, the recurrent episodes of apnea, coupled with cycles of hypoxia and reoxygenation, lead to the release of substantial inflammatory mediators (33). These inflammatory and oxidative stress responses further exacerbate the pathophysiological mechanisms underlying PCOS. Notably, OSAS enhances both muscle and cardiac sympathetic nerve activity, which are pivotal in the development of PCOS by fostering chronic inflammation, inducing changes in ovarian function, and facilitating the polycystic transformation of ovarian morphology (34). Studies involving rodent models for polycystic ovary syndrome demonstrated that an increase in sympathetic ovarian nerve activity and a rise in nerve growth factor synthesis within the ovaries contribute to the pathology's onset and progression (35). Further research has confirmed that patients with PCOS show greater cardiac rhythm variability, diminished heart rate recuperation following exercise, and heightened muscle and cardiac sympathetic nerve activity, even when controlling for age and BMI (29). Ibrahim et al. have indicated that individuals with OSAS face a higher risk of infertility and miscarriage (36). This elevated risk may stem from the association of OSAS with an increased likelihood of developing polycystic ovary syndrome (PCOS), which is known to contribute to female infertility. This corresponds with the conclusions drawn from our Mendelian randomization analysis, which indicate that OSAS could participate in the development of PCOS, impacting women regardless of their obesity status, with obesity amplifying this relationship.

High androgen levels in PCOS may lead to alterations in the upper airway anatomy, predisposing patients to OSAS. Conversely, OSAS may directly or via the link to insulin resistance and decreased sex hormone-binding protein levels, play a part in increasing androgen levels in PCOS (37). Moreover, the increased sympathetic nerve activity and oxidative stress associated with PCOS can promote insulin resistance, with OSAS exacerbating these metabolic abnormalities through similar mechanisms (38). Thus, a vicious cycle between PCOS and OSA emerges, posing significant health risks. Firstly, it compromises sleep quality; sleep quality is impacted in both OSA and PCOS patients, with those suffering from both conditions experiencing more severe effects (39). Secondly, it may lead to sexual dysfunction and infertility: both OSAS and PCOS affect sexual function, with PCOS women reporting lower levels of sexual satisfaction compared to those without PCOS (40). The inflammation, oxidative stress, and increased sympathetic excitability caused by OSAS, along with fragmented sleep and abnormal sleep architecture, can reduce the secretion of gonadotropins and gonadotropin-releasing hormones, thus impairing reproductive function and leading to infertility in PCOS patients. Thirdly, it amplifies the risk of metabolic disorders: studies indicate that women suffering from both PCOS and OSAS experience more pronounced metabolic imbalances, such as increased fasting blood sugar, diminished glucose tolerance, and reduced insulin sensitivity, thereby increasing their susceptibility to metabolic diseases (41). Finally, it escalates the risk of cardiovascular incidents: women with both PCOS and OSAS display increased levels of cardiac contraction and relaxation pressure levels, along with triglyceride concentrations relative to individuals not afflicted with OSAS, a disparity that persists even when controlling for BMI (42).

Hence, future research should not only explore the actual incidence of OSAS among a more indicative sample of females diagnosed with PCOS and compare incidences across different ethnic groups but also ensure that women with OSAS undergo pelvic ultrasound examinations for early treatment. It is advisable to screen women with PCOS for sleep-related breathing disorders and provide them with appropriate treatment as needed. Continuous positive airway pressure can alleviate symptoms in individuals with OSAS, and improve insulin function, oxidative stress, and sympathetic excitability, thereby reducing blood pressure and decreasing catecholamine levels (43).

However, it is important to acknowledge the restrictions present in our investigation. Although our bidirectional MR analysis sheds light on the PCOS-OSAS causal relationship, the evidence from the

various MR methods used does not consistently support a direct causal link between these conditions. Future research could be enriched by implementing clinical RCTs to delve deeper into and confirm the dynamics of the relationship between PCOS and OSAS. Furthermore, our reliance on publicly available summary statistics limited our ability to include comprehensive demographic variables such as age, gender, and comorbidities in our analysis, thus representing a notable limitation in our approach. Nevertheless, the strength of MR analysis lies in its ability to apply genetic instruments to elucidate possible causative links between exposures and outcomes, eliminating the necessity for intricate demographic details. Despite these acknowledged limitations, our study represents a substantial stride in enhancing comprehension of the genetic associations and causal connections between PCOS and OSAS. This work lays a strong basis for future pursuits in diagnostics and preventive strategies targeting these disorders.

5 Conclusion

Our study conclusively establishes the bidirectional causal link between PCOS and OSAS, underlining the complexity of their interaction. Through Mendelian Randomization analysis, we demonstrated significant causal links from OSAS to PCOS and vice versa, with robust odds ratios confirming these associations. Our study paves the way for developing targeted screening and preventative strategies, emphasizing the need to address both conditions concurrently in clinical practice.

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.

Ethics statement

Our investigations utilized data from published research or GWAS summaries that are in the public domain. These studies received clearance from relevant ethics committees, negating the need for further ethical consent.

Author contributions

PL: Conceptualization, Investigation, Methodology, Writing – original draft. QZ: Formal analysis, Investigation, Writing – original draft. HD: Validation, Visualization, Writing – review & editing. HZ: Funding acquisition, Software, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the Natural Science Foundation of Enshi, China (No. D20230070).

Acknowledgments

We extend our gratitude to the participants and researchers involved in the FinnGen and GWAS studies.

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.2024.1429783/full#supplementary-material

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 12 July 2024
DOI 10.3389/fonc.2024.1346809

OPEN ACCESS

EDITED BY
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RECEIVED 29 November 2023
ACCEPTED 18 June 2024
PUBLISHED 12 July 2024

CITATION
Yao J, Duan R, Li Q, Mo R, Zheng P and Feng T (2024) Association between obstructive sleep apnea and risk of lung cancer: findings from a collection of cohort studies and Mendelian randomization analysis. *Front. Oncol.* 14:1346809. doi: 10.3389/fonc.2024.1346809

Association between obstructive sleep apnea and risk of lung cancer: findings from a collection of cohort studies and Mendelian randomization analysis

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Background: Previous cohort studies conducted on large populations have suggested a potential association between obstructive sleep apnea (OSA) and an elevated risk of developing lung cancer. However, limited research has comprehensively investigated the correlation between the two conditions, and the causal effect remains unknown.

Methods: A comprehensive and systematic search was conducted across various databases, including PubMed, Web of Science, Cochrane Library, and Embase, from their inception dates to November 1, 2023. To assess the relationship between OSA and lung cancer, a meta-analysis was performed. Additionally, a two-sample Mendelian randomization (MR) study was conducted using summary data. The datasets included 336,659 individuals from the FinnGen study for OSA and 27,209 individuals from the International Lung Cancer Consortium study, as well as 420,473 individuals from the UK Biobank study for lung cancer. The estimates from each study were aggregated using the inverse variance-weighted method.

Results: Data from six population-based cohort studies, encompassing 6,589,725 individuals, indicated a significant increase in the risk of developing lung cancer among patients with OSA (HR 1.28, 95% CI 1.07-1.54). However, the MR analysis did not support a causal relationship between OSA and lung cancer (OR 1.001, 95% CI 0.929–1.100). This lack of association was consistent across specific subtypes of lung cancer, including non-small-cell lung cancer (OR 1.000, 95% CI 0.999–1.000, p = 0.974), lung adenocarcinoma (OR 0.996, 95% CI 0.906–1.094, p = 0.927), and squamous cell lung carcinoma (OR 1.034, 95% CI 0.937–1.140, p = 0.507).

Conclusions: Our meta-analysis findings suggest an elevated risk of lung cancer among individuals with OSA. However, the MR analysis did not provide evidence supporting a causal relationship between OSA and lung cancer. Further investigation is required to uncover the underlying factors contributing to the observed association between OSA and lung cancer risk.

KEYWORDS

lung cancer risk, obstructive sleep apnea, meta-analysis, Mendelian randomization, cohort studies

1 Introduction

Cancer remains a pressing global health concern and is responsible for a staggering number of deaths on a worldwide scale. In particular, lung cancer emerges as the foremost culprit, being the leading cause of cancer-related fatalities and contributing to a staggering 1.8 million lives lost. Recent data from the year 2020 delineates that lung cancer constituted a significant proportion of newly diagnosed cases, accounting for 11.4% of all cancer diagnoses (1). Obstructive sleep apnea (OSA), a condition characterized by interrupted breathing during sleep, affects a staggering number of adults globally, with estimates suggesting that nearly one billion adults suffer from this sleep disorder (2). Growing evidence indicates that OSA plays a significant role for various types of lung cancer. The underlying mechanisms involve intermittent hypoxia, oxidative stress, and inflammation, all of which contribute to the development and progression of cancer within the body (3). Various observational studies have provided evidence indicating a greater incidence of lung cancer in individuals with OSA (4, 5), and patients diagnosed with lung cancer also exhibit a higher incidence of OSA (6, 7). Nevertheless, conflicting evidence from other observational studies undermines the establishment of this association (8, 9). Moreover, it is vital to acknowledge and carefully consider the limitations present in prior research, which encompass factors such as small sample sizes, dependence on local registries, and ambiguous diagnostic criteria. These limitations have the potential to impact the findings.

The main objective of our study was to conduct a comprehensive meta-analysis of existing population-based cohort studies in order to thoroughly examine the relationship between OSA and lung cancer. It is imperative to recognize that observational studies possess inherent limitations, as they solely establish correlations without determining causation between OSA and lung cancer. This limitation arises from the potential impact of confounding variables or reverse causation. Additionally, while meta-analysis yields valuable insights, it does not definitively establish a causal relationship between OSA and lung cancer. Since most studies rely on observational data, there is a potential for reverse causation bias, where the association may not be due to OSA itself but rather the lung cancer causing OSA. Traditional observational studies may have limitations, including the presence of confounding biases. OSA and lung cancer share common risk factors and comorbidities, such as obesity, male gender, advanced age, smoking, and chronic obstructive pulmonary disease (COPD) (10, 11). These shared factors can complicate efforts to establish a causal relationship between OSA and lung cancer, making it challenging to accurately determine the impact of OSA on the development of specific lung cancers. Therefore, a more comprehensive understanding of the causal association between OSA and lung cancer is crucial for preventing potential adverse outcomes.

Mendelian randomization (MR) is a widely employed technique for inferring credible causal relationships in cases where conducting randomized controlled trials (RCTs) is impracticable (12). By capitalizing on the genetic variations that occur during meiosis, independent of any environmental or acquired factors, the MR design offers a valuable tool for randomization. This mechanism helps reduce the impact of any remaining confounding variables and potential reverse causality, making it an ideal approach for minimizing interference in studies (13). Recent MR studies have successfully identified causal associations between body mass index (BMI) and the development of lung cancer (14, 15). However, a dearth of MR evidence currently exists to support a causal relationship between OSA and lung cancer.

Given this knowledge gap, our study aims to address this lacuna by conducting an two-sample MR analyses on two large databases, aiming to achieve a sufficient sample size, which had been typically constrained due to the low occurrence of lung cancer in previous observational studies. Through examining the causal effect of OSA

Abbreviations: OSA, Obstructive sleep apnea; MR, Mendelian randomization; RCTs, Randomized controlled trials; SNPs, Single nucleotide polymorphisms; IVs, Instrumental variables; BMI, Body mass index; HR, Hazard ratio; CI, Confidence intervals; GWAS, Genome-wide association study; AHI, Apnea-hypopnea index; REI, Respiratory event index; ILCCO, Lung Cancer Consortium; COPD, Chronic obstructive pulmonary disease; GSCAN, Sequencing Consortium of Alcohol and Nicotine use; GIANT, Genetic Investigation of Anthropometric Traits; IVW, Instrumental variable-weighted; OR, Odds ratio; HIFs, Hypoxia-inducible factors.

on the lung cancer, we seek to provide compelling evidence for its role in the genesis of this disease. Such findings would offer a novel perspective on the early detection of lung cancer, ultimately enhancing patient outcomes.

2 Methods

The current investigation followed the protocols and recommendations outlined in Cochrane's Handbook for its research methodology. Report list for strengthening meta analysis can be found in Supplementary Table 1. To ensure transparency and credibility, the registration of our study has been completed and recorded, with a unique identifier assigned as PROSPERO ID 480577. Detailed methodology is provided in the Supplementary Materials.

2.1 Meta analysis

We conducted comprehensive searches on PubMed, Web of Science, Cochrane Library, and Embase on November 1, 2023, using terms related to OSA and various cancers, and reviewed references of relevant articles. Included studies were longitudinal follow-up studies with OSA patients, assessing OSA and lung cancer incidence over at least 3 years, and reporting hazard ratios (HR) adjusted for confounders. We excluded non-cohort studies, those only reporting lung cancer mortality, case reports, conference papers, reviews, animal studies, and non-English studies. Two reviewers independently extracted data on author, publication year, participant characteristics, OSA assessment methods, follow-up duration, lung cancer validation, and covariates. We used the Newcastle-Ottawa Scale (NOS) to assess study quality, categorizing them into high, medium, and low quality. We synthesized HRs and 95% confidence intervals (CI) using meta-analysis, assessed heterogeneity with Cochran's Q test and the I^2 statistic, and used random-effects or fixed-effects models accordingly. Sensitivity analyses included studies accounting for smoking status, and pre-specified subgroup analyses were based on follow-up duration. Limited study numbers prevented in-depth subgroup analyses or funnel plot asymmetry assessments. Statistical analyses were performed using RevMan software (Version 5.3; Cochrane Collaboration, Oxford, UK). Detailed methodology is provided in the Supplementary Materials.

2.2 Study design of MR analysis

Figure 1 presents a comprehensive overview of the study design. To comprehensively understand the causal effects of OSA on total lung cancer and its various histological types, we utilized the most extensive available dataset on OSA as well as two extensive lung cancer datasets.To ensure the validity of our results, we relied on three key assumptions concerning the genetic variants used in our analysis (16). First, these variants were selected based on their reliable and robust association with the exposure under investigation. Second, we assumed that they were independent of any factors that could potentially confound the relationship between the exposure and the outcome. Lastly, we assumed that these variants solely influenced the outcome through their impact on the exposure variable. All the genome-wide association study (GWAS) summary statistics employed in our study were openly accessible, and we sought ethical approval from the original studies.

2.3 Data sources and instrument variables

2.3.1 Obstructive sleep apnea

In this study, we meticulously selected a total of twenty single nucleotide polymorphisms (SNPs) that have recently demonstrated a significant association with traits relevant to OSA in individuals of European descent. The cohort for this GWAS comprised 336,659 individuals of European ancestry (17). The data for OSA patients

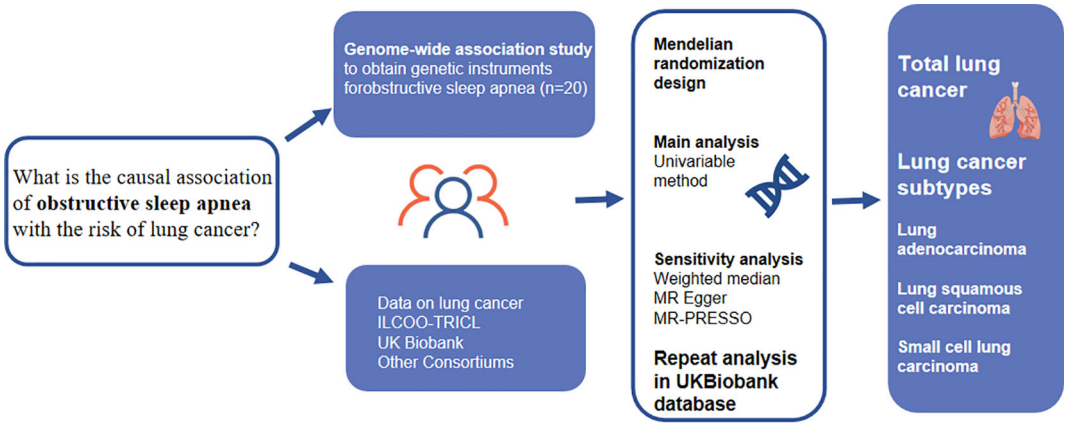

FIGURE 1
Overview of the design and main findings from a Mendelian randomization (MR) study. MR, Mendelian randomization. MR-PRESSO, MR pleiotropy residual sum and outlier test; IVW, inverse-variance weighted.

were obtained from nationwide health registries in Finland, with a total of 38,998 patients identified as having OSA based on the diagnosis criteria. The diagnosis involved considering OSA-related symptoms, conducting clinical examinations, and analyzing national insurance data using the apnea-hypopnea index (AHI), with thresholds set at a minimum of 5 events per hour (17). Further information regarding the selected SNPs as instrumental variables can be found in Supplementary Table 4.

2.3.2 Lung cancer

The data for lung cancer obtained in this study came from two reliable and extensive databases - the International Lung Cancer Consortium (ILCCO) and the UK Biobank. The ILCCO is a collaborative project focused on investigating the genetic variations associated with lung cancer (18). On the other hand, the UK Biobank is a comprehensive research endeavor that includes a large population-based cohort of over 500,000 individuals from diverse regions across Great Britain, providing valuable biological samples (19). For our analysis, we utilized two sets of GWAS summary statistics from ILCCO and the UK Biobank as our primary outcomes. The ILCCO data set comprised 11,348 cases and 15,861 controls, while the UK Biobank data set included 4,030 cases and 238,678 controls. In addition to these primary outcomes, we also examined GWAS statistics for specific subtypes of lung cancer. This includes lung adenocarcinoma (3,442 cases and 14,894 controls), lung squamous cell carcinoma (3,275 cases and 15,038 controls), and small cell lung carcinoma (2,791 cases and 20,580 controls) from the ILCCO database. These secondary outcomes aimed to investigate the association between OSA and the various pathological subtypes of lung cancer. To ensure the reliability of our analysis, we implemented a filter that only included variants with a minimum variant allele frequency greater than 0.01. For a more detailed representation of the data sources for the outcomes, please refer to Supplementary Table 5.

2.3.3 Potential pleiotropy

In order to investigate the potential mediating role of OSA on established risk factors for lung cancer, including body mass index (BMI), smoking, and chronic obstructive pulmonary disease (COPD), an analysis was conducted using the inverse variance weighted (IVW) method. The objective was to uncover any mediating effects of OSA on the development of lung cancer, taking into account these known risk factors.To evaluate the connection between OSA and smoking, we utilized genetic instruments obtained from the Sequencing Consortium of Alcohol and Nicotine use (GSCAN) project. This particular project offered a comprehensive genetic analysis of smoking-related traits, such as smoking initiation, smoking duration, and smoking frequency (20). With a dataset of 632,802 individuals of European ancestry, the GSCAN project offers the largest and most reliable source of genetic data for this investigation. In order to investigate the association between OSA and COPD, as well as BMI, summary statistics data were obtained from two reputable sources: the UK Biobank and the Genetic Investigation of Anthropometric Traits (GIANT) (21). These studies are well-established providers of genetic data and include a large sample size of 462,933 individuals for COPD and 681,275 individuals for BMI (Supplementary Table 5).

2.3.4 SNP selection

Significant single nucleotide polymorphisms (SNPs) associated with our study outcomes were identified using a threshold criterion of P < 5E-8. These SNPs were found in various gene regions and showed no evidence of linkage disequilibrium, as determined by the 1000 Genomes European reference panel (22). In order to enhance the robustness of our MR design, we excluded SNPs that were strongly linked to the lung cancer (P < 5E-8) to mitigate potential biases. Additionally, we standardized the impact of each SNP on both the outcome and exposure to ensure consistency across alleles (refer to Supplementary Table 6). To assess the likelihood of weak instrument bias in the instrumental variables employed, we utilized the F-statistic. This statistical measure was calculated using the equation $F = R^2/(1 - R^2) * (N - k - 1)/k$ (23). In this equation, R^2 represents the proportion of variability in the risk factor that can be attributed to genotype, N represents the sample size, and k represents the number of instrumental variables used (24). An F-statistic value exceeding 10 suggests a low probability of weak instrument bias.

2.4 Statistical analyses in MR analysis

2.4.1 Main Mendelian randomization analyses

In our analysis, we employed IVW models as the primary methods of study. These models were individually implemented in each cohort. To aggregate odds ratio (OR) estimates for a specific endpoint from various sources, we adopted a fixed-effects meta-analysis approach. Despite the high accuracy of the IVW method in providing estimates, it does not account for potential biases arising from invalid instruments or pleiotropic effects (25). To ensure the reliability and consistency of our findings, we conducted analyses using both the ILCCO and UK Biobank databases. In the IVW analysis, we utilized the Q statistic and I^2 index to evaluate the heterogeneity. If there is heterogeneity, we use a random forest model.

2.4.2 Sensitivity analyses

In order to ensure the accuracy and strength of our findings, this investigation employed several sensitivity analyses. The weighted median approach permits a maximum of 50% of instrumental variables to violate the MR assumption in the presence of horizontal pleiotropy (26). In order to identify directional pleiotropy, the intercept derived from MR-Egger regression was utilized (27). To evaluate and rectify horizontal pleiotropy, we utilized the MR-PRESSO technique, which is composed of three components: (a) identification of horizontal pleiotropy, (b) correction by removing outliers, and (c) examination of significant differences in causal estimates before and after outlier correction (28). It is important to emphasize that the MR-PRESSO method is less biased and offers improved precision when

compared to both IVW and MR-Egger. Furthermore, a leave-one-out analysis was conducted to assess whether a single SNP was exerting influence or biasing the MR estimate.

All statistical analyses were conducted using the R project version 4.1.3, with the TwoSample MR package utilized for the MR analysis (29).

3 Results

3.1 Search results and study characteristics

Initially, our database search yielded 2867 articles, but after eliminating duplicate studies, we were left with 2823 articles that were not relevant to our meta-analysis based on their titles and abstracts. Subsequently, we thoroughly examined the remaining 43 studies through full-text reading. Out of these, we excluded 36 studies for reasons outlined in Figure 2, resulting in 7 studies for inclusion in our meta-analysis.

All 7 articles were population-based cohort studies, with 4 originating from America and one each from Korea, Canada, and Australia (5, 8, 9, 30–33).Overall, these studies encompassed a total of 6,589,725 individuals, with 18,879 cases of lung cancer. The duration of follow-up varied between 3 and 11 years across the studies. We present the characteristics of these studies in Table 1 and Newcastle-Ottawa Scale (NOS) in Table 2.

3.2 Overall lung cancer risk in OSA patients

Regarding the evaluation of quality, all 7 studies incorporated in our meta-analysis indicated a moderate or low potential for bias. However, one particular study conducted by Sillah was not included in the meta-analysis due to inadequate adjustments for age and sex. Moreover, this study did not take into account other coexisting medical conditions, which significantly differed from the rest of the studies.The combined HR for the overall risk of developing lung cancer among individuals with OSA was calculated as 1.11 (95% CI 0.93–1.33). This finding suggests that there is no notable increase in lung cancer risk among individuals with OSA. It is worth noting that the 6 remaining studies exhibited significant heterogeneity ($I2 = 97\%$, $p < 0.001$), as depicted in Figure 3 of the comparative analysis.

3.3 Subgroup analysis

Further subgroup analysis based on the length of follow-up suggested that studies with a median follow-up of 7 years or longer

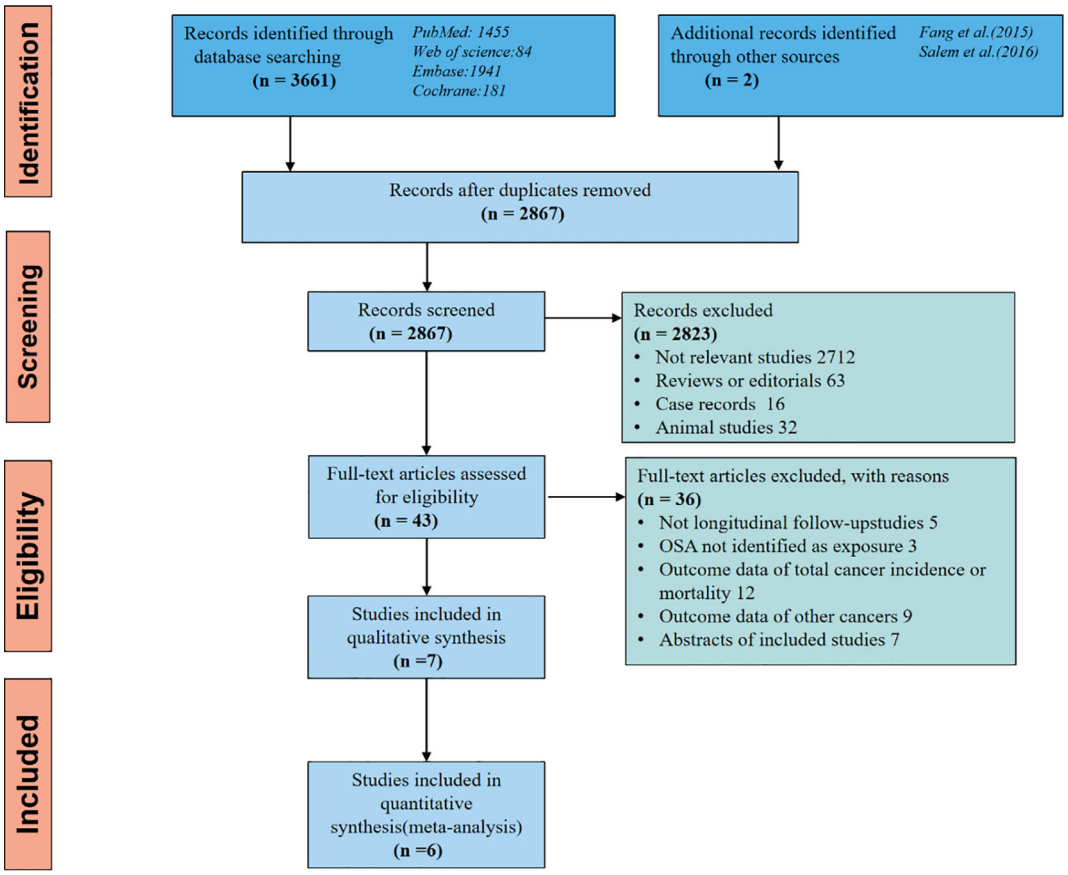

FIGURE 2
The flow diagram of a detailed overview of the search strategy and the process used for identifying studies included in the meta-analysis.

TABLE 1 Characteristics of the included studies in the meta-analysis.

Study	Study Design	Sample Size	Total Incident Lung Cancer	OSA Diagnosis	Lung cancer validation	Setting/ Country	Mean Age	Male (%)	Covariates	Median Follow-Up Duration (Yr)
Gozal 2016 (34)	Retrospective cohort	3,408,906	NR	ICD	ICD	USA	NR	50.2	Age, sex, morbid obesity, hypertension, type 2 diabetes, ischemic heart disease, coronary heart failure, stroke, cardiac arrhythmias, and depression	3,20, 3.75, and 3.91 for different subgroups
Sillah 2018 (33)	Retrospective cohort	34,402	115,	ICD	ICD	USA	51.6	57.4	Age, sex	5.3
Jara 2020 (30)	Retrospective cohort	1,377,285	10,595	ICD	ICD	USA	55.2	94	Age, sex, year of cohort entry, smoking status, alcohol use, obesity, and comorbidity	7.4
Kendzerska 2021 (9)	Retrospective cohort	33,711	241	Polysomnography	Medical chart review	Canada	50	58	Age, study year, clinic site, alcohol use, and comorbidities including hypertension, diabetes mellitus, CVD, and COPD	7
Huang 2021 (5)	Prospective cohort	65,330	492	Self-reported clinical diagnosis of OSA	ICD	USA	73	0	Age, race, family history of cancer, body mass index, height, pack-years of smoking, alcohol drinking, physical activity, sleep duration, duration of hormonal therapy use by type, history of type 2 diabetes, aspirin use, and recent physical examination	8
Marriott 2023 (8)	Retrospective cohort	20,289	173	Polysomnography	ICD	Australian	50	69	age and, in some cases, sex, BMI and smoking status,	11.2
Park 2023 (32)	Retrospective cohort	1,649,802	7263	ICD	ICD	Korea	45.6	75.8	sex, age, subjects' income levels, diabetes, hypertension, dyslipidemia, stroke, chronic obstructive pulmonary disease, and ischemic heart disease.	5.9

NR, No results.

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TABLE 2 Evaluation of risk of bias using the Newcastle-Ottawa Scale (NOS) Cohort NOS.

Study	Representativenes of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure (secure record, structured interview)	Demonstrate s that cancer was not initially present	Adjusts for age	Adjusts for obesity	Assessment of outcome (record linkage)	Follow -up at least 3 years	Enough long follow-up duration	Total	Risk of bias*
Gozal 2016	1	1	1	1	1	1	1	1	0	8	Low
Huang 2021 (5)	0	1	0	1	0	1	1	1	0	5	Moderate
Jara 2020 (30)	0	1	1	1	1	1	1	1	0	7	Moderate
Kendzersa 2021 (9)	1	1	1	1	1	0	1	1	0	7	Moderate
Sillah 2018 (33)	1	1	1	0	1	0	1	1	0	6	Moderate
Marriott 2023 (8)	1	1	1	1	1	1	1	1	0	8	Low
Park 2023 (32)	1	1	1	1	1	1	1	1	0	8	Low

*high (<5 stars), moderate (5-7 stars), low risk of bias (≥8 stars).

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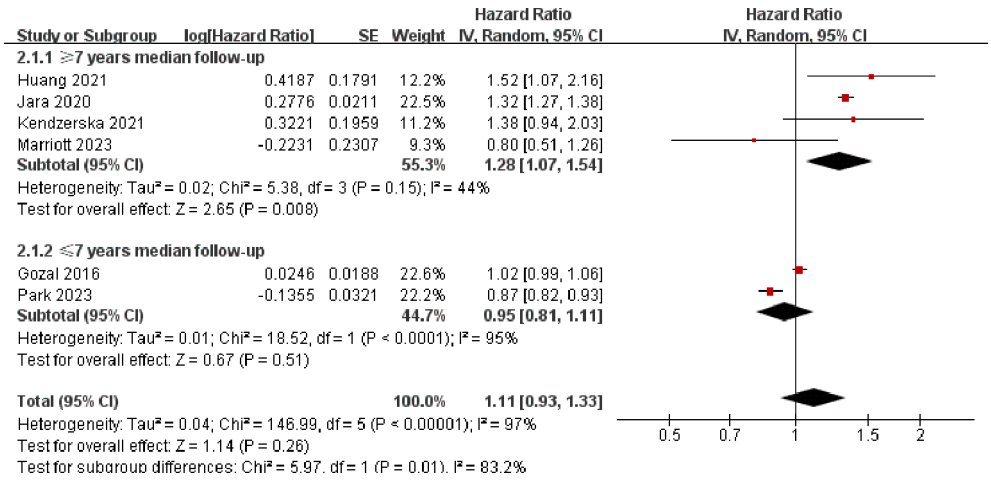

FIGURE 3
Comparing of Lung Cancer Incidence in Patients With or Without OSA Based on Meta-Analysis.

had a higher pooled HR of 1.28 (95% CI 1.07–1.54) with reduced heterogeneity (I^2 = 44%, p = 0.15), as shown in Figure 4. Moreover, a sensitivity analysis conducted exclusively on studies adjusting for smoking consistently yielded similar results. In particular, three studies that adjusted for smoking reported an HR of 1.32 (95% CI 1.26–1.37, P=0.07, I^2=63%).

3.4 Certainty of evidence

Due to the limitations of observational studies, the quality of initial evidence for observational studies in Grading of Recommendations Assessment is low. The evidence quality regarding the lung cancer incidence was determined to be of low quality. This downgrade occurred due to two factors. First, there was a significant statistical heterogeneity, indicating variations in study findings. Second, there was a potential for publication bias, which could not be adequately assessed due to a limited number of studies. Additionally, it should be noted that the evidence quality for our specific subgroup of studies, characterized by a mean follow-up duration of at least 7 years, is also low (Supplementary Table 2).

3.5 Genetic instruments

Following the criteria for genetic instrument selection, a total of 17 independent SNPs were chosen as instruments for analyzing

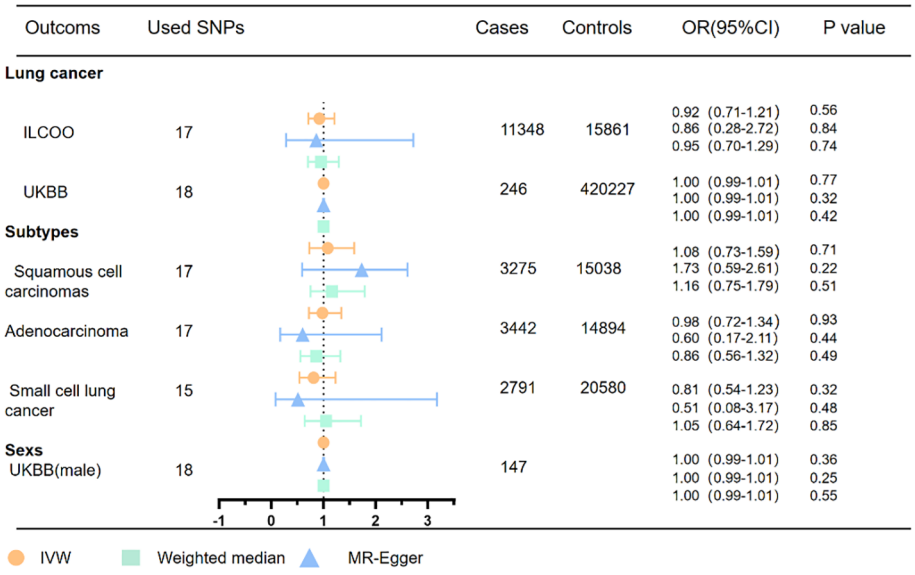

FIGURE 4
MR analyses of OSA with risk of lung cancer and pathological subtypes. OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted method; ILCCO, International Lung Cancer Consortium.

OSA in the ILCCO database, while 18 independent SNPs were selected for the UK Biobank database. More detailed information about the instruments used for each exposure can be found in Supplementary Tables 4, 6. Importantly, all F statistics for the instruments used in the MR analyses were greater than 10, indicating the presence of robust instrument variables (Supplementary Table 4). Supplementary Figure 1 illustrates the process of IV selection conducted in this study.

3.6 Causal effects of OSA on lung cancer and pathological subtypes

Within the scope of OSA genetic instrumental variables, the results of the univariate MR analysis indicate no significant association between OSA and an increased risk of total lung cancer, as demonstrated in Figure 4 and confirmed by the ILCCO database (IVW: OR = 0.92, 95% CI 0.71–1.21, P =0.56). These findings are consistent with the results obtained from the UK Biobank database (IVW: OR =1.00, 95%CI 0.99–1.01, P =0.77). Moreover, the examination of specific pathological subtypes of lung cancer did not reveal any significant associations between genetically predicted OSA and the risk of lung adenocarcinoma (IVW: OR = 0.98, 95% CI 0.72–1.34, P =0.93), small cell lung cancer (IVW: OR =0.81, 95% CI 0.54–1.23, P = 0.32), and lung squamous cell carcinomas (IVW: OR = 1.08, 95% CI 0.73–1.59, P = 0.71).

Consistently, the effect estimator exhibited a consistent direction in the weighted median analysis. While the analysis of total lung cancer and lung squamous cell carcinomas in the ILCCO database identified an outlier through MRPRESSO, excluding this outlier variant did not alter the results. Heterogeneity tests indicated the presence of some heterogeneity among the individual SNP effect estimates. Furthermore, the MR-Egger intercept tests did not detect any horizontal pleiotropy in any of the conducted MR analyses (Supplementary Figures 3-5) (Supplementary Tables 7, 8).

3.7 Causal effect from OSA on potential lung cancer risk factors

Utilizing the IVW method, we conducted a study to investigate the potential impact of various lung cancer-related factors on the association between genetically determined OSA and lung cancer. Our analysis focused on assessing the relationship between OSA and several risk factors for lung cancer, such as smoking, COPD, and body mass index, as shown in Supplementary Figure 2. However, our investigation did not reveal any supportive evidence indicating a causal relationship between OSA and these potential risk factors for lung cancer, as summarized in Supplementary Table 9.

4 Discussion

This paragraph presents the findings of a comprehensive meta-analysis involving a combined cohort of 6,589,725 patients. The analysis revealed that individuals with OSA had an incidence of lung cancer that was 11% higher compared to those without OSA. The study emphasized the significance of long-term monitoring in studies focused on detecting lung cancer incidence, as this difference was observed over a follow-up period of more than 7 years. Both OSA and lung cancer are chronic disease, and the time interval between their onset and detection can stretch out for several years. To establish a link between the physiological effects of OSA and the development of cancer, it is crucial for OSA to be present, even if undiagnosed, several years preceding the diagnosis of cancer. For instance, the research findings indicated that the typical time for squamous cell lung carcinoma to reach a diagnostic size is 8 years (35).

We then employed a two-sample MR approach to comprehensively investigate the potential causal effect of OSA on the incidence of lung cancer. Based on our analysis, the evidence produced inconclusive results regarding the existence of a causal relationship between genetically predicted OSA and the lung cancer. Among various lung cancer cell lines, H520 (human squamous cell lung cancer) demonstrated the most significant proliferation in response to hypoxemia. Different subtypes of lung cancer may respond differently to hypoxia (36). Nevertheless, our analysis did not reveal any notable correlations between genetically predicted OSA and the specific pathological subtypes of lung cancer, such as lung adenocarcinoma, small cell lung cancer, and lung squamous cell carcinomas. The findings of the meta-analysis depicting a significant increase in lung cancer risk seem to be at odds with the outcomes derived from the MR analysis. This inconsistency can be attributed to the inherent disparities and constraints inherent in observational studies. The majority of the studies included in this analysis are retrospective, which inherently brings limitations in the quality of the collected data. Maximize the sample size and enhance the accuracy of analyses related to specific cancer sites, numerous epidemiological studies have utilized national insurance health databases (5, 8, 31–33). These databases are used to identify individuals with OSA by examining recorded diagnostic codes. While these resources are valuable, they also introduce potential biases. Within these databases, certain confounding factors, such as obesity and smoking status, are of great importance but frequently unattainable. The insufficient management of these influential factors can significantly influence the interpretation of findings and produce varying repercussions across different studies, contingent upon the prevalence of these risk factors. The utilization of administrative databases to identify individuals with OSA introduces the potential for selection bias and the misclassification of exposure (37). Hence, the control group categorized as “unexposed” due to the lack of an OSA diagnosis might encompass numerous patients who are actually undiagnosed with OSA. This issue becomes more prominent in clinical settings where patients often possess risk factors for OSA, such as obesity. Conversely, individuals who have received a diagnosis of OSA may not adequately represent the entire population of OSA patients. Overcoming these limitations can be achieved through studies conducted in community settings, utilizing objective indicators to determine the presence of OSA. However, it is essential to acknowledge that such studies require significant resources and are consequently constrained in terms of sample size (38).

Although our findings suggest no causality between OSA and lung cancer incidence, it is possible that OSA may have an impact on the progression of lung cancer. At both the biological and behavioral levels, there is widespread acceptance of the numerous underlying pathways connecting OSA and lung cancer. One potential pathway is the effect of OSA on sleep fragmentation. Sleep fragmentation, a covert form of sleep deprivation, may contribute to the development of cancer. Notably, research indicates that sleep fragmentation can stimulate the migration of macrophages to the artery, resulting in metabolic alterations that potentially facilitate the progression of malignancy. Furthermore, the influence of sleep fragmentation on tumorigenesis and advancement could be attributed to the disruption of the tightly linked biological clock associated with sleep disorders (39). Another potential pathway is the effect of intermittent hypoxia. Intermittent hypoxia has been associated with tumor growth and progression. Hypoxia-inducible factor (HIF)-1 and metabolic pathway-related molecules in lung cancer cells undergo significant changes under hypoxic conditions, playing a crucial role in the response of lung cancer cells to hypoxia. Animal experiments have revealed that in a mouse model of melanoma-induced lung metastasis, the OSA model not only promotes melanoma growth but also induces alterations in tumor-related macrophages, increasing invasiveness and facilitating the metastatic process. Intermittent hypoxia, resulting from cycles of hypoxia and reoxygenation, induces the generation of reactive oxygen species (ROS) or oxygen free radicals, triggering an activation of the oxidative stress response. This leads to an imbalance in the body's oxidation and antioxidant substances, thereby causing acute and chronic deterioration of cellular function and structure, DNA damage, and genomic instability. Consequently, these processes promote cell proliferation and malignant transformation. Moreover, oxidative stress-induced nuclear factor-kappa B (NF-κB) activation can contribute to an increased cancer incidence. Patients with OSA experience both systemic and local inflammatory reactions. The disrupted balance of antioxidant production and increased ROS production further elevate levels of inflammatory factors such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-8, all of which can further stimulate NF-κB activation, thereby promoting cancer occurrence and progression (3, 34, 40). Intermittent hypoxia (IH) in OSA promotes cancer progression by upregulating HIF-1α and transforming growth factor β1 (TGF-β1), which alter cytokine levels, increase TNF-α and IL-10, and decrease IL-17, suppressing antitumor immunity (41). IH also elevates paraspeckle protein-1 (PSPC1), activating the TGF-β-SMAD pathway, and promoting epithelial-mesenchymal transition (EMT) and cancer stem cell (CSC)-like features (42–44). Furthermore, IH induces an immunosuppressive phenotype in monocytes, impairing NK cell function, and increases soluble immune checkpoints (PD-1/PD-L1) and midkine, facilitating immune evasion and lymphangiogenesis (45). These mechanisms collectively enhance tumor aggressiveness and progression in OSA patients. In addition, cancer can be influenced by various indirect pathways associated with behavior pattern of living, including smoking and obesity (Figure 5).

Our study possesses several notable strengths. Firstly, while traditional observational studies and RCTs serve as prominent research methods, the former is prone to bias, confounding factors, and reverse causality when investigating causal relationships. In contrast, MR draws upon the concept of instrumental variable methods utilized in economics, skillfully addressing issues of interference in causal inference. Notably, MR offers an effective alternative to the limitations associated with RCT research. Secondly, we conducted our causal estimation using two extensive databases, ensuring the consistency of our findings and providing reliable causal inference. This robustness strengthens the reliability of our results. Thirdly, while our study reveals an

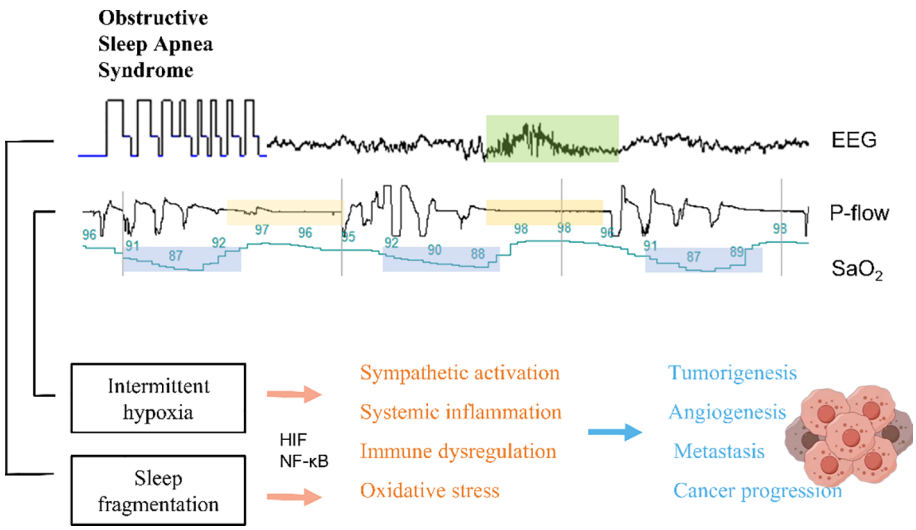

FIGURE 5
Potential mechanisms affected by either sleep disruption or intermittent hypoxia in the context of OSA.

association between OSA and lung cancer, the lack of conclusive evidence for a causal relationship suggests that further research is needed to fully understand the public health implications. Current findings are not sufficient to directly influence public health policies, but they provide a foundation for future investigations. Our findings suggest that there may be limited value in enhancing lung cancer screening solely in patients with genetically predicted OSA. Therefore, it is crucial to direct greater attention towards uncovering the correlation between environment-induced OSA and lung carcinogenesis, as well as exploring the connection between OSA and the prognosis of lung cancer.

However, our study has certain limitations that need to be acknowledged. Firstly, It is important to highlight that not all of the studies analyzed in our research accounted for smoking status. This is due to a lack of available data on smoking habits among participants in certain studies. However, it is noteworthy that Kendzerska et al. conducted a sensitivity analysis, which included smoking status as a subgroup. Secondly, because only summary-level statistics were available, we encountered limitations in conducting stratified analyses involving age, as well as other covariates like specific subtypes of lung cancer, gender, and smoking status. One possible limitation to our MR analysis was the possibility of potential overlap, due to restriction to European populations (40). Although we utilized data from both the UK Biobank and ILCCO databases. It is important to note that OSA is a binary exposure, and the instrumental variable estimate we obtained represents the average causal estimate in individuals influenced by the genetic variants used to determine OSA presence or absence (46). When applying MR analysis to binary exposures, it is possible to obtain relative risk values that are not precisely identifiable but have identifiable boundaries. Additionally, it is worth mentioning that all the GWAS data used in our study were derived from European populations. Therefore, it is crucial to examine whether our findings remain consistent in other populations.

5 Conclusion

In our research, we discovered a clear connection between OSA and an increased likelihood of developing lung cancer, as observed in population-based cohort studies. However, it is important to note that the study using MR did not establish a direct cause-and-effect relationship between OSA and lung cancer. The significant association seen in the observational studies may be influenced by biases inherent in these types of studies, such as inaccurate diagnoses of OSA, inadequate adjustment for factors that may confound the results, and other potential limitations. Additionally, to validate our findings and provide more definitive evidence regarding the association between OSA and lung cancer, it would be advantageous to conduct well-orchestrated epidemiological studies and MR studies that incorporate a larger number of instrumental variables and samples. This would help strengthen the reliability of our findings and provide more compelling insights into the relationship between OSA and lung cancer.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: ILCCO, FinnGen (https://www.finngen.fi/en), GSCAN GIANT, and the UK Biobank study.

Ethics statement

The cited genome-wide association studies incorporated in this paper were granted approval by the appropriate review board, and all participants had provided written informed consent.

Author contributions

JY: Writing – original draft. RD: Conceptualization, Writing – original draft. QL: Conceptualization, Data curation, Formal analysis, Writing – original draft. RM: Validation, Software, Writing – original draft, Writing – review & editing. PZ: Project administration, Writing – review & editing. TF: Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We express our gratitude to ILCCO, FinnGen (https://www.finngen.fi/en), GSCAN GIANT, and the UK Biobank study for their valuable contribution in making the summary statistics utilized in this research readily accessible to the public.

Declaration of AI and AI-assisted technologies in the writing process during the preparation of this work, the authors used GPT-4 for proofreading and editing the paper. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1346809/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 21 August 2024
DOI 10.3389/fmed.2024.1401309

OPEN ACCESS

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RECEIVED 15 March 2024
ACCEPTED 05 August 2024
PUBLISHED 21 August 2024

CITATION
Weng L, Luo Y, Luo X, Yao K, Zhang Q, Tan J and Yin Y (2024) The common link between sleep apnea syndrome and osteoarthritis: a literature review. *Front. Med.* 11:1401309. doi: 10.3389/fmed.2024.1401309

The common link between sleep apnea syndrome and osteoarthritis: a literature review

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Patients with Osteoarthritis (OA) often also suffer from Sleep Apnea Syndrome (SAS), and many scholars have started to notice this link, although the relationship between the two is still unclear. In this review, we aim to summarize the current literature on these two diseases, integrate evidence of the OA and OSA connection, explore and discuss their potential common mechanisms, and thus identify effective treatment methods for patients with both OA and SAS. Some shared characteristics of the two conditions have been identified, notably aging and obesity as mutual risk factors. Both diseases are associated with various biological processes or molecular pathways, including mitochondrial dysfunction, reactive oxygen species production, the NF-kB pathway, HIF, IL-6, and IL-8. SAS serves as a risk factor for OA, and conversely, OA may influence the progression of SAS. The effects of OA on SAS are underreported in the literature and require more investigation. To effectively manage these patients, timely intervention for SAS is necessary while treating OA, with weight reduction being a primary requirement, alongside combined treatments such as Continuous positive airway pressure (CPAP) and medications. Additionally, numerous studies in drug development are now aimed at inhibiting or clearing certain molecular pathways, including ROS, NF-KB, IL-6, and IL-8. Improving mitochondrial function might represent a viable new strategy, with further research into mitochondrial updates or transplants being essential.

KEYWORDS

sleep apnea syndrome, osteoarthritis, obesity, age, comorbidity

Background

Sleep apnea syndrome (SAS) is a breathing-related disorder during sleep, where breathing frequently pauses or becomes significantly shallow. These pause events may last 10 s or longer and occur more than 5 times per hour. Recent studies show that approximately half of the global population is affected by SAS (1). Research investigating the Asian obese population has discovered a SAS prevalence rate of up to 80.5% (2). Osteoarthritis (OA), a chronic degenerative disease occurring in the joints, has been seeing a rise in prevalence with the aging of the population.

A close relationship exists between SAS and OA. In a cross-sectional study, Asiye Kanbay et al. (3) identified SAS as a risk factor for OA. Furthermore, Andressa Silva et al. (4) observed that patients diagnosed with both OA and SAS exhibited poorer knee joint function than those

without SAS. Present evidence suggests the importance of focusing on the connection between OA and SAS. Hence, this review aims to summarize the shared aspects between the two, providing directions for further research into their comorbid issues.

Method

Searches were performed in PubMed and Google Scholar using keywords like "sleep apnea syndrome," "osteoarthritis," "obstructive sleep apnea," and terms such as "arthritis," "arthropathy," "joint pain." By continuously recombining search terms and filtering through titles and abstracts, we identified relevant documents concerning the relationship between SAS and OA. Using the snowballing method, we summarized the content of retrieved literature and identified additional search terms related to OA and SAS, which facilitated further searches. Inclusion criteria included that the full text be in English and published in this century. Excluded were those studies that did not meet the objectives of this review and were unrelated to the topic.

Common risk factors for SAS and OA

Obesity

Obesity is a risk factor for SAS. Compared to individuals of normal weight, those who are obese or overweight are significantly more likely to suffer from SAS, and they tend to experience a higher severity of the condition. As the Body Mass Index (BMI) and the circumference of the neck and waist increase, the incidence of SAS escalates, and sleep quality deteriorates significantly (5–7).

Bariatric surgery demonstrates remarkable outcomes in treating obstructive sleep apnea in obese patients, particularly in cases of morbid obesity. These surgeries are effective in not only reducing apnea-hypopnea events but also in decreasing body weight, and improving oxygen saturation, deep N3 sleep, and REM (Rapid Eye Movement) sleep stages. Moreover, the surgery improves pulmonary function by increasing Forced Vital Capacity (FVC) (8). Additionally, research shows that managing obesity-related body metrics through pharmacological intervention can reduce symptoms of sleep apnea (9). Wyszomirski et al. (10) discovered that sleep apnea can exacerbate obesity. However, research by Caliendo et al. (11) suggests there may not be a direct correlation between obesity and sleep apnea, yet a positive relationship exists between BMI and the severity of AHI. In summary, obesity is a risk factor for SAS, and managing obesity can play a key role in the prevention and control of sleep apnea.

Obesity is closely related to OA. Research shows that both overall and abdominal obesity elevate the risk of knee OA, with the risk peaking when these two types of obesity are present simultaneously (12). In South Korea's aged population, obesity significantly raises the risk of OA (13). Research in Saudi Arabia has discovered a close relationship between obesity and bilateral knee OA (14). Within an OA animal model, researchers induced obesity in mice with a high-fat diet, thereby speeding up the mice's OA progression (15). Further research indicates a causal link between obesity and hip OA (16). Interestingly, there is an association between metabolic syndrome and hip OA in women, but in men, this link is not evident. However, for men, obesity is directly associated with hip OA, yet in women, this association is less clear. The mechanical impact of obesity may be the main mechanism behind hip OA in men, while in women, metabolic actions are believed to take precedence (17). Not only do obesity and metabolic syndrome foster knee OA through increased mechanical loading, but they also do so via systemic inflammation caused by obesity (18). Moreover, obesity could intensify OA pain, with class III obese patients suffering from notably greater pain than those who are overweight or have class I or II obesity (19).

OA may in turn worsen obesity. Research indicates a higher incidence of obesity, sarcopenia, and sarcopenic obesity in patients with end-stage knee OA. Patients with bilateral knee OA exhibit a higher rate of sarcopenic obesity compared to those with unilateral knee OA (20), underscoring the significance of focusing on the interplay between obesity and OA. Interestingly, bariatric surgery can alleviate symptoms of OA and even potentially slow its progression (21).

Age

Age has an impact on SAS. With advancing age, the severity of SAS tends to intensify, particularly among men (22). For women, transitioning into menopause significantly raises the risk of developing SAS (23). The prevalence of SAS in elderly women is on the rise, with this increase possibly due to aging causing a decrease in the reactivity of upper airway muscle activity, thereby making the airway more prone to collapse (24).

SAS may accelerate the aging process, acting as a contributing factor to aging-related conditions (25). SAS is associated with aging characteristics such as metabolic syndrome, vascular dysfunction, decline in quality of life and cognitive scores, accelerated brain aging, increased insulin resistance, and elevated levels of plasma hydrogen peroxide, GSH, IL-6, hsCRP, and leptin (26). For those under 50, sleep apnea patients are particularly susceptible to aging-related mechanisms such as altered cell communication, impaired nutrient sensing, telomere shortening, mitochondrial dysfunction, and genomic instability (26). SAS can affect the cognition of the elderly. Research indicates that obstructive sleep apnea is linked to a decline in cognitive abilities, particularly in attention and processing speed, among middle-aged and older people (27, 28). This could be attributed to minor alterations in the local brain structures of individuals with SAS (29).

Age significantly impacts OA. Research analyzing data from 36 Organization for Economic Cooperation and Development countries (OECD) countries identified aging and obesity as critical risk factors for OA (30). Both obesity and age are closely related to the severity of knee OA, with age being an independent risk factor for its severity (31). In studies on aged female mice, increased knee cartilage degeneration was observed, alongside more severe mechanical allodynia, knee joint hyperalgesia, and decreased grip strength (32). Di et al. (33) observed that the incidence of knee OA increased most significantly in the age groups of 35 to 39 and 40 to 44 years. A meta-analysis highlighted age as a risk factor for scapulothoracic OA (34). Furthermore, age also influences the hand strength in patients with hand OA (35).

Common mechanism of SAS and OA

Mitochondrial dysfunction

Mitochondrial dysfunction plays a crucial role in the context of SAS. A diet high in fats causes mitochondrial dysfunction and

oxidative stress, which damages the genioglossus muscle and could lead to SAS (36). Moreover, research has shown that in the whole blood DNA of patients with SAS, the copy number of mitochondrial DNA (mtDNA) is reduced, with this reduction being associated with the severity of the patient's condition (37). However, Lacedonia D et al. found that: in patients, intermittent hypoxia intensifies oxidative stress, resulting in mitochondrial damage, and consequently, a increase in the number of mitochondrial DNA copies (38).

Chronic intermittent hypoxia in patients can lead to mitochondrial dysfunction, triggering neuroinflammation, an increase in reactive oxygen species (ROS) (39). Furthermore, mitochondrial dysfunction is associated with metabolic disorders, and the level of mitochondrial-derived peptide MOTS-c in serum is closely related to SAS. MOTS-c emerges as a new and useful marker for early metabolic disorder in patients (40). Interestingly, enhancing mitochondrial autophagy to remove damaged mitochondria can alleviate tissue cell damage caused by the syndrome. Research has found that silencing NLRP3 in mice activates the PINK1-Parkin pathway to promote mitochondrial autophagy, thereby preventing the neuroinflammation and production of reactive oxygen species induced by intermittent hypoxia (41).

Mitochondrial dysfunction is indeed a significant factor contributing to the development of OA. Cytokine stimulation triggers mitochondrial dysfunction through signaling pathways such as JNK, PI3K/Akt, NF-κB, and p38 MAPK, which is characterized by decreased transmembrane potential, reduced ATP production, and increased ROS, all of which contribute to cartilage cell damage (42). The ensuing ROS chain reaction caused by mitochondrial dysfunction damages mitochondrial DNA (mtDNA) and cardiolipin, leading to a decrease in mitochondrial membrane potential and the opening of mitochondrial permeability transition pores (PTP). This facilitates the influx of calcium ions (Ca2+) and thus triggers an inflammatory response. During this process, the inflammasome NLRP3 is activated, enabling the conversion from pro-Caspase-1 to Caspase-1 and initiating a caspase cascade, ultimately leading to pyroptosis. Moreover, ROS can further activate NF-κB, resulting in changes in gene transcription that lead to cell cycle arrest, cellular senescence, and degradation of the extracellular matrix (43).

Reactive oxygen species (ROS)

Intermittent hypoxia caused by SAS leads to the activation of NADPH oxidase and xanthine oxidase, mitochondrial dysfunction, and uncoupling of nitric oxide synthase (NOS) (44, 45). These reactions result in increased ROS levels, further activating transcription factors such as NF-kB and AP-1, which then trigger the release of inflammatory mediators and pro-inflammatory cytokines (45, 46), ultimately causing tissue and cellular damage (Table 1).

Additionally, intermittent hypoxic conditions during apnea lead to an increase in mtROS and activation of NLRP3 inflammasomes, these inflammatory reactions may cause damage to other organs (41).

TABLE 1 The role of ROS in SAS and OA.

Impact/Drug	Molecule/pathway	Function	
Hypoxia	mtROS(+)	Activation of the NLRP3 inflammasome	Wu et al. (41)
Hypoxia	ROS(+)，NF-κB(+)，HIF-1α(+)	Pyroptosis of muscle cells	Yu et al. (47)
Hypoxia	ROS(+)，NF-kB(+)，AP-1(+)	Promotes the release of inflammatory mediators and proinflammatory cytokines	Lavie (45)
Synovial inflammation	ROS/NLRP3(+)	Chondrocyte apoptosis accelerates cartilage degeneration in osteoarthritis	Liu et al. (48)
Nitidine chloride	ROS(−)	Reduces inflammation and cellular senescence in mice with osteoarthritis	Lin et al. (49)
Mn(3)O (4)/UIO-TPP nano-enzyme	ROS(−)	Restore mitochondrial function and relieve osteoarthritis	Zhang et al. (50)
Fucoxanthin	ROS(−)	It plays a protective role in chondrocytes and effectively reduces the development of osteoarthritis	Wu et al. (51)
Polydopamine-Pd nanozymes	ROS(−)	Anti-oxidant and anti-inflammatory	Hu et al. (52)
Nodakenin	Drp1/ROS/NLRP3 (−)	Reduce cartilage degradation and inflammation	Yi et al. (53)
TRPV4(−)	ROS/NLRP3 (−)	M1 macrophage polarization was hindered and osteoarthritis was delayed	Sun et al. (54)
NP@Poly(RHAPM)	ROS(−)，Macrophage repolarization (+)	Repolarization of M1 macrophages to the M2 phenotype enhanced chondrocyte proliferation and viability	Li et al. (55)
PIM-1(−)	ROS/Cl(−)(−)	Inhibition of NLRP3 inflammasome activation can alleviate osteoarthritis	Zhang et al. (56)
Pt@PCN222-Mn cascade nanase	ROS-NF-κB(−)，MAPK (−)	It also inhibited the production of inflammatory factors, ECM degradation and chondrocyte apoptosis	Zhang et al. (57)
Dendrobine	ROS/NF-κB (−)	Reduce osteoarthritis	Chen et al. (58)
Astragalus polysaccharide	ASK1/p38 MAPK(−)	Thioredoxin is activated and apoptosis is inhibited	Xu et al. (59)
++GLX351322(GLX)	NOX4(−)，ROS(−)	Inhibition of inflammatory responses	Zhen et al. (60) and Huang et al. (61)
Angelica Polysaccharide	PPARγ(+)，SOD2(+)，ROS(−)	Improve mitochondrial metabolism of chondrocytes in osteoarthritis	Ni et al. (62)

* "+" represents facilitation, "−" represents inhibition.

Hypoxia-induced increase in ROS also promotes cell apoptosis through the activation of the NF-κB/HIF-1α signaling pathway (47).

ROS plays a crucial role in the development mechanism of OA (Table 1). Research indicates that synovitis-induced activation of the ROS/NLRP3 pathway can enhance chondrocyte apoptosis, thereby speeding up the degeneration of joint cartilage in OA (48). Efficiently clearing ROS can alleviate the symptoms of OA. For instance, nitidine chloride, acting as a reactive oxygen species scavenger, can reduce inflammatory responses and cell senescence in a mouse model of OA (49). Moreover, mitochondria-targeted Mn(3)O (4)/UIO-TPP nanozymes restore mitochondrial function by eliminating ROS, thus effectively combating OA (50). Molybdenum-based polyoxometalate (POM) nanoclusters leverage their near-infrared photosensitivity to enhance ROS scavenging capability, markedly improving clinical symptoms of OA (63). Additionally, Nodakenin can mitigate cartilage degeneration and inflammatory responses in a mouse model of OA by modulating the mitochondrial Drp1/ROS/NLRP3 axis (53).

The ROS/NLRP3 pathway also impedes M1 macrophage polarization, leading to OA. By inhibiting the ROS/NLRP3 pathway, the progression of OA can be delayed (54). Researchers have created a nanomaterial NP@Poly(RHAPM) that is capable of significantly lowering ROS levels within cells, thereby leading to the repolarization of M1 macrophages to the M2 phenotype, enhancing the proliferation and vitality of chondrocytes, as well as preventing cell apoptosis (55). Similarly, BTZ@PTK reduces ROS levels, activates apoptosis in M1 macrophages, inhibits M1 macrophage-mediated inflammatory responses, and thus improves OA (64).

ROS regulate the NF-κB and MAPK pathways, thus contributing to OA. The Pt@PCN222-Mn cascaded nanoenzyme, developed by Zhang et al. (57), can delay the progression of temporomandibular joint OA in rat models by inhibiting the ROS-NF-κB and MAPK signaling pathways. Moreover, Dendrobine targets chondrocytes via the ROS/NF-κB axis, inhibiting the expression of aging-related secretory phenotype factors, thus helping to alleviate OA (58). Additionally, Astragalus polysaccharides inhibit apoptosis and improve OA symptoms by suppressing ROS-mediated activation of the ASK1/p38 MAPK signaling pathway, subsequently activating thioredoxins (59).

NF-κB pathway

Chronic hypoxia mediated by SAS can cause damage to multiple organ tissues throughout the body via the NF-κB pathway (Table 2). Hypoxia-induced ROS promotes myoblast apoptosis in obstructive sleep apnea via the NF-κB/HIF-1α signaling pathway (47). Additionally, hypoxia accelerates lung fibrosis in mouse lung injury by regulating the NF-κB/Nrf2 signaling pathway (65). Hypoxia further mediates adipocyte insulin resistance through the RAGE/NF-κB pathway (66). The activation of the TLR4/NF-κB/VEGF pathway enhances vascular dysfunction in the soft palate, aggravating SAS (67).

Intervening in the NF-κB pathway offers a therapeutic avenue for neurological and cardiovascular diseases caused by SAS. Liu et al. (68) demonstrated that inhibiting NF-κB activation can alleviate cognitive impairment in sleep apnea. Similarly, PDTC and Rapa, by inhibiting the mTOR and NF-κB pathways, can prevent damage to hippocampal neurons induced by hypoxia (69). Song et al. (99) showed that inhibiting endothelial NF-κB signaling can alleviate arteriosclerosis induced by chronic intermittent hypoxia in mice. Furthermore, enhanced O-GlcNAcylation can inhibit NFAT and NF-κB activity in mice to attenuate cardiac remodeling induced by intermittent hypoxia (70). Also, overexpressing miR-15b-5p/miR-92b-3p and inhibiting the PTGS1-NF-κB-SP1 signaling pathway provides a potential treatment for depression related to SAS (71).

There's a significant link between the NF-κB pathway and OA (Table 2); suppressing NF-κB can significantly mitigate OA. Pelagonidin effectively improves OA by inhibiting the NF-κB pathway, thus reducing inflammation and cartilage degeneration (76). Exosomal miR-4738-3p helps relieve mild inflammatory symptoms of OA by regulating COL1A2 through the NF-kB and inflammatory signaling pathways (78). Atractylenolide III effectively alleviates OA and chondrocyte aging by inhibiting the NF-κB signaling pathway (100). Shihuakalin targets cellular aging and OA via the ROS/NF-κB pathway (58). Quercitrin acts to slow down OA by inhibiting the NF-κB signaling pathway and enhancing glucose transport capability (101). Indole-3-propionic acid offers relief to chondrocyte inflammation and OA through the AhR/NF-κB axis (72).

Furthermore, NF-κB is known to promote chondrocyte apoptosis, and inhibiting NF-κB can effectively protect chondrocytes. Paroxetine has been shown to alleviate chondrocyte apoptosis and inhibit osteoclast formation by suppressing NF-κB (85). Stevioside reduces chondrocyte inflammation and apoptosis *in vivo* via the NF-κB and MAPK pathways, thereby improving OA (86). Forkhead box O3 plays a crucial role in inhibiting chondrocyte ferroptosis and alleviating OA by suppressing the NF-κB/MAPK signaling (87).

NF-κB plays a pivotal role in OA through its influence on macrophages. Suramin effectively ameliorates OA by targeting the Nrf2/HO-1 and NF-κB signaling pathways in chondrocytes and by promoting the M2 polarization of macrophages (88). Additionally, κ-opioid receptor activation can modulate macrophage polarization through the NF-κB pathway and help alleviate osteoarthritic synovitis (89).

Some miRNAs significantly influence OA through the NF-κB pathway. The MicroRNA-15a/β1, 4-galt-i axis is involved in the degeneration of osteoarthritic cartilage via the NF-κB signaling pathway (102). MiR-203a-3p plays a role in alleviating chondrocyte apoptosis by regulating the MYD88/NF-κB pathway (91).

Physical factors also impact OA via the NF-κB pathway. Mechanical stress works to avert chondrocyte apoptosis by suppressing the NF-κB signaling pathway (92). Non-weight-bearing exercise has been shown to reduce rat knee OA through the TLR4/MyD88/NF-κB signaling pathway (93). Tendon adjustments and bone grafting are effective in facilitating the healing of synovitis in rabbit osteoarthritic knees via the TLR4-MyD88-NF-κB pathway (94). Moderate-intensity physical activity can mitigate inflammation and cellular apoptosis by enhancing metrnl release, thereby acting to suppress the PI3K/Akt/NF-κB and NLRP3/caspase-1/GSDMD pathways (95).

Upregulating Nrf2 to inhibit NF-κB activity offers a promising approach to alleviate OA. Li et al. (103) found that the Nrf2/HMGB1/NF-κB axis regulates chondrocyte apoptosis and extracellular matrix degradation in OA. Phillygenin improves OA in mice by inhibiting chondrocyte inflammation via the Nrf2/NF-κB axis (73). Oxymatrine

TABLE 2 The role of NF-κB pathway in SAS and OA.

Impact/Drug	Molecule/pathway	Function	
Hypoxia	NF-κB(+), Nrf2(−)	Pulmonary fibrosis that accelerates lung injury in mice	Kang et al. (65)
Hypoxia	RAGE(+), NF-κB (+)	Increased insulin resistance in adipocytes	Tang et al. (66)
HMGB1(+)	TLR4/NF-κB/VEGF(+)	Promote soft palate vascular dysfunction in patients with obstructive sleep apnea	Su et al. (67)
NF-κ b(+)	JNK(+)	Hippocampal neuronal apoptosis and cognitive dysfunction	Liu et al. (68)
PDTC, Rapa	mTOR (−), NF-κB (−)	Prevention of hypoxia-induced hippocampal neuronal damage	Zhang et al. (69)
o-glcn acylation	NFAT(−), NF-κB(−)	Attenuated intermittent hypoxia-induced cardiac remodeling	Nakagawa et al. (70)
miR-15b-5p/miR-92b-3p(−)	PTGS1-NF-κB-SP1(+)	Oxidative stress and MAOA hyperactivation	Chen et al. (71)
Indole-3-propionic acid	AhR/NF-κB (−)	Reduces chondrocyte inflammation and osteoarthritis	Zhuang et al. (72)
Phillygenin	Nrf2(+), NF-κB (−)	Inhibition of chondrocyte inflammation	Zhang et al. (73)
Orientin	Nrf2/HO-1(+), SIRT6 pathway(+), NF-κB (−)	Inhibits the development of osteoarthritis	Xia et al. (74)
Pachymic acid	Sirtuin 6(+), NF-κB(−)	It can inhibit the inflammatory response of chondrocytes and alleviate the progression of osteoarthritis	Wu et al. (75)
Pelagonidin	NF-κB(−)	Improve inflammation and cartilage degeneration in osteoarthritis	Zeng et al. (76)
Sakuranetin	PI3K/AKT/NF-κB (−)	Reduces inflammation and chondrocyte dysfunction in osteoarthritis	Deng et al. (77)
miR-4738-3p	NF-kB(−),COL1A2(−)	Relieve the symptoms of low-grade inflammation in osteoarthritis	Xu et al. (78)
Dendrobine	ROS/NF-κB(−)	Alleviates cellular senescence and osteoarthritis	Chen et al. (58)
Oxymatrine	Nrf2(+), NF-κB(−)	Reduced proinflammatory cytokines, ECM degradation and OA progression	Zhou et al. (79)
Chrysophanol	Sirt6(+), Nrf2(+), NF-κB(−)	Alleviates inflammation and ECM degradation in osteoarthritis	Lu et al. (80)
Rutaecarpine	PI3K/AKT/NF—κB(−), MAPK(−)	Improving osteoarthritis	Wan et al. (81)
Mulberroside A	MAPK(−), NF-κB(−), PI3K-AKT–mTOR (−)	Relieving Osteoarthritis	Lu et al. (82)
Ergothioneine	Sirt6(+), NF-κB(−)	Inhibit the progression of osteoarthritis	Wang et al. (83)
Plantamajoside	NF-κB(−), MAPK(−)	Relieving Osteoarthritis	Lin et al. (84)
Paroxetine	NF-κB (−)	Reduce chondrocyte apoptosis and inhibit osteoclast formation	Zheng et al. (85)
Stevioside	NF-κB(−), MAPK (−)	Inhibition of chondrocyte inflammation and apoptosis	Cai et al. (86)
Forkhead box O3	NF-κB(−), MAPK(−)	Inhibition of ferroptosis in chondrocytes	Zhao et al. (87)
Suramin	Nrf2/HO-1(+), NF-κB (−)	Improving osteoarthritis	Shen et al. (88)
κ-opioid receptor	NF-κB (−)	Promote macrophage polarization and reduce osteoarthritis synovitis	Shi et al. (89)
miR-181a-5p	DDX3X(−), NF-KB(−)	Inhibit the progression of osteoarthritis	Zhao et al. (90)
MiR-203a-3p	MYD88/NF-κB (−)	Reduce the progression of osteoarthritis	Chen et al. (91)
Mechanical stress	tgf—β 1/Smad2/Smad3 axis(+), NF-KB(−)	Prevent pyroptosis of chondrocytes	Wang et al. (92)
Non-weight bearing exercise	TLR4/MyD88/NF-κB (−)	It can reduce the levels of inflammatory cytokines il-1β, IL-6 and tnf-α, and slow down the degeneration of articular cartilage	Wang et al. (93)
Regulating tendons and bone-setting techniques	TLR4-MyD88-NF-κB (−)	Reduce synovial inflammation of the knee joint	Jin et al. (94)
Moderate exercise	metrnl(+), PI3K/Akt/NF-κB(−), NLRP3/caspase-1/GSDMD (−)	Improves inflammation and pyroptosis	Liu et al. (95)
ROR1(+)	STAT3(+), NF-κB (+)	There was an imbalance between anabolism and catabolism in chondrocytes	Huang et al. (96)
SNIP1(+)	NF-κB(−)	Reduces extracellular matrix degradation and inflammation	Chen et al. (97)
FTO(+)	TLR4/MyD88/NF-κB(−)	Relieve osteoarthritis	Cai et al. (98)

* "+" represents facilitation, "-" represents inhibition.

enhances OA treatment *in vitro* and *in vivo* via the Nrf2/NF-κB axis (79). Chrysophanol acts to prevent OA inflammation and extracellular matrix degradation via the Nrf2/NF-κB axis (80).

The Sirtuin 6/NF-κB signaling pathway holds significance in OA treatment. Orientin effectively mitigates OA through activation of the SIRT6 signaling pathway and suppression of the NF-κB pathway (74).

Pachymic acid targets chondrocyte inflammation by modulating the Sirtuin 6/NF-κB signaling axis (75). Emodin again demonstrates its efficacy in preventing OA inflammation and extracellular matrix degradation in chondrocytes via the Sirt6/NF-κB pathway (80). Ergothioneine is proven to inhibit the progression of OA both *in vitro* and *in vivo* via the Sirt6/NF-κB axis (83).

The PI3K/AKT/NF-κB and MAPK signaling pathways are closely associated with the onset and progression of OA. Sakuranetin acts to reduce inflammation and chondrocyte dysfunction in OA by targeting the PI3K/AKT/NF-κB pathway (77). Rutaecarpine demonstrates effectiveness in improving OA by inhibiting PI3K/AKT/NF-κB and MAPK signal transduction through integrin αVβ3 (81). Mulberroside A contributes to alleviating OA by restoring damaged autophagy and inhibiting the MAPK/NF-κB/PI3K-AKT–mTOR signaling pathway (82). Furthermore, Plantamajoside beneficially impacts the development of OA by suppressing the activation of NF-κB and MAPK (84).

HIF (hypoxia-inducible factors)

HIF-1α is recognized as a biomarker for SAS (104). In patients with sleep apnea, the HIF-1α protein expression levels are notably elevated, correlating with the chronic hypoxia state (105). This chronic hypoxia not only leads to other diseases, through HIF-1 (106) but also results in an increase in ROS, which further promotes tissue cells apoptosis via the NF-κB/HIF-1α signaling pathway (47). Moreover, elevated HIF-1α levels are tied to excessive expression of circadian rhythm proteins, thereby increasing the risk of circadian rhythm disturbances in SAS patients (107). SAS may harm other tissues and organs via HIF-1, SAS can accelerate the progression of aortic dissection through the ROS-HIF-1α-MMPs related pathway (108), as well as exacerbate neuroinflammation and apoptosis in early brain injury after subarachnoid hemorrhage via the ASC/HIF-1α pathway (109).

HIF-2α is a subtype of the HIF. HIF-2α increases the expression of Superoxide Dismutase 2 (SOD2), an antioxidant enzyme that can reduce ROS (110). Chronic hypoxia from SAS causes an increase in ROS, subsequently triggering a rise in intracellular calcium levels ([Ca(2+)]i), which stimulates increased synthesis of HIF-1α and enhanced degradation of HIF-2α, as a result, the normal balance between HIF-1α-dependent pro-oxidants and HIF-2α-dependent antioxidants is broken, resulting in an additional increase in ROS, this exacerbates damage to multiple tissues throughout the body (111).

Some studies indicate that HIF-1 plays a protective role in OA (Table 3). HIF-1α may protect articular cartilage by promoting chondrocyte phenotype, maintaining chondrocyte vitality, and supporting metabolic adaptation in hypoxic conditions (128). In hypoxic conditions, the activity of HIF-1α is enhanced, and it accelerates angiogenesis in cartilage through the vascular endothelial growth factor VEGF and Notch signaling pathway (112). Sunli Hu et al. (129) found that HIF-1α-mediated mitochondrial autophagy can alleviate OA. The dysregulation of the HIF-1α/CRAT/miR-144-3p signaling axis has a significant relationship with OA; silencing HIF-1α leads to downregulation of CRAT, which then results in increased expression of miR-144-3p causing dysfunction of peroxisomes and accumulation of long-chain fatty acids, promoting the development of OA (118).

Nonetheless, certain studies refute the protective role of HIF-1 in OA. For instance, in knee OA, elevated HIF-1α may exacerbate synovial fibrosis and fibroblast-like synoviocyte apoptosis (130). Moreover, LncHIFCAR has been shown to positively regulate HIF-1α and its target genes (including VEGF, BNIP3) along with the PI3K/AKT/mTOR pathway, thereby promoting chondrocyte apoptosis (114). Interestingly, Li et al. (115) discovered that Casticin mitigates knee OA through the suppression of HIF-1α/NLRP3 inflammasome signaling. In a similar vein, Agnuside alleviates synovitis and fibrosis in experimental knee OA by inhibiting the accumulation of HIF-1α and the activation of the NLRP3 inflammasome (116). Additionally, Vitexin targets the HIF-1α pathway to reduce inflammatory responses in osteoarthritic chondrocytes (117). Likewise, CircRNA-UBE2G1 modulates chondrocyte damage via the miR-373/HIF-1α pathway (119). Finally, Capsiate metabolites are found to reduce the progression of ferroptosis-associated OA by enhancing SLC2A1 expression, thereby effectively inhibiting HIF-1α expression (120).

HIF-2α is recognized as a crucial regulator of catabolic metabolism and the inflammatory cascade in OA (131). It can directly induce the expression of catabolic metabolic factors in chondrocytes and also enhance the expression of Fas in mature chondrocytes, thus mediating chondrocyte apoptosis and autophagy regulation (128). Moreover, mechanical stress has been found to exacerbate cartilage degradation through NF-κB and HIF-2α. Remarkably, inhibiting p65 has been shown to significantly reduce the expression of HIF-2α, thereby decreasing cartilage degradation and the production of related factors (121). Furthermore, HIF-2α is known to enhance the influx of Zn(2+) in chondrocytes by activating the Zn-ZIP8-MTF1 axis, consequently promoting the expression of matrix metalloproteinases and amplifying the regulatory effect on cartilage destruction in OA (125).

Suppressing HIF-2α offers a therapeutic strategy to relieve OA. Osthole has been demonstrated to alleviate cartilage degeneration by inhibiting the NF-κB and HIF-2α pathways (122). Intra-articular resveratrol injections activate SIRT1, thereby effectively inhibiting HIF-2α and preventing the progression of OA (123). Additionally, chemically modified curcumin targets the NF-κB/Hif-2α axis while stabilizing the extracellular matrix, showing potential in slowing the progression of OA (132). D-Mannose reduces the sensitivity of chondrocytes to ferroptosis by inhibiting HIF-2α, aiming to alleviate OA (124).

Exploring further, additional strategies targeting HIF-2α involve employing IkappaBalpha kinase inhibitors and syndecan-4 inhibitors to address associated pathways. The inhibition of syndecan-4 has been found to reduce cartilage degradation in osteoarthritic mouse models by downregulating HIF-2α via miR-96-5p (126). Similarly, IkappaBalpha kinase inhibitors are reported to reduce cartilage degradation in mouse models by downregulating the NF-κB/HIF-2α axis (127).

IL-6 and IL-8

Cytokines IL-6 and IL-8 play a significant role in sleep apnea. Research has shown increased levels of IL-6, TNF-α, and IL-8 in the serum and plasma of SAS patients, which are positively correlated with disease severity, age, and BMI (133). Furthermore, a consistent

TABLE 3 The role of HIF in SAS and OA.

Impact/Drug	Molecule/pathway	Function	
Hypoxia	HIF-1α(+)	It can be used as a biomarker of sleep apnea and is related to the overexpression of circadian clock proteins	Gabryelska et al. (105), Gabryelska et al. (106), and Liu et al. (104)
Hypoxia	NF-κB/HIF-1α (+)	Myoblast pyrosis	Yu et al. (47)
Hypoxia	ROS-HIF-1α-MMPs(+)	Aortic dissection	Liu et al. (108)
Hypoxia	ASC/HIF-1α(+)	Aggravated neuroinflammation and pyroptosis in early brain injury after subarachnoid hemorrhage	Xu et al. (109)
Hypoxia	HIF-1α(+),VEGF(+),Notch (+)	It can accelerate the angiogenesis of cartilage and regulate the autophagy and apoptosis of chondrocytes	Chen et al. (112) and Zeng et al. (113)
LncHIFCAR(−)	HIF-1α(+),VEGF(+),BNIP3(+),PI3K/AKT/mTOR (+)	It has a protective effect on chondrocytes	Sun et al. (114)
Casticin	HIF-1α/NLRP3 inflammasome(−)	Reduce osteoarthritis	Li et al. (115)
Agnuside	HIF-1α(−),NLRP3 inflammasome(−)	Reduces synovitis and fibrosis in experimental osteoarthritis	Zhang et al. (116)
Vitexin	HIF-1α(−)	It alleviates the inflammatory response of chondrocytes	Yang et al. (117)
HIF-1α(−)	HIF-1α(−),CRAT(−),miR-144-3p(+)	Peroxisome dysfunction and long-chain fatty acid accumulation	Song et al. (118)
CircRNA-UBE2G1(+)	HIF-1α(+)	It also increases the expression of pro-inflammatory cytokines and promotes the formation of osteoarthritis	Chen et al. (119)
miR-373(−)	HIF-1α(+)	It also increases the expression of pro-inflammatory cytokines and promotes the formation of osteoarthritis	Chen et al. (119)
Capsiate	SLC2A1(+),HIF-1α(−)	Slowing the progression of ferroptosis-related osteoarthritis	Guan et al. (120)
Mechanical stress	NF-κB(+),HIF-2α(+),MMP13(+),ADAMTs-4(+)	Aggravated cartilage degradation	Li et al. (121)
Osthole	NF-κB(−),HIF-2α(−),	The cartilage degradation was alleviated	Chern et al. (122)
Resveratrol	SIRT1(+),HIF-2α(−)	The progression of osteoarthritis was prevented	Li et al. (123)
D-mannose	HIF-2α(−)	Reduce the sensitivity of chondrocytes to ferroptosis	Zhou et al. (124)
HIF-2α	Zn -ZIP8-MTF1 (+)	It also increases the influx of Zn(2+) into chondrocytes and further promotes the expression of matrix-degrading enzymes	Lee et al. (125)
Syndecan-4(−)	miR-96-5p(+),HIF-2α(−)	Reduce cartilage degradation in osteoarthritis	Zhou et al. (126)
IkappaBalpha kinase inhibitor	NF-κB/HIF-2α (−)	Reduced cartilage degradation	Murahashi et al. (127)

* "+" represents facilitation, "−" represents inhibition.

conclusion from another study is that IL-6 levels are associated with both glucose metabolism and sleep apnea (134). This increase in IL-6 levels might be linked to the reduced oxygen consumption observed in sleep apnea patients (135). However, Kurt et al. (136) reported no significant variance in plasma IL-6 levels between the SAS group and a control group. As for the levels of IL-8, they are closely associated with obesity. Carpagnano et al. (137) observed a significant increase in the levels of IL-8, ICAM, and neutrophil percentage in induced saliva of obese sleep apnea patients, non-obese sleep apnea patients, and obese non-sleep apnea participants, compared to healthy individuals.

It remains contentious whether treating sleep apnea can influence the levels of IL-6 and IL-8. Previous findings suggest that adenotonsillectomy can improve clinical symptoms and signs, but has a minimal effect on TNF-α and IL-6 inflammatory levels (138). However, recent studies offer a different view, showing a decrease in circulating polymorphonuclear leukocyte levels of IL-6, IL-8, and β2-adrenergic receptor mRNA after adenotonsillectomy in children with obstructive SAS (139). One study found elevated IL-6 levels in patients with SAS, but Continuous positive airway pressure (CPAP) had no significant inhibitory effect on IL-6 levels in adults with SAS (140). In contrast, another study, by comparing untreated SAS patients and a control group, found that untreated SAS patients had significantly higher levels of IL-8 in peripheral blood than the control group. Moreover, this study suggests that nCPAP treatment can reduce hypoxia and the production of inflammatory mediators induced by SAS (141).

IL-6 and IL-8 are associated with OA. Senescent chondroprogenitor cells from the articular cartilage of knee OA patients contribute to the senescence-associated secretory phenotype by releasing IL-6 and IL-8 (142). Notably, IL-6 increases the production of inflammatory cytokines and expression of hypertrophic markers in primary mouse chondrocytes by activating JAK2/STAT3 (143). Blocking IL-6 can enhance Treg function and mitigate the progression of OA (144). Interestingly, IL-6 inhibits the spheroid size of osteophyte cells in OA by inducing apoptosis and reducing extracellular matrix molecules, highlighting its suppressive role in the regulation of pathological osteophyte formation (145).

Long non-coding RNA can influence the expression of IL-6 in OA. In OA patients, long non-coding RNA FER1L4 is downregulated, while IL-6 is upregulated. Importantly, the upregulation of FER1L4 can inhibit IL-6 expression in human chondrocytes (146).

Overexpression of IL-6 can exacerbate OA, and notably, PM2.5 can increase the production of IL-6 in human OA, worsening the condition (147). Moreover, Platelet response protein 2 promotes the production of IL-6 in OA synovial fibroblasts via the PI3K/AKT/NF-κB pathway (148).

Inhibiting IL-6 can alleviate OA. For instance, Tofacitinib relieves OA by upregulating miR-149-5p levels, thereby inhibiting the expression of JAK1/TNF-α/IL-6 (149). Similarly, Achyranthes root demonstrates anti-inflammatory and antioxidative treatment effects on OA and rheumatoid arthritis models by inhibiting the expression of IL-6 mediated matrix metalloproteinase-3 and -13 (150). Additionally, inhibition of the nuclear receptor RORα alleviates cartilage damage in OA by regulating the IL-6/STAT3 pathway (151). Furthermore, Genistein reduces obesity-induced OA in mice by inhibiting IL-6 and MMP-13 (152). Research has shown that fibroblast growth factor 10 delays the progression of OA by inhibiting the IL-6/JAK2/STAT3 signaling pathway, reducing synovial fibrosis (153). Physical therapy can also affect IL-6 expression in OA. Notably, rapid walking exercise significantly improves patients' daily functioning and physical ability, while notably reducing TNF-α and IL-6 levels (154). Additionally, pulsed electromagnetic fields improve cartilage matrix, chondrocyte apoptosis, and autophagy by inhibiting TNF-α and IL-6 signaling (155). It is also suggested that IL-8 may be a risk factor for OA, with serum IL-8 levels being associated with aggravated knee joint symptoms (156). Moreover, research indicates that IL-8/Kc is highly responsive to mechanical, inflammatory, and metabolic stress (157).

Discussion

SAS and OA not only exhibit numerous common features, epidemiological studies reveal a tight correlation between them. Patients with both OA and SAS exhibit more severe symptoms of knee arthritis than those with only OA. Additional research has identified SAS as a risk factor for OA (3). There are numerous complex mechanisms involved (Figure 1). SAS results in intermittent hypoxia, which over time leads to mitochondrial dysfunction and significant ROS activation that stimulates inflammasomes (NLRP3), causing inflammation. ROS activates the NF-kB pathway, enhancing the production of inflammatory markers like IL-6 and TNF-α, which can expand the inflammatory response in joint synovium and lead to the breakdown of the extracellular matrix in cartilage cells, exacerbating OA.

Conversely, is OA a risk factor for SAS? Research in this area is still limited; however, Karla Diaz et al. (159) found a certain correlation between newly diagnosed SAS and prior OA. OA patients suffer from poor proprioception, reduced joint mobility, and weak muscle strength (160), leading to a loss of normal activity. A decrease in physical activity can result in becoming overweight and obese (161). Obesity further aggravates SAS. Overall, there is a bidirectional link between OA and SAS. SAS exacerbates OA, and decreased activity among OA sufferers could lead to obesity, thereby intensifying SAS. Owing to insufficient literature, it remains uncertain whether OA is a risk factor for SAS, but there appears to be a significant relationship between the two. Whether this relationship is causal or merely correlational needs more experimental evidence in the future.

In treating OA patients with SAS, intervention for SAS must not be neglected alongside OA treatment. Reducing weight is both essential and primary, and must be combined with correcting hypoventilation. CPAP is the gold standard for addressing hypoxia in SAS; however, its effectiveness on certain complications of SAS remains debated, potentially due to issues like patient compliance (162). Reduced patient compliance can result in poorer treatment effectiveness. Surgery to enhance hypoventilation is another method; Uvulopalatopharyngoplasty (UPPP) is the most frequently performed surgery for OSA. In traditional UPPP, tissue surrounding the blockage is removed to expand the airway and relieve obstruction (163). The success rate of the surgery is also related to the anatomical staging system; for stage IV patients, the success rate is only 20% (164). Excessive removal of obstructive parts and surrounding tissue to enlarge the airway space can cause complications such as nasopharyngeal narrowing and palatopharyngeal dysfunction (158). Hence, surgery is neither the preferred nor compulsory option, as its effectiveness in relieving small and multiple airway obstructions is limited.

For patients treating OA combined with SAS, relying solely on CPAP is insufficient; medication is also necessary (Tables 1–3), which targets and inhibits certain key molecules or pathways (Tables 1–3) to achieve therapeutic effects. Mitochondrial dysfunction is an upstream factor in these molecular pathways, and improving mitochondrial function might be a more effective method. In the future, treatment for patients with OA combined with SAS may involve improving or renewing mitochondrial function. Currently, a prevalent strategy includes the use of agents such as Urolithin A to boost mitochondrial functionality (165). Additionally, activating mitochondrial autophagy to clear damaged mitochondria can be achieved; for instance, artemisinin reduces TNFSF11 expression in cartilage and inhibits the PI3K/AKT/mTOR signaling pathway, thereby activating mitochondrial autophagy (166). Mitochondrial transplantation is another strategy; Lee et al. (167) have used mitochondrial transplantation to mitigate the progression of OA. Recently, liposomes have emerged as a new tool for transporting mitochondria (168), facilitating mitochondrial regeneration, representing a promising therapeutic strategy. Zhang et al. (169) have discovered that sustained release of melatonin can reactivate mitochondria in cartilage cells. Developing a sustained-release system for melatonin may also be a viable treatment method in the future.

Conclusion

There is a close relationship between OA and SAS. SAS is a risk factor for OA, and OA might influence the progression of SAS, though the specifics of this influence require further experimental investigation. For patients with OA who have SAS, treating OA while also intervening timely in SAS is necessary, with weight reduction being a primary and essential step, alongside combined treatments

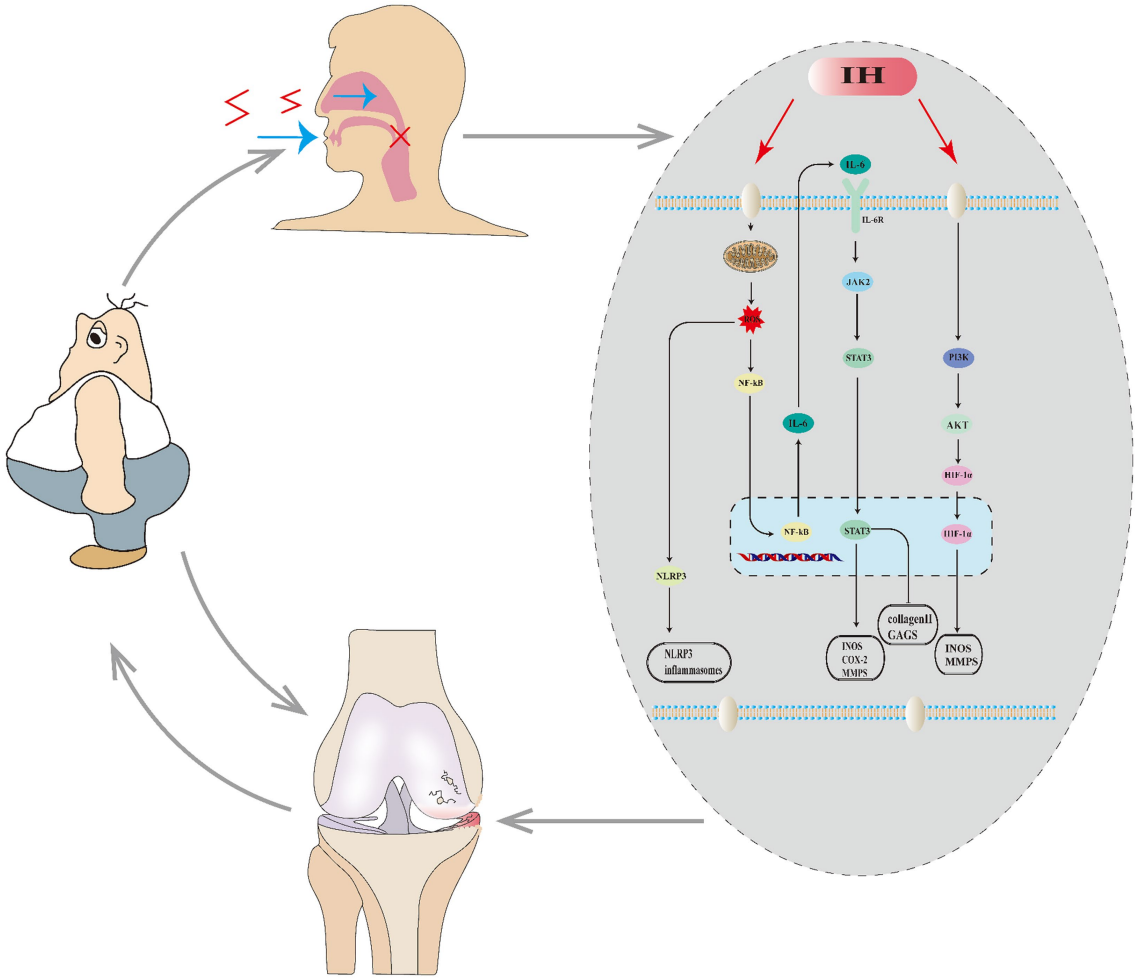

FIGURE 1
Relationship between OA and SAS. SAS causes intermittent hypoxia (IH) in the body, which affects a series of molecules and pathways, leading to the worsening of OA. OA, in turn, promotes obesity, which can further exacerbate both SAS and OA.

such as CPAP and medications. Current drug development efforts involve numerous studies aimed at inhibiting or clearing molecular pathways, including ROS, NF-KB pathway, IL-6, and IL-8. Improving mitochondrial function may be an effective new method; renewing or transplanting mitochondria is a promising direction.

Author contributions

LW: Conceptualization, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. YL: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. XL: Software, Visualization, Writing – review & editing. KY: Conceptualization, Data curation, Software, Visualization, Writing – review & editing. QZ: Data curation, Software, Visualization, Writing – review & editing. JT: Data curation, Software, Visualization, Writing – review & editing. YY: Conceptualization, Data curation, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 10 December 2024
DOI 10.3389/fneur.2024.1420391

OPEN ACCESS

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RECEIVED 20 April 2024
ACCEPTED 28 November 2024
PUBLISHED 10 December 2024

CITATION
Zhao M, Huang X, Zheng H, Cai Y, Han W, Wang Y and Chen R (2024) Association between hypothyroidism and obstructive sleep apnea: a bidirectional Mendelian randomization study combined with the geo database.
Front. Neurol. 15:1420391.
doi: 10.3389/fneur.2024.1420391

Association between hypothyroidism and obstructive sleep apnea: a bidirectional Mendelian randomization study combined with the geo database

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Background: The causal relationship between hypothyroidism and obstructive sleep apnea (OSA) remains controversial. Therefore, our research used a bidirectional Mendelian randomization (MR) method in an attempt to determine the causal relationship between hypothyroidism and OSA.

Methods: From the publicly accessible genome-wide association analysis (GWAS) summary database, we obtained single nucleotide polymorphism (SNPs) data pertaining to hypothyroidism and OSA. Inverse variance weighting (IVW) was the principal method of analysis utilized, with validation also conducted via weighted median, MR-Egger, simple model, and weighted model approaches. To further evaluate the robustness of the results, heterogeneity testing, pleiotropy testing, and the "leave-one-out" sensitivity analysis were performed. Differentially expressed genes (DEGs) from the OSA dataset (GSE135917) and hypothyroidism dataset (GSE176153) derived from the Gene Expression Omnibus (GEO) database were screened using the "limma" package. The "clusterProfiler" and "GO plot" packages were used for further enrichment analysis in order to validate the findings of the MR study. The Cytoscape software was utilized to build a protein–protein interaction (PPI) network of DEGs and to screen for hub genes.

Results: The MR analysis showed that genetically predicted hypothyroidism was associated with an increased risk of OSA [IVW odds ratio (OR) = 1.734; 95% confidence interval (CI) = 1.073–2.801; p = 0.025]. The trend of the outcomes of the other approaches is consistent with the trend of the IVW outcome. However, the reverse MR analysis suggested no evidence for the causal effect of OSA on hypothyroidism (IVW OR = 1.002, 95% CI: 0.996–1.009, p = 0.454). The robustness of the results was confirmed by the sensitivity analysis. Bioinformatics analysis revealed that there were DEGs that hypothyroidism and OSA have in common.

Conclusion: Our findings suggested that hypothyroidism may increase the risk of OSA, while the effect of OSA on hypothyroidism was not found in this MR study. Thus, patients with hypothyroidism should be enhanced with screening for OSA for early diagnosis and appropriate treatment.

KEYWORDS

hypothyroidism, obstructive sleep apnea, GEO, Mendelian randomization, causality

TABLE 1 Details on GWAS datasets that were used for the Mendelian randomization analysis.

Trait	Consortium	Case/Control	Sample size	Population	Year
Hypothyroidism	MRC-IEU	22,687/440,246	462,933	European	2018
OSA	FinnGen	38,998/336,659	375,657	European	2023

GWAS, genome-wide association study; OSA, obstructive sleep apnea.

Introduction

Obstructive sleep apnea (OSA) is a widely observed disease that is distinguished by repeated, partial, or total blockage of the upper respiratory tract while sleeping. This obstruction causes intermittent decreases in blood oxygen saturation, blood oxygen partial pressure, as well as hypercapnia (1). About 1 billion individuals between aged of 30 and 69 are estimated to have obstructive sleep apnea (2). Individuals suffering OSA are more probable to experience daytime sleepiness, lethargy, poor concentration, memory loss, or headaches, all of which can negatively impact quality of life and life expectancy (3). In addition, OSA has the potential to result in complications such as stroke, type 2 diabetes mellitus, hypertension, and even nocturnal abrupt death (4–6).

It has been shown that OSA is associated with thyroid disease, especially hypothyroidism, and that patients with hypothyroidism and those with OSA often exhibit similar symptoms (7). Hypothyroidism is a systemic hypometabolic syndrome resulting from thyroid hormoneemia or thyroid hormone resistance due to autoimmunity, iodine metabolism disorders, thyroid surgery, etc. (8). Clinical hypothyroidism is a prevalent condition, with prevalence rates ranging from 0.3 to 3.7% in the overall population of United States and from 0.2 to 5.3% in the Europe (9). Hypothyroidism can result in a higher risk to hyperlipidemia, cardiovascular illness, reproductive abnormalities, somatic and neuromuscular symptoms and other unfavorable consequences (10).

Although the association between hypothyroidism and OSA has been studied, it remains unclear, and a recent meta-analysis also suggests that the relationship between OSA and thyroid dysfunction remains controversial (11). Some observational studies have demonstrated a greater occurrence of hypothyroidism in individuals with OSA, while hypothyroidism can also increase the risk to have OSA (12–14). A multivariate logistic regression analysis by Thavaraputta et al. (2019) demonstrated a strong correlation between OSA and hypothyroidism after adjusting for potential confounding variables (15). However, a study evaluating 271 patients with OSA by Bahammam et al. revealed that the incidence of clinical hypothyroidism newly diagnosed in patients with OSA was comparatively low (16). Besides, the present studies are predominantly grounded in observational epidemiology methodologies. Limitations of traditional observational research methods include susceptibility to reverse causality and unmeasured confounders. Because of the potential bias of confounders, the correlation inference of these previous observational studies may be limited, and the conclusions may even be considered controversial (17). Thus, further research is still needed to determine the causal relationship between hypothyroidism and OSA.

Mendelian randomization is an effective analytical method that utilizes genetic variations as instrumental variables (IVs) (18). Because genetic mutations are innate and independent of environmental factors, MR research approach could effectively manage confounding factor interference, similarly to randomized trials. Moreover, since genetic mutations can influence outcomes, but outcomes are unable to influence genes, no inference about reverse causality could be derived. In order to ensure the validity of the causal relationships obtained from MR studies, the instrumental variables (IVs) must meet three fundamental assumptions: (1) The relevance assumption states that IVs should be strongly correlated with the exposure traits; (2) The independence assumption states that IVs should not be correlated with confounding variables.; and (3) The exclusivity assumption states that IVs should only affect outcomes via exposure variables and not via other pathways (19). The identification of thousands of genetic variations associated with a variety of complicated diseases through genome-wide association studies (GWASs) has boosted the use of MR (20). In this study, we investigated the causal relationship between hypothyroidism and OSA by employing a bidirectional MR analysis with large-scale GWAS data and verifying the results of the MR analysis with bioinformatics analysis.

Materials and methods

GWAS data acquisition

The hypothyroidism GWAS data (GWAS ID: ukb-b-19732) was acquired from the IEU GWAS database.[1] There were 462,933 individuals of European descent in the hypothyroidism GWAS data, comprising 22,687 cases and 440,0.246 controls. The definition of hypothyroidism cases was established using clinical diagnosis and self-report measures. The OSA GWAS data were acquired from Round 9 of the FinnGen consortium and included 38,998 OSA patients and 336,659 controls from Europe. The complete OSA GWAS was made available to the public through the FinnGen research project.[2] The project's main objective is to identify new targets for treatment by analyzing genotype–phenotype correlations. The OSA cases was diagnosed according to International Statistical Classification of Diseases (ICD) codes (ICD-9: 3472 A, ICD-10: G47.3). More specifically, OSA cases were identified using clinical examination, subjective symptoms, and sleep registry with a respiratory event index (REI) or apnea-hypopnea index (AHI) of no less than 5 per hour. Table 1 presents the details of the two GWAS datasets. As a reanalysis of previously gathered and published data, this research did not need further ethical clearance.

Selection of instrumental variables

Rigorous SNP screening was performed for the forward analysis with hypothyroidism as the exposure. Firstly, we selected independent SNPs that showed a significant correlation with the exposure variable,

1 https://gwas.mrcieu.ac.uk/

2 https://www.finngen.fi/en

meeting the threshold of genome-wide significance [$p < 5 \times 10–8$, linkage disequilibrium (LD) r2 < 0.001 within a 10,000 kb window]. Secondly, the PhenoScanner V2 database[3] was used to identify and exclude SNPs that may be associated with confounding. Thirdly, in order to determine whether or not the retained SNPs were susceptible to weak instrument bias, the F statistic was calculated and utilized as in the prior research (21). SNPs with a F statistic below 10 were deemed to be weak instruments and were subsequently excluded from the analysis (22). Fourthly, the retained SNPs were extracted from the outcome dataset, with undetected SNPs and those directly associated with the outcome variable ($p < 5 \times 10–8$) being excluded. Fifthly, to exclude those that were incompatible or palindromic, we harmonized the SNPs. Mendelian randomization analysis was finally conducted on the SNPs that remained after the previously mentioned filtration stages. The instrument selection for reverse analysis was identical to that of the forward analysis.

MR analysis

In both forward and reverse MR analyses, the inverse variance weighted (IVW) method was employed as the principal analysis to explore the causal relationship between hypothyroidism and OSA. The IVW approach has the greatest statistical power if all assumptions are satisfied (23). To assess the robustness of the MR estimates, several of other well-established MR approaches, include MR-Egger, weighted median, simple model, and weighted model, were used in comparison with the IVW method's results. Assuming instrument strength independent of direct influence, the MR-Egger approach can consistently provide results (24). Even though 50% of IVs are invalid, the weighted median approach can still result in a consistent estimate (25). Consistency of direction and magnitude of several kinds of methods can strengthen the robustness of inference of causality.

In order to assess whether the causality obtained was biased, we further performed sensitivity analyses. The Cochran's *Q* test was employed to assess heterogeneity. When heterogeneity was identified, the random-effect IVW approach was used. The MR-Egger regression test was subsequently employed to evaluate horizontal pleiotropy. The intercept reflects pleiotropic effects across genetic variations (24). In addition, the leave-one-out analysis was conducted to find any outliers which could significantly skew the pooled IVW estimations. The "TwoSampleMR" package (version 0.5.7) in the R (version 4.3.1) were used for all MR analyses (26).

Bioinformatic analysis

From the Gene Expression Omnibus (GEO) database,[4] the hypothyroidism-related dataset GSE176153 and OSA-related dataset GSE135917 were extracted. The "limma" package (27) was applied to conduct differential expression analysis in order to identify Differential Expression Genes (DEGs) meeting the following criteria: *p* value <0.05 and |log2(FC)| > 0.5, and the "ggplot2" package (28) and "pheatmap" package (29) were employed to visualize the results. The results of MR analyses were verified by using a Venn diagram to determine whether common DEGs existed between hypothyroidism-DEGs and OSA-DEGs. Gene Ontology (GO) enrichment analysis was performed on the derived common DEGs through the "clusterProfiler" package (30) and "GO plot" package (31) in order to identify the principal pathways and functions implicated in the common DEGs. All of the packages used above are part of the R software statistical environment. The STRING database,[5] a free online tool for identifying and predicting protein interactions, was used to build the PPI network of the shared DEGs. Cytoscape software (version 3.9.0) was employed to display the network, and the hub genes were identified using the Cytohubba plugin in Cytoscape.

Results

Selection of genetic instrument

According to the predetermined criteria, forward MR analysis was performed on 110 SNPs linked to hypothyroidism, while reverse MR analysis was performed on 18 SNPs linked to OSA. All of the F statistics were more than 10, indicating that our research did not include any weak instruments. Supplementary Tables S1, S2 provide details on the included instrumentation variations on hypothyroidism and OSA.

Casual effect of hypothyroidism on OSA

The MR results of hypothyroidism on OSA are listed in Figure 1A. The included IVs showed no indication of horizontal pleiotropy, according to MR-Egger regression analysis (intercept = 6.123e-05, $p = 0.980$; Table 2). The heterogeneity of the results was assessed using the IVW (Cochran's $Q = 174.344$; $p < 0.05$) and MR-Egger (Cochran's $Q = 174.343$; $p < 0.05$) approaches, which indicated that there was heterogeneity in the included IVs (Table 2). Therefore, the inverse variance weighted method under random effect was used to evaluate the causal associations of hypothyroidism on OSA. Genetically predicted hypothyroidism was associated with an increased risk of OSA, according to the IVW method [odds ratio (OR) = 1.734; 95% confidence interval (CI) = 1.073–2.801; $p = 0.025$]. All five approaches exhibit positive ORs and similarly directional correlations were detected using the other approaches (weighted mode, OR = 2.740, 95% CI = 1.233–6.084, $p = 0.015$; weighted median, OR = 2.226, 95% CI = 1.176–4.213, $p = 0.014$), despite the fact that the results of the simple mode and MR Egger methods were not statistically significant (MR Egger, OR = 1.713, 95% CI = 0.578–5.070, $p = 0.333$; Simple mode, OR = 1.695, 95% CI = 0.353–8.135, $p = 0.511$).

A leave-one-out sensitivity analysis was carried out for each SNP on the causal effect of hypothyroidism on OSA. Regardless of whether any SNP was eliminated, we observed that the outcome

3 http://www.phenoscanner.medschl.cam.ac.uk/

4 http://ncbi.nlm.nih.gov/geo

5 http://www.string-db.org/

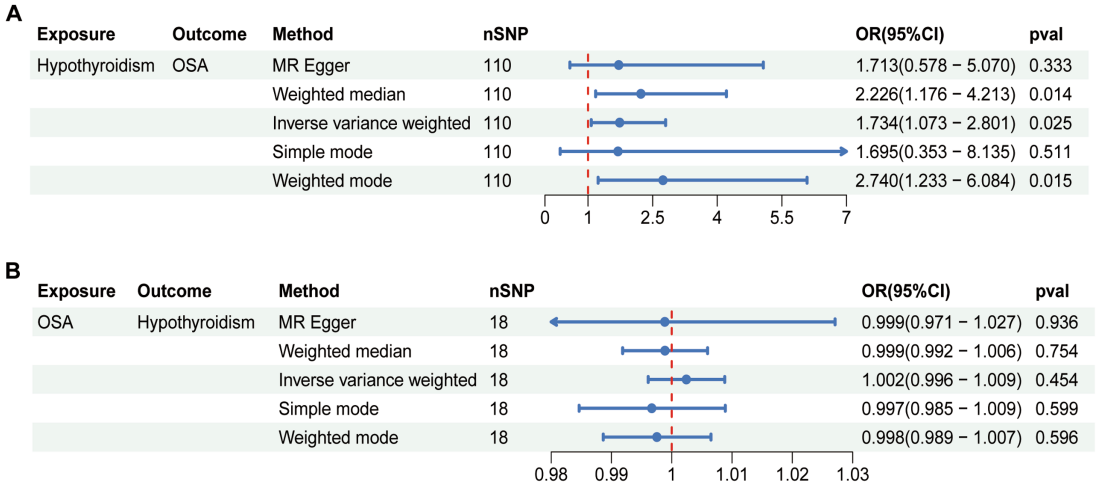

FIGURE 1
Bidirectional causal relationship between hypothyroidism and OSA. **(A)** The causal effect of hypothyroidism on OSA. **(B)** The causal effect of OSA on hypothyroidism. OSA, obstructive sleep apnea; nSNP, number of SNPs employed in this study; OR, odds ratio; CI, confidence interval.

TABLE 2 Sensitivity analysis of the associations between hypothyroidism and OSA.

Exposure	Outcome	Heterogeneity test				Pleiotropy test	
		IVW		MR-Egger		MR-Egger intercept	
		Q	*p*-value	*Q*	*p*-value	Intercept	*p*-value
Hypothyroidism	OSA	174.344	7.099E-05	174.343	5.502E-05	6.123E-05	0.980
OSA	Hypothyroidism	33.384	0.010	33.246	0.007	2.113E-04	0.800

OSA, obstructive sleep apnea; IVW, inverse variance weighted.

was always on one side of the zero line (Figure 2A). Also, by visualizing the effect size of IVW and MR-Egger using 110 SNPs, we found that the two outcomes of roughly the same (Figure 2B). In addition, the tendencies of various MR methods were comparatively consistent (Figure 2C). Finally, funnel plot demonstrated that, in both IVW and MR-Egger analysis, the distribution of each SNPs is uniformly distributed on both sides of the vertical line (Figure 2D).

Casual effect of OSA on hypothyroidism

Reverse analysis was performed to further assess the causal relationship between OSA and hypothyroidism. The random effect IVW methods suggested no evidence for the causal effect of OSA on hypothyroidism (OR = 1.002, 95% CI = 0.996–1.009, $p = 0.454$; Figure 1B). Meanwhile, no statistical significance was observed in the results from other MR approaches (Figure 1B). According to the results of Cochran's Q test, heterogeneity was found in sensitivity analysis (MR Egger, Q = 33.246, $p = 0.007$; IVW, Q = 33.384, $p = 0.010$; Table 2). There was no indication of horizontal pleiotropy according to the MR-Egger regression (intercept = 2.113e-04, $p = 0.800$; Table 2). The leave-one-out analysis indicated that the total effect of OSA on hypothyroidism was not altered by any one SNP. Supplementary Figure S1 displayed the leave-one-out analysis, forest, scatter, and funnel plots of the sensitivity analysis of casual effect of OSA on hypothyroidism.

Bioinformatic analysis

Analysis of the hypothyroidism-related dataset GSE176153 resulted in a total of 979 DEGs, 557 of which were downregulated and 422 of which were upregulated (Figures 3A,B). Analysis of the OSA-related dataset GSE135917 resulted in a grand total of 1,469 DEGs, 587 of which were downregulated and 882 of which were elevated (Figures 3C,D). The Venn graphic shows the DEGs common to hypothyroidism and OSA (Figure 3E), including AGT, RANBP3L, ACTA2, TCEANC2, FGR, RAMP3, IMPA2, RGS4, PLK3, UCN3, PFKFB3, MARCO, CXCL2, NLRP3, TREM2, TMSB15B, SKA3, OR51E1, ZNF252P, MSTO1, IL1RL1, FAIM, RAB20, EPPIN, CAPNS1, PIGF, CD300LB, NR4A1, NRIP1, PCDHB10, ATF3, NUDT7, MOGS, ZFP36L1, PSMD14, ERRFI1, ENC1, SLC5A3, SLC35G1, HIGD1A, TM4SF18, PTGES3, OR56A4, KIF5C, MMRN1, PLBD2, MCL1, and RPL29. These findings genetically support the close association between hypothyroidism and OSA and that hypothyroidism may cause OSA. The GO enrichment analysis showed the DEGs shared between hypothyroidism and OSA primarily play roles in functions including ERK1 and ERK2 cascade, cellular response to decreased oxygen levels, cellular response to hypoxia, inositol metabolic process, negative regulation of interleukin-1 production, neuron intrinsic apoptotic signaling pathway in response to oxidative stress, and so on (Figure 3F). We employed the STRING database for PPI network analysis of common DEGs and Cytoscape software to visualize the PPI network (Figure 3G). The hub genes might potentially serve critical physiological regulatory functions in

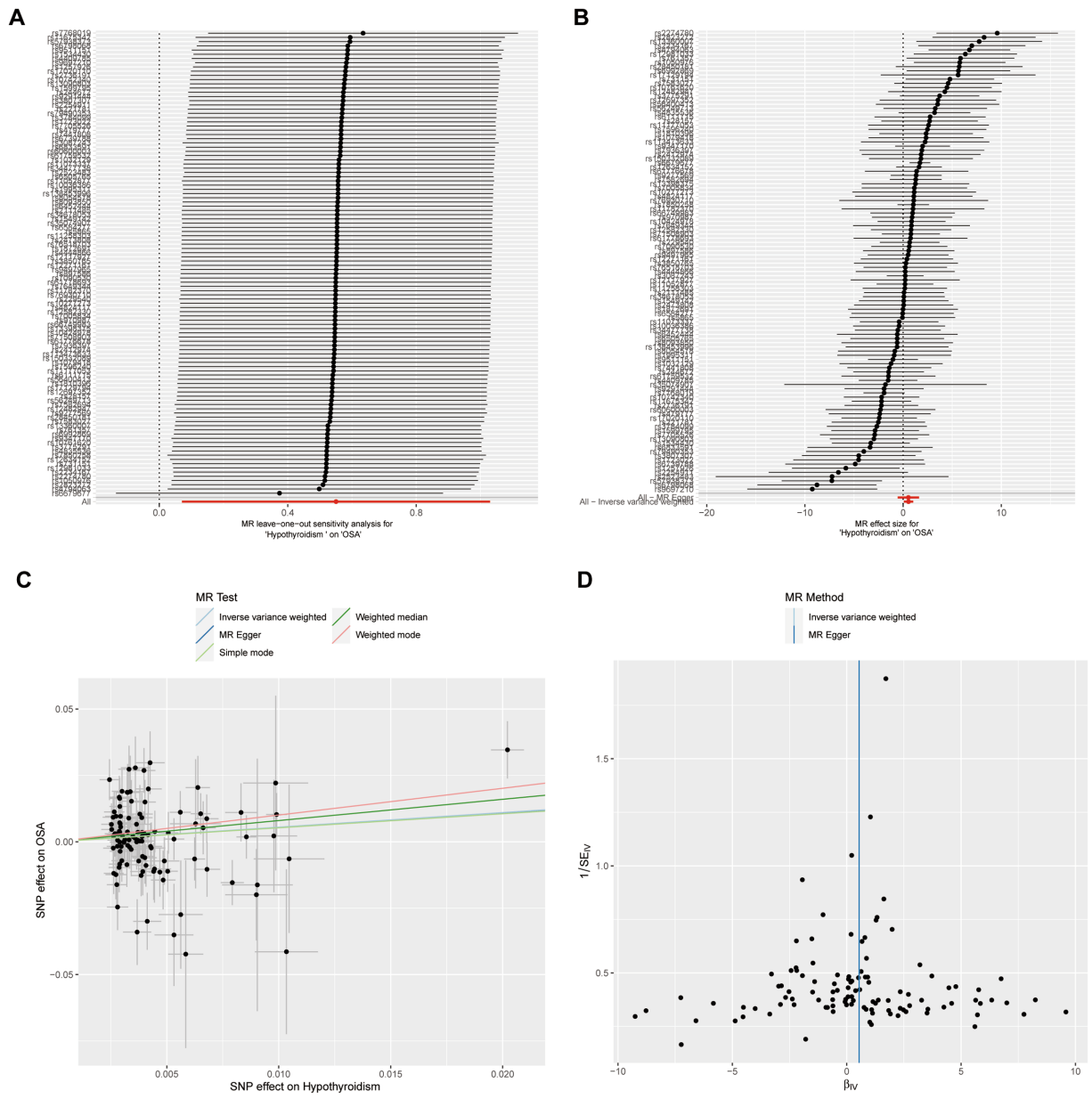

FIGURE 2
Sensitivity analysis of casual effect of hypothyroidism on OSA. **(A)** MR leave-one out analysis of hypothyroidism on OSA. **(B)** MR effect size for hypothyroidism on OSA. **(C)** MR test scatterplot of five methods. **(D)** Funnel plot of individual SNP analyses.

the PPI analysis. The hub genes were identified using Cytohubba plugin in Cytoscape, which determined the top 10 genes with the greatest number of connections (NR4A1, ATF3, NLRP3, CXCL2, TREM2, AGT, MCL1, ZFP36L1, IL1RL1, and PFKFB3).

Discussion

The causal relationship between hypothyroidism and OSA is still controversial. The present study employed MR analysis to investigate the causal relationship between hypothyroidism and OSA, and the findings of the MR analysis were subsequently validated through bioinformatics analysis. Due to the influence of ethical considerations and confounding variables, conventional observational epidemiologic approaches are unable to determine accurate causal relationships (32). Therefore, the usage of MR analysis was able to compensate for the incapacity of conventional statistical approaches to eliminate confounding variables (33), and the findings of the present study were further strengthened in terms of reliability by the bioinformatics analysis validation.

In this study, the two-sample MR analysis revealed a correlation between genetically predicted hypothyroidism and an increased risk of OSA. This aligns with the results reported in several prior research investigations (34, 35). Clinical researchers have identified a number of clinical characteristics shared by hypothyroidism and OSA, including obesity, apathy, diminished cognitive function, and excessive

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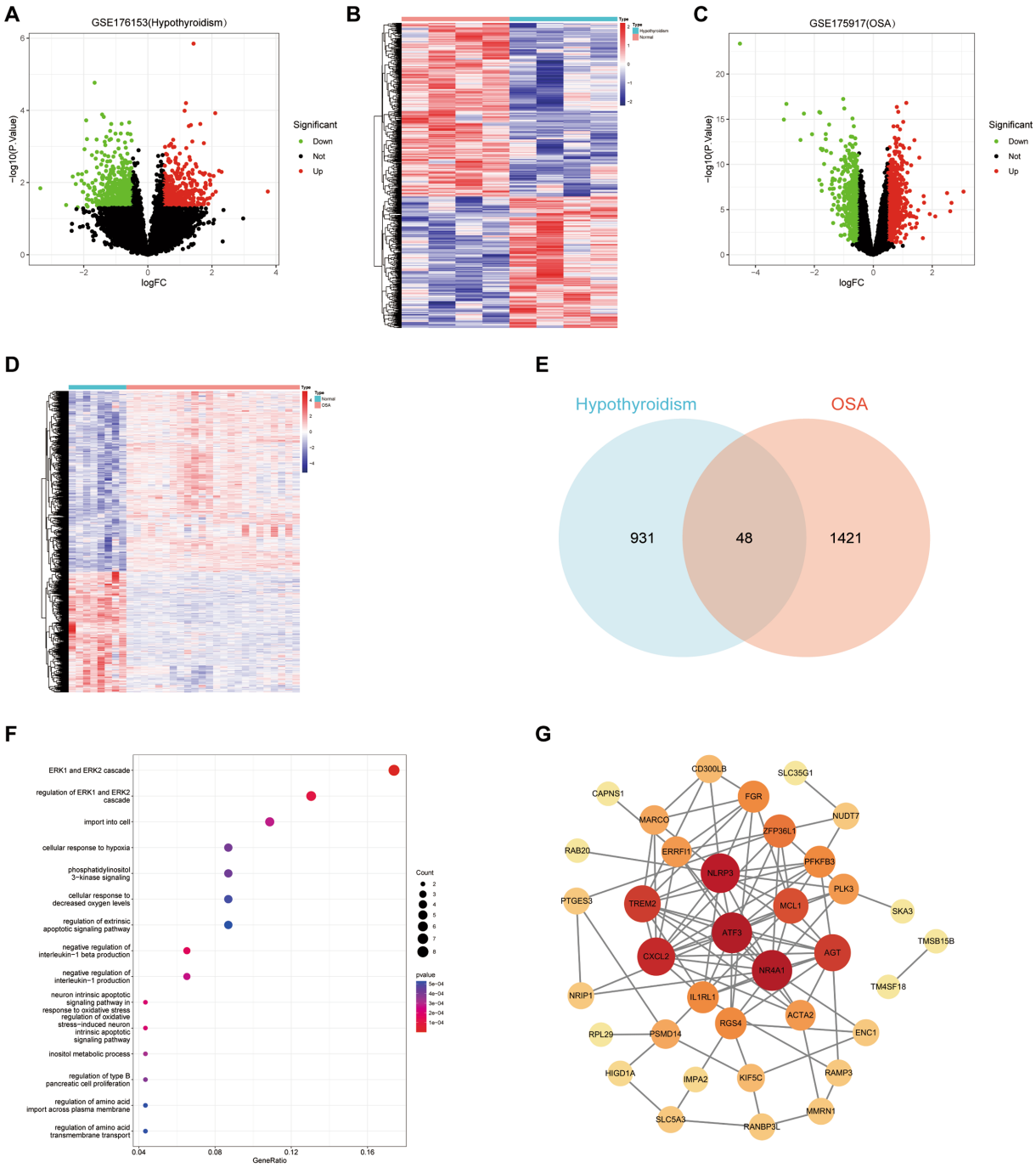

FIGURE 3
Bioinfonnatic analysis. **(A,B)** Volcano plot and heatmap of DEGs for hypothyroidism. **(C,D)** Volcano plot and heatmap of DEGs for hypothyroidism. **(E)** Venn graphic of DEGs that hypothyroidism and OSA have in common. **(F)** Gene Ontology enrichment analysis of common DEGs. **(G)** The PPI network of common DEGs. Node size increases in proportion to the number of other nodes to which it is connected.

daytime lethargy (12). These symptoms in hypothyroidism are due to a drop in basal metabolic rate and a reduction in sympathetic nervous system activity. Regarding OSA, these symptoms are the result of repetitive nocturnal episodes of cessation of breathing, which cause increased carbon dioxide levels, intermittent hypoxia, disturbances in sleep structure, and frequent awakenings (36, 37). The effect of thyroid hormones on the proper functioning of the central nervous system is very significant. Researchers have found that patients with Hashimoto's encephalopathy, which is expected to be the most serious neurological complication in autoimmune hypothyroidism, present with electroencephalography abnormalities and disturbances in the metabolic composition of the brain: a notable decrease in the Nacetylaspartate/creatine ratio in the white matter of the left parietal lobe and the posterior cingulate regions (38). This may affect proper brain bioelectrical function and sleep. In addition, several presumptions from previous studies may explain the increased risk of

OSA caused by hypothyroidism. First, hypothyroidism can cause muscle dysfunction that affects respiratory muscle strength, resulting in hypotonia of the respiratory muscles (39, 40). Second, Submucosal glycosaminoglycan deposition due to hypothyroidism leads to narrowing of the pharynx (41). Furthermore, low metabolic rate due to hypothyroidism can cause obesity, and further accumulation of fat in the abdomen and neck leads to obesity hyperventilation (42). Therefore, patients with hypothyroidism should be screened for OSA for early diagnosis.

The susceptibility to hypothyroidism was not found to be altered by genetic predisposition to OSA in our MR analysis. This result is in accordance with a number of observational studies that demonstrate that individuals with OSA had the same prevalence of hypothyroidism as the general population (43, 44). Although some observational studies have reported a comparatively significant prevalence of hypothyroidism in OSA individuals (13, 45), there are some possible explanations for this discrepancy in results. First, these observational studies may often be subject to reverse causality. In addition, this discrepancy can be attributed to unmeasured confounding factors in observational research, including gender, age, and iodine nutrition status. Further research is necessary in order to illuminate pertinent discrepancies.

Bioinformatics has been a vital tool in biomedical research in recent years, particularly in the identification of potential treatment targets and the clarification of disease mechanisms. In this study, bioinformatics methods, including Venn diagrams and GO enrichment analysis, were utilized to provide insight into the potential connection between hypothyroidism and OSA. The analysis of the Venn diagrams revealed a number of DEGs that hypothyroidism and OSA have in common. This provides genetic support for the idea that hypothyroidism and OSA are strongly correlated. PPI network analysis of common DEGs identified the top 10 hub genes. NLRP3 is an inflammasome which activity is directly correlated with apnea-hypoventilation index and hypoxemia index in patients with OSA, and the damage that OSA causes to endothelial cells, neurons, the kidney, and the lung can be made worse by the activation of NLRP3 inflammasomes (46, 47). At the same time, studies show that hypothyroidism activates the inflammasome-NLRP3 pathway and thyroid hormone deficiency increases the amount of cardiac NLRP3 protein in rats (48, 49). Both NR4A1 and TREM2 are regulated by thyroid hormones and promote papillary thyroid cancer progression (50–53). Furthermore, NR4A1 is upregulated in hypothyroid juvenile mouse liver and higher sTREM2 in cerebrospinal fluid is associated with poor self-reported sleep characteristics and sleep indicators (54, 55). ATF3 is a hypoxia-associated gene biomarker for OSA and acts as a tumor suppressor in thyroid cancer (56, 57). GO enrichment analysis of the DEGs in common between hypothyroidism and OSA revealed the involvement of ERK signaling pathway, regulation of interleukin-1, and oxidative stress process. Previous studies have shown that hypothyroidism promotes increased phosphorylation of ERK1 and ERK2 and that the ERK signaling pathway is robustly activated in OSA (58, 59). The serum levels of the proinflammatory cytokine IL-1β are significantly elevated in patients with OSA (60), and high concentrations of IL-1β inhibit thyroid cell function (61). OSA results in intermittent hypoxia during sleep due to recurrent upper airway obstruction, and the resulting oxidative stress can lead not only to complications of sleep–wake rhythms, but also systemic dysfunction (62). Hypothyroidism has been shown to be associated with oxidative stress in animals and humans, thyroid hormones can modulate antioxidant levels and tissue hypothyroidism exacerbates oxidative stress (63). Thus, we consider that hypothyroidism and OSA share a common pathogenesis that may involve ERK signaling pathway, interleukin-1, and oxidative stress process. Synthesizing these bioinformatics analyses, we consider that there are complex interactions between hypothyroidism and OSA, including multiple biological pathways and mechanisms, which provided further validation of the findings of the MR analyses in the present research.

There are advantageous and limited aspects to this research. The present study is the initial effort to synergistically integrate GWAS and GEO data, using MR analysis and bioinformatics analysis to clarify the relationship of causation between hypothyroidism and OSA. To guarantee the robustness and timeliness of the findings, we used the recent large-scale GWAS data in our study. In addition, the MR analysis of the present research underwent strict quality control based on three fundamental assumptions and sensitivity analysis. There were several limitations on this study as well. Firstly, this study primarily investigates the genetic causality between hypothyroidism and OSA, while some non-genetic factors such as environmental and lifestyle factors might also have some influence. Secondly, the ability to generalize to other ethnic groups is limited due to the fact that the present study's participants were predominantly of European descent. Furthermore, the lack of comprehensive demographic detail in the GWAS summary data prevented the conduct of in-depth subgroup analyses, including those that accounted for age and gender. As a result, subsequent research should endeavor to conduct further subgroup analyses, and where conditions permit, it could be worthwhile to conduct high-quality randomized controlled trials in an effort to derive more dependable conclusions.

Conclusion

In conclusion, we have provided evidence that genetically predicted hypothyroidism increases the risk of OSA. Therefore, patients suffering from hypothyroidism should be intensively screened for OSA for early diagnosis and appropriate treatment. However, the effect of OSA on hypothyroidism was not found in this MR study. Further research is needed regarding the exact mechanism that contribute to the relationship of causation between hypothyroidism and OSA.

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

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin

in accordance with the national legislation and the institutional requirements.

Author contributions

MZ: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. XH: Data curation, Validation, Visualization, Writing – review & editing. HZ: Data curation, Validation, Writing – review & editing. YC: Writing – review & editing. WH: Data curation, Methodology, Writing – review & editing. YW: Funding acquisition, Supervision, Writing – review & editing. RC: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by Health Research Program of Anhu (AHWJ2023BAa20131), Research Fund of Anhui Institute of translational medicine (2022zhyx-C86) and 2022 Disciplinary Construction Project in School of Dentistry, Anhui Medical University (2022xkfyhz01).

Acknowledgments

The authors thank all investigators for sharing these data.

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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1420391/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 03 March 2025
DOI 10.3389/fmed.2025.1369393

OPEN ACCESS

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RECEIVED 12 January 2024
ACCEPTED 17 February 2025
PUBLISHED 03 March 2025

CITATION
Zhou P, Li H, Li H, Chen Y and Lv Y (2025) A possible important regulatory role of estrogen in obstructive sleep apnea hypoventilation syndrome.
Front. Med. 12:1369393.
doi: 10.3389/fmed.2025.1369393

A possible important regulatory role of estrogen in obstructive sleep apnea hypoventilation syndrome

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Obstructive sleep apnea-hypoventilation syndrome (OSAHS) is a prevalent clinical sleep breathing disorder that affects both pediatric and adult populations. If left untreated, OSAHS can induce or aggravate systemic dysfunction across multiple organ systems, with a particularly pronounced impact on cardiovascular health, thereby posing a substantial threat to overall human well-being. Notably, there exists a significant sex disparity in the prevalence and severity of OSAHS, with a higher incidence and greater severity observed in males. However, this disparity tends to diminish post-menopause. Research indicates that sex differences in OSAHS are associated with gonadal function, wherein estrogen exerts a protective effect by modulating pharyngeal muscle tone and mitigating oxidative stress. This regulatory role of estrogen partially reduces the incidence of OSAHS and attenuates its pathological impact. Conversely, OSAHS may adversely affect gonadal function, resulting in decreased estrogen levels, which can exacerbate the condition. This review examines the beneficial role of estrogen in the progression of OSAHS and explores the potential impact of OSAHS on estrogen levels.

KEYWORDS

sleep apnea, obstructive, CIH, estrogen, ERα, HIF-1α

1 Introduction

OSAHS is primarily characterized by the recurrent partial or complete obstruction of the upper airway during sleep, leading to chronic intermittent hypoxemia and associated pathophysiological consequences, including disrupted sleep architecture, prolonged sympathetic activation, and carbon dioxide retention (1). Epidemiological data suggest that the prevalence of OSAHS is on the rise annually, with an estimated 425 million adults aged 30 to 69 years affected by moderate to severe forms of the condition worldwide (2). Furthermore, the prevalence is notably higher in males compared to premenopausal females, with a male-to-female ratio of approximately 2:1 (3, 4). In females, the incidence of OSAHS increases with age, particularly following menopause (3, 5, 6), exhibiting minimal differences when compared to males (1, 7). For instance, the HypnoLaus cohort study conducted by Heinzer et al. (8) (n = 2,121) revealed a significantly greater prevalence of OSAHS in males compared to premenopausal females (83.8% vs. 35.1%). However, this prevalence gap was considerably reduced when comparing males to postmenopausal females (83.8% vs. 71.6%). Additionally, the prevalence of OSAHS was markedly higher in postmenopausal females not undergoing hormone replacement therapy than in both premenopausal females and postmenopausal females receiving hormone replacement therapy, particularly when controlling for

confounding variables such as body mass index (BMI) and neck circumference (5, 6). Alarmingly, over 90% of perimenopausal and postmenopausal females with OSAHS remain undiagnosed (8). In comparison to premenopausal females, postmenopausal females with OSAHS exhibit more severe symptoms and elevated apnea-hypopnea index (AHI) levels (9, 10), with serum estradiol (E2) levels demonstrating a significant negative correlation with both AHI and arousal index (11).

Research has indicated that hormone replacement therapy is associated with a decreased prevalence of sleep apnea in postmenopausal women, even after controlling for confounding variables such as age, body mass index (BMI), and neck circumference (12). Notably, estrogen, which is crucial for the physiological response and adaptation to hypoxic conditions (13), significantly influences the gender-specific effects of obstructive sleep apnea-hypopnea syndrome (OSAHS) on cardiovascular outcomes. It has been shown to lower the incidence of cardiovascular diseases associated with OSAHS, as well as related morbidity and mortality (4, 14), and to mitigate the risk of depression (8, 11). Estrogen's protective role in OSAHS operates through various mechanisms, and a comprehensive investigation of these mechanisms could provide a theoretical foundation for identifying new therapeutic targets for OSAHS. Such insights could enhance clinicians' understanding of sleep-related disorders and their complications in postmenopausal women, thereby reducing the likelihood of missed diagnoses and delays in clinical intervention.

In addition, a chronic systemic inflammatory response in OSAHS adversely affects multiple organs throughout the body. Despite the protective effect of estrogen on OSAHS, it also suffers from the pathologic damage of OSAHS (Figure 1). Significantly, sleep deprivation disrupts the circadian rhythm of estrogen secretion and causes a variety of endocrine disorders, leading to a decline in estrogen levels (15). In theory, this would further exacerbate the condition of OSAHS. As there are few studies on this, we discuss the adverse effects of estrogen in terms of the common pathomechanisms of OSAHS, aiming to provide ideas for future research.

2 Important protective role of estrogen in OSAHS

The most biologically active form of estrogen is estradiol (E2), whose genomic effects are facilitated by two receptor subtypes, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), both of which are classified as nuclear receptors. The distribution and expression levels of ERα and ERβ differ across various tissues, which underlies the diverse biological effects of estrogen (16). It has been established that E2 exerts its protective effects on OSAHS primarily through ERα and Erβ (Figure 2).

2.1 Airway protection

Sex hormones play a protective role in maintaining the patency of the upper airway in premenopausal females. The condition of the upper airway is influenced by the interplay between the positive intraluminal pressure that keeps the airway open and the opposing surface tension that tends to close it (17). Research indicates that upper airway collapsibility may be more pronounced in males than females, as evidenced by measurements of critical closure pressure, defined as the pressure at which airflow ceases due to airway collapse (18). The pharyngeal muscle, a key skeletal muscle responsible for dilating the upper airway, significantly impacts airway patency through its functional status. This muscle is particularly important in the pathogenesis of OSAHS, especially regarding its pathomorphological characteristics (19). The genioglossus muscle is crucial for maintaining an open airway to facilitate adequate respiration among the pharyngeal muscles (17, 20). Furthermore,

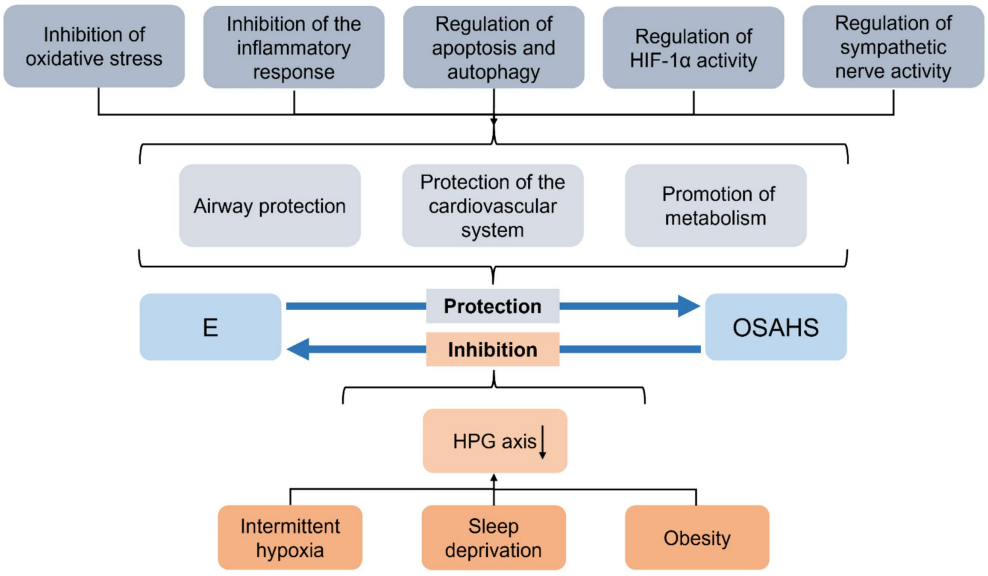

FIGURE 1
Summary of the interaction between OSAHS and estrogen. E, estrogen; OSAHS, obstructive sleep apnea-hypopnea syndrome; HPG, hypothalamic–pituitary-gonadal.

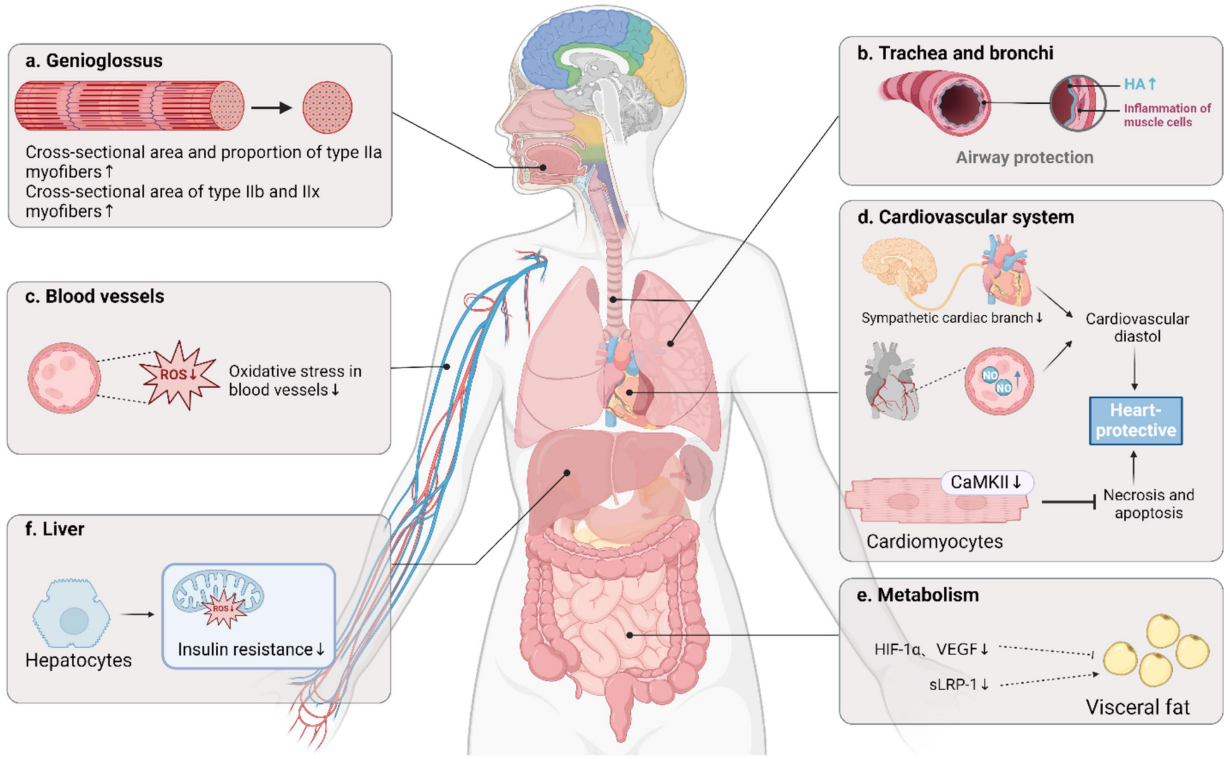

FIGURE 2
Important protective role of estrogen in OSAHS. OSAHS: Obstructive sleep apnea-hypopnea syndrome; HA, hyaluronic acid; ROS, reactive oxygen species; CaMKII, calcium/calmodulin-dependent protein kinase II; HIF-1α, hypoxia-inducible factor-1α; VEGF, vascular endothelial growth factor; sLRP-1, soluble low-density lipoprotein receptor-related protein-1. Created in BioRender.

exposure to chronic intermittent hypoxia (CIH) enhances the body's ventilatory response to hypoxia, leading to prolonged respiratory motor output, whether sublingual or diaphragmatic. This prolonged output can increase the susceptibility of skeletal muscles to fatigue and atrophy, ultimately impairing muscle function and potentially exacerbating sleep apnea (21).

The functional characteristics of mammalian skeletal muscle are influenced by the various types of muscle fibers present, with the rate of force production, fatigue resistance, and energy metabolism being contingent upon the composition of these fibers, which include both slow and fast types (21, 22). Slow muscle fibers, classified as type I, and fast muscle fibers, categorized as type II (encompassing types IIa, IIb, and IIx), exhibit distinct physiological properties. In healthy individuals, approximately 90% of the pharyngeal muscles consist of fatigue-resistant fibers (types I and IIa), while only 10% comprise fatigue-sensitive fibers (type IIb). The predominance of fatigue-resistant fibers in human pharyngeal muscle can be attributed to the high mitochondrial content of type I fibers, which utilize fatty acids oxidatively to generate acetyl-coenzyme A, and the enhanced oxidative capacity of type IIa fibers (23). Conversely, individuals with OSAHS demonstrate a reduced ratio of type I to type IIb fibers, alongside an increased proportion of type IIa fibers (23). Notably, the ratio of type I fibers is positively correlated with the lowest oxygen saturation levels (24), contributing to pharyngeal muscle fatigue and an increased vulnerability to pharyngeal collapse during sleep (21, 23, 25). Research indicates that CIH leads to a diminished contractile function of the genioglossus muscle, a condition that is further aggravated by menopause in human females (26) or ovariectomy (OVX) in rats (27, 28). Estrogen has been shown to enhance myoelectric activity and tonic muscle tone in the genioglossus (26–28), counteracting the reduction in cross-sectional area and proportion of type IIa fibers associated with estrogen deficiency and hypoxia, while also increasing the cross-sectional area of type IIb and IIx fibers (27). These findings suggest that estrogen plays a significant role in the positive regulation of genioglossus muscle function.

ERα is extensively present in mouse skeletal muscle, and it is posited that estrogen may enhance muscle endurance by modulating muscle fiber composition via the ERα signaling pathway (24). Research conducted by Cabelka et al. (29) demonstrated that mice with a skeletal muscle-specific knockout of ERα exhibited increased susceptibility to fatigue compared to control mice, and they showed impaired recovery of strength, indicating the critical role of ERα in mitigating skeletal muscle fatigue and facilitating recovery. Additionally, a significant concentration of ERα is found in the genioglossus muscle, where E2 influences its contractility primarily through the ERα pathway, while also promoting the expression of ERα mRNA and protein, with no observed effect on ERβ (30). Chen et al. (24) reported a reduction in the expression levels of ERα and type I muscle fibers in the palatopharyngeal tissues of patients with OSAHS, revealing a significant positive correlation between the two. Most studies indicate that OSAHS is linked to an increase in type II muscle fibers and a decrease in type I fibers. As the severity of OSAHS progresses, there is a gradual decline in the proportion of type I fibers, accompanied by a corresponding increase in type II fibers (21).

However, Chen et al. (24) specifically noted an increase in type IIx muscle fibers in the palatopharyngeal tissues of OSAHS patients, rather than an increase in type II fibers. Furthermore, animal studies have shown that ERα expression and a decrease in type I muscle fibers were observed in the sternohyoid muscle of OVX rats, with no significant alterations in type IIb muscle fiber expression (24). The underlying changes in muscle fiber types associated with OSAHS remain unclear and may be influenced by various factors, including age, sex, and the specific biopsy site. The direct contribution of these fiber type changes to OSAHS is still uncertain. Current evidence suggests a beneficial effect of estrogen on skeletal muscle contractility; however, further research is warranted to confirm this effect and to investigate the mechanisms through which estrogen interacts with different receptors.

A recent investigation revealed diminished plasma concentrations of hyaluronic acid (HA) and markedly elevated levels of hyaluronidases (HYAL) in individuals diagnosed with OSAHS (31). HA, a glycosaminoglycan, serves as a crucial component of the extracellular matrix within tracheal and bronchial mucosa and endothelial cells (32, 33). High-molecular weight HA (HMW-HA) functions as a vital anti-inflammatory and antioxidant agent, whereas low molecular weight HA is associated with promoting inflammatory processes (34). The metabolism of HA is primarily facilitated by HYAL, particularly HYAL1 and HYAL2, which are present in various tissues, including the lungs. This metabolic process generates low molecular weight fragments that can exacerbate inflammatory responses, thereby intensifying inflammatory damage (35). Alterations in HA synthesis and metabolism have been identified in airway diseases characterized by chronic inflammation and oxidative stress, such as bronchial asthma and chronic obstructive pulmonary disease (COPD). These alterations increase lung inflammation and remodeling, reducing lung compliance and airway obstruction (33, 35, 36). Klagas et al. (33) reported that HA levels were significantly lower in primary human airway smooth muscle cells derived from patients with asthma and COPD. This reduction was correlated with a notable decrease in HA synthase-1 and -2 expression, alongside a significant increase in HYAL1, indicating a suppression of HA synthesis and an enhancement of its catabolism. Furthermore, Klagas et al. observed a decline in CD44 receptor expression, which hindered the clearance of HA degradation products, thereby perpetuating inflammation (33). Meszaros et al. (31) found a significant negative correlation between plasma levels of HMW-HA and the apnea-hypopnea index (AHI) in patients with OSAHS, while HYAL-1 exhibited a significant positive correlation with both AHI and the oxygen desaturation index (ODI). This suggests that chronic hypoxia is linked to elevated plasma concentrations of HYAL-1 and accelerated degradation of HMW-HA (31). Additionally, one study indicated that estrogen treatment resulted in increased skin HA levels in mice, an effect that could be inhibited by estrogen receptor antagonists, implying that estrogen elevates HA levels through the activation of its specific receptors (37). However, more studies need to address this topic, necessitating further investigation into the alterations in lung HA levels among OSAHS patients. It is also imperative to consider the effects of sleep deprivation and to evaluate changes in these indices following treatments such as continuous positive airway pressure (CPAP) and estrogen therapy. Such research will enhance our understanding of HA's role in airway inflammation in OSAHS and provide additional evidence regarding the airway protective effects of estrogen.

2.2 Promotion of metabolism

In postmenopausal women and the OVX rat model, a reduction in estrogen levels has been linked to the onset of central obesity, dyslipidemia, insulin resistance, and an elevated risk of developing non-alcoholic fatty liver disease, type 2 diabetes, and cardiovascular disease (10, 38, 39). Following the decline in ovarian estrogen production in postmenopausal women, estrone becomes the predominant form of estrogen, primarily synthesized through the peripheral aromatization of androstenedione in muscle and adipose tissues. This process often increases body mass and visceral fat accumulation during the postmenopausal phase (40–42). A metabolic syndrome characterized by visceral obesity is associated with the onset and progression of OSAHS (1, 8). Research indicates that CIH further contributes to an increase in body mass (43) and a reduction in rectal temperature (44) in OVX rats, implying that OSAHS may exacerbate the hypo-metabolic condition induced by decreased estrogen levels.

The regulation of metabolism by estrogen is predominantly mediated through ERα. Administration of E2 has been shown to enhance mitochondrial function in the liver while simultaneously decreasing the production of reactive oxygen species (ROS) and mitigating insulin resistance in rat models (45). Furthermore, E2 treatment reduces the expression of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor in the periaortic and intra-abdominal adipose tissue of OVX rats. This reduction contributes to decreased visceral fat accumulation and improved insulin sensitivity, as evidenced by restored blood glucose and serum leptin levels, thereby providing a comprehensive improvement in metabolic syndrome (39). Additionally, multiple studies have substantiated the beneficial effects of E2 on metabolic and visceral obesity and its protective role in OSAHS (43, 44). However, Boukari et al. (46) conducted a study involving OVX rats exposed to CIH and treated with selective ERα receptor agonists, which revealed no significant alterations in body mass. This lack of change may be attributed to the brief duration of hypoxic exposure.

Recent research has indicated that soluble low-density lipoprotein receptor-related protein-1 (sLRP-1) levels are significantly diminished in patients diagnosed with OSAHS. This reduction has been correlated with severe nocturnal hypoxia and disrupted lipid metabolism *in vivo* (47). sLRP-1 plays a crucial role in anti-inflammatory and metabolic processes within the body, and its low concentrations are linked to metabolic irregularities associated with OSAHS, implying its function as a protective protein. It has been suggested that OSAHS may elevate LRP1 expression through the action of HIF-1α, which could result in the accumulation of low-density lipoprotein cholesterol esters in cardiomyocytes (48) and vascular smooth muscle cells (49). It is plausible that other inhibitory mechanisms may counteract this stimulatory effect, leading to the observed decline in sLRP-1 concentrations in OSAHS. The inhibitory influence of estrogen on HIF-1α is discussed further, and we postulate that estrogen may suppress sLRP1 expression. This hypothesis was substantiated by an animal study involving tilapia, which demonstrated a significant reduction in LRP1 levels following treatment with a high dose (50 mg/kg) of E2 accompanied by hepatic lipid accumulation (50). The conclusion must be considered with caution due to species differences, which suggests that we need to pay attention to the dual effects of estrogen on OSAHS metabolism. The mechanism of interaction

between estrogen and adipose function and metabolic disorders needs to be clarified by further studies.

Conversely, postmenopausal women who received estrogen therapy exhibited greater physical activity and engaged in higher levels of moderate to vigorous exercise compared to their untreated counterparts (51). This indicates that estrogen is crucial in modulating physical activity levels following menopause. In a study conducted by Cabelka et al. (29), OVX rats were administered estrogen, progesterone, and a combination of both hormone treatments, with subsequent comparisons regarding changes in activity levels before and after treatment. The findings revealed that the activity levels of rats receiving estrogen and the combined hormone treatment were significantly elevated compared to the control group, with the increase particularly pronounced in the latter. These results suggest that estrogen is the primary ovarian hormone influencing physical activity, while progesterone may enhance the effects of estrogen. Estrogen can potentially elevate metabolism to a certain degree by influencing physical activity levels.

2.3 Protection of the cardiovascular system

OSAHS has been associated with numerous adverse effects on the cardiovascular system, potentially inducing or exacerbating pre-existing conditions (1). This phenomenon is particularly pronounced in postmenopausal women, who demonstrate an elevated risk for hypertension, arrhythmias, and heart failure (52, 53).

Research conducted by Lan et al. (14) indicates that the surgical removal of ovaries in rats leads to hypoxia-induced oxidative stress and damage to the vascular endothelium. This damage is characterized by disorganization, hypertrophy, and proliferation of vascular smooth muscle cells, as well as the destruction of endothelial cells and thickening of the middle layer of the endothelium, all of which contribute to an increased risk of atherosclerosis. Estrogen has been shown to mitigate vascular oxidative stress in OVX rats subjected to intermittent hypoxia (3). Furthermore, treatment with E2 may offer protective benefits against vascular complications in female patients with OSAHS (46). Additionally, ERαis highly expressed in the carotid body and central structures that regulate sympathetic nerve activity and vascular function (54). E2 has been found to decrease cardiac output, heart rate, and arterial pressure during CIH exposure by activating ERα, which in turn inhibits the activation of the cardiac branch of the sympathetic nervous system and enhances nitric oxide-mediated vasodilatory responses (3).

Heart failure represents a significant comorbidity associated with OSAHS. Research indicates that female patients with OSAHS exhibit a higher propensity for developing heart failure with preserved ejection fraction compared to those with heart failure characterized by reduced ejection fraction (53, 55). Furthermore, echocardiographic parameters have been found to correlate significantly with the severity of OSAHS. Notably, diastolic left ventricular filling is more frequently compromised in female patients than in their male counterparts, with this impairment showing a significant correlation to minimum oxygen saturation levels and the duration of oxygen saturation below 90%. Additionally, ventricular diastolic sarcoplasmic reticulum calcium leakage has been closely linked to ventricular systolic dysfunction and arrhythmias. Lebek et al. (56) reported an increase in calcium/calmodulin-dependent protein kinase II (CaMKII)-induced sarcoplasmic reticulum calcium leakage among patients with OSAHS, a phenomenon potentially associated with elevated production of ROS resulting from the condition. E2 has been shown to confer cardioprotective effects by mitigating oxidative stress, reducing ROS production, inhibiting CaMKII expression, and decreasing cardiomyocyte necrosis and apoptosis (57). Consequently, diminished levels of estrogen render postmenopausal female patients with OSAHS more vulnerable to severe cardiovascular complications, while E2 appears to alleviate the cardiovascular damage associated with OSAHS.

3 Important protective mechanisms of estrogen in OSAHS

The presence of considerable oxidative stress, inflammatory responses, and sympathetic activation in OSAHS has the potential to harm various tissues and organs within the body. Estrogen may play a protective role by mitigating these pathological response mechanisms (Figure 3).

3.1 Inhibition of oxidative stress

An imbalance between pro-oxidants and antioxidants can result in tissue and organ damage, known as "oxidative stress." This imbalance may arise from excessive production of ROS or deficiencies in the antioxidant defence mechanisms (14). The primary sources of ROS include mitochondria, NADPH oxidase, and xanthine oxidase (58, 59). In patients with OSAHS, recurrent nocturnal hypoxemia leads to significant ROS production and diminished antioxidant capacity within the organism. The accumulation of excessive ROS can induce cellular damage (60–62), impairing tissues and organs' normal functioning.

E2, recognized as the most biologically active form of estrogen, has been shown to exhibit antioxidant properties. It promotes the synthesis of antioxidant enzymes by binding to specific receptors that enhance the expression of nuclear genes related to antioxidant enzymes within mitochondria, thereby reducing intracellular levels of ROS (44, 59, 63). A substantial body of research indicates that CIH exposure induces oxidative stress across various tissues, including lung tissue, the cerebral cortex, the brainstem, adrenal glands, vascular endothelium, and other organs in OVX rats. Furthermore, E2 supplementation has been found to mitigate the elevated oxidative stress levels induced by CIH significantly and to enhance the activity of antioxidant enzymes, such as zinc/manganese superoxide dismutase and glutathione peroxidase, which protect against oxidative stress-related damage (14, 44, 64, 65). In a study conducted by Ribon-Demars et al. (61), E2 treatment was observed to increase the activity of antioxidant enzymes in the tissues of OVX rats while concurrently exacerbating oxidative stress levels. This observation suggests that E2 may stimulate mitochondrial ROS production, potentially influenced by the concentration of supplemental estrogen or the distribution of receptors; however, the overall effect on oxidative stress appears to be inhibitory. Irwin et al. (64) further clarified that only ERβ, and not ERα, affected the expression of genes encoded by mitochondrial DNA in brain tissue, with ERα activation serving as the primary mechanism for initiating the scavenging of lipid peroxides in brain mitochondria. Consequently, there are notable differences in the distribution and

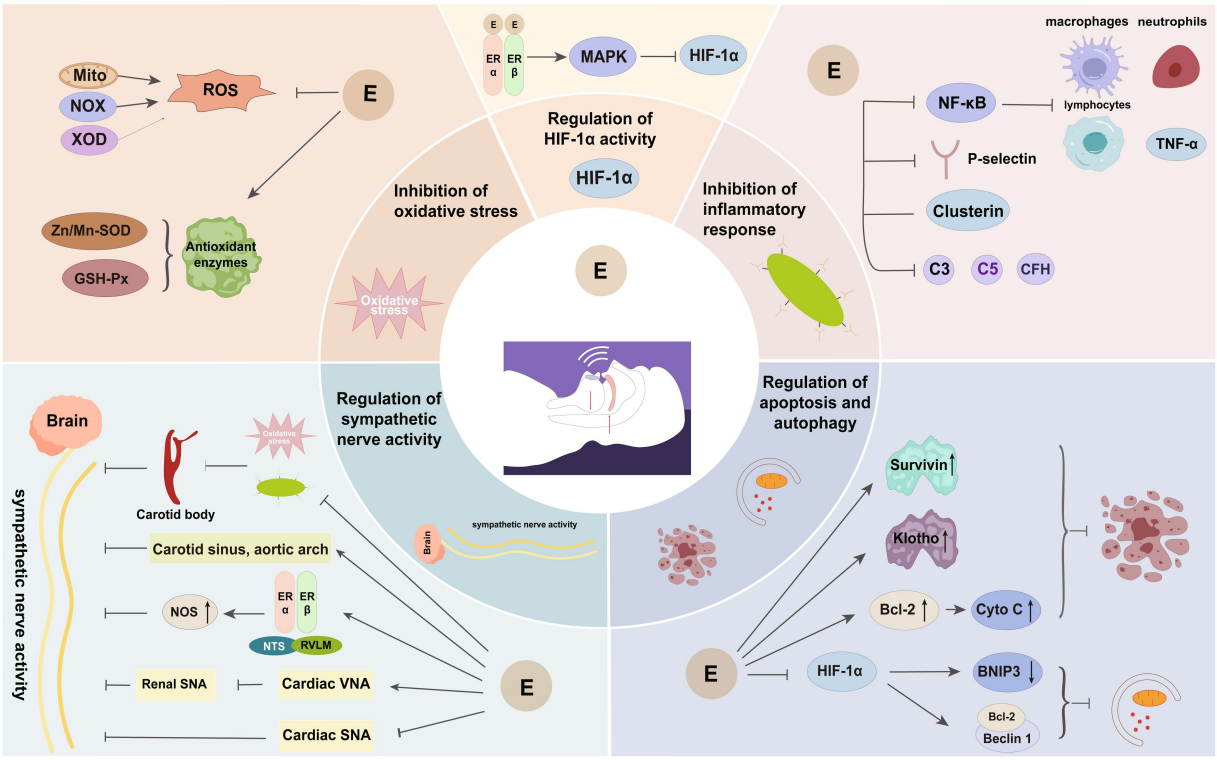

FIGURE 3
Important protective mechanisms of estrogen in OSAHS. E, estrogen; Mito, mitochondria; NOX, reduced nicotinamide adenine dinucleotide phosphate oxidase; XOD, xanthine oxidase; ROS, reactive oxygen species; Zn/Mn-SOD, zinc-manganese superoxide dismutase; GSH-Px, glutathione peroxidase; MAPK, mitogen-activated protein kinase; HIF-1α, hypoxia-inducible factor-1α; NF-κB, nuclear factor kappa B; CFH, complement factor H; Bcl-2, B cell lymphoma-2; Cyto C, cytochrome c; NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla; NOS, nitric oxide synthase; VNA, vagus nerve activity; SNA, sympathetic nerve activity.

function of various estrogen receptor subtypes across different tissues, with ERβ playing a pivotal role in mitigating oxidative stress.

3.2 Inhibition of the inflammatory response

In the context of OSAHS, CIH activates the nuclear factor-κB (NF-κB) and HIF-1αsignaling pathways, with NF-κB serving as a pivotal transcription factor in the inflammatory response (62). NF-κB can also induce muscle atrophy, leading to the loss of slow-twitch muscle fibers and affecting muscle tone (66). Estrogen has been shown to inhibit NF-κB activity by activating its receptor (67). Research indicates a pronounced inflammatory response in the lung tissues of female rats subjected to hypoxia, characterized by a significant increase in the nuclear levels of the NF-κB p65 subunit protein, which was further exacerbated following ovariectomy (13). Additionally, a notable inflammatory response was detected in the bronchoalveolar lavage fluid of ovariectomized rats exposed to CIH, evidenced by elevated levels of total proteins, inflammatory cells (including macrophages, neutrophils, and lymphocytes), tumor necrosis factor-alpha (TNF-α), and lipid peroxides (13). Conversely, a study conducted by Torres et al. (43) found that while intermittent hypoxia intensified the inflammatory response (as indicated by the overexpression of IL-6 and IL-8 genes) in the cardiac and cerebral tissues of rats, it did not further elevate inflammatory markers in ovariectomized rats, aligning with the observations of Ribon-Demars et al. (61). This phenomenon may be attributed to estrogen's role in stabilizing HIF-1α activity, which activates NF-κB to facilitate inflammatory responses (62). Under hypoxic conditions, estrogen enhances the stability of HIF-1αand promotes NF-κB activation, thereby increasing the expression of IL-6 and IL-8. In contrast, a reduction in estrogen levels leads to diminished HIF-1α activity in ovariectomized rats, resulting in decreased NF-κB activity and the expression of its target genes, IL-6 and IL-8 (43). However, numerous studies have demonstrated that E2 can inhibit HIF-1α expression via ERα (17, 28, 68) or ERβ (69), presenting contradictory evidence that suggests the existence of alternative pathways through which estrogen may influence HIF-1α. Notably, Torres did not further investigate this inflammatory response mechanism through estrogen replacement therapy, whereas Huang et al. (13) reported a significant reduction in the inflammatory response following the administration of a low dose of E2 to ovariectomized rats, indicating a more reliable outcome and suggesting that estrogen may mitigate hypoxia-induced inflammatory responses in the lung.

Numerous inflammatory diseases are characterized by increased recruitment of immune cells to vascular sites. P-selectin, an inflammatory adhesion molecule, plays a crucial role in this mechanism, particularly atherogenesis (70). Research conducted by Horváth et al. (71) demonstrated that plasma levels of P-selectin were significantly elevated in patients suffering from severe OSAHS, although these levels did not correlate with the arousal index. This finding indicates that P-selectin is implicated in the

inflammatory response associated with OSAHS, which is influenced by nocturnal hypoxia. Furthermore, estrogen has been shown to modulate P-selectin levels; for instance, P-selectin levels decrease in response to elevated E2 during the menstrual cycle in females, and similarly, levels in males decline following intramuscular E2 administration (72). This observation provides additional evidence supporting the anti-inflammatory properties of estrogen.

Additionally, clusterin, a heterodimeric protein known for its anti-apoptotic and anti-inflammatory functions (73), is involved in the inflammatory processes related to OSAHS. Elevated clusterin levels in OSAHS patients have been linked to nocturnal hypoxic stimulation and have shown a positive correlation with the severity of the disease (74). This suggests clusterin may be a protective mechanism against OSAHS and could partially inhibit NF-κB activity (75). However, a study indicated that estrogen downregulates clusterin gene expression in the rat endometrium (76), which appears to contradict the anti-inflammatory effects of estrogen. It is essential to consider the tissue-specific variability in estrogen action, which may be influenced by the distribution of its receptor subtypes (77). Further research is necessary to validate these findings.

The overexpression of complement components C3, C5, and C9 has been observed in patients with OSAHS (78), indicating an activation of the complement system (78, 79). This system plays a crucial role in the hazard perception cascade response and is integral to humoral innate immunity, encompassing functions such as antimicrobial defense, immunomodulation, clearance of immune complexes, and apoptosis (80, 81). Research conducted by Horvath et al. (79) identified a significant association between elevated levels of C3a and CIH in OSAHS patients; however, no notable alterations were detected in the levels of C5a or SC5b-9. C3a is generated through the cleavage of C3 by the C3 converting enzyme, while the binding of C5b-9, known as the membrane attack complex (MAC), to S-protein results in the formation of the inactive stabilized form SC5b-9 (80). The activation of the complement system may be linked to a decrease in the expression of complement component 4-binding protein alpha in OSAHS (78), as this protein serves as an inhibitor of both the classical and clusterin pathways and obstructs the formation of C3b and C4b2b. The stable levels of plasma C5a and SC5b-9 suggest a potential attenuation of the complement cascade or the existence of a protective feedback mechanism in OSAHS (79). Complement factor H (CFH) is a crucial regulator of the alternative pathway within the complement system, inhibiting the activity of the C5 converting enzyme, reducing C5 cleavage, and exerting anti-inflammatory effects (81). Nevertheless, no significant changes in CFH levels were noted in OSAHS patients, which complicates understanding the observed attenuation of the complement cascade. Additionally, clusterin, which inhibits MAC formation and thereby mitigates cytolysis and the inflammatory response (81), may account for the unchanged levels of SC5b-9. The proposition of a sluggish complement cascade necessitates further investigation. Lastly, the impact of estrogen on the complement system has been evaluated, albeit with limited studies available. One investigation indicated that estrogen enhances C3 secretion in rat uterine epithelium, a phenomenon not replicated in the liver (82), suggesting that the effects of estrogen may be tissue-specific and cannot be generalized as universally activating the complement system. Further research is warranted to elucidate this relationship.

The inflammatory response associated with OSAHS is intricate, and there exists a diversity of perspectives regarding the influence of estrogen. Comprehensive research is required to investigate this phenomenon across various tissues and organs, allowing for adequate consideration of environmental exposures. Such investigations are essential to elucidate whether the inflammatory response is tissue-specific or if it involves more profound molecular mechanisms. Furthermore, clinical studies should focus on monitoring changes in pertinent indices following OSAHS treatment while also accounting for the impacts of obesity, sleep deprivation, and other confounding variables.

3.3 Regulation of apoptosis and autophagy

CIH is a well-established trigger for apoptosis, with numerous studies indicating that hypoxia prompts pharyngeal myocytes in rat models to generate ROS excessively. This overproduction subsequently influences the expression of genes associated with apoptosis, ultimately resulting in organ dysfunction (20, 21, 62). Survivin (83) and Klotho (84) are pivotal anti-apoptotic proteins in inflammation and immune regulation. In individuals diagnosed with OSAHS, hypoxia has been shown to inhibit these two proteins, with their regulation being influenced by estrogen; however, there is a notable absence of data regarding their status following CPAP treatment. Kunos et al. (85) were the first to document the impact of OSAHS on Survivin levels, revealing a significant reduction in plasma Survivin among OSAHS patients, which correlated with nocturnal hypoxia and elevated C-reactive protein levels. Estrogen has been found to enhance Survivin gene expression (86, 87), thereby inhibiting both inflammation and apoptosis, an effect that is dependent on ERα (87). Additionally, Pákó et al. (88) reported a significant decrease in Klotho protein levels in the plasma of OSAHS patients, which was also associated with nocturnal hypoxia. Nonetheless, there is insufficient direct evidence to elucidate the relationship between Klotho protein and markers of inflammation and apoptosis in OSAHS patients. Research has demonstrated that estrogen exerts varying effects on Klotho protein expression. For instance, Oz et al. (89) observed that Klotho protein levels were markedly elevated in aromatase-deficient mice, while estrogen pretreatment normalized these levels, suggesting that estrogen may lead to a reduction in Klotho protein. Conversely, Sárvári et al. (90) reported a significant upregulation of Klotho mRNA in the hippocampi of OVX rats subjected to continuous E2 treatment for 29 days. The underlying reasons for these discrepancies in findings are currently unclear, indicating the potential involvement of additional mechanisms that may influence the effects of estrogen on Klotho proteins. In summary, the regulation of apoptosis appears to be dysregulated in OSAHS and is modulated by estrogen.

The regulation of cell viability through the apoptotic process is a critical function of mitochondria. Increasing mitochondrial cytochrome c levels enhances electron flow within the respiratory chain, which may reduce the rate of ROS production (59). The B cell lymphoma-2 (Bcl-2) protein, known for its anti-apoptotic properties, plays a significant role in the mitochondria-mediated apoptotic pathway. It can diminish ROS production and mitigate apoptosis and hypoxia-induced damage by elevating cytochrome c levels within mitochondria (58). Furthermore, estrogen receptors, ERα and ERβ, regulate mitochondrial respiration and can ameliorate CIH-induced

mitochondrial dysfunction and metabolic reprogramming through distinct pathways, thereby enhancing cognitive function (64, 65). Genistein, a soy isoflavone that preferentially binds to ERβ, has been shown to reduce hypoxia-induced hydrogen peroxide (H_2O_2) production, increase Bcl-2 expression, decrease cytochrome c release from mitochondria, and significantly lower apoptosis rates associated with hypoxia (69). This action resembles E2 while potentially mitigating the adverse effects of E2 on the reproductive system (20). Hsu et al. (91) demonstrated that resveratrol enhances the expression of Klotho mRNA and protein in mouse kidneys both *in vivo* and *in vitro*. In summary, E2 has the potential to modulate apoptosis, thereby improving the functional status of tissues and organs in patients with OSAHS. However, further research is necessary to substantiate the protective effects of E2 and to elucidate the specific molecular regulatory mechanisms involved, which could lead to the development of additional therapeutic strategies.

In contrast to apoptosis, autophagy is characterized by the self-degradation of intracellular proteins and damaged organelles, serving a crucial regulatory function during hypoxic stress. Autophagy induced by hypoxia is acknowledged as a mechanism that promotes cell survival and provides cytoprotection; however, it can also lead to cell death in specific contexts (92, 93). BNIP3, a member of the pro-apoptotic protein family, is upregulated in response to hypoxic conditions and has been implicated in the induction of autophagic cell death (93). Autophagy contributes to cell survival by dismantling dysfunctional mitochondria and decreasing ROS levels, a process contingent upon the hypoxia-induced expression of HIF-1α, which involves the HIF-1α/BNIP3 signaling pathway (94). Beclin 1 is a pivotal intersection among cellular autophagy, apoptosis, and proliferation, and it inhibits autophagy through its interaction with Bcl-2 (95). Research indicates that in genioglossus myogenic stem cells, hypoxia leads to increased HIF-1α expression and the formation of HIF-1 heterodimers, subsequently upregulating BNIP3 expression. This upregulation disrupts the Beclin 1/Bcl-2 complex, releasing Beclin 1, which then promotes autophagy under hypoxic conditions (96). Consequently, the damage to genioglossus tissue resulting from chronic hypoxia exposure in OSAHS is partially associated with autophagy-induced cell death. Numerous studies have demonstrated that E2 exerts an inhibitory effect on HIF-1α expression (17, 28, 68), aligning with the mechanisms through which OSAHS induces cellular autophagy, suggesting that E2 may modulate autophagy via the HIF-1α pathway. This hypothesis was substantiated by research conducted by Hsieh et al. (69), which revealed that E2 inhibited cardiomyocyte autophagy by suppressing hypoxia-induced HIF-1α expression, consequently limiting the expression of genes associated with autophagy. Nevertheless, a significant body of literature indicates that the regulatory effects of E2 on autophagy levels are complex and, in many instances, exhibit a stimulatory effect (97). Therefore, further investigation is warranted to elucidate the regulatory role of E2 on OSAHS-induced cellular autophagy across various tissues and organs, particularly emphasizing the mechanisms governing the interaction between E2 and HIF-1α.

3.4 Regulation of HIF-1α activity

HIF-1 is a heterodimeric protein consisting of HIF-1α and HIF-1β subunits, with the expression of HIF-1α being meticulously regulated by intracellular oxygen levels. Under hypoxic conditions, the stabilization of the HIF-1α protein occurs, leading to the translocation of the HIF-1 complex into the nucleus, which activates target genes crucial for cellular proliferation, survival, and differentiation (17, 62). The overexpression of HIF-1α induces a transformation of slow-twitch muscle fibers into fast-twitch muscle fibers, thereby influencing muscle tone (98). Research indicates that HIF-1α plays a significant role in regulating myogenic cell proliferation in hypoxic environments. Specifically, inhibiting HIF-1α expression in myoblasts exposed to CIH has enhanced myoblastogenesis (28). Furthermore, estrogen has been observed to downregulate HIF-1α expression in the genioglossus muscle of CIH-exposed rats, thereby improving the endurance of upper airway muscles (68). This suggests that estrogen may confer protective effects on the upper airway by inhibiting CIH-induced HIF-1α expression (17, 28, 68), with ERα mediating this effect (17). The mitogen-activated protein kinase (MAPK) signaling pathway is well-established in regulating various cellular processes, including proliferation, calcification, inflammation, and oxidative stress. A study conducted by Li et al. (17) demonstrated that the activation of the p38 MAPK pathway is further stimulated by the binding of E2 to ERα, as evidenced by a notable increase in phosphorylated p38 MAPK levels. The inhibitory effect of a p38 MAPK inhibitor on E2's action suggests that the p38 MAPK pathway is integral to suppressing HIF-1α by E2 in myofibroblasts. Similarly, ERβ has also been shown to downregulate the hypoxia-induced increase in HIF-1α levels (65, 69).

However, research by Ding et al. (20) revealed that p38 MAPK protein levels did not significantly change in rat genioglossus muscle myoblasts subjected to hypoxia. Instead, this study found that hypoxia inhibited the expression of PI3K-Akt and ERK1/2 MAPK proteins while suppressing Bcl-2-mediated apoptosis in genioglossus myogenic cells. Notably, the effects observed with hypoxia treatment were replicated using Akt and ERK1/2 MAPK inhibitors (20), indicating that hypoxia-induced tissue damage may involve multiple pathways. Additionally, in vascular smooth muscle cells, inhibiting the MAPK pathway by E2 resulted in reduced proliferation and oxidative stress, a process associated with the upregulation of BHLHE40 (45), a transcriptional repressor, although the precise mechanism underlying this action remains unclear.

In conclusion, HIF-1α is a critical regulator for the protective effects of E2. The MAPK pathway plays a significant role in mediating the protective actions of E2 against apoptosis and oxidative stress. However, the underlying mechanisms are intricate and multifaceted, warranting further investigation to elucidate this relationship.

3.5 Regulation of sympathetic activity

Cyclic enhancement of sympathetic nerve activity is observed in OSAHS, as indicated by increased muscle sympathetic nerve activity (MSNA) (99), elevated urinary norepinephrine concentrations (100), and reduced heart rate variability (101), which persists during wakefulness (102). The overactivation of the sympathetic nervous system is a critical factor in the pathogenesis of cardiovascular disease among individuals with OSAHS.

Recent research has identified that the sympathetic nerve activity (SNA) associated with OSAHS is primarily linked to changes in the chemosensitivity of the carotid body (CB) induced by CIH (103, 104). The CB is the principal peripheral oxygen sensor, initiating reflex

physiological responses to acute hypoxemia and facilitating ventilatory adaptation to sustained chronic hypoxemia (105). ROS produced by CIH activate chemoreflex mechanisms, thereby enhancing the chemosensitivity and responsiveness of the CB to hypoxic conditions and stimulating sympathetic nervous system activity (105, 106). This mechanism is crucial in the pathway through which CIH contributes to elevated blood pressure and arrhythmias (103, 104). Evidence suggests that pro-inflammatory mediators downstream of ROS, such as IL-1β, IL-6, and TNF-α (107, 108), are significant contributors to the increased sensitivity of CB chemoreceptors (105, 109). Gassmann et al. (110) demonstrated that chronic hypoxia-induced elevations in rats' erythropoietin (EPO) levels led to the sensitization of CB chemoreceptors and enhanced hypoxic ventilatory responses. Additionally, mice with a heterozygous deficiency in hypoxia-inducible factor 1 (HIF-1 +/−) exhibited impaired carotid body function and diminished adaptive responses to chronic hypoxia (111). Consequently, the hypoxic adaptation and inflammatory responses induced by CIH may result in altered CB sensitivity, with HIF-1 potentially playing a pivotal role.

Further investigations have indicated that E2 reduces the ventilatory response to hypoxia in OVX rats without affecting responses to hypercapnia (44). E2 has been shown to inhibit the upregulation of EPO and mitigate the hypoxic ventilatory response in the CB of hypoxic rats (110). This suggests that E2 exerts a modulatory influence on the CB, thereby indirectly alleviating CIH-induced SNA. However, there is a paucity of research regarding the role of estrogen in modulating CB chemoreceptor-associated SNA, a vital aspect of the protective effects against OSAHS. The protective mechanisms of E2 against oxidative stress and inflammatory responses have been previously discussed, primarily through the downregulation of HIF levels. Future research should pursue this avenue to elucidate further the underlying mechanisms involved.

Recent research has elucidated the role of estrogen in regulating SNA in females. Notably, variations in SNA among females are linked to physiological cycles and menopause. In younger females, fluctuations in resting MSNA throughout the menstrual cycle negatively correlate with changes in plasma E2 levels (112). Premenopausal females demonstrate lower levels of sympathetic nerve activity compared to their male counterparts of the same age, while a relative increase in sympathetic nerve activity is observed post-menopause (113–115). Furthermore, many studies conducted on both animal models and human subjects have indicated that estrogen supplementation can mitigate SNA (115–119). The underlying mechanism is believed to be associated with estrogen's influence on critical brainstem regions integral to neurocardiovascular regulation (54).

Research has identified the presence of estrogen receptors in autonomic centres of the rat brainstem, including the nucleus tractus solitarius and the rostral ventral lateral medulla (RVLM), where mRNA expression for estrogen receptor subtypes ERα and ERβ has been documented. These regions receive, integrate, and coordinate input signals to elicit appropriate autonomic responses (54, 120). For instance, localized administration of E2 into the RVLM of OVX rats has decreased sympathetic nervous tension and blood pressure (121). Additionally, E2 appears to diminish sympathetic excitation induced by the RVLM in OVX rats through the antagonism of cannabinoid receptors (118). Moreover, evidence suggests that estrogen may enhance the sensitivity of the sympathetic stress reflex, thereby inhibiting SNA (122–124). In conditions such as OSAHS, CIH typically leads to a suppression of the stress reflex, indicating that estrogen may also ameliorate SNA in OSAHS through this pathway. However, some studies have reported that E2 does not influence sympathetic stress reflex sensitivity in postmenopausal women (115, 119) This phenomenon may be related to the duration of estrogen treatment, with sympathetic activation decreasing only following chronic, rather than acute, administration. Estrogen may exert its effects by activating an inducible NO synthase signaling pathway (125). NO has been shown to inhibit noradrenergic neurotransmission at pre-sympathetic junctions and in various tissues (126, 127). Chronic estrogen treatment has been demonstrated to have a central effect in rats by enhancing the expression of neuronal NO synthase, which plays a role in the inhibitory regulation of brainstem sympathetic outflow (117, 128). Additionally, a study involving rats indicated that decreased E2 levels could diminish cardiac vagal inhibition of renal sympathetic nerves while simultaneously enhancing cardiac sympathetic excitation, leading to a significant overall increase in reflex-driven sympathetic excitability (116). This finding suggests that vagal reflexes also play a role in the estrogen-mediated regulation of sympathetic nerves.

4 Effect of OSAHS on estrogen levels

Numerous studies have indicated that female patients with OSAHS exhibit reduced estrogen levels (129–132), which correlate negatively with the severity of the condition (11, 133). This observation suggests a complex interplay between OSAHS and estrogen. Specifically, a decline in estrogen levels, which may result from various conditions such as polycystic ovary syndrome or premature ovarian failure, as well as from natural physiological changes like menopause, appears to facilitate the onset and progression of OSAHS. Consequently, estrogen may be considered a protective factor against this syndrome. Furthermore, the intermittent hypoxia, sleep deprivation, and other pathological processes associated with OSAHS may further contribute to decreased estrogen levels. Research conducted by Stavaras et al. (132) on pre- and postmenopausal women, after controlling for BMI, revealed a correlation between the Female Sexual Function Index (FSFI) scores and the severity of OSAHS, with significantly lower estrogen levels observed in patients with severe OSAHS. This finding implies a detrimental impact of OSAHS on female sexual function, potentially linked to variations in sex hormone levels (132). While CPAP treatment has been shown to improve sexual dysfunction in females (134, 135), some studies have reported no significant changes in sex hormone levels following such treatment (136).

In male patients with OSAHS, a robust association between the severity of the condition and sexual dysfunction has been documented (137–140). Notably, a decrease in testosterone levels has been observed (137, 139, 141, 142), alongside increases in follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone levels after one month of CPAP treatment (139). However, certain studies have found no significant differences in sex hormone levels between male OSAHS patients and healthy controls, nor any substantial changes after three months of CPAP treatment (140). These discrepancies may be attributed to factors such as small sample sizes, variations in age and BMI, and the circadian rhythm of sex hormone

secretion, which may have influenced the results due to the lack of sleep assessments in the studies.

There is a paucity of research examining the effects of OSAHS on estrogen levels in females, with the majority of studies concentrating on sexual function. It is important to note that sexual function is influenced by a multitude of factors, including psychological, neurological, endocrine, and vascular abnormalities, which cannot be solely ascribed to sex hormone levels. Therefore, further validation through rigorous clinical and animal studies is warranted. Based on the current findings, we propose the hypothesis that OSAHS may impact estrogen secretion in females and briefly discuss the underlying mechanisms involved (Figure 4).

4.1 CIH

CIH represents a significant pathological consequence of OSAHS, resulting in excessive oxidative stress within the body and initiating both local and systemic inflammatory responses. These responses can ultimately lead to tissue and organ dysfunction or failure (60–62). However, there is a notable paucity of research examining the impact of CIH on the structural integrity of ovarian tissue. Yang et al. (143) elucidated the adverse effects of oxidative stress and chronic inflammation on ovarian functionality, suggesting that exogenous estrogen supplementation may mitigate chronic low-grade inflammation and enhance follicular development. Furthermore, Yang et al. (144) demonstrated that CIH adversely affected the function and cellular ultrastructure of the hypothalamic–pituitary-gonadal (HPG) axis in male rats, evidenced by nuclear deformation and consolidation, vacuole formation within the cellular matrix, and mild mitochondrial swelling, which collectively resulted in diminished levels of FSH, LH, and testosterone. The study also reported elevated levels of the oxidative stress marker malondialdehyde and increased inflammatory cytokines IL-6 and TNF-α, alongside reduced activity of antioxidant enzymes; these alterations were ameliorated by pretreatment with reduced glutathione (144). This evidence indirectly supports the detrimental impact of CIH on the HPG axis in females.

Additional research has indicated that OSAHS is correlated with elevated prolactin levels (145), which may inhibit the secretion of hypothalamic gonadotropin-releasing hormone (GnRH), thereby indirectly influencing the release of sex hormones (146). Notably, prolactin levels can be decreased through CPAP treatment (145). These findings suggest that CIH may directly or indirectly impair the secretory function of the HPG axis via oxidative stress and inflammatory mechanisms, ultimately leading to reduced levels of sex hormones.

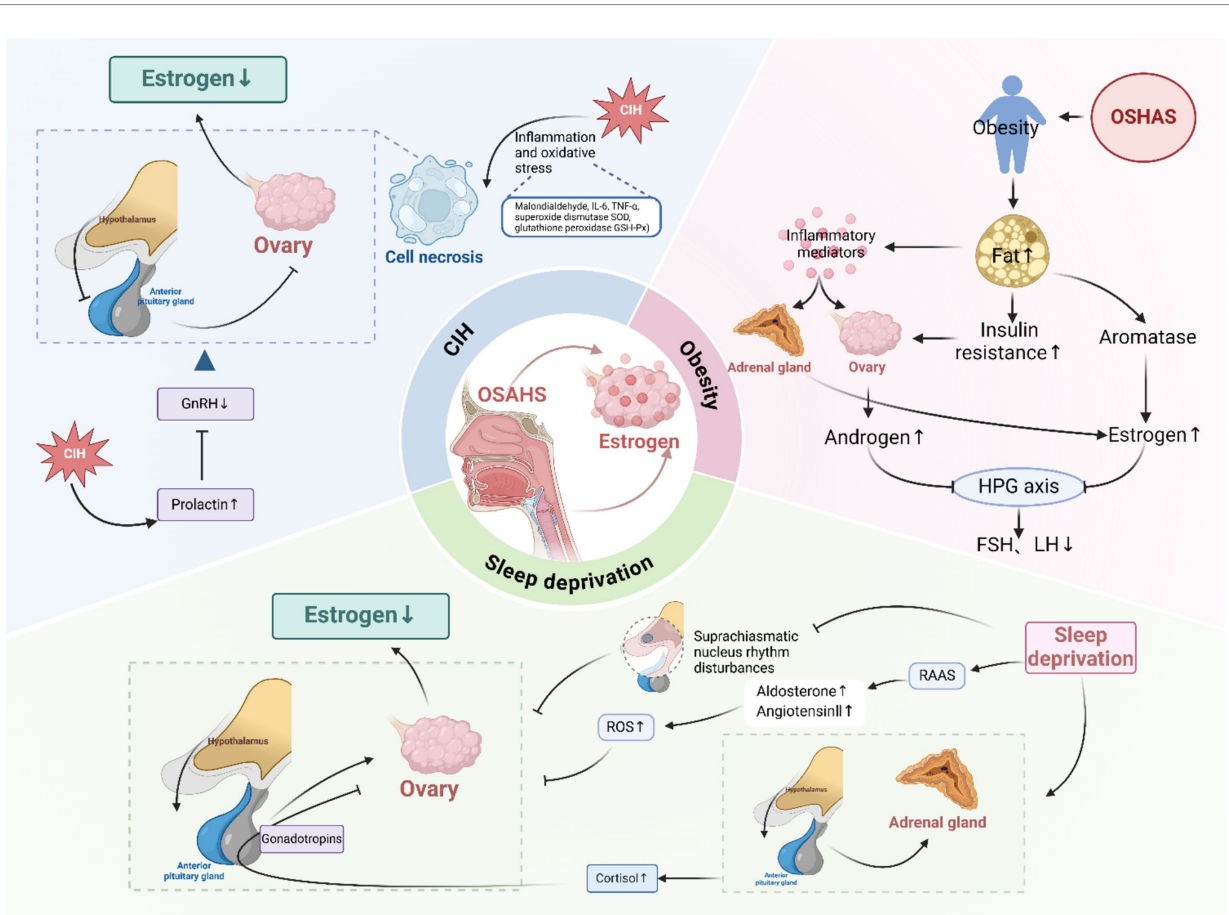

FIGURE 4
Effect of OSAHS on estrogen levels. CIH, chronic intermittent hypoxia; ROS, reactive oxygen species; GnRH, gonadotropin-releasing hormone; HPG, hypothalamic–pituitary-gonadal; FSH, follicle-stimulating hormone; LH, luteinizing hormone; RAAS, renin-angiotensin-aldosterone system. Created in BioRender.

4.2 Sleep deprivation

Sleep deprivation, commonly characterized by frequent nocturnal awakenings and disrupted sleep patterns in individuals with OSAHS (1), has several implications for estrogen secretion. Firstly, estrogen secretion follows a circadian rhythm regulated by the supraoptic nucleus of the hypothalamus. Disruption of this rhythmicity due to sleep deprivation can impair the functioning of the HPG axis (15). A cross-sectional study conducted by Sowers et al. (147) involving 365 participants indicated a negative correlation between E2 levels and sleep quality in females. Furthermore, a prospective study by Michels et al. (148), which included 259 regularly menstruating women, demonstrated that an additional hour of sleep per day was associated with a significant increase of 3.9% in mean E2 concentration.

Secondly, sleep plays a crucial role in regulating the activity of the hypothalamic–pituitary–adrenal (HPA) axis. In patients with OSAHS, nocturnal hypoxic stress and sleep deprivation can activate the HPA axis, leading to disturbances in cortisol secretion rhythms (133, 142). Notably, cortisol levels have been found to correlate significantly with the AHI and minimum oxygen saturation (142), with reductions in cortisol levels observed following treatment with CPAP (149). Elevated cortisol levels can cause direct damage to ovarian tissue (150) and, when affecting the pituitary gland, can disrupt the synthesis and release of gonadotropins, thereby indirectly influencing ovarian secretory function (151).

Thirdly, sleep deprivation activates the renin-angiotensin-aldosterone system (RAAS), resulting in increased aldosterone and angiotensin II secretion (152), which may contribute to oxidative stress damage within the HPG axis. Lastly, TNF-α levels exhibit a circadian pattern, and sleep deprivation has been associated with elevated levels of TNF-α and IL-6 (153), which may inflict damage on ovarian tissue through the activation of inflammatory responses.

The impact of sleep deprivation on estrogen levels within the body is well-documented; however, it remains relatively underexplored in individuals diagnosed with OSAHS. The direct influence of alterations in sleep architecture on estrogen levels can be assessed through PSG monitoring.

4.3 Obesity

There exists a reciprocal promotional relationship between OSAHS and obesity, wherein OSAHS exacerbates endocrine dysfunction, thereby worsening obesity in individuals with obesity (1). In obese female patients, insulin resistance leads to increased ovarian production of androgens. At the same time, excess adipose tissue enhances aromatase activity, facilitating the conversion of androgens to estrogens, predominantly estrone (42, 145). Additionally, visceral adipose tissue releases significant inflammatory and immune mediators (143), stimulating the ovaries and adrenal glands to secrete these hormones (154). Elevated levels of androgens and estrogens disrupt the negative feedback mechanism of the HPG axis, resulting in the inhibition of FSH and LH secretion. Consequently, obese females may exhibit low FSH, LH, estrogen metabolites, and urinary progesterone (155). These hormonal imbalances can lead to impaired follicle development, ovulatory dysfunction, and menstrual irregularities (145, 156), often presenting as polycystic ovary syndrome (PCOS) in female patients.

A meta-analysis indicated that bariatric surgery significantly improved the signs and symptoms of PCOS and reduced free testosterone and estrogen levels in females (154). Another meta-analysis focusing on obese females without PCOS reached similar conclusions, noting that bariatric surgery ameliorated menstrual irregularities, improved insulin resistance, decreased testosterone and estrogen levels, and increased sex hormone-binding globulin levels. However, no significant changes in LH and FSH levels were observed (156). Some studies involving females (145, 157) and males (154) have reported elevated FSH and LH levels post-bariatric surgery, with this variation potentially influenced by the menstrual cycle during which the samples were collected. Sarwer et al. (157) conducted a four-year follow-up study involving 106 females post-bariatric weight loss, revealing an average weight reduction of 30% at four years post-surgery, alongside a significant decrease in estrogen levels after the procedure, with a notable increase in estrogen levels from the third year onward. This finding suggests that the inhibition of the HPG axis is alleviated following weight loss, leading to the normalization of hormone regulation. In summary, obesity results from multiple endocrine dysfunctions that inhibit the HPG axis, and weight loss surgery can mitigate pathological estrogen levels and relieve this inhibition.

In conclusion, OSAHS may influence estrogen production through various mechanisms, with sleep deprivation likely being the predominant factor. It is important to note that while examining the impact of reduced estrogen levels on OSAHS, one must also consider the reciprocal effects of OSAHS on estrogen synthesis and secretion. There is a notable scarcity of research investigating the fluctuations in sex hormone levels before and after treatment in female patients with OSAHS. This gap in the literature can be attributed to the inherent variability in the female menstrual cycle, which poses challenges in standardization and is further influenced by factors such as age, pregnancy, and the use of steroid hormones.

5 Exploration of the application of estrogen in the treatment of OSAHS

In the United States, more than 1.3 million women undergo menopause annually. A cross-sectional study assessed the trends in the utilization of menopausal hormone therapy among postmenopausal women in the United States from 1999 to March 2020, indicating a decrease in prevalence from 26.9% in 1999 to 4.7% in 2020 (158). During the menopausal transition, it is estimated that between 50 and 75% of women experience vasomotor symptoms, such as hot flashes and night sweats, which may lead to increased anxiety and insomnia. Additionally, over 50% of women report experiencing genitourinary symptoms (159), which can have a profound effect on their personal and social well-being (160). Estrogen therapy is recognized as the primary treatment for both vasomotor symptoms and menopausal genitourinary syndrome (159).

5.1 Effects of estrogen therapy on humans

The adverse effects of estrogen therapy primarily pertain to the associated risks of neoplasms, cardiovascular disease (CVD), and stroke. The existing literature on the implications of estrogen therapy

for human health presents inconsistencies, particularly regarding the risks of CVD and breast cancer. Estrogen was previously advocated for the management of menopausal symptoms in women; however, its utilization significantly declined following findings from the Heart and Estrogen/Progestin Replacement Study (HERS) (161)and the Women's Health Initiative (WHI) (162, 163) randomized trials. These studies revealed an elevated risk of CVD and breast cancer linked to the oral administration of 0.625 mg/d conjugated equine estrogens (CEE) in conjunction with 2.5 mg/d medroxyprogesterone acetate (MPA) (161–163). The concerns surrounding hormone therapy extend beyond CVD and breast cancer, as it has also been correlated with an increased risk of venous thromboembolism, overall mortality, and cancer-related deaths (164, 165). Recent research indicates that these risks may be more closely associated with progestogens, given that contraceptives containing both estrogen and progestogen, as well as progestogen-only formulations, have been shown to elevate the risk of breast cancer (166, 167). Notably, the WHI randomized trials (163, 168) and a meta-analysis (169) have demonstrated that treatment with CEE alone significantly decreases the risk of breast cancer. Furthermore, estrogen therapy does not appear to be linked to all-cause, cardiovascular, or cancer-related mortality risks (170). A meta-analysis involving over 2.5 million menopausal women suggests that oral hormone therapy is not associated with an increased risk of heart disease, and that low-dose oral and transdermal hormone therapies may confer cardioprotective benefits (171). Recent findings from the KEEPS trial indicate that oral CEE may slow the accumulation of epicardial fat tissue and impede the progression of coronary atherosclerosis (172). It is crucial to acknowledge that the studies focusing on estrogen monotherapy predominantly involve women who have undergone hysterectomy. For women with an intact uterus, the administration of CEE alone may heighten the risk of endometrial cancer, while combined treatment with MPA can mitigate this risk (173). Additionally, the WHI has reported that postmenopausal women receiving estrogen alone face an increased risk of stroke (174), as well as heightened incidence and mortality rates of ovarian cancer (173).

The etiology of organ damage linked to hormone therapy may be influenced by the age at which treatment commences, especially in relation to the age of menopause. Additionally, factors such as the type, dosage, and method of administration of estrogen, along with the concurrent use of progestogens, may also play a significant role (171).There is substantial evidence indicating that estrogen therapy may confer cardioprotective benefits when initiated around the time of menopause. In contrast, its initiation during the late menopausal period (more than ten years post-menopause) may be detrimental (171). This phenomenon can be attributed to the less favorable CVD risk profile observed in women who are further along in the menopausal transition, rendering them more susceptible to CVD (175). A secondary analysis of the WHI revealed that women aged 50 to 59 years, or those who are less than ten years post-menopause, exhibited a decreased risk of heart disease, a lower likelihood of mortality from all causes, and no significant increase in stroke risk, in contrast to women who commenced hormone therapy after the age of 60 (176). Furthermore, early initiation of estrogen replacement therapy has been shown to significantly impede the progression of coronary atherosclerosis, diminish the risk of colon cancer, and potentially reduce all-cause mortality by 20–40% (177). Conversely, the initiation of hormone replacement therapy a decade post-menopause may elevate the risk of cardiovascular disease, among other health concerns (177). Consequently, the timing of hormone therapy initiation relative to menopause is a critical determinant of its effects on chronic disease risk (165). The duration of estrogen's absence prior to therapy is particularly relevant, as it influences the risk of atherosclerosis. Additionally, it is essential to note that while estrogen is not inherently carcinogenic, it can promote the growth of pre-existing tumors; thus, timely screening for tumors is essential for menopausal women, particularly prior to the commencement of hormone therapy (165). Unless contraindicated, patients may opt to continue hormone therapy until the associated risks surpass the benefits (165). Regular reassessment of a woman's health status is necessary throughout treatment.

In summary, the formulation of a personalized approach to estrogen therapy is of paramount importance (178). A comprehensive evaluation of various factors, including the dosage of the medication, the administration route, the specific type of hormonal agent utilized (whether combined estrogen or progestin), the timing of treatment initiation, the patient's age, her cardiovascular disease history, and the thromboembolic characteristics associated with estrogen and progestin, is essential for postmenopausal hormone replacement therapy (171). The debate surrounding the advantages and disadvantages of estrogen therapy remains unresolved.

5.2 Clinical studies of estrogen therapy for OSAHS

Wesström et al. (179) administered a regimen of hormone replacement therapy consisting of 2 mg/d of estradiol and 0.5 mg/d of trimegeston orally for a duration of 5–6 weeks to four postmenopausal women and one perimenopausal woman diagnosed with OSAHS via PSG monitoring. The results indicated a significant average reduction of 75% in the AHI post-treatment. In a separate study conducted by Keefe et al. (180), treatment with oral estrogen (2 mg/d) and combined progesterone (10 mg/d) yielded reductions in AHI of 25 and 50%, respectively. Additionally, Heinzer et al. (8) reported that postmenopausal women undergoing hormone replacement therapy exhibited comparatively lower AHI values. Conversely, Cistulli et al. (181) conducted a study involving 15 postmenopausal women with moderate OSAHS, administering estrogen (either oral CEE at 0.625 mg/d, estradiol valerate at 1 mg/d, or transdermal estradiol at 8 mg/week) in conjunction with combined progesterone (MPA at 2.5–10 mg/d) over a period of 50 days, and found no significant reduction in sleep-disordered breathing events. Notably, both the studies by Keefe and Cistulli were unblinded and lacked a control group. Additionally, Wesström's investigation was a small-sample clinical trial without a placebo control, leading to ongoing debates regarding the validity of the results. Currently, there is insufficient conclusive evidence to ascertain the efficacy of estrogen alone or estrogen-progestin combination therapy in postmenopausal women with OSAHS. Nevertheless, findings from various animal studies and clinical investigations suggest that estrogen therapy may confer a protective effect against the onset and progression of OSAHS and its associated complications in postmenopausal women, with the combination of progestin potentially enhancing therapeutic efficacy (6). Further extensive and methodologically rigorous clinical studies are warranted to substantiate these conclusions.

5.3 Basic research on estrogen therapy for OSAHS

The impact of CIH on female patients with OSAHS is influenced by various stages of ovarian hormone production, including the physiological menstrual cycle, pregnancy, and menopause. This observation indicates that hormonal therapies aimed at contraception, alleviating menopausal symptoms, or treating estrogen receptor-positive breast cancer may interact with CIH, potentially modifying the responses of other tissues such as the lungs, cardiovascular system, brain, and kidneys in female OSAHS patients (61). Research has demonstrated that low doses of E2 can reduce inflammatory and immune responses (67), while physiologically elevated levels of E2 may intensify these responses (182). In a study conducted by Huang et al. (13), the subcutaneous implantation of E2 silicone capsules demonstrated that supplementation with low concentrations of E2 (30 mg/mL) significantly diminished the apnea reflex induced by CIH in OVX rats, as well as the afferent response to chemical stimuli and the pulmonary inflammatory response; conversely, higher concentrations of E2 (50 and 150 mg/mL) did not yield significant effects.

These findings suggest that the influence of estrogen on the inflammatory response induced by CIH may be concentration-dependent, warranting further investigation to determine whether similar concentration-dependent effects of estrogen are observed in other tissues.

Recent investigations into the utilization of phytoestrogens have yielded promising results. Genistein, a polyphenolic nonsteroidal compound derived from plants, is among the most extensively studied phytoestrogens, exhibiting estrogen-like bioactivity without significant toxic effects during prolonged use (183). A study conducted by Zhou et al. (28) demonstrated that genistein enhances the endurance of upper airway muscles and mitigates airway collapse by down-regulating the expression of HIF-1α in the genioglossus of CIH rats. However, this effect was less pronounced than that of estrogen. Subsequent research indicated that genistein reduces oxidative stress and myogenic apoptosis through various mechanisms, including the regulation of ROS, lipid peroxidation, Bcl-2, and the apoptosis marker caspase-3 via the PI3K-Akt and ERK1/2 MAPK signaling pathways, with its effects remaining unaffected by estrogen receptor antagonists [28]. This suggests that the protective role of genistein against hypoxia-induced damage to genioglossus myogenic cells may operate through a non-genomic pathway rather than a genomic pathway mediated by estrogen receptors (28).

Moreover, genistein exhibits a high affinity for ERβ, while ERα is predominantly distributed in skeletal muscle. Experimental findings indicate that low concentrations of genistein confer a more pronounced protective effect against adult myocyte injury, suggesting that this protective effect may be both tissue-specific and concentration-dependent (20). Further research is warranted to elucidate its physiological effects and mechanisms in other tissues. Additionally, other phytoestrogens, such as resveratrol dimer (a derivative of resveratrol), which possesses superior estrogenic properties and minimal cytotoxicity, can enhance ERα expression by binding to ERα, thereby activating the p38 MAPK pathway to inhibit HIF-1α expression, ultimately improving the function of the genioglossus (17).

In conclusion, the utilization of estrogen for the management of OSAHS presents specific practical considerations; however, there is a deficiency of robust clinical evidence to substantiate its efficacy. Phytoestrogens exhibit various protective effects against OSAHS and may mitigate the adverse effects of conventional estrogens. Further investigation into their mechanisms of action is essential, as this research holds considerable importance for preventing and treating OSAHS in postmenopausal women. Additionally, hormone replacement therapy for postmenopausal women with OSAHS carries inherent risks and potential benefits.

6 Conclusion

A substantial body of evidence indicates that the chronic systemic inflammatory response associated with OSAHS impacts the body's estrogen levels. Notably, estrogen serves a crucial protective function in the context of OSAHS. Disruption of this balance may exacerbate the condition. Future research should focus on a more comprehensive examination of the interplay between OSAHS and estrogen. The advancement and utilization of phytoestrogens have partially mitigated the severe complications associated with traditional estrogen therapy, positioning them as a promising therapeutic adjunct for postmenopausal patients with OSAHS. Given the significant relationship between OSAHS and estrogen, we propose that a combination therapy involving CPAP and E2 could be explored to substantially enhance the clinical symptoms of affected individuals, at least in the short term. However, this approach necessitates robust empirical support through extensive experimental data.

Author contributions

PZ: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Supervision. HML: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. HYL: Conceptualization, Investigation, Writing – original draft. YC: Conceptualization, Resources, Writing – original draft. YL: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research was funded by the National Natural Science Foundation of China, Number: 1760022; Hanfang Expert Workstation in Yunnan Province, No. 202105AF150022. Yunnan Province "Xing Dian Talent Support Program" Project, No. XDYC-MY-2022-0013.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 29 April 2025
DOI 10.3389/fmed.2025.1400376

OPEN ACCESS

EDITED BY
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RECEIVED 13 March 2024
ACCEPTED 01 April 2025
PUBLISHED 29 April 2025

CITATION
Xie K, Tang X, Zhou J, Liu X, Zhang Y and Cui X (2025) Intermittent hypoxia index: a new indicator for assessing the degree of intermittent hypoxia in obstructive sleep apnea.
Front. Med. 12:1400376.
doi: 10.3389/fmed.2025.1400376

Intermittent hypoxia index: a new indicator for assessing the degree of intermittent hypoxia in obstructive sleep apnea

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Objective: In order to objectively and accurately evaluate the degree of nocturnal intermittent hypoxia (IH) in patients with obstructive sleep apnea (OSA), we developed the Newton quadrature low oxygen load assessment system (NLAS) to seek a new, quantifiable, comprehensive evaluation index of intermittent hypoxia (intermittent hypoxia index, IHI).

Methods: Demographic characteristics, anthropometric measurements, and polysomnography (PSG) parameters [oxygen desaturation index (ODI), lowest oxygen saturation ($LSpO_2$), time below 90% saturation (T90)] of 732 patients with OSA who underwent multi-channel sleep monitoring at the Sleep Center of Affiliated Wuxi People's Hospital, Nanjing Medical University, from 2019 to 2023 were retrospectively collected. The IHI was calculated using the NLAS (Certificate of Registration Number for Computer Software Copyright of the People's Republic of China: 12208933), and its threshold was defined. Additionally, correlation analysis was performed between IHI and T90, $LSpO_2$, and ODI.

Results: Among the 732 patients with OSA, IHI showed significant correlations with T90 (r = 0.922) and $LSpO_2$ (r = 0.866), and moderate correlation with ODI (r = 0.675). The threshold for diagnosing hypoxia in OSA patients using IHI was 7.178 (%s/min).

Conclusion: This study demonstrates that IHI calculated using NLAS covers various dimensions of IH indices in OSA patients undergoing multi-channel sleep monitoring. It correlates with parameters such as T90, $LSpO_2$, and ODI. Independent of existing IH assessment indices, IHI holds promise as a new comprehensive assessment index for evaluating the degree of nocturnal IH in OSA.

KEYWORDS

intermittent hypoxia, Newton quadrature low oxygen load assessment system, intermittent hypoxia index, obstructive sleep apnea, Newton-cotes formula

1 Introduction

According to epidemiological statistics, one billion people worldwide suffer from obstructive sleep apnea (OSA) (1). OSA is associated with many comorbidities such as hypertension, diabetes, arrhythmia, pulmonary arterial hypertension, and congestive heart failure (2).OSA is mainly characterized by recurrent episodes of upper airway collapse and obstruction during sleep (3), which can result in repeated hypoxia-reoxygenation of the body, i.e., intermittent hypoxia (IH), which is one of the main mechanisms underlying the pathophysiology of OSA-associated cardiovascular diseases and metabolic syndrome (4, 5). At present, the main indicators used to evaluate IH in OSA are lowest oxygen saturation ($LSpO_2$), sleep time with oxygen saturation below 90% (T90), and oxygen desaturation index (ODI). However, these indicators can only reflect a single pathophysiological feature of IH, evaluating only the duration, length or frequency of oxygen reduction, and cannot capture its overall characteristics, thus failing to serve as a comprehensive hypoxia evaluation indicator in clinical practice (6). In order to more accurately assess the severity of IH and its pathophysiological characteristics in OSA patients, Azarbarzin (7) et al. proposed hypoxic burden (HB). However, there is no relevant literature report on HB showing that it can be specifically measured directly from polysomnographic monitoring data. Based on this, we developed the NLAS to calculate the IHI using the Newton-Cotes formula and to assess its correlation with traditional hypoxic assessment metrics.

2 Methods

2.1 Study subjects

This was a retrospective study. Subjects were selected according to the inclusion criteria: (1) patients who met the diagnostic criteria and efficacy standards for OSA-hypopnea proposed by the American Academy of Sleep Medicine (AASM), and whose apnea-hypopnea index (AHI) was ≥ 5;. (2) Age 18–80 years old, male or female. Exclusion criteria: (1) AHI < 5; (2) unable to obtain original blood oxygen saturation information or complete PSG monitoring information; (3) diagnosed with chronic obstructive pulmonary disease, bronchial asthma, chronic bronchitis, restrictive lung disease, acute respiratory distress syndrome or other respiratory diseases, or having a minimum blood oxygen saturation when awake of less than 90%. Polysomnography data of 732 patients who underwent polysomnography monitoring using the Philips Alice polysomnography device at the Sleep Center of Wuxi People's Hospital Affiliated to Nanjing Medical University between January 1, 2019 and December 31, 2023 were included in the study. This study was approved by the Clinical Research Ethics Committee of Wuxi People's Hospital Affiliated to Nanjing Medical University (Ethics Number: KY24016).

2.2 Newton quadrature low oxygen load assessment system (NLAS)

NLAS is a computing software program that can be opened to all users after registration and login. For details, see File 1.The NLAS mainly consists of three modules: data collection, data analysis and data storage. The data collection module calculates and displays the duration, depth, and frequency of desaturation and IHI during the monitoring period; the main function of the data analysis module is comparative analysis, which displays the differences between oxygen desaturation index and IHI and the comparison of T90, T85, and T80 duration and oxygen desaturation index and hypoxic area. The data storage module has a memory function that can record all historical uploaded data and store it by time period. Users can click the query button to query. There is a scroll bar at the bottom of any module interface, and the left side shows the time of desaturation episodes, called abnormal results. Dragging the scroll bar or clicking the abnormal results on the left will produce data on the corresponding duration, depth, graphics and other information of desaturation.

Using NLAS, we analyzed the corresponding parameters of nocturnal IH and calculated the IHI value (Table 1). The specific method is as follows: NLAS uses the Newton-Cotes formula to calculate the area under the desaturation curve (If the decrease in

TABLE 1 Name and explanation of parameters involved in the Newton assessment system software for hypoxic load.

Parameter name (Unit)	Explanation
Total area (%*s)	The sum of the areas under all desaturation curves, that is, using the Newton-Cotes formula to calculate the area of a single desaturation curve, and then add them up to get the total area
Maximum area (%*s)	The maximum area under a single oxygen descent event
Average area (%*s)	The average area of all oxygen descent events, Average area = Total area / Number of desaturations
Maximum duration(s)	The longest time SPO_2 < 90% lasts in a single oxygen descent event, i.e., the longest oxygen reduction time
Minimum duration(s)	The shortest time SPO_2 < 90% lasts in a single oxygen descent event
Average duration(s)	The average time of all oxygen descent events, Average Duration = Sum of all oxygen descent times / Number of Desaturations
Maximum depth (%)	The amplitude at which the SPO_2 drops from the baseline to the lowest value in a single oxygen descent event, i.e., the maximum oxygen reduction
Average depth (%)	The average amplitude of SPO_2 drops in all oxygen descent events, Average Depth = Sum of SPO_2 drop amplitudes in all oxygen descents / Number of desaturations, i.e., average SPO2 drop amplitude
IHI (%s/min)	The total area under the desaturation curve calculated by NLAS using the Newton-Cotes formula divided by the total sleep time in minutes. The total area under the desaturation curve is calculated by the Newton-Cotes formula

oxygen saturation (SpO_2) was ≥ 3% of the baseline value, it was counted as one desaturation). This area is divided by the total sleep time (TST) in minutes to obtain the IHI (IHI is calculated in Supplementary file 1). In addition to IHI, the NLAS system can also calculate the maximum desaturated area, the average desaturated area, the longest duration, and the average desaturated depth of the patient's overnight desaturation event, and allows the user to view the time and frequency of the desaturation distribution, the duration of each desaturation event, the degree of oxygen drop and other information. It can provide data support for studying the relationship between the duration of respiratory related events, attack frequency, oxygen drop depth and comorbidities in OSA patients. The Newton-Cotes formula is a commonly-used formula that uses interpolation to calculate numerical integration. It is a special calculation method when the nodes are equidistant with the integration interval equally divided. It reflects the correlation between data and the integration of fluctuations. Because the values are simple by themselves without high-order derivatives, the result error is small. From the following formula, it can be seen that the trapezoidal formula only has first-order algebraic accuracy, while the Newton-Cotes formula can have fifth-order algebraic accuracy (different algebraic precision graphs are shown in Figure 1). Therefore, it has better stability and smaller errors. Unlike Excel and other calculation tools, Excel is only a calculation tool, there is no coding function, can not automatically identify desaturation, if it is used to calculate the hypoxic load, it is necessary to manually identify the graphs and data of each desaturation, and enter the calculation law one by one, and finally excel can calculate the AUC. Then the same piece of data, counted by different technicians will get different then the same data, counted by different technicians will get different results, which will affect the accuracy of the data. It is with this in mind that we have endeavored to solve this problem effectively by developing a calculation software.

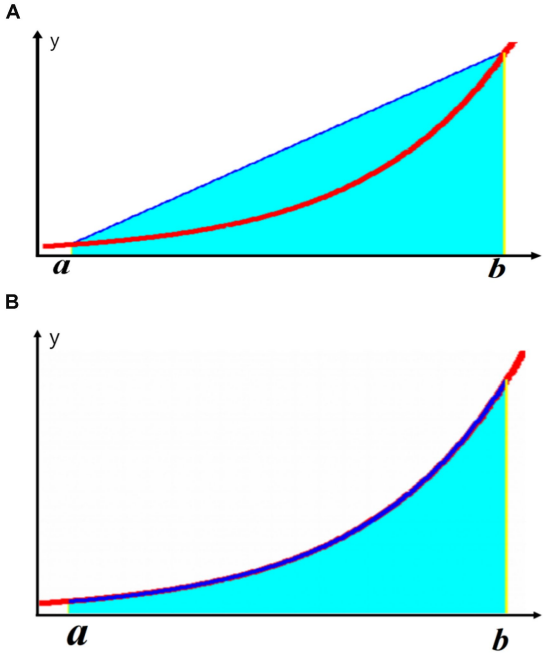

FIGURE 1
Illustration of different algebraic accuracies: **(A)** Trapezoidal formula; **(B)** Newton-Cotes formula.

Interpolating integration formula (8):

$$\int_a^b f(x)dx \approx \int_a^b P(x)dx = \sum_{k=o}^{n} A_k f(x)$$

$$\int_a^b f(x)dx \approx (b-a)\sum_{k=0}^{n} c_k^{(n)} f(x)$$

$$C_k^{(n)} = \frac{(-1)^{n-k}}{k!(n-k)!n}\int_0^n \prod_{\substack{j=0 \\ j\neq k}}^{n} (t-j)dt$$

2.3 Polysomnography (PSG) and intermittent hypoxia index (IHI)

2.3.1 PSG

We collected demographic and anthropometric characteristics of the study subjects, including gender, age, neck circumference, abdominal circumference, body mass index (BMI), and medical history. Sleep monitoring data were analyzed using Phillip G3 software. All patients included in the study underwent at least 8 h of overnight PSG. Standard electroencephalography (EEG) was used for PSG recordings, including frontal leads (F1, F2), central leads (C3, C4), occipital leads (O1, O2) and mastoid reference leads (M1, M2), electromyography (EMG), electrooculography (EOG) and monitoring of thoracoabdominal movements. Oxygen saturation was measured by pulse oximetry. Recordings and analyses were performed by experienced sleep lab technicians following the standard protocols recommended by the AASM. Apnea was defined as a drop of ≥ 90% of baseline in the peak signal of respiratory airflow monitored by nasal pressure, accompanied by persistent or enhanced inspiratory effort (thoracoabdominal movement present). Hypopnea was defined as a drop of ≥ 30% of baseline peak signal of respiratory airflow monitored by nasal pressure, lasting ≥ 2 breathing cycles, accompanied by ≥ 3% oxygen desaturation from pre-event baseline or with arousal. Regarding hypoxemia parameters, the lowest SpO_2 ($LSpO_2$) was the lowest oxygen saturation during sleep; T90 was the total sleep time spent with oxygen saturation below 90%; ODI was defined as the average number of desaturations per hour, if average oxygen saturation decreased ≥ 3% from baseline value, lasting for at least 10 s, it was counted as one desaturation event.

2.3.2 IHI and calculation method

Regarding the concept of hypoxic load, the research literature reports so far have mainly used the rectangular formula (9), trapezoidal formula (2) or triangular formula (7, 10) methods to calculate the total area under the desaturation curve. The rectangular area formula involves individually selecting the values corresponding to each time point as the length and width of the rectangle, and finally summing the rectangular area of the time period (see Figure 2A); the trapezoidal area formula is similar to the rectangular

area formula, but divides each figure into multiple small trapezoids, and finally sums the area (see Figure 2B). Wenhao (10) took the duration of apnea or hypopnea as the base, the depth of oxygen desaturation as the height, and approximated the desaturation graph as a triangle, using the triangular formula to calculate the total area under the desaturation curve (see Figure 2C). By observing the blood oxygen trend graph of PSG monitoring, it can be seen that the area under the desaturation curve formed when IH occurs at night in patients with OSA is mostly an irregular and dynamically-changing graph (see Figure 2D), and thus neither the triangular formula, trapezoidal formula, nor the rectangular formula can accurately reflect and calculate the actual hypoxic load in patients with OSA. In order to calculate the area under the desaturation curve more accurately, we tried different calculation methods, and finally, according to the characteristics of the nocturnal dynamic desaturation graphs of OSA patients, we chose the Newton-Cotes formula, which is a function formula with algebraic precision (see Figure 2E, the red line is the area under the desaturation curve calculated by the Newton-Cotes formula with lower algebraic precision, and the dashed line is the Newton-Cotes formula with higher algebraic precision; it can be seen that more accurate results can be obtained when the algebraic precision is high). The NLAS was developed to calculate the IHI by dividing the total area under the desaturation curve calculated using the Newton-Cotes formula by the TST in minutes (see Figure 3), and the NLAS was used to calculate the IHI by dividing the area under the desaturation curve by the TST in minutes. If the decrease in oxygen saturation (SpO_2) was ≥ 3% of the baseline value, it was counted as one desaturation, with the time at which SpO_2 began to fall as the starting point and the time at which oxygen saturation returned to its maximum value as the endpoint, and the graph of the starting point, endpoint, and the oxygen drop and reoxygenation delineating the area of desaturation was plotted (shaded in Figure 3). The portion of the curve where the SpO_2 was less than 30% was regarded as the error of measurement and excluded.

2.4 Statistical analysis

Normally-distributed variables are expressed as mean ± standard deviation (X ± SD). Non-normally-distributed measurement data are expressed as quartile spacing M (P25, P75). Categorical data are described using frequency and percentage. A receiver operating characteristic (ROC) curve was used to calculate the threshold of IHI. The Pearson correlation coefficient was used to analyze the correlation between IHI and the hypoxic indicators ODI, T90, $LSpO_2$ and the indicators representing the various dimensions of IH calculated by the software described above. $p < 0.05$ was considered statistically significant. All data analyses were performed using SPSS 26 statistical software (IBM SPSS Statistics for Windows, Armonk, NY, USA).

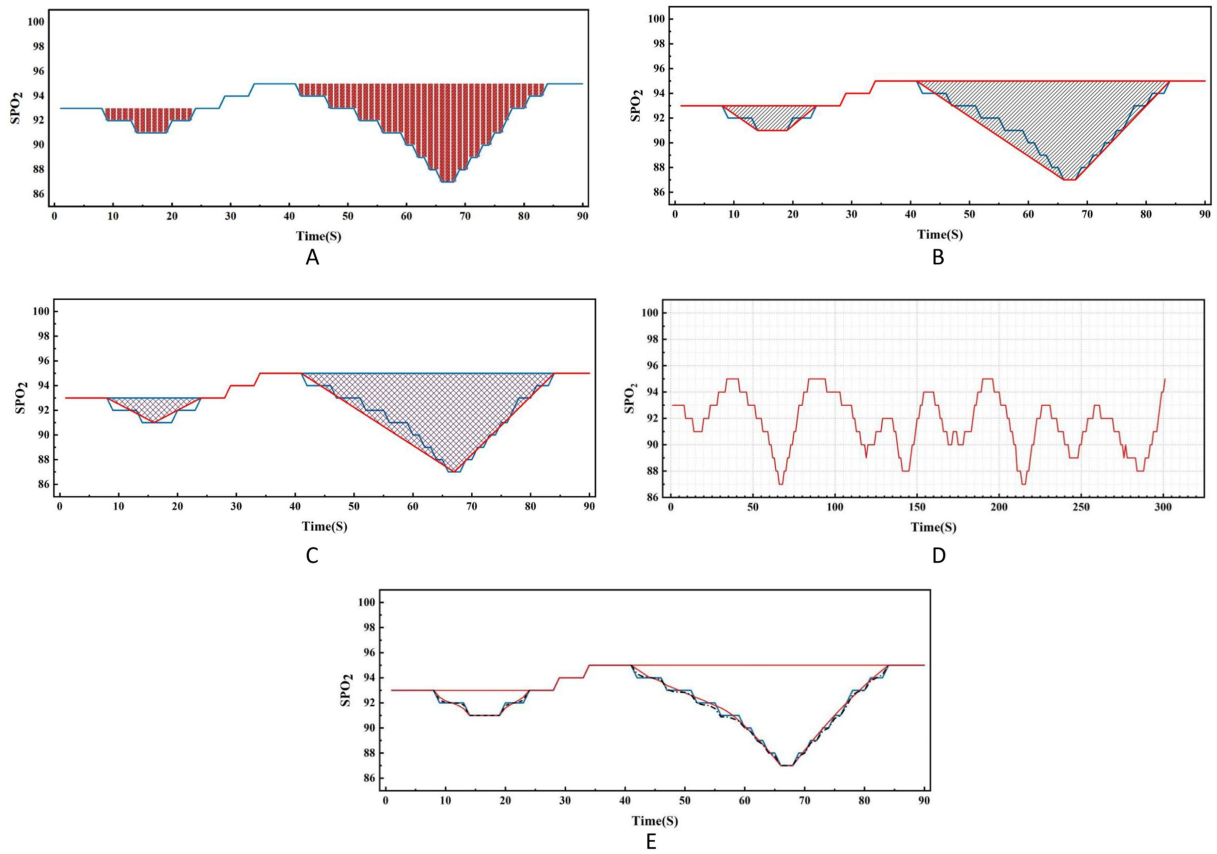

FIGURE 2
Comparison of nocturnal desaturation graph of OSA patient and various calculation methods.

3 Results

3.1 General information

Table 2 presents the general information of the study subjects. A total of 732 patients with OSA were included in this study, with an average age of 44.58 years. Among them, there were 647 male patients (88.40%) and 85 female patients (11.60%). The mean values for neck circumference, waist circumference, and BMI were 40.61 cm, 102.53 cm, and 29.75 kg/m^2, respectively. The median value of the AHI was 47.20, ranging from 5 to 138.3. The proportions of mild, moderate, and severe OSA were 14.10, 17.90, and 68%, respectively. The median values for ODI and time spent below 90% oxygen saturation (T90) were 41.30 and 23.60, respectively. The median value of the lowest oxygen saturation ($LSpO_2$) was 76.00% (ranging from 30 to 94%). Based on the grouping of patients according to the lowest blood oxygen saturation, the proportions of mild, moderate, and severe hypoxia were 18.17, 17.90, and 58.73%, respectively.

3.2 Calculation of IHI threshold value

A lowest oxygen saturation value of less than 90% is considered a state of hypoxia (7, 11), that is, the IHI value corresponding to a minimum blood oxygen saturation of 90% is the threshold for determining whether a patient has hypoxia. Taking the current $LSpO_2$ as the standard for judging the degree of hypoxia, the ROC curve of IHI and $LSpO_2$ (Figure 4) had an AUC of 0.397 (95% confidence interval 0.913–0.960, $p < 0.001$, see Table 3), with an optimal cutoff value of 7.178. That is, the threshold for using IHI to diagnose intermittent hypoxia was 7.178 (%s/min).

3.3 Correlation between IHI and PSG parameters

Pearson's chi-squared test showed that the participants' IHI was strongly correlated with T90 ($r = 0.922$, $p < 0.001$, Figure 5A); there was a significant negative correlation between IHI and $LSpO_2$ ($r = 0.866$, $p < 0.001$, Figure 5B); IHI also showed good correlations with ODI ($r = 0.675$, $p < 0.001$, Figure 5C).

4 Discussion

Currently, $LSpO_2$, ODI, and T90 are the main clinical assessment indicators for determining the occurrence of IH and the severity of hypoxia in patients with OSA (6). Kainulainen et al. (11) found that the depth of desaturation negatively affects vigilance and the ability to maintain attention, which may lead to cognitive deficits in patients with OSA. ODI is the most widely used oxygen saturation parameter for assessing OSA and its co-morbidities (9), and is associated with subclinical atherosclerosis associated with OSA, all-cause mortality in heart failure, and post-procedural complications (6), as well as the QT variability index (QTVI), a measure of ventricular repolarization instability that predicts ventricular arrhythmias and sudden cardiac death (12). An article by Solhjoo (12) and others demonstrated that T90 is a predictor of QTVI. These studies suggest the need for an objective assessment of the degree of hypoxia in OSA in terms of the frequency, depth, and duration of desaturation in multiple dimensions.

To provide a more comprehensive assessment of nocturnal hypoxia in patients with OSA, Azarbarzin et al. (7) introduced the concept of hypoxic burden (HB). For clinical convenience, Fengwei Chen et al. (9) proposed the hypoxic burden index (HBI) as an alternative indicator to HB. Similar indices include hypoxic load (HL_{100}) (2) and sleep breathing impairment index (SBII) (10). With these different measures, the degree of hypoxia in OSA patients cannot be accurately assessed clinically. However, all these indices have shortcomings in accurately calculating the total area under the desaturation curve. Researchers have mainly used rectangular, trapezoidal and triangular fixed graphical patterns to simulate and calculate the total area under the desaturation curve (2, 9, 10), but the area under the nightly desaturation curve in OSA patients is mostly irregular and dynamic, and the simulation method of fixed graphical patterns ignores and removes the correlation and fluctuation between the values. The rectangle method divides the area into numerous small rectangles, using individual values at each time point as the length and width of the rectangle. While it may seem precise, it does not consider the relationships between the numerical values. The trapezoid method faces similar issues, and the triangle method approximates the

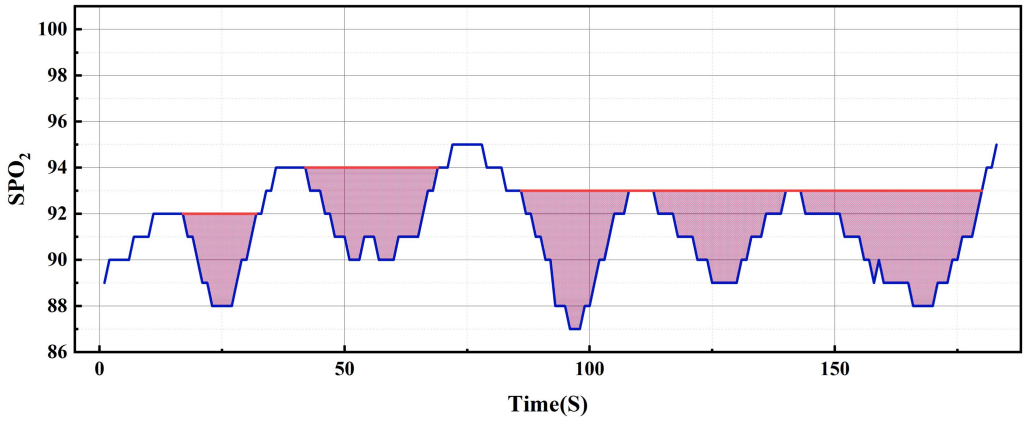

FIGURE 3
Graphical representation of the calculation of the intermittent hypoxia.

TABLE 2 General information of study subjects.

Characteristics of study subjects (n = 732)	Numerical values
Age (years)	44 ± 13
Men, n (%)	647 (88.40%)
Women, n (%)	85 (11.60%)
neck circumference	40.61 ± 3.85
waist circumference	102.53 ± 17.69
BMI	29.75 ± 5.00
AHI (times per hour)	47.2 (24.1, 71.2)
Mild OSA, n (%)	103 (14.10%)
Moderate OSA, n (%)	131 (17.90%)
Severe OSA, n (%)	498 (68%)
ODI (times per hour)	41.30 (20.50, 69.70)
T90 (min)	23.60 (3.1, 111.35)
$LSPO_2$%	76.00 (64.00, 84.00)
Non hypoxia, n (%).	38 (5.20%)
Mild hypoxia, n (%)	133 (18.17%)
Moderate hypoxia, n (%)	131 (17.90%)
Severe hypoxia, n (%)	430 (58.73%)

Note: Normally-distributed variables are expressed as the means ± SD, whereas the non-normally distributed measures are expressed as interquartile spacing M (P25, P75), and categorical data are described by frequencies and percentages. Mild OSA: 5 ≤ AHI ≤ 15; Moderate OSA: 15 < AHI ≤ 30; Severe OSA: AHI > 30; Non hypoxia: $LSpO_2$ > 90%; Mild hypoxia: 85% ≤ $LSpO_2$ < 90%; Moderate hypoxia: 80% ≤ $LSpO_2$ ≤ 84%; Severe hypoxia: $LSpO_2$ < 80%.

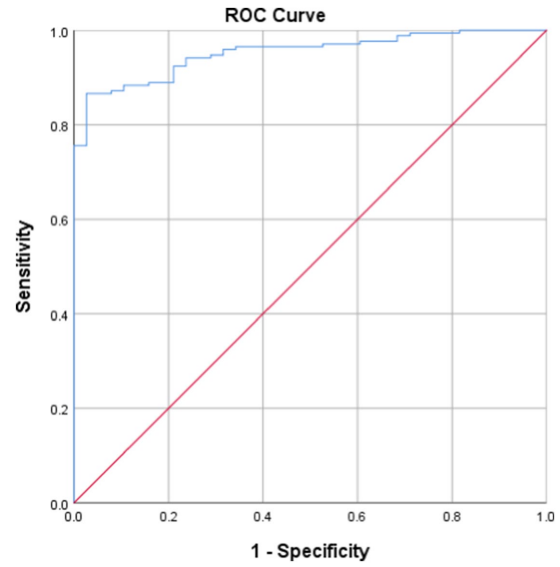

FIGURE 4
ROC Curve.

TABLE 3 ROC curve analysis.

95% Confidence interval					
AUC	p-value	Lower limit	Upper limit	Odds ratio	Optimal cutoff value
0.937	<0.001	0.913	0.960	0.805	7.178

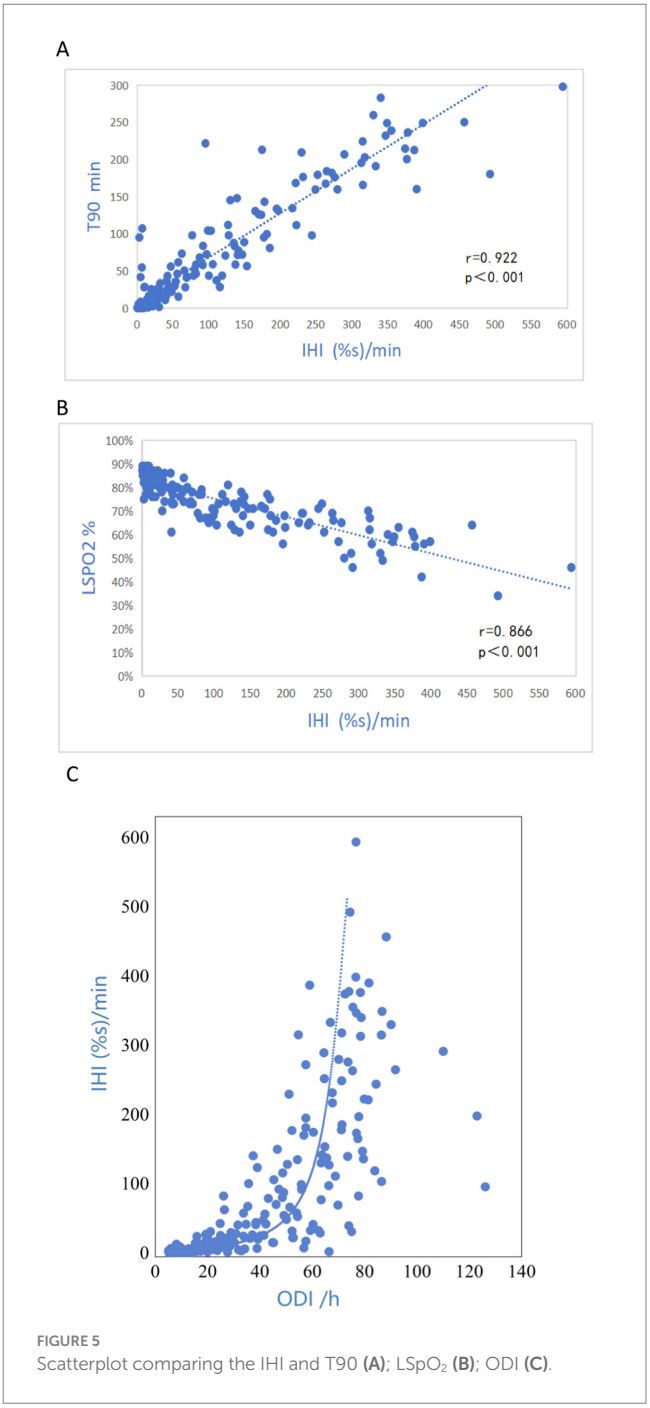

FIGURE 5
Scatterplot comparing the IHI and T90 **(A)**; $LSpO_2$ **(B)**; ODI **(C)**.

desaturation curve as a triangle, which can lead to significant errors. For example, Trzepizur et al. (13) reported that the median HB value they calculated was approximately 10 (% min)/h lower than that derived from a similar sample in the Sleep Heart Health Study (SHHS) conducted by the National Heart, Lung, and Blood Institute in the United States. There is a lack of standardized calculation criteria for HB, and given the graphical characteristics of dynamic changes in nocturnal IH shown under PSG monitoring, software is needed to assist in calculating the area

under the desaturation curve (14). To address the shortcomings of previous calculation methods, our research team developed the Newton-Cotes formula-based NLAS. This formula allows for the calculation of the total area under the desaturation curve with different degrees of algebraic accuracy based on numerical changes. It reflects the integral situation of the correlation and fluctuation changes between data. Utilizing NLAS, we identified a new comprehensive evaluation index called the IHI, which simultaneously reflects information on the duration, frequency, and depth of desaturation, providing a more comprehensive characterization of the severity of IH in OSA patients.

Existing studies suggest that when oxygen saturation is above 90% and oxygen partial pressure exceeds 60 mmHg, mild decreases in blood oxygen should not impact cellular physiological functions and should not be considered as hypoxia (15, 16). The prognosis of OSA is closely associated with blood oxygen saturation falling below 90%, with $SpO_2 < 90\%$ considered an independent predictor of mortality (17, 18). Therefore, in this study we defined hypoxia as having the lowest blood oxygen saturation below 90%. As mentioned above, IHI=S/TST, calculate the total area under the desaturation curve S by the following steps:

$$\int_a^b f(x)dx \approx (b-a)\sum_{k=0}^{n} c_k^{(n)} f(x)$$

$$C_k^{(n)} = \frac{(-1)^{n-k}}{k!(n-k)!n}\int_0^n \prod_{\substack{j=0 \\ j\neq k}}^{n} (t-j)dt$$

The parameters T90, LSPO2, and ODI are not included in the calculation of the IHI. They reflect individual pathophysiological characteristics of intermittent hypoxia, such as the duration, length, or frequency of oxygen desaturation. The IHI encompasses different dimensions of intermittent hypoxia indicators currently used in polysomnography for OSA patients and has a correlation with indicators such as T90, LSPO2, and ODI. The IHI is independent of existing intermittent hypoxia assessment indicators. This indicated that IHI, as a comprehensive evaluation index for IH, objectively reflected the severity of nocturnal hypoxia from multiple dimensions, including the duration, frequency, and depth of desaturation.

It is inescapable that this study has some limitations. First, our sample included more patients with severe OSA than other groups and the male-to-female ratio was unbalanced; second, the fact that the nocturnal minimum oxygen saturation in OSA patients was generally lower than 90% resulted in a higher positive rate of diagnosing hypoxia in patients using $LSpO_2$, which may have caused a certain degree of error in the calculation of the threshold.

In summary, the IHI established based on NLAS covers different dimensions of hypoxia assessment indexes during sleep in OSA patients, and is expected to become an independent and comprehensive assessment index for nocturnal hypoxemia in OSA patients to compensate for the shortcomings of the existing IH assessment indexes.

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 humans were approved by the Clinical Research Ethics Committee of Wuxi People's Hospital Affiliated to Nanjing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

KX: Writing – review & editing, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing – original draft. XT: Data curation, Writing – original draft. JZ: Data curation, Writing – original draft. XL: Software, Writing – original draft. YZ: Resources, Writing – review & editing. XC: Methodology, Resources, Software, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

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.2025.1400376/full#supplementary-material

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