

Novel technologies in the diagnosis and management of sleep-disordered breathing, volume II

Edited by

Ding Zou and Henri Korkalainen

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Novel technologies in the diagnosis and management of sleep-disordered breathing, volume II

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Editorial: Novel technologies in the diagnosis and management of sleep-disordered breathing, volume II

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Editorial on the Research Topic

Novel technologies in the diagnosis and management of sleep-disordered breathing, volume II

Volume II of our *Frontiers* Research Topic Series was completed in September 2024. Although nearly a year passed before we began drafting the editorial, this delay proved advantageous. The intervening period witnessed notable advances in the field of sleep-disordered breathing (SDB), allowing us to reflect not only on the contributions of this volume but also on the rapidly evolving scientific landscape in which these studies are situated. For example, key regulatory milestones were achieved, including the approval of the first pharmacological treatment for obese patients with obstructive sleep apnea (OSA) by the U.S. Food and Drug Administration (Lisik and Zou, 2025). The American Academy of Sleep Medicine also released guidelines for the treatment of central sleep apnea, underscoring the dynamic and evidence-based evolution of clinical practice (Badr et al., 2025). Furthermore, projections indicate that by 2050 nearly 77 million U.S. adults aged 30–69 will be living with OSA, a 35% increase compared with 2020 (Boers et al., 2025). The global health and economic costs are enormous: health systems are strained by diagnosis delays (overnight polysomnography is resource-intensive) and low adherence to conventional therapies (e.g. CPAP). These challenges have motivated the development of novel diagnostic and management technologies for SDB and the recent developments provide important context for the diverse contributions featured in this volume.

Genetic insights

Genetic research has long contributed to our understanding of SDB, from early candidate gene studies implicating pathways related to obesity, craniofacial development, and ventilatory control, to more recent genome-wide association studies. Within this broader context, Mendelian randomization (MR) has emerged as a methodological framework that leverages genetic variation to make causal inferences about the relationship between exposures and outcomes. MR is often

described as a form of “nature’s randomized trial,” because the random allocation of alleles during meiosis approximates the randomization process used in clinical trials (Smith and Ebrahim, 2003). This approach has gained traction in sleep research because it helps disentangle correlation from causation, a particularly pressing challenge given the multifactorial nature of OSA and its numerous comorbidities.

Three studies in this volume applied MR to examine associations between OSA and diverse outcomes. Gong et al. utilized the GSE135917 OSA gene dataset, derived from subcutaneous adipose tissue samples of OSA patients. Through weighted gene co-expression network analysis, they identified two critical genes, CETN3 and GTF2A2, that may contribute to OSA pathogenesis. These findings suggest new molecular targets for further investigation, potentially paving the way toward biomarker-driven precision medicine. Yang et al., drawing on data from the National Health and Nutrition Examination Survey (NHANES), reported a causal link between OSA and increased risk of osteoarthritis, with body mass index serving as a mediator. This highlights the intertwined relationship between SDB, obesity, and musculoskeletal health, and suggests that comprehensive management of OSA may also confer benefits beyond sleep, particularly in reducing osteoarthritis burden. In contrast, Hou et al. analyzed data from the FinnGen database and found no causal evidence that genetically predicted OSA leads to chronic kidney disease, contradicting the findings from observational studies. However, higher blood urea nitrogen (BUN; a marker of renal dysfunction) predicted increased OSA risk. This suggests that renal impairment may exacerbate OSA or share common pathways, but specific pathways remain elusive. Although negative findings often receive less attention, this helps refine hypotheses and redirect future efforts.

Together, these MR studies emphasize the complexity of OSA as both a consequence of genetic predisposition and a risk factor for systemic disease. However, the rise of MR has not been without controversy. The method depends on strong assumptions: namely, that the selected genetic variants influence the outcome only through the exposure of interest, are not linked to other pathways (no horizontal pleiotropy), and are robustly associated with the exposure. When these conditions are not met, results can be biased and misleading (Evans et al., 2025). Given the methodological intricacies of MR, it is recommended that future investigations adhere to the MR-SLEEP guidelines, which provide a structured framework for robust study design and interpretation (Evans et al., 2025).

Epidemiology, comorbidities, and the burden of OSA

Several contributions in this volume highlight the global prevalence of SDB and its far-reaching clinical consequences. Wang et al. reported striking differences in SDB prevalence among patients with multiple system atrophy, documenting a prevalence of 79% in an Asian cohort compared with 42% reported in European populations. These findings raise important questions about genetic, environmental, and diagnostic factors that may

account for the disparity. Moreover, the results highlight the need for efficient screening in populations with a high likelihood of SDB.

The interplay between OSA and infectious disease was examined by Dinh et al., who demonstrated that moderate-to-high risk of OSA is associated with more severe manifestations of COVID-19. The authors postulated that dysregulated inflammatory responses in OSA patients contribute to worse outcomes, reinforcing the concept that sleep health is integrally tied to immune function. Mental health comorbidities were also explored. Li et al. applied latent profile analysis to depressive symptoms in NHANES participants with OSA symptoms, identifying distinct clusters in the population, illustrating the heterogeneity of psychological burden in OSA patients. Collectively, these studies reinforce the urgent need to improve diagnostic pathways for OSA and to acknowledge its systemic consequences.

In line with these findings, Pittman et al. convened a group of experts to critically evaluate the challenges of OSA management facing in the United States. They identified five domains requiring urgent reform: (1) simplify the patient journey, (2) bridge the communication gaps, (3) expand the monitoring over several nights for serial assessments and therapy titration, (4) update the care models to avoid provider shortages and burnout, and (5) align the financial models to reward high-quality care. Their work represents a call to action for structural change and highlights the necessity of aligning healthcare delivery with the realities of OSA’s widespread burden.

Mechanistic and biomarker studies

To advance mechanistic understanding of OSA and explore novel biomarkers, Howarth et al. investigated electroencephalogram (EEG) power spectral densities in patients with mild OSA. They reported a positive association between relative delta frequency power and excessive daytime sleepiness as assessed by the multiple sleep latency test. These results suggest that mild OSA patients with elevated delta activity may experience increased sleep drive, a finding that raises conceptual questions about how to distinguish excessive sleepiness from excessive need for sleep. Biomarker discovery was advanced by Liu et al., who conducted the first study of claudin (CLDN) proteins, key regulators of barrier function, in OSA. Their analysis revealed that plasma and urine CLDN levels decreased in OSA patients, and especially urinary CLDN3 was inversely associated with OSA severity. These findings are intriguing, as they suggest a possible mechanistic link between intermittent hypoxia, intestinal mucosal integrity, and altered biomarker expression. Future studies are needed to determine whether disrupted epithelial barriers contribute to systemic consequences of OSA.

Cardiovascular insights and heart rate dynamics

Cardiovascular complications represent one of the most significant consequences of OSA. While physiological signals representing the cardiovascular status are routinely measured

during sleep recordings, they often remain underutilized. Heart rate, for example, has traditionally been viewed as supplementary to respiratory or oxygenation metrics in sleep studies. However, emerging research underscores its value as a sensitive marker of autonomic and cardiovascular stress. Hilmisson et al. employed photoplethysmography (PPG) based cardiopulmonary coupling analysis (Thomas et al., 2005) to derive heart rate measures during sleep. They reported that each one beat per minute increase during stable non-REM sleep corresponded to a 4.4% higher likelihood of nocturnal non-dipping blood pressure, an established cardiovascular risk factor. These findings support the proposition that nocturnal heart rate dynamics may serve as accessible and clinically relevant markers for cardiovascular health assessment in OSA patients (Azarbarzin et al., 2025).

Technological innovations and protocol development

Innovation in therapeutic strategies and methodological rigor is also reflected in this volume. O'Connor Reina et al. clarified the development of a smartphone-based application for myofunctional therapy, designed to strengthen pharyngeal dilator muscle control in OSA patients. This work reflects the broader trend toward digital therapeutics, which offer scalability and accessibility for tailored therapy.

Additionally, Kobayashi Frisk et al. presented a systematic review protocol aimed at synthesizing evidence on multidimensional sleep health (Buysse, 2014) and cardiovascular disease. Protocol publications are valuable for enhancing transparency and reducing bias, and this initiative signals a growing recognition of the need to move beyond unidimensional measures of sleep (e.g., sleep duration) toward more holistic conceptualizations.

Future directions in OSA management

Taken together, the studies in this volume underscore that the field of sleep medicine is progressing rapidly, both in diagnostic precision and therapeutic innovation. Yet, realizing the benefits of these advancements will require systemic transformation. The World Health Organization's recent report envisions care pathways that integrate home sleep apnea testing, telemonitoring, and virtual consultations to accelerate access and tailor management (WHO, 2025). Such pathways not only streamline diagnosis and treatment but also hold promise for improving patient outcomes by reducing delays and increasing personalization (Zou et al., 2023).

At the same time, the integration of machine learning, advanced diagnostic modalities, and novel therapies heralds a new era of personalized medicine in sleep care. However, successful translation of advanced diagnostics and personalized treatments from research into clinical practice will require careful validation in large-scale, diverse populations (McNicholas and Korkalainen, 2023; Oks et al., 2025). Moreover, innovations must be accompanied by health system reforms to ensure equitable access, particularly for underserved populations disproportionately affected by OSA. Equally critical is the training of healthcare professionals as new diagnostic technologies, digital health

platforms, and personalized therapeutic strategies will necessitate continuous education and interdisciplinary collaboration (McNicholas et al., 2025a). Sleep medicine increasingly intersects with respirology, cardiology, endocrinology, neurology, and psychiatry, reinforcing the need for collaborative approaches that transcend traditional disciplinary boundaries. Finally, addressing the systemic burden of OSA requires not only technological and clinical innovation but also policy-level interventions (McNicholas et al., 2025b). Financial models must evolve to reward high-quality, patient-centered care, and workforce challenges must be mitigated through strategic planning and resource allocation.

Conclusion

Volume II of our *Frontiers* Research Topic series captures a pivotal moment in sleep medicine, showcasing studies that range from molecular genetics to health policy. Together, these contributions reinforce the view of OSA as a complex, multifactorial disorder with implications across nearly every organ system. At the same time, they illuminate new avenues for diagnosis, treatment, and health system reform. The field stands at the threshold of a transformative era, and the challenge ahead is to translate these scientific advances into tangible benefits for patients worldwide (Kryger and Thomas, 2025).

Author contributions

DZ: Conceptualization, Project administration, Writing – original draft, Writing – review & editing. HK: Conceptualization, Writing – original draft, Writing – review & editing.

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The future of sleep apnea management: we can either ride the bus or drive it

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This consensus conference report summarizes discussions on sleep apnea care and management. Our goal is to simplify the journey to optimize success for individuals at risk of obstructive sleep apnea and to facilitate diagnostics, monitoring and communication among the entire healthcare team including patients, primary care physicians, sleep specialists, sleep dentists and other key providers. The statement identifies five key problems or unmet needs and contemplates four potential future directions.

KEYWORDS

obstructive sleep apnea (OSA), continuous positive air pressure (CPAP), home sleep apnea test (HSAT), value-based care, patient journey, oral appliance therapy

Our goal is to simplify the journey to successful diagnosis and treatment of obstructive sleep apnea (OSA) and to facilitate communication among providers and between patients and providers. Such providers may include primary care physicians, sleep specialists, sleep dentists and others.

OSA is thought to affect up to 1 billion people worldwide although, due to logistics, current diagnostic strategies are challenging (Benjafield et al., 2019). The current gold standard approach of seeing a board-certified sleep specialist followed by polysomnography or home sleep apnea testing with a technically adequate device is unlikely to be scalable to assess the global burden of disease particularly given that many more patients are at risk of OSA. Further complicating scalability is the expected increase in prevalence due to the obesity pandemic and the aging of the population (Mulgrew et al., 2007; Rosen et al., 2012). We convened a consensus conference of key stakeholders to discuss potential future approaches to sleep apnea care and management. The conference was sponsored by Wesper, but the sponsor had no role in guiding the discussion or summarizing conclusions which were at the discretion of the co-chairs (SDP, AM).

1 Introduction

The group met via Zoom teleconference in March 2022 with a robust discussion moderated by the co-chairs. Three session topics were used to guide discussions: personnel + communication, equipment, and financial models. Documents were circulated to seek input yielding this proceedings summary. The participants were chosen to provide diversity both from the perspective of training background (e.g., dentist, physician, technologist, health economist, and patient advocate) and various health systems (e.g., Veteran Affairs, Kaiser Permanente, academic medical centers, non-academic medical centers, private practice, and industry). We further sought input via follow-up calls from key opinion leaders who were unable to participate in the interactive discussion, but whose opinions were valued. Their comments contributed to the final summary. A few topics like financial models were taken offline to dive deeper into these topics with subject matter experts. The details of these more granular topics were summarized in this final document.

2 Problems and unmet needs

The current framework for this document uses the conference discussions to define problem(s) and identify unmet needs rather than attention on specific solutions. Our goal in agreeing on problems and unmet needs was to establish a strong foundation or baseline on which to propose future directions toward solutions for the benefit of all OSA patients.

2.1 Patient journey needs to be simplified

At present, some health systems encourage an initial evaluation by a primary care physician followed by a sleep consultation and evaluation with a specialist (Hwang et al., 2018). The specialist may then order a polysomnogram or home sleep apnea test. The patient is scheduled for a subsequent follow-up visit where the patient returns to the specialist to discuss the results and may be prescribed treatment, usually PAP therapy. Though some practices incorporate the distribution of durable medical equipment (DME) into their clinical flow, oftentimes the patient receives the PAP therapy through a home care company, only to have to return to the specialist a few months later for monitoring and evaluation. While multiple visits may be appropriate, they can be perceived as burdensome to patients and thus alternative care models to improve efficiency may be well received. In principle, a subset of patients at risk of OSA could undergo diagnostic testing at the discretion of a provider or at the request of a concerned patient. In such a model, patients could be prescribed therapy without the need for multiple visits to confirm what may be clinically obvious. One common example is the high volume of patients undergoing

bariatric surgery (Lee et al., 2009; Sareli et al., 2011; Rodbard, 2016; Horvath et al., 2018; Kreitinger et al., 2020; Raphelson et al., 2022). Such patients have high pre-test probability for OSA and the data suggest increased risk of perioperative complications in people with OSA undergoing bariatric surgery (Glazer et al., 2018; Ahlin et al., 2019). Thus, a reasonable approach could involve an initial diagnostic test in these patients without the need for additional visits for routine cases. One challenge exists when serial nights of data are required for optimal patient care (Lechat et al., 2023). Currently, the patient would repeatedly return to clinic or receive serial mailings to get diagnostic equipment because most existing medical technology does not allow serial assessments over multiple nights. While objective testing is an important aspect of the patient journey, explanation of testing results, review of appropriate treatment options, and long-term monitoring of therapeutic outcomes remain essential steps in the journey to ensure optimal patient outcomes.

2.2 Enhanced communication is needed

A number of participants expressed concern about the lack of communication that sometimes occurs between various providers e.g., dentists and doctors, sleep providers and surgeons, providers and durable medical equipment (DME) companies, etc. In some cases, the participants described competition rather than collaboration despite general acknowledgment that the pool of patients potentially seeking treatment is vast. Secure communication is often a challenge since various providers may not use the same electronic health records system, e.g., many dental offices use dental software that does not typically integrate with medical electronic health record (EHR) platforms. Alternative communication methods such as text messaging and email may not be HIPAA compliant. In some cases, experienced providers reported receiving the most difficult cases (sometimes described using the pejorative term “train wrecks”) after other therapies had been exhausted. For example, patients who are morbidly obese and have failed positive airway pressure (PAP) therapy going to a dentist for an oral appliance as a last resort (Mohammadih et al., 2022). There was general agreement that secure communication strategies using universally accepted standards for communication and data should be enhanced and that identifying patients with high likelihood for success would be helpful to all parties involved. Future collaborative communications might include, but not limited to, monitoring patients via telemedicine and employing wearable technology, particularly cloud-based systems that can be accessed by the diverse healthcare team.

2.3 Expanded scope for monitoring is needed for serial assessments and therapy titration

Most diagnostic approaches currently provide one night of data. Many factors can contribute to night-to-night variability including patient familiarity with the equipment, changes in body

Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; DME, durable medical equipment; HIPAA, Health Information Portability and Accountability Act; HIV, human immunodeficiency viruses; OSA, obstructive sleep apnea; PAP, positive airway pressure; US, United States.

posture, sleep stage distribution, alcohol intake, nasal congestion, etc. Multiple nights of data would be helpful in solidifying or informing context toward diagnosis (Stoberl et al., 2017). In addition, over time many factors can change including body weight or during titration of therapy, such that serial data over weeks or months would be helpful in guiding treatment for some patients.

A major contributor to optimizing therapy adherence is patient engagement which can be enhanced by providing objective data (Malhotra et al., 2018), e.g., improvement in OSA and metabolic risk in the context of weight loss (Chirinos et al., 2014). In the case of oral appliances, tracking residual OSA while using treatment can be helpful since additional mandibular advancement and/or other adjustments could be made, guided by objective data (Cistulli and Gotsopoulos, 2004). In patients with substantial comorbidities, e.g., COPD or CHF, serial data would be helpful in guiding sleep therapy particularly given the dynamic nature of these diseases. In some cases, exacerbations of COPD or CHF may be predicted by deterioration in sleep parameters as a harbinger of impending decompensation (Shorofsky et al., 2019; Do et al., 2022a,b). Early identification of patients at risk of hospitalization or readmission may allow targeted interventions potentially resulting in reduced healthcare costs (Light et al., 2018; Sterling et al., 2022).

2.4 Provider shortage and burnout accelerate need for updated care models

As previously stated, given the global burden of disease, the number of board-certified sleep specialists is unlikely adequate to address the volume of patients affected and at risk. Even among sleep technologists, respiratory therapists and nurses, there are current shortages in adequately trained personnel as many are choosing alternative job opportunities. Existing providers and staff are experiencing burn out due to multiple complex factors. However, the addition of extra data may impose a further burden on some individuals. For example, endocrinologists experienced a considerable workload with the advent of continuous glucose monitoring since the volume of data markedly increased, placing a burden on already stretched providers (Rodbard, 2016; Verbraecken, 2021).

Automation may be one solution to simplify routine tasks since a sophisticated algorithm could provide robust summary data and perhaps flag any outliers requiring expert review. Patient engagement is another strategy whereby the extra data become the responsibility of the patient (with appropriate disclaimers) and can be used to create peer group motivation rather than an extra burden on providers (Hoy et al., 1999). Nonetheless, expert providers will clearly be required on an ongoing basis for review of outlier data, for quality control performing routine audits of a percentage of patients to provide reassurance, and for concierge patients who prefer traditional models of care. Members of the sleep team like psychologists, nurse practitioners, physician assistants and sleep navigators with specialized and focused training are also a resource for consideration.

2.5 Financial models are needed that reward high quality care

Today, many US health systems use volume-based purchasing rather than value-based purchasing. The volume approach rewards *quantity* of care whereas in theory the value-based system rewards *quality* of care. Clearly, both approaches have merit since a variety of financial models are needed as the cost to provide care increases and budgets become more constrained. In a volume-based scenario, the development of care management service codes by US Medicare could be used to reward efforts used for remote patient or physiological monitoring (RPM) and may be one tool to improve outcomes and generate revenue. In addition, if increasing automation and assistant scoring of sleep studies occurs, the loss of professional revenue from interpreting reports could be addressed by rewarding high quality care based on avoiding subsequent health care costs (Pittman et al., 2004; Malhotra et al., 2013). However, we anticipate with improved efficiencies, increased volume would preserve financial viability.

In a value-based scenario, careful consideration must be given to the selection of robust validated quality metrics. Objectively captured data could be used to identify and define leading indicator(s) that predict important patient centric outcomes which are often lagging indicators. Some recent data suggest physician time expended on trying to achieve certain quality metrics does not yield better patient outcomes (Panzer et al., 2013; Saver et al., 2015; Adler, 2018). It is possible that OSA may be a disease that that could be part of a well-designed value-based care model, as evidence grows about the associated benefits of OSA treatment with cardiovascular risk reduction, reduction of hypertension, improvement of neurocognitive outcomes, etc. Additionally, evidence is growing with respect to the association of OSA treatment and reductions in health care resource use and costs. For example, treating OSA may reduce costs of various other interventions by preventing medical complications, motor vehicle accidents, etc. (Ayas et al., 2006; Strohl et al., 2013). In the case of chronic obstructive pulmonary disease, recent data showed a reduction in ER visits and hospitalizations with the consistent use of PAP therapy for OSA as compared to patients not consistently using PAP (Sterling et al., 2022).

3 Future directions and models

3.1 Establish a centralized specialist model

One solution that has been proposed for highly prevalent diseases is to develop specialized expertise for the care of these patients. In Africa, both HIV and tuberculosis are highly prevalent, and the volume of patients can easily overwhelm the existing infrastructure. Some providers have been specifically trained for the care and management of these patients to allow highly efficient/high-quality care. This approach allows up to 20 medications to be prescribed at one time with the experience of the provider enabling rigorous management of medication side-effects, drug interactions and identification of outliers that may require sub-specialty care. In the case of OSA, in theory one provider with multispecialty training could manage obesity,

diabetes, hypertension and OSA rather than multiple individual sub-specialists. Recent data suggest weight loss through diet and exercise in conjunction with PAP therapy may be an effective treatment strategy for cardiometabolic risk in OSA (Chirinos et al., 2014; Carneiro-Barrera et al., 2022). Thus, OSA therapy including risk factor modification may yield superb outcomes. Clearly, these specialized providers would need to work within the context of a supportive environment including excellent communication with sub-specialists (Kalonji and Mahomed, 2019).

3.2 Triage to fast-track straight-forward cases model

For patients with high pre-test probability, an expedited pathway could be designed whereby patients have a telemedicine evaluation to initiate care management. Diagnostic testing and treatment could then be facilitated by telemedicine for straight-forward cases. This model can also evolve over time with a focus on continually simplifying the patient journey to access care. Adaptation during the crisis of the recent pandemic have helped to realize what could be the model for the future of clinical sleep medicine (Malhotra and Ayas, 2020). Likewise, more difficult cases would be scheduled with the appropriate specialist consult to coordinate more involved care management.

3.3 Tiered-care model

Given that management of some OSA patients is straight-forward, many patients do not require a face-to-face meeting with a physician specialist. A percentage of patients could likely be managed by primary care nurse practitioners, physician assistants, respiratory therapists, or sleep technologists (under a physician's supervision) though the more complicated cases may need direct physician evaluation, but only a subset would require seeing a sleep expert. Such an approach would need to be studied rigorously to ensure optimum care is provided. Clearly, communication would need to be robust between all tiers of care providers. Sleep navigators have been used effectively to triage patients within referring practices and to improve end-to-end patient care.

3.4 Predictive model(s)

In theory, predictive models and patient preferences could drive treatment decisions regarding who should receive oral appliances, upper airway surgery, or PAP therapy rather than based on "first come-first serve" approaches.

4 Discussion

Problems and unmet needs persist regarding the management of OSA following a consensus conference of key stakeholders to discuss potential future approaches to improve sleep apnea care and management. Other stakeholders will expand the scope of their

solutions to close the gaps between problems, unmet needs, and available solutions. This scenario results in riding the bus driven by others. Or we can drive the bus to have more control over possible outcomes.

We should aim to simplify the patient's journey to achieve successful diagnosis and treatment. Delete what isn't required. Barriers to effective communication between providers and between providers and patients should be eliminated. Serial monitoring for OSA should be routine to establish reliable baseline measurements or monitor response to therapy over weeks and months. Provider shortages and burnout persist. These pose challenges when the demand for services increases, but the supply cannot. And most financial models still reward the quantity of care vs. the quality of care.

Solutions are possible when the entire ecosystem is engaged that manages and delivers care to patients. Communication between a sleep specialist and a sleep dentist to provide effective oral appliance therapy to a patient should not be limited to fax machines just because medical and dental information systems are not interoperable. We need to find solutions. This allows data regarding patient progress to also flow from the sleep dentist back to the sleep specialist.

Future directions and models should deliver more value to patients and improve the quality of their care. In value-based models, these are the core outcomes on which payment to treat patients is based. The efficiency in which a care team provides this care is also important to help manage resources. The entire ecosystem will need to be engaged to design, test, measure and iterate the technology, processes and care delivered through these models. Patients should win if we are successful.

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

SP: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. BC: Conceptualization, Writing – original draft, Writing – review & editing. DG: Writing – review & editing. DH: Writing – review & editing. DK: Writing – review & editing. NS: Writing – review & editing. KS: Writing – review & editing. KT: Writing – review & editing. TB: Writing – review & editing. JT: Writing – review & editing. KC: Writing – review & editing. RB: Writing – review & editing. AR: Writing – review & editing. SA-I: Writing – review & editing. AM: Conceptualization, Writing – original draft, Writing – review & editing.

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Association between risk of obstructive sleep apnea severity and risk of severe COVID-19 symptoms: insights from salivary and serum cytokines

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Objectives: Obstructive sleep apnea (OSA) can adversely affect the immune response through clinical factors such as hypoxia, inflammation, and sleep disturbance. Since SARS-CoV-2 heavily relies on local and systemic host immune responses, this study aims to examine the links between the severity of OSA risk, cytokine levels, and the severity of symptoms associated with SARS-CoV-2 infection.

Methods: Saliva and blood samples from 50 COVID-19 patients and 30 non-infected hospital staff members were collected. Using Luminex multiplex analysis, 65 blood and salivary cytokines were examined from the collected samples. Ordinal logistic regression analysis was utilized to examine the association between the self-reported risk of OSA, assessed through the STOP-Bang questionnaire, and the likelihood of experiencing severe symptoms of COVID-19. Mann-Whitney test was then performed to compare the cytokine levels between individuals with moderate to severe risk of OSA to those with a mild risk of OSA.

Results: Ordinal logistic regression analysis revealed that individuals with a moderate to severe risk of OSA were 7.60 times more likely to experience more severe symptoms of COVID-19 compared to those with a mild risk of OSA (OR = 7.60, 95%CI: 3.03, 19.06, $p < 0.001$). Moreover, among COVID-19-positive patients with a moderate to severe risk of OSA, there was a statistically significant negative correlation with serum IL-6 ($p < 0.05$), Eotaxin (CCL11) ($p = 0.04$), and salivary MIP-3 α /CCL20 ($p = 0.04$). In contrast, individuals without COVID-19 who had a moderate to severe risk of OSA exhibited a significant positive correlation with serum IL-6 ($p = 0.04$).

Conclusion: Individuals with moderate to severe risk of OSA were more likely to experience severe COVID-19 symptoms than those with mild risk for OSA. Additional analysis from the present studies revealed distinct patterns of oral and systemic immune responses between individuals with mild and moderate to

severe risk of OSA. Findings from the present study underscores the importance of early detection and management of OSA to improve clinical outcomes, particularly when faced with the subsequent superimposed infection such as COVID-19.

KEYWORDS

COVID-19, SARS-CoV-2, obstructive sleep apnea, IL-6, cytokines

Introduction

Obstructive sleep apnea (OSA) affects approximately one billion individuals globally and is characterized by periodic interruptions in breathing during sleep, either partially or completely (1, 2). Individuals with OSA face an elevated risk of developing cardiovascular disease, hypertension, and various other chronic health issues (2, 3). The potential link between OSA and COVID-19 has been of particular interest due to the respiratory nature of both conditions, their overlapping comorbidities, and notable risk factors, particularly obesity (4).

Persistent, episodic collapse of airway during sleep results in chronic intermittent hypoxia, a state of decreased oxygen saturation and increased carbon dioxide arterial blood partial pressure (5). Each time this occurs, the process of desaturation and reoxygenation results in oxidative stress and a generation of reactive oxygen species (ROS) (5). Ultimately, chronic intermittent hypoxia can result in immune dysfunction both locally and systemically, predisposing individuals with OSA to developing subsequent superimposed infections (6, 7).

In recent years, the SARS-CoV-2 and the successive variants has had a significant, widespread impact worldwide. The World Health Organization (WHO) reported over 761 million cases and 6.8 million deaths to date (8). In particular, COVID-19 is caused by SARS-CoV-2 and primarily affects the respiratory system. Symptoms range from asymptomatic to severe Acute Respiratory Distress Syndrome (ARDS), requiring hospitalization and potentially leading to mortality (9). Multiple risk factors, including obesity, age, diabetes mellitus (DM), and cardiovascular disease, have been linked with an increase in severity of COVID-19 symptoms (10).

Previous studies illustrated the presence of similar risk factors in individuals with OSA, hinting at a possible connection between OSA and the severity of COVID-19 symptoms (11, 12). Earlier investigations also revealed that individuals who had both OSA and contracted COVID-19 faced an elevated risk of hospitalization, mechanical ventilation, admission to intensive care units (ICUs), and mortality when compared to COVID-19 patients with OSA (4, 13, 14). Despite these notable findings, there remains a substantial gap in the existing body of literature, prompting the current study to focus on investigating the relationship between risk of OSA, the severity of COVID-19 symptoms, and their association with relevant serum and salivary biomarkers.

Methods

The present study was conducted in collaboration with the Dasman Diabetes Institute in Kuwait, the J Craig Venter Institute

(JCVI), the Ministry of Health in Kuwait, and the University of Alberta. Ethics approval was granted by the Institution Review Boards (IRB) of JCVI, the Ministry of Health in Kuwait, and the University of Alberta. All enrolled participants provided their informed consent for participation in the study, with the respective ethics approval references as follows: Kuwait Ministry of Health #2020/1462, the University of Alberta #Pro00125245, and JCVI, which received an exemption due to the secondary analysis of de-identified samples.

Study design

The present study employed a convenience sampling approach, enrolling patients from AlFarwaniyah, Jaber Al Ahmed, and Kuwait Field hospitals in Kuwait between 24 July and 4 September 2020. Individuals who tested positive for SARS-CoV-2 by RT-PCR ($n = 50$) provided consent and underwent nasopharyngeal swab collection. For the control group, nasopharyngeal swabs were obtained from hospital staff members ($n = 30$) who had no contact with COVID-19 case(s).

Using a Qualtrics questionnaire on an iPad, comprehensive demographic and clinical data were gathered from the participants. This included details about their medical history, medication use, smoking habits, sleep patterns, weight, height, waist circumference, neck circumference, blood type, respiratory rate, COVID-19 symptoms, and, for those using supplemental oxygen, the specific liter amount.

Saliva collection

In preparation for saliva collection, 15 mL plastic centrifuge tubes were pre-labeled with the date and subject number, along with a clear demarcation at the 4 mL level. The saliva collection tubes were then placed on ice. Before proceeding with sample collection, a hospital nurse provided detailed instructions and demonstrated to the participants the process of saliva collection, including how to use the parafilm to stimulate saliva production and how to collect the saliva in the pre-marked tubes. The participants were directed to swish a sip of water in their mouth, swallow it, and then chew on a piece of parafilm. When saliva formed, the participants used their tongue to push the saliva into the pre-marked tube, which was placed back in an ice-filled cup. Saliva collection continued until it reached the 4 mL mark, accounting for the meniscus. After completing the task, participants notified the nurse, who then sealed and sanitized the tube before storing it in an ice-filled collection rack and disposing of any unused materials.

Blood collection

All serum samples were collected in 7.5 mL BD Vacutainer Serum tubes with clot activator using standardized venipuncture techniques.

Sample processing

The samples were packed in containers with dry ice and transferred to the Jaber Alahmad Hospital laboratory. The samples were received and processed within the same day, ensuring a maximum of 3 h elapsed between collection and processing. Salivary samples were centrifuged at 2000xg for 5 min. The separated supernatant and pellets were transferred into distinct tubes. Serum samples were centrifuged at 2000xg for 10 min after a 30-min interval of equilibration at room temperature on vertical racks. All processed samples were stored at -80°C . During samples transfer from the laboratory to JCVI, the samples were placed on dry ice along with a specialized monitoring apparatus to guarantee their sustained frozen condition throughout the transportation process.

Cytokine abundance measurements

The serum analysis was conducted with the Luminex 200 system (Luminex Corporation, Austin, Texas, United States) using the Immune Monitoring 65-Plex Human ProcartaPlex Panel (Cat# EPX650-16500-901; ThermoFisher Scientific, Vienna, Austria) following the manufacturer's instructions. This comprehensive kit assessed immune function by examining 65 protein targets in a single well, encompassing cytokines, chemokines, growth factors/regulators, and soluble receptors. To establish a standard curve, the provided standard was diluted fourfold, and both high and low controls were incorporated into the analysis.

Outcome variable

COVID status

COVID-19 severity was categorized into four distinct groups as follows: (1) Mild symptoms, which included individuals who were hospitalized without the need for oxygen therapy ($n=11$); (2) Moderate symptoms, involving hospitalized patients requiring low-flow oxygen support ($<10\text{ L/min}$) ($n=28$); (3) Severe symptoms, comprising of hospitalized patients who need high-flow oxygen support ($>10\text{ L/min}$) ($n=11$); and (4) the control group, composed of hospital administrative staff members who had no contact with COVID-19 patients ($n=30$). The control group underwent daily visual triage by the hospital, including temperature and symptom checks, although they did not undergo PCR testing nor have a confirmed negative PCR test. The control group was age- and sex-matched with the COVID-19 subjects. Two variables were generated for analysis, a binary variable and a categorical variable. Stratification of the participants into COVID-19 vs. no COVID-19 groups yielded a binary variable for the descriptive statistics. For the ordinal logistic regression analysis, a categorical variable was generated after grouping participants into one of four categories: (1)

control (non-infected); (2) mild symptoms; (3) moderate symptoms; and (4) severe symptoms.

Exposure variable and covariates

Obstructive sleep apnea

The risk of OSA was evaluated using the STOP-Bang questionnaire, a well-validated screening tool known for its high sensitivity of 96% and a negative predictive value of 90% (15). Participants were asked the following questions: (1) Do you snore loudly (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)? (2) Do you often feel tired, fatigued, or sleepy during the daytime (such as falling asleep during driving or talking to someone)? (3) Has anyone observed you stop breathing or choking/gasping during your sleep? (16). Participants received one point for each affirmative response to the aforementioned questions. An extra point was included if they were male, aged 50 or older, had a body mass index (BMI) exceeding 35 kg/m^2 (2), possessed a neck circumference exceeding 40 cm, or had a history of high blood pressure. Participants who accumulated three or fewer points were classified as having a low risk of OSA, whereas those with more than three points were categorized as having a moderate to severe risk of OSA (16).

Body measurements

Measurements for height, weight, waist, and neck circumferences were collected using the Qualtrics software on an iPad. Weight was assessed using a standard scale, while height was determined with the integrated stadiometer. Waist circumference was measured using a paper anthropometry tape, specifically at the midpoint between the bottom of the rib cage and the top of the iliac crest. These measurements were taken for each participant during minimal respiration and recorded to the nearest 0.1 cm. For neck circumference measurement, participants were advised to stand in a relaxed posture with their head held upright, looking straight ahead. The measurement was taken just above the midpoint of the participant's neck, usually below the thyroid cartilage (commonly known as the Adam's apple), at the end of a normal expiration. All measurements were recorded to the nearest millimeter.

Statistical analysis

All statistical analyses were carried out utilizing STATA 17 software, where a significance threshold of 0.05 was set. To create demographic data represented in Tables 1, 2, categorical variables were examined using chi-square tests, resulting in counts and percentages. To explore the connection between COVID-19 status and OSA risk, an ordinal logistic regression analysis was conducted after adjusting for gender and age. Moreover, an analysis of sixty-five serum and salivary biomarkers was performed. For each of these biomarkers, calculations were conducted to determine both the median and interquartile range (IQR) with a distinction between individuals with a mild risk of OSA and those with a moderate to severe risk. Following this, a two-sample Mann-Whitney test was employed to assess the statistical significance of differences between these two groups for each respective biomarker.

TABLE 1 Descriptive summary of sample characteristics stratified by risk of obstructive sleep apnea.

Characteristics	Mild risk of obstructive sleep apnea N = 46 (%)	Moderate/severe risk of obstructive sleep apnea N = 34 (%)	p-values
Age ≤ 50 years	40/46 (87)	11/33 (32.3)	<0.001
Age > 50 years	6/46 (13)	23/33 (68.7)	
Female	24/46 (52.1)	12/34 (35.3)	0.13
Male	22/46 (47.9)	22/34 (64.7)	
Diabetic	7/46 (15.2)	16/34 (47)	0.002
Non-diabetic	39/46 (84.8)	18/34 (53)	
Heart disease	1/46 (2.2)	7/34 (20.6)	0.007
No heart disease	45/46 (97.8)	27/34 (79.4)	
Hypertension	2/46 (4.4)	20/34 (58.8)	0.000
No hypertension	44/46 (95.6)	14/34 (41.2)	
BMI ≤ 35	39/46 (84.8)	18/34 (52.9)	0.002
BMI > 35	7/46 (15.2)	16/33 (47.1)	
Smoker	15/43 (34.9)	3/34 (8.8)	0.007
Non-Smoker	28/43 (65.1)	31/34 (91.2)	
Asthma	2/45 (4.4)	3/34 (8.8)	0.43
No asthma	43/45 (95.6)	31/34 (91.2)	
Emphysema	6/46 (13.1)	0/34 (0)	0.03
No emphysema	40/46 (86.9)	34/34 (100)	
Male waist circumference ≤ 94	3/22 (13.6)	2/22 (9.1)	0.64
Male waist circumference > 94	19/22 (86.4)	20/22 (90.1)	
Female waist circumference ≤ 80	6/24 (25)	0/12 (0)	0.06
Female waist circumference > 80	18/24 (75)	12/12 (100)	
Male neck circumference ≤ 43	20/22 (90.9)	19/22 (86.4)	0.64
Male neck circumference > 43	2/22 (9.1)	3/22 (13.6)	
Female neck circumference ≤ 41	21/24 (87.5)	10/12 (83.3)	0.73
Female neck circumference > 41	3/24 (12.5)	2/12 (16.7)	

p-values were determined using chi-square tests. Waist circumference cut off was based on the International Diabetes Federation. Cut off for males was 94 cm, while for females it was 80 cm. Neck circumference cut off was based on the WHO guidelines. Cut off for males was 43 cm, while for females it was 41 cm.

Results

Among the 80 participants of this study, 42.5% of individuals had moderate to severe risk of OSA while 57.5% had mild risk of OSA. For those with moderate to severe risk of OSA, 64.7% were male, 68.7% were > 50 years old, 47.1% had a BMI > 35 kg/m², and 91.2% were smokers (Table 1).

87% of individuals who experienced moderate and severe COVID-19 symptoms had a moderate to severe risk of OSA (Table 2).

COVID-19 positive individuals with a moderate to severe risk of OSA exhibited lower serum IL-6 levels (median 4, IQR 28) compared to individuals with a mild risk of OSA (median 21, IQR 38, $p < 0.05$). In contrast, individuals without a COVID-19 but who have a moderate to severe risk of OSA displayed higher serum IL-6 levels (median 14, IQR 25.5) than those with a mild risk of OSA (median-8, IQR 5, $p < 0.05$) (Table 3).

Among individuals who tested positive for COVID-19, those with a moderate to severe risk of OSA exhibited lower levels of salivary

MIP-3α/CCL20 (Median 0.205, IQR 0.286) compared to those with a mild OSA risk (Median 0.293, IQR 0.688, $p < 0.05$). Furthermore, in COVID-19-positive individuals with a moderate to severe OSA risk, lower levels of serum Eotaxin-1/CCL11 (median 1332.5, IQR 1178) were observed in contrast to those with a mild OSA risk (median 1933, IQR 1210, $p < 0.05$) (Table 3).

Individuals with a moderate to severe risk of OSA exhibit a 7.60-fold increased likelihood of falling within higher categories of COVID-19 symptom severity (OR: 7.60, 95%CI: 3.03–19.06, $p < 0.001$). Specifically, the probability of transitioning from lower (control or mild) to higher (mild to moderate, moderate to severe) COVID-19 symptom categories is 7.60 times higher among individuals with a moderate to severe risk of OSA compared to those with a mild risk (Table 4).

Sensitivity analysis was conducted using the same sleep apnea variable while excluding BMI from the variable. Individuals at a moderate/severe risk of OSA still exhibited a 5.85 fold increased likelihood of falling within the higher categories of COVID-19 symptom severity (OR: 5.85, 95%CI: 2.38–14.41, $p < 0.001$).

TABLE 2 Descriptive summary of COVID-19 symptoms stratified by risk of obstructive sleep apnea.

Characteristics	Mild risk of obstructive sleep apnea N = 46 (%)	Moderate/severe risk of obstructive sleep apnea N = 34 (%)	p-values
Mild COVID-19 symptoms	7/19 (36.84)	4/31 (12.90)	0.56
Moderate/severe COVID-19 symptoms	12/19 (63.16)	27/31 (87.10)	
Shortness of breath	11/19 (57.9)	21/31 (67.7)	0.48
No shortness of breath	8/19 (42.1)	10/31 (32.3)	
respiratory distress $\leq$ 20/min	5/46 (10.9)	9/34 (26.5)	0.07
Respiratory distress >20/min	41/46 (89.1)	25/34 (73.5)	
Chest pain	9/45 (20)	6/34 (17.7)	0.79
No chest pain	36/45 (80)	28/34 (82.3)	
Sputum production	8/19 (42.1)	15/31 (48.4)	0.67
No sputum production	11/19 (57.9)	16/31 (51.6)	
Cough	17/19 (89.5)	25/31 (80.6)	0.41
No cough	2/19 (10.5)	6/31 (19.3)	
Congestion	4/19 (21.1)	4/31 (12.9)	0.45
No congestion	15/19 (78.9)	27/31 (87.1)	
Sore throat	6/19 (31.6)	8/31 (25.8)	0.66
No sore throat	13/19 (68.4)	23/31 (74.2)	

Symptom severity was based on oxygen supplementation requirements. Subjects were placed in the Mild symptoms category if they were hospitalized without the need for oxygen therapy. Moderate if they required less than 10 L/min and severe if they required > 10 L/min of 100% O₂ supplementation. Subjects were placed in the severe symptoms category if they required > 10 L/min of 100% O₂ supplementation. Respiratory distress cut off was based on 20 breaths/min.

TABLE 3 Descriptive summary of statistically significant differences between serum and salivary biomarker levels stratified by COVID-19 status and risk of OSA.

Biomarkers:		No COVID		p-values	COVID		p-values
		Mild risk of OSA Median (IQR)	Moderate/Severe risk of OSA Median (IQR)		Mild risk of OSA Median (IQR)	Moderate/Severe risk of OSA Median (IQR)	
Serum (pg/ml)	IL-6	−8 (5)	14 (25.5)	0.04	21 (38)	4 (28)	0.04
	MIP-3 α /CCL20	0 (4)	−1 (1)	0.15	3 (7)	4 (7)	0.42
	Eotaxin-1/CCL11	2056 (1503.5)	1,124 (1017)	0.32	1933 (1210)	1332.5 (1178)	0.04
Saliva (pg/ml)	IL-6	0.067 (0.248)	0.015 (0.072)	0.33	0.014 (0.154)	0.007 (0.366)	0.95
	MIP-3 α /CCL20	0.276 (0.404)	0.08 (0.196)	0.12	0.293 (0.688)	0.205 (0.286)	0.04
	Eotaxin-1/CCL11	0.106 (0.235)	0.106 (0.059)	0.70	0.117 (0.161)	0.146 (0.198)	0.94

Mann–Whitney test was used to determine the p-values. IQR, interquartile range.

Discussion

The present study investigated the association between the risk of OSA and the likelihood of individuals experiencing heightened COVID-19 symptoms, while also examining the associated inflammatory patterns of the disease versus the non-diseased state. We demonstrated that individuals with moderate to severe risk for OSA were more likely to experience more severe symptoms than individuals with mild risk for OSA. Additionally, the sensitivity analysis revealed that our results remained statistically significant despite BMI being excluded from the sleep apnea variable, suggesting that the association between risk of OSA

and COVID-19 symptom severity is not solely driven by obesity, rather by the combination of the different components of the STOP-Bang model (gender, age, BMI, hypertension, snoring, gasping for air during sleep, feeling sleepy during the daytime, and neck circumference).

Furthermore, individuals with a moderate to severe risk of OSA, in the absence of concurrent COVID-19, exhibited elevated levels of serum IL-6 in contrast to those with a mild risk of OSA. Conversely, individuals at moderate to severe risk of OSA with concurrent COVID-19 showed reduced levels of serum IL-6, Eotaxin-1/CCL11, and salivary MIP-3 α /CCL20 compared to those with mild OSA risk and concurrent COVID-19. Since it is widely recognized that OSA can

TABLE 4 Ordinal logistic regression analysis of the association between COVID-19 status and risk of OSA.

Covariate	Odds ratio	95% confidence interval	p-values
Sleep apnea	7.60	3.03–19.06	<0.001
Adjusted sleep apnea*	5.85	2.38–14.41	<0.001

*The adjusted sleep apnea variable was determined using the STOP-Bang model while excluding BMI.

compromise the immune system, rendering individuals with preexisting OSA more susceptible to experiencing severe symptoms due to their weakened immune response against the virus.

The increased serum levels of IL-6 in patients with a moderate to severe risk of OSA, without concurrent COVID-19, aligns with the findings made by Imani et al. (17). Specifically, IL-6 plays various roles in inflammation and the immune system, including the stimulation of immunoglobulin secretion and the initiation of vascular inflammation (17). Among OSA patients, chronic intermittent hypoxia induces the release of proinflammatory cytokines like IL-6, resulting in a sustained condition of mild but persistent inflammation (18).

However, for patients with moderate to severe risk for OSA with concurrent COVID-19, there is a decrease in serum IL-6, Eotaxin-1/CCL11, and salivary MIP-3 α /CCL20. Eotaxin-1/CCL11 is a chemokine primarily responsible for recruiting eosinophils to inflammation sites, especially in the context of allergic reactions (19). Conversely, MIP-3 α /CCL20 is a chemokine that exhibits selective binding to CCR6, a receptor predominantly found on immature dendritic cells (DC) (20). Therefore, MIP-3 α /CCL20 facilitates the migration of immature DCs to the site of injury, and studies conducted by Reibman et al. have provided insight into the role of MIP-3 α /CCL20 in shaping the adaptive immune response within the airway mucosa (20). The observed attenuated immune response in patients with a moderate to severe risk of OSA and concurrent SARS-CoV-2 infections may be attributed to two potential mechanisms. First, OSA-mediated chronic inflammation due to persistent intermittent hypoxia could result in immune dysfunction (21). This pre-existing immune impairment could potentially exacerbate when individuals with OSA contract SARS-CoV-2, resulting in decreased secretion of cytokines. For instance, obesity, a shared risk factor for both OSA and COVID-19, impairs the immune response through chronic low-grade inflammation, hyperinsulinemia, hyperglycemia, and hyperleptinemia (22). Additionally, the deposition of adipose tissues can impede respiratory function, increasing susceptibility to respiratory infections like COVID-19 (22). Alternatively, SARS-CoV-2 infection could directly induce an “immunological collapse,” a state of reduced inflammatory reactions, unchecked viral replication, widespread dissemination, and direct host cell cytotoxicity (23). Nonetheless, the latter theory falls short of providing a comprehensive explanation for the observed reduction in IL-6 in the current study. This is evident as Remy et al. noted an increase in IL-6 when compared to the healthy control group in their own study (23). The discrepancies between the findings further reinforces the former theory that a synergistic effect exists between OSA and the concurrent COVID-19.

Limitations

It is important to note, however, that while the results of our cross-sectional study suggest a possible association between OSA, impaired

inflammatory reaction, and increased COVID-19 severity, additional research is required to establish a definitive causal relationship. One notable limitation of this study is the relatively small sample size, which may constrain the generalizability of our findings and limit the statistical power to detect subtle associations between variables. Another limitation of our study lies in the composition of the control group, consisting of hospital staff, while the experimental group comprises hospitalized patients. The inherent differences between these groups may introduce confounding variables related to occupational exposures, health behaviors, or access to healthcare, potentially impacting the generalizability of our findings. Furthermore, the exclusive focus on hospitalized patients within our experimental groups may inadvertently disregard potential variations in cytokine profiles among non-hospitalized individuals with COVID-19, constraining the generalizability of our findings. Additionally, in the present study, polysomnography confirmation of OSA was not feasible due to the clinical status of the patients and the infection control measures implemented during the pandemic. Thus, the patients in the study were never formally diagnosed with OSA. Likewise, we did not confirm participants' prior OSA diagnosis. This decision was influenced by the potential for introducing recall bias, and the survey's limited length constrained the comprehensive collection of accurate historical data on past OSA diagnosis. The absence of polysomnography or stratification of participants with a prior diagnosis of OSA limits the interpretation of the results, limiting our ability to assess the impact of pre-existing OSA on the observed outcome. However, the STOP-Bang questionnaire, a validated screening tool, was employed to assess the risk for OSA (15). While the STOP-Bang questionnaire is a valuable tool, it has inherent limitations. Future investigations should explore the inclusion of prior OSA diagnoses and polysomnography confirmation. Additionally, considerations such as sample size, representative sample, controlling for additional covariates and confounding variables, and investigating potential mechanisms through which OSA may impact immune response warrant attention in future studies.

Conclusion

Findings from the present study demonstrated an association between a moderate to high risk of OSA and the manifestation of severe COVID-19 symptoms. Moreover, the study has unveiled a link between the levels of inflammatory cytokines in individuals with OSA, some of which exhibited distinct differences based on the presence or absence of acute COVID-19. These findings substantiate the initial hypothesis, implying that individuals at higher risk of OSA may display an impaired inflammatory response, potentially intensifying the severity of COVID-19 symptoms.

Consequently, it becomes imperative to address and target OSA as a potential risk factor to mitigate the onset of severe COVID-19 symptoms

in subsequent variants and respiratory infections. By identifying and implementing appropriate interventions for individuals with OSA, healthcare professionals have the potential to diminish the susceptibility to COVID-19 symptoms and the associated complications they entail. Despite the ongoing endeavors to study COVID-19, further research is imperative to attain a more comprehensive grasp of the contributing factors that exacerbate the manifestation of symptoms related to COVID-19 and other respiratory infectious diseases.

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 Kuwait Ministry of health ethics approval: #2020/1462 Harvard: IRB21-1492, University of Alberta: Pro00125245. 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.

Author contributions

YD: Data curation, Formal analysis, Investigation, Writing – original draft, Conceptualization. AA: Data curation, Formal analysis, Software, Conceptualization, Investigation, Writing – original draft. HesA: Conceptualization, Formal analysis, Writing – review & editing. KA: Writing – review & editing, Formal analysis, Investigation, Software. MF: Data curation, Writing – review & editing, Methodology. MA: Writing – review & editing, Conceptualization, Resources. SD: Funding acquisition, Project administration, Resources, Writing – review & editing. FA: Funding acquisition, Project administration,

Resources, Writing – review & editing. SB-H: Conceptualization, Data curation, Methodology, Project administration, Supervision, Funding acquisition, Investigation, Resources, Validation, Writing – review & editing. HenA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Association of CLDN molecules with sleep apnea hypopnea syndrome: new biomarker candidates

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Introduction: Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder, and has become a serious threat to public health. Intermittent hypoxia caused by OSA results in a low-grade inflammatory response that leads to impaired mucosal barrier function. Claudin (CLDN) molecules are important for the permeability of the mucosal epithelium. This study aimed to explore whether CLDN molecules can be a potential biomarker of OSA.

Methods: A total of 37 healthy controls and 40 OSA patients underwent a physical assessment for OSA and filled out the STOP-Bang Questionnaire (SBQ) and Epworth Sleepiness Scale (ESS). Clinical specimens of plasma and urine were obtained to observe the difference between OSA patients and healthy controls and diagnostic accuracy of CLDN molecules for OSA.

Results: CLDN1, CLDN2, and CLDN3 molecules in plasma and urine decreased in OSA patients (both $p < 0.05$). The areas under the receiver operating characteristic curve (AUCs) of urinary CLDN1, plasma CLDN1, urinary CLDN2, plasma CLDN2, urinary CLDN3, and plasma CLDN3 were 0.887, 0.724, 0.779, 0.676, 0.828, and 0.665, respectively. The AUC of urinary CLDN1 + CLDN2 + CLDN3 was 0.906 (95% confidence interval (CI), 0.831–0.981). The AUC of plasma CLDN1 + CLDN2 + CLDN3 was 0.776 (95% CI, 0.645–0.878). The AUC of urinary CLDN3 + SBQ was 0.899 (95% CI, 0.832–0.967). The AUC of urinary CLDN3 + ESS was 0.896 (95% CI, 0.826–0.966). In addition, Urinary CLDN-3 was negative associated with the severity of OSA.

Conclusion: CLDN molecules are promising as useful biomarkers for OSA, which may be related to the impaired barrier function related to OSA.

KEYWORDS

CLDN family, obstructive sleep apnea, biomarker, diagnosis, barrier

1 Introduction

Obstructive sleep apnea (OSA) is characterized by repeated closure of the upper airway during sleep, which leads to intermittent hypoxia (IH), hypercapnia, and increased sympathetic nerve activity (1). Currently, the STOP-Bang Questionnaire (SBQ) and other questionnaires are used in many medical centers for initial screening of patients with suspected OSA, followed by polysomnography (PSG) for high-risk patients (2). PSG, which is the gold standard for diagnosing OSA, requires the patient to wear the device all night in a specific room,

and the staff must observe the machine at all times, which consumes considerable time and human resources. In addition, the examination is expensive. It is estimated that approximately one in seven of the world's adult population has OSA. However, the diagnosis rate is very low (3), and testing may be one of the many obstacles to diagnosis. Laborious and expensive PSG is a prohibitive treatment for many patients with suspected OSA. Therefore, qualified biomarkers can help streamline the screening and diagnostic processes for OSA and reduce the financial burden of OSA as a serious public health problem.

Studies have shown that the disruption of mucosal barrier is a common pathological process in OSA. There is evidence to suggest that IH cause changes in the blood-brain barrier (BBB) through oxidative stress, oxygen sensors, increased inflammation, and also influences microvessel permeability of BBB (4). Baronio et al. (5) report higher overall brain water and lower levels of aquaporin 1 in the hippocampus and cerebellum of mice exposed to chronic IH. The pathological damage of intestinal mucosa has also been confirmed. In the presence of hypoxia, intestinal dysfunction leads to necrosis and detachment of the intestinal mucosal epithelium. Once the intestinal mucosa is damaged, the permeability of the intestinal barrier changes. Hypoxia can induce inflammation, and tissues with inflammatory reactions often exacerbate hypoxia, which is a positive feedback phenomenon (6). At the same time, the inflammatory response caused by OSA can also damage the lung mucosa and vascular intima, leading to more serious comorbidities (7).

The CLDN protein family is an important junction protein in barrier function. Currently, more than 20 subtypes of CLDN proteins related to mammals have been identified (8). Partial subtyping of genes has identified defects that are associated with diseases (9), and differential expression of eight subtypes has been found in various diseases (10). However, there is currently not a lot of research on CLDN molecules and OSA. Given the importance of disruption of mucosal barrier in OSA, more studies focus on OSA and barrier function are warranted. Therefore, the aim of our study was to explore the changes of CLDN molecules in patients with OSA, and whether the CLDN molecules can be a biomarker for assessment of OSA.

2 Materials and methods

2.1 Study design and participants

The present investigation was a study that enrolled consecutive adults who underwent an in-laboratory sleep recording and were diagnosed with OSA from July 2022 to December 2022 at the Sleep Medical Center, Tianjin Medical University General Hospital (Heping, China). All data were anonymous and complied with the requirements of authorities for personal data protection. The study protocol was approved by the Ethical Committee of Tianjin Medical University General Hospital (IRB2019-WZ-175). Healthy participants were also recruited. They underwent PSG to assess whether they should be classified as healthy controls or OSA patients. No participant was undergoing continuous positive airway pressure treatment or had any other lung diseases.

TABLE 1 Clinical characteristics of the study population.

	Controls (<i>n</i> = 37)	OSA (<i>n</i> = 40)	<i>p</i> -value
Age (years)	44.3 ± 12.81	50.33 ± 13.47	0.065
Male, <i>n</i> (%)	54.05%	72.50%	0.095
Hypertension (%)	5.41%	70%	<0.001
Diabetes (%)	0%	7.50%	0.091
MetS (%)	8.11%	62.50%	<0.001
TG (mg/dl)	129.23 ± 61.64	190.35 ± 96.67	0.002
HDL-C (mg/dl)	54.94 ± 16.12	41.37 ± 11.97	<0.001
BMI (kg/m ²)	27.03 ± 6.71	29.85 ± 5.08	0.043
Neck circumference (cm)	38.03 ± 3.22	41.68 ± 3.49	<0.001
Waist circumference (cm)	93.30 ± 7.75	103.9 ± 11.24	<0.001
SE (%)	87.01 ± 7.98	76.94 ± 11.86	<0.001
AHI (events/h)	2.43 ± 1.35	54.51 ± 27.69	<0.001
Arousal (events/h)	8.52 ± 4.82	30.58 ± 22.50	<0.001
AI (events/h)	0.55 ± 0.71	31.81 ± 31.11	<0.001
ODI (events/h)	2.04 ± 2.01	44.85 ± 26.69	<0.001
Mean SpO ₂ (%)	96.59 ± 1.07	92.08 ± 3.25	<0.001
SPO ₂ min (%)	91.89 ± 2.58	72.75 ± 12.54	<0.001
T90 (%)	0	17.76 ± 19.98	<0.001
Plasma CLDN1 (ng/ml)	371.40 ± 44.34	332.59 ± 47.05	0.0006
Urine CLDN1 (ng/ml)	350.53 ± 39.17	269.58 ± 51.43	<0.001
Plasma CLDN2 (ng/ml)	2.21 ± 0.27	2.20 ± 0.29	0.0084
Urine CLDN2 (ng/ml)	2.10 ± 0.28	1.71 ± 0.33	<0.001
Plasma CLDN3 (ng/ml)	4.98 ± 0.64	4.45 ± 0.66	0.0131
Urine CLDN3 (ng/ml)	4.82 ± 0.63	3.70 ± 0.84	<0.001
SBQ	2.18 ± 1.25	3.33 ± 1.01	0.0034
ESS	9.81 ± 3.67	13.88 ± 3.53	<0.001

Data are shown as mean ± SD or median (IQR). OSA, obstructive sleep apnea; MetS, metabolic syndrome; TG, triglycerides; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; AHI, apnea-hypopnea index; SpO₂ min, minimum peripheral capillary oxygen saturation; T90, total sleep time spent with oxygen saturation below 90%; AI, apnea index; ODI, oxygen desaturation index; SE, sleep efficiency; SD, standard deviation; SBQ, OP-Bang Questionnaire; ESS, Epworth Sleepiness Scale.

2.2 Sleep monitoring

All participants underwent a full night of sleep recording at the Sleep Medical Center. They were allowed to follow their habitual sleep time from 21:00 to 22:00 to 06:00–07:00 hours. Each patient's sleep was continuously monitored using a PSG device (Alice 5; Philips Respironics, Murrysville, PA, USA) by two technicians. Sleep parameters were scored manually using the American Academy of Sleep Medicine Manual v2.3 2016. Respiratory sleep patterns were studied according to the recommendations of the American Academy of Sleep Medicine. The PSG parameters evaluated included sleep latency, sleep efficiency, total sleep time, and duration of each sleep stage. Apnea was defined as the cessation of airflow for at least 10 s in the presence of respiratory effort.

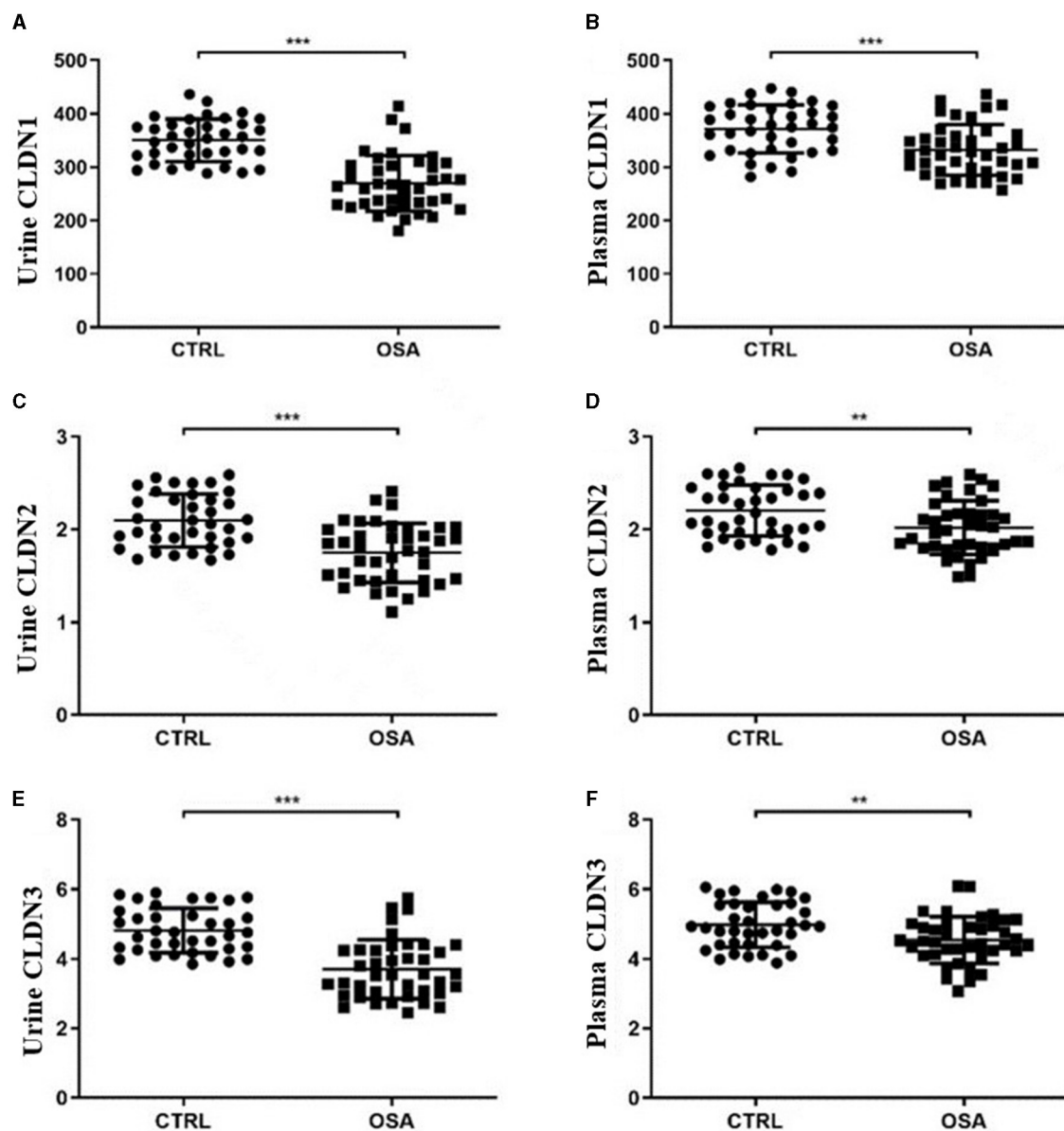


FIGURE 1

Scatter plot of CLDN molecules in the OSA and control groups. Differences in the expression of CLDN1 in (A) urine and (B) plasma. Differences in the expression of CLDN2 in (C) urine and (D) plasma. Differences in the expression of CLDN3 in (E) urine and (F) plasma. OSA, obstructive sleep apnea.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Hypopnea was identified as a $>30\%$ reduction in airflow for at least 10 s and was associated with either a $>3\%$ decrease in oxygen saturation or arousal. The apnea–hypopnea index (AHI) was calculated as the average number of apnea and hypopnea events per hour. Participants with OSA were diagnosed according to an AHI of >5 , whereas those with an AHI of <5 were diagnosed as primary snorers. The percentage of time spent in sleep with an oxygen saturation of $<90\%$ was defined as T90.

2.3 Clinical data and laboratory tests

During the visit, lifestyle questionnaires, SBQ, ESS, medical tests (i.e., electrocardiogram and plasma pressure measurement), anthropometric measurements (i.e., weight, height, and waist and

neck circumference), and biochemical tests (fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides) were performed. The venous plasma samples and urine samples were collected early in the morning before breakfast. Enzyme-linked immunosorbent assay kits for human CLDN1, CLDN2, and CLDN3 were purchased from J&L Biological Industrial Co., Ltd. (Shanghai, China), and analyses were performed according to the recommended protocols. Participants were considered to have a metabolic syndrome if they had at least three of the following criteria: increased waist circumference (≥ 94 cm for men and 80 cm for women), increased triglycerides (≥ 150 mg/dl), decreased high-density lipoprotein cholesterol (<40 mg/dl for men and <50 mg/dl for women), increased plasma pressure (systolic ≥ 130 and/or diastolic ≥ 85 mmHg), and increased fasting glucose (≥ 100 mg/dl) (11).

TABLE 2 Accuracies of indicators in the diagnosis of OSA.

Markers	AUC (95% CI)	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Urinary CLDN1 (ng/ml)	0.887 (0.811–0.964)	258.7	100.0	67.5	76.9	100	84.4
Plasma CLDN1 (ng/ml)	0.724 (0.611–0.837)	359.41	62.2	75	72.9	64.3	68.4
Urinary CLDN2 (ng/ml)	0.779 (0.679–0.880)	1.7	100.0	42.5	65.3	100	72.4
Plasma CLDN2 (ng/ml)	0.676 (0.557–0.795)	1.9	85.6	42.5	61.7	73.3	64.9
Urinary CLDN3 (ng/ml)	0.828 (0.735–0.922)	3.83	100.0	56.1	71.1	100	78.9
Plasma CLDN3 (ng/ml)	0.665 (0.543–0.786)	4.65	70.3	57.5	64.1	64.2	64.1
Urinary CLDN1 + CLDN2 + CLDN3	0.906 (0.831–0.981)	–	97.3	82.5	85.7	96.6	90.2
Plasma CLDN1 + CLDN2 + CLDN3	0.776 (0.645–0.878)	–	95.5	52.5	68.5	91.5	74.8
Plasma CLDN3 + urinary CLDN3	0.872 (0.786–0.959)	–	95.5	52.5	68.5	91.5	74.8

Cutoff values were selected based on Youden's index.

AUC, area under the receiver operating characteristic curve; CI, confidence interval; OSA, obstructive sleep apnea; PPV, positive predictive value; NPV, negative predictive value.

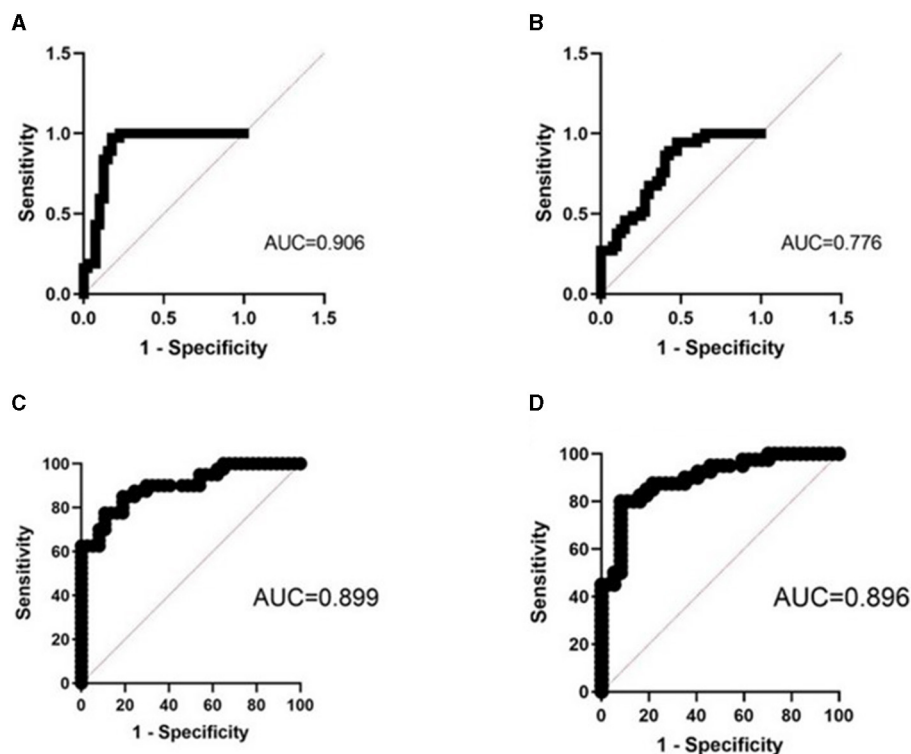


FIGURE 2

ROC curve of the joint indicator. (A) Combined ROC curve of urinary CLDN1 + CLDN2 + CLDN3. (B) Combined ROC curve of plasma CLDN1 + CLDN2 + CLDN3. (C) Combined ROC curve of urinary CLDN3 + SBQ. (D) Combined ROC curve of urinary CLDN3 + ESS. AUC, area under the ROC curve; ROC, receiver operating characteristic; ESS, Epworth Sleepiness Scale; SBQ, STOP-Bang Questionnaire.

2.4 Statistical analysis

The results for variables that were normally distributed are presented as the means $\pm$ standard deviations. The results for variables that were not normally distributed are summarized as medians and compared using the Mann–Whitney *U* test. Student's *t* test was used to compare the means of two independent variables. Spearman's correlation analysis was used to evaluate the relationship between two variables. Receiver

operating characteristic (ROC) curves were generated to estimate the area under the curve (AUC), and optimal cutoffs were estimated via the highest Youden's index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated through the crosstabs. Binary logistic analysis was used to analyze the ROC curve of the joint indicator. *p* values < 0.05 were considered statistically significant. Error bars were used to indicate the standard deviation. All statistical analyses were performed using SPSS

TABLE 3 Accuracies of indicators in the diagnosis of OSA.

Markers	AUC (95% CI)	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
SBQ	0.754 (0.644–0.864)	3.5	70.7	59.4	65.3	65.2	65.3
ESS	0.786 (0.682–0.891)	14.5	72.5	73	74.4	71.7	72.7
Urinary CLDN3 + SBQ	0.899 (0.832–0.967)	–	85.0	81.1	82.9	83.3	83.1
Urinary CLDN3 + ESS	0.896 (0.826–0.966)	–	80.0	91.9	91.4	81.0	85.7

SBQ, STOP-Bang Questionnaire; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; and AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value.

20.0 (IBM, New York, NY, USA) and Graphpad Prism v.9.0 (California, USA).

3 Results

3.1 General clinical characteristics of the OSA and control groups

A total of 40 OSA patients and 37 healthy controls were enrolled in the cohort. The OSA patients and controls were matched by age ($p = 0.065$) and sex ($p = 0.095$). The demographic and polysomnographic characteristics of the groups were presented in Table 1.

3.2 There were significant differences in plasma and urinary CLDN1, CLDN2, and CLDN3 between the OSA and control groups

The plasma CLDN1, CLDN2, and CLDN3 levels were significantly decreased between the OSA and control groups ($p = 0.006$, $p = 0.0084$, and $p = 0.0131$). The urinary CLDN1, CLDN2, and CLDN3 levels were significantly decreased between the OSA and control groups (both $p < 0.001$; Table 1; Figure 1).

3.3 The diagnostic efficacy of CLDN molecules in OSA

We used ROC curves to assess the diagnostic efficacy of CLDN molecules for OSA. The AUC of urinary CLDN1 was 0.827 (95% CI, 0.811–0.964), with a sensitivity of 100%, specificity of 67.5%, PPV of 76.9%, NPV of 100%, and accuracy of 84.4%; the AUC of plasma CLDN1 was 0.724 (95% CI, 0.611–0.837), with a sensitivity of 62.2%, specificity of 75%, PPV of 72.9%, NPV of 64.3%, and accuracy of 68.4%; the AUC of urinary CLDN2 was 0.779 (95% CI, 0.679–0.880), with a sensitivity of 100%, specificity of 42.5%, PPV of 65.3%, NPV of 100%, and accuracy of 72.4%; the AUC of plasma CLDN2 was 0.676 (95% CI, 0.557–0.795), with a sensitivity of 85.6%, specificity of 42.5%, PPV of 61.7%, NPV of 73.3%, and accuracy of 64.9%; the AUC of urinary CLDN3 was 0.828 (95% CI, 0.735–0.922), with a sensitivity of 100%,

specificity of 56.1%, PPV of 71.1%, NPV of 100%, and accuracy of 78.9%; the AUC of plasma CLDN3 was 0.665 (95% CI, 0.543–0.786), with a sensitivity of 70.3%, specificity of 57.5% PPV of 64.1%, NPV of 64.2%, and accuracy of 64.1%. It can be seen that the predictive power of urinary CLDN1 is the best among single indicators.

The AUC of urinary CLDN1 + CLDN2 + CLDN3 was 0.906 (95% CI, 0.831–0.981), with a sensitivity of 97.3%, specificity of 82.5%, PPV of 85.7%, NPV of 96.6%, and accuracy of 90.2%; the AUC of plasma CLDN1 + CLDN2 + CLDN3 was 0.776 (95% CI, 0.645–0.878), with a sensitivity of 95.5%, specificity of 52.5%, PPV of 68.5%, NPV of 91.5%, and accuracy of 74.8%; the AUC of plasma CLDN3 + urinary CLDN3 was 0.872 (95% CI, 0.786–0.959), with a sensitivity of 95.5%, specificity of 52.5%, PPV of 68.5%, NPV of 91.5%, and accuracy of 74.8%. Among the joint indicators, urinary CLDN1 + CLDN2 + CLDN3 has the best predictive ability. And the predictive ability of the combined index is higher than that of the single index (Table 2; Figure 2).

3.4 The diagnostic efficacy of CLDN molecules combined SBQ or ESS in OSA

The AUC of SBQ was 0.754 (95% CI, 0.644–0.864), with a sensitivity of 70.7%, specificity of 59.4%, PPV of 65.3%, NPV of 65.2%, and accuracy of 65.3%; the AUC of ESS was 0.786 (95% CI, 0.682–0.891), with a sensitivity of 72.5%, specificity of 73%, PPV of 74.4%, NPV of 71.7%, and accuracy of 72.7%; the AUC of urinary CLDN3 + SBQ was 0.899 (95% CI, 0.832–0.967), with a sensitivity of 85%, specificity of 81.1%, PPV of 82.9%, NPV of 83.3%, and accuracy of 83.1%; the AUC of urinary CLDN3 + ESS was 0.896 (95% CI, 0.826–0.966), with a sensitivity of 80.0%, specificity of 91.9%, PPV of 91.4%, NPV of 81.0%, and accuracy of 85.7%. We found that the combination of urine CLDN3 molecules improved the ability to predict OSA (Table 3; Figure 2).

3.5 Correlation analysis suggests that urinary CLDN3 can predict the severity of OSA

We found that urinary CLDN3 was significantly correlated with AHI and T90 ($r = -0.36$, $p = 0.023$; $r = 0.33$, $p = 0.035$; Table 4; Figure 3). This suggested that the more severe OSA, the lower the concentration of urinary CLDN3.

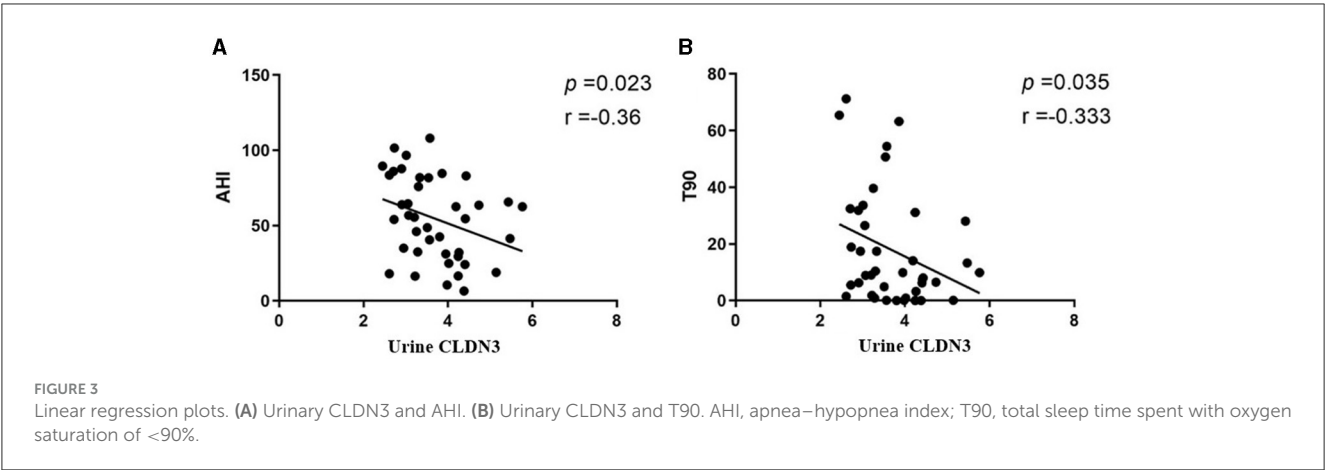


TABLE 4 Correlation analysis of urinary CLDN3, AHI, and T90.

Factor		Urinary CLDN3	AHI	T90
Urinary CLDN3	<i>r</i>	–	–0.36	–0.33
	<i>p</i>	–	0.023	0.035
AHI	<i>r</i>	–0.36	–	–
	<i>p</i>	0.023	–	–
T90	<i>r</i>	–0.33	–	–
	<i>p</i>	0.035	–	–

AHI, apnea–hypopnea index; T90, total sleep time spent with oxygen saturation of <90%.

4 Discussion

In this study, the association of CLDN1, CLDN2, and CLDN3 molecules with OSA is proposed for the first time. We found that the concentrations of CLDN1, CLDN2, and CLDN3 molecules in the plasma and urine of OSA patients decreased. CLDN1 and CLDN3 are called “pore-sealing CLDNs,” and the increase in the expression of the sealing CLDNs will lead to the increase of the tight junctions of the mucosa. CLDN2 is called “pore-forming CLDNs,” which can form paracellular anion/cation pores and water channels, results in reducing epithelial tightness and increasing solute permeability (12). Our study is based on the assumption that IH damages the intestinal mucosal epithelium and thereby impairs expression of CLDN molecules, resulting in decreases in plasma and urine, but the specific mechanism needs to be further explored.

Previous studies have found that IH can cause impairment of barrier function. Baronio et al. reported higher overall brain water and lower levels of aquaporin 1 in the mice exposed to chronic IH (5). A study has shown the brain diffusion alteration in patients with OSA, and neuronal damage and vasogenic edema in the different brain regions of OSA patients due to IH (13). In addition, in the study of intestinal permeability by D-lactate, high intestinal permeability was found in middle-aged male non-obese OSA patients, so there may be subclinical intestinal damage in some OSA patients (14). In this study, we speculated that the decrease of CLDN1 and CLDN2 may lead to the decrease of barrier permeability, while the decrease of CLDN2 may lead

to the decrease of water passage, and result in tissue edema. As important molecules in maintaining barrier function, CLDNs have rarely appeared in the study of OSA. Our exploration also provides a promising idea for subsequent basic research.

In addition, the diagnostic efficacy of urinary CLDN3 was 82.8%, and there is a correlation between CLDN3 and the severity of OSA. The AUC of Urinary CLDN1 + CLDN2 + CLDN3 was 90.6%. Urine is an easily obtainable specimen in clinical practice. Therefore, the urine CLDNs are expected to become promising biomarkers for OSA. These findings are very important for further studying biomarkers for the prediction of OSA.

In previous studies, many OSA biomarkers have been discovered, such as I-FABP, D-LA, LPS, and LBP (15). In our previous study, Liu et al. (11) found that neutrophil-to-lymphocyte ratio, lymphocyte, and CD4 counts are associated with “overlap syndrome (OVS)” and have a moderate diagnostic value. These are promising biomarkers for exploring OSA from the perspective of metabolic processes and inflammatory responses. However, there are few researches focus on the barrier function in OSA. We believe that this will help us further explore the impact of OSA on other organ complications.

Combined CLDN molecules, CLDN + SBQ and CLDN + ESS have high AUC, which also provides us with a direction for the screening of OSA. As subjective factors, SBQ and ESS usually have low specificity and accuracy (16). Combined urinary CLDN3 with SBQ and ESS, we found that the specificity and accuracy were significantly increased. In addition, the sensitivity of CLDN1, CLDN2, and CLDN3 molecules in plasma is 100%. Therefore, we believe that adding the CLDN molecules to SBQ and ESS may have more satisfactory results in OSA screening. Future large-scale clinical studies are warranted to confirm our hypothesis.

OSA is frequently associated with comorbidities that include metabolic, cardiovascular, renal, pulmonary, and neuropsychiatric, and there is growing evidence of bidirectional relationships between OSA and comorbidity, especially for heart failure, metabolic syndrome, and stroke (17). And severe OSA was an independent predictor of all-cause death (18). The possible mechanisms include oxidative stress, sympathetic nerve activation, vascular endothelial injury, and endothelial dysfunction. The underlying mechanisms have not yet been

explored (19). OSA increases the risk of stroke by 60% (20). Alvarez-Sabin et al. found that in patients with hypertension, moderate-to-severe OSA is independently associated with lacunar silent cerebral infarct (21). Therefore, it is very important to strengthen the screening of OSA in the population. Early detection of patients with moderate and severe OSA can reduce the number of patients with cardiovascular and cerebrovascular diseases and avoid a large amount of waste of public resources.

This study mainly focuses on patients with moderate to severe OSA. We first propose the association of CLDN levels with OSA patients, which provides clues for further understanding of the impaired barrier function related to OSA. Next, we will conduct a large-sample study based on the results of this study to determine whether CLDN molecules can be used to screen patients with moderate and severe OSA, and the potential value of CLDN molecules in mild patients.

5 Conclusions

This study mainly explored the association of CLDN1, CLDN2, and CLDN3 molecules with OSA. We found that CLDN molecules have good predictive ability. Urinary CLDN3 was inversely associated with the severity of OSA. The combination of urine CLDN3 and SBQ or ESS can significantly improve specificity for diagnose of OSA, indicating the CLDN molecules as novel biomarker candidates.

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

The studies involving humans were approved by Ethical Committee of Tianjin Medical University General Hospital. 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.

Author contributions

DL: Writing – original draft. HM: Writing – original draft. NW: Writing – review & editing. JF: Writing – review & editing.

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Conflict of interest

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

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Commentary: Physical therapy for sleep apnea: a smartphone application for home-based physical therapy for patients with obstructive sleep apnea

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KEYWORDS

obstructive sleep apnea, home-based physical therapy, smartphone application, physical therapy, respiratory muscle training

A Commentary on

Physical therapy for sleep apnea: a smartphone application for home-based physical therapy for patients with obstructive sleep apnea

by Bui-Diem, K., Hung, C.-H., Zhu, G.-C., Tho, N. V., Nguyen-Binh, T., Vu-Tran-Thien, Q., To-Truong, D., Ngo-Thanh, H., and Duong-Quy, S. (2023). *Front. Neurol.* 14:1124059.
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Background

Obstructive sleep apnea (OSA) is the most common respiratory disease, with an increasing incidence worldwide. Telemedicine based on smartphone apps to treat this disease seems worthwhile. Myofunctional therapy is one of the options to treat OSA, and it has been recommended only for specific cases seeking alternative treatments and who are reluctant to undertake surgical or mechanical strategies (1).

State of the art

In this journal, a recent manuscript published by Bui-Diem et al. (2) raised some issues we would like to address here. Our group designed an app called Airway Gym (3) to treat obstructive sleep apnea (OSA) that promotes proprioceptive rehabilitation and coordination of the airway muscles (4). This app includes nine exercises based on myofunctional therapy aimed at improving the tonicity of the various muscles involved in the pathogenesis of OSA (5). Before each exercise, an animated demonstration and a video with a real person are shown to the patient (Figure 1) so that they learn how to perform the exercise. After each exercise, the patient receives visual, acoustic, and tactile feedback about the success of their performance as a point score. When the patient finishes the exercises, the results are saved on a networked online storage (in the cloud),

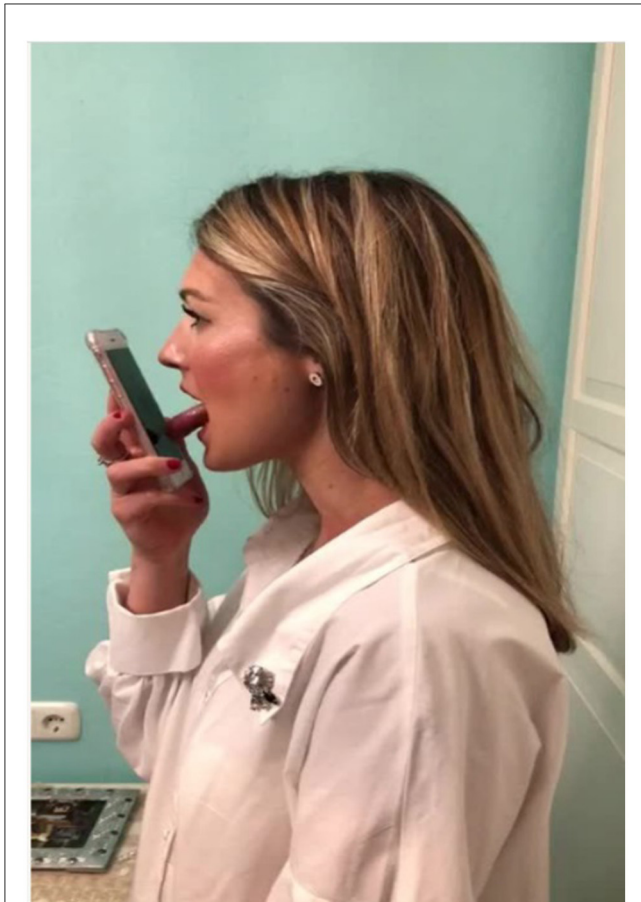


FIGURE 1
Video of a real person performing an oropharyngeal exercise.

and a therapist can evaluate the patient's adherence and performance of the exercises. Users of the app can follow the progress of their daily activity over time. A chat function is available through which the patient can contact the therapist directly. Additional information can be found on the AirwayGym webpage <https://airwaygym.app/en/gymnasts-homepage>.

Randomized clinical trial with an app

We have already performed a randomized clinical trial (6) where the intervention group with severe OSA showed significant improvements in most metrics of OSA scores. The control group just performed sham therapy. The apnea-hypopnea index decreased by 53.4% from 44.7 (range 33.8–55.6) to 20.9 (14.0–27.7) events/h (p -value <0.001). The oxygen desaturation index decreased by 46.5% from 36.3 (27.2–43.4) to 19.4 (12.9–26.0) events/h ($p = 0.003$). The Epworth Sleepiness Scale score decreased from 10.3 (8.7–12.2) to 5.4 (3.4–7.3) in the app group ($p < 0.001$). Since Eckert (7) defined non-anatomical factors or 'phenotypes' as crucial determinants of OSA for many people, our group has focused on investigating those with a weakness in pharyngeal dilator muscle control known as "Hypotonic." Studies performed with our app demonstrated that this was the best phenotype to improve adherence and receive myofunctional therapy (8).

In their article, Bui-Diem et al. (2) designed an app that, to the best of their knowledge, is the first application designed to assist patients with OSA in performing rehabilitation programs at home. However, they mentioned Airway Gym in their article and considered it an application for sleep apnea to practice upper airway muscle strength, although they erroneously mentioned that the video of our app does not show a real person. Furthermore, the use of their app (1) is clearly very similar to how we use ours, and they did not reference any of our works that would support this assertion.

Conclusion

We believe that our app has been underestimated by the authors and truly was the first designed to perform a rehabilitation program at home using real-person videos based on enhanced tone and proprioceptive deficit of upper airway muscles in OSA patients. Future publications by Bui-Diem et al. should always reference articles on which they have based their idea; in this case, we consider it based on the concept from our research.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

Author contributions

CO'C: Writing – original draft, Writing – review & editing. PB: Conceptualization, Writing – original draft. GP: Investigation, Writing – review & editing.

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Conflict of interest

CO'C is the author of Airway Gym and has a financial interest in this app.

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

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Excessive daytime sleepiness is associated with relative delta frequency power among patients with mild OSA

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Background: Excessive daytime sleepiness (EDS) is a cause of low quality of life among obstructive sleep apnoea (OSA) patients. Current methods of assessing and predicting EDS are limited due to time constraints or differences in subjective experience and scoring. Electroencephalogram (EEG) power spectral densities (PSDs) have shown differences between OSA and non-OSA patients, and fatigued and non-fatigued patients. Therefore, polysomnographic EEG PSDs may be useful to assess the extent of EDS among patients with OSA.

Methods: Patients presenting to Israel Loewenstein hospital reporting daytime sleepiness who recorded mild OSA on polysomnography and undertook a multiple sleep latency test. Alpha, beta, and delta relative powers were assessed between patients categorized as non-sleepy (mean sleep latency (MSL) ≥ 10 min) and sleepy (MSL < 10 min).

Results: 139 patients (74% male) were included for analysis. 73 (53%) were categorized as sleepy (median MSL 6.5 min). There were no significant differences in demographics or polysomnographic parameters between sleepy and non-sleepy groups. In multivariate analysis, increasing relative delta frequency power was associated with increased odds of sleepiness (OR 1.025 (95% CI 1.024–1.026)), while relative alpha and beta powers were associated with decreased odds. The effect size of delta PSD on sleepiness was significantly greater than that of either alpha or beta frequencies.

Conclusion: Delta PSD during polysomnography is significantly associated with a greater degree of objective daytime sleepiness among patients with mild OSA. Further research is needed to corroborate our findings and identify the direction of potential causal correlation between delta PSD and EDS.

KEYWORDS

excessive daytime sleepiness, MSLT, OSA, ESS, power spectral densities

Introduction

Excessive daytime sleepiness (EDS) is highly prevalent across populations, estimated to affect up to one in five people (1). EDS is associated with an increased risk of motor vehicle accidents (2, 3), decreased quality of life (4, 5), reduced work productivity (4, 6), and significant economic burden (7, 8). In addition, EDS has shown significant associations with psychological distress (9, 10), depression and bipolar disorder (11–15), and seasonal affective disorder (11). EDS is often associated with sleep disorders, such as insomnia, narcolepsy, or obstructive sleep apnoea (OSA). Among patients with OSA, a greater severity as judged by the apnoea-hypopnoea index (AHI) has been associated with EDS (16). Yet, alongside increasing OSA severity there appears to be a concurrent increase in comorbidities (17, 18), which are also associated with increased daytime sleepiness (19–22), and may thus confound the effect of OSA on EDS. However, EDS is common even among patients with only mild OSA (AHI 5–15), without concomitant insomnia or narcolepsy (16), and a significant proportion of patients who are receiving continuous positive airway pressure (CPAP) therapy still suffer from EDS (23–25). The current prevailing theory suggests that EDS in the context of OSA is caused by a combination of sleep fragmentation and intermittent hypoxia, which over time lead to neuronal damage (26). Yet, although these markers are less common among patients with mild OSA, these patients are still prone to EDS, and therefore further exploration into the potential underlying mechanisms is warranted. Furthermore, studies which have utilised subjective markers of sleepiness have found contradictory results in polysomnographic parameters between sleepy and non-sleepy patients (27, 28).

Alternate parameters assessed through polysomnography (PSG) are being increasingly investigated for their relationship with EDS. Oxygen desaturation severity and power spectral densities (PSDs) for example have shown greater correlations with EDS as measured via multiple sleep latency tests (MSLTs) mean sleep latency (MSL) than either the AHI or the oxygen desaturation index (ODI) (29, 30). Although power spectral analyses are commonly used to quantify electroencephalogram (EEG) outcomes, the association of these with EDS is sparsely reported, though associations with other somnolence or psychiatric disorders have been (31–34). Within the sleep field, EEG-based PSDs are typically analysed at four frequency bands – delta (δ) (0.5–4 Hz), theta (θ) (4–8 Hz), alpha (α) (8–12 Hz), and beta (β) (12–30 Hz), though the exact thresholds used between studies may differ. Among patients with insomnia, beta frequency power has been found to be higher in non-rapid eye movement (NREM) stages, but lower in rapid eye movement (REM) stages compared to patients without insomnia (35). Among patients with narcolepsy, alpha power has been found to be higher in REM stages and delta power lower in NREM stage 1 (N1) compared to controls (36). Concerning EDS, one recent study reported increased delta and reduced alpha and beta power prior to sleep among patients classified as sleepy [Epworth sleepiness scale (ESS) score > 20] compared to non-sleepy patients (ESS score < 5) (37). Another reported greater alpha power among drowsy compared to non-drowsy patients (also assessed via ESS) – though in a resting but non-sleep state (38). To date, however, no studies have reported on associations between sleep EEG PSDs and objectively measured EDS via MSLTs which may have higher generalisability than subjective measures of EDS (39).

Therefore, this study aimed to describe the associations between objectively measured EDS and the EEG PSDs assessed over the whole

night among patients with mild OSA. Based on previous findings in different patient populations, we hypothesised that during N3 and REM sleep, alpha PSD would be increased, and delta PSD decreased among suspected OSA patients with EDS compared to those without. Furthermore, we hypothesised there would be a significant positive correlation between delta PSD and MSL.

Methods

Dataset

Between the years 2001 and 2011, patients were referred to Loewenstein Hospital rehabilitation centre (Raana Israel) for an overnight PSG [level 1 study, analysed with REMbrandt Manager System (Medcare CO, Amsterdam, Netherlands) and following day MSLT] [following AASM guidelines (40)] based on suspicion for OSA alongside complaints of daytime sleepiness. The PSG data were rescored for research purposes at Kuopio University Hospital according to the AASM 2007 guidelines and clinical practices at the time. The MSL was determined by calculating the mean of the four nap recordings in the MSLT.

Patient demographic and anthropometric information were collected by the sleep technologist prior to the PSG. From the initial cohort ($n=937$), patients with missing demographic/clinical data ($n=104$), absence of sleep stage scoring ($n=2$), less than 6 h of total sleep time ($n=29$), or failed MSLTs ($n=10$) were excluded from the analysis. Furthermore, this study focused on patients with mild OSA ($5 \leq \text{AHI} < 15$ events/h), and thus 139 patients were included in the final analysis. Patients were categorized as ‘sleepy’ or ‘non-sleepy’ based on their MSL with the sleepy group including patients with an MSL < 10 min.

EEG processing

Six EEG recordings were conducted across the frontal, central, and occipital regions, and the placement of electrodes for these recordings followed the International 10–20 System guidelines (41). These signals were sampled at 256 Hz and imported to MATLAB 2021b (MathWorks Inc., Natick, Massachusetts, United States) for further analysis. The central EEG signals (C3–A2 and C4–A1), being more prevalent among the patients, were selected for comparison between the sleepy and non-sleepy groups. For this purpose, the EEG signals were filtered using a fifth-order Chebyshev Type I bandpass filter with 0.3 and 35 Hz cutoff frequencies. The filtered signals were divided into 30-s epochs according to sleep stages. The analysis included epochs identified as light sleep (N1 + N2), deep sleep (N3), and REM.

In frequency domain analyses, the PSD was estimated within each 30-s epoch by Welch's method with 50% overlap and employing a Hamming window with size 1,000 points. The relative PSDs were calculated across various frequency bands, and for this study defined as slow oscillation (0.3–1 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–35 Hz). Relative PSDs were determined by dividing the PSD values for each specific frequency band (alpha, beta, and delta) by the total PSD calculated over the frequency range of 0.3 to 35 Hz. Then, the median relative PSDs were calculated for each signal in each sleep stage. Based on preliminary results, the frequency bands delta, alpha, and beta were selected for further analysis.

Ethics approval

Data collection and processing were approved by the Ethical Committee of the Loewenstein Hospital – Rehabilitation Center (0006-17-LOE).

Statistical analysis

The Mann–Whitney U test was used to test for statistically significant differences in continuous variables in demographics, polysomnography variables (total sleep time, night sleep latency, wakening after sleep onset (WASO), percentage time in NREM (N1 + N2 + N3) and REM stages, apnoea-hypopnea index, oxygen desaturation index (defined as a drop of $\geq 4\%$) and time under 90% oxygen saturation as a percentage of total sleep time (T90%)), and relative EEG frequency band powers between sleepy and non-sleepy groups. Furthermore, the Chi-squared test was employed to evaluate the statistical significance of categorical values.

To explore the predictive efficacy of EEG PSDs on EDS, six binomial logistic regression models were developed utilising relative PSD in each frequency band (alpha, beta and delta in both C3A2 and C4A1 channels) as the primary predictor. For the regression analyses, the relative band powers were scaled to the range of 0 to 100 by

multiplying the values by 100 to make reported odds ratios (ORs) and 95% confidence intervals (CIs) more easily interpretable and comparable. The models were adjusted for age, sex, BMI, REM, and T90. Due to potential multiple comparison issues, a *p*-value threshold of 0.01 was considered for statistical significance. Post-hoc Wilcoxon tests were employed to compute the effect size and to allow comparisons of effect between frequency bands (alpha, beta, and delta) and between the C3A2 and C4A1 channels. The Wilcoxon effect size was calculated as the *z*-statistic dividing by the square root of the sample size.

Results

Of the 139 patients with mild OSA included, 66 (47%) were categorised as non-sleepy (median MSL = 14 min) and 73 (53%) as sleepy (median MSL = 6.5 min). Patients in the sleepy and non-sleepy groups were predominantly males; however, there was a statistically significant difference in gender distribution between the groups (*p* = 0.007; Table 1). Sleep architecture, AHI and ODI did not significantly differ between sleepy and non-sleepy groups.

Significant differences in relative PSDs between sleepy and non-sleepy patients were noted in each sleep stage, in both C3A2 and C4A1 channels (Figure 1, values provided in Supplementary Table S1). During N1 + N2 stages sleepy patients

TABLE 1 Demographic data and sleep characteristics of sleepy and non-sleepy groups.

Demographic				
	All patients (<i>n</i> = 139)	Non-sleepy (<i>n</i> = 66)	Sleepy (<i>n</i> = 73)	<i>p</i> -value
Age (years)	51 (42–57)	51 (42–58)	50 (44–57)	0.86
Male <i>n</i> (%)	103 (74.1%)	42 (63.6%)	61 (83.5%)	0.007
BMI (Kg/m ²)	28.9 (26.3–32.6)	28.9 (26.5–32.9)	29.1 (25.9–31.5)	0.71
Normal weight (18.5 ≤ BMI < 25)	19 (13.7%)	9 (13.6%)	10 (13.7%)	0.99
Overweight (25 ≤ BMI < 30)	59 (42.4%)	28 (42.4%)	31 (42.5%)	0.10
Obese (BMI ≥ 30)	61 (43.8%)	29 (43.9%)	32 (43.8%)	0.99
Polysomnography				
Total sleep time (min)	405 (390.6–420.2)	400.2 (391.0–419.5)	407 (390.4–421.1)	0.50
Night sleep latency (min)	8.1 (5.0–13.4)	9.4 (4.9–19.5)	7.5 (5.0–10.5)	0.02
WASO (min)	22 (11.6–43.8)	22.2 (11.0–46.5)	22.0 (12.8–38.2)	0.91
Wake (%)	8.2 (4.6–14.5)	9.4 (4.6–15.6)	8.0 (4.9–11.6)	0.45
N1 (%)	1.8 (0.4–3.5)	1.8 (0.2–3.5)	1.9 (0.5–3.5)	0.54
N2 (%)	48.1 (42.6–55.5)	48.4 (40.8–56.2)	48.0 (43.3–55.4)	0.83
N3 (%)	20.6 (15.4–26.4)	19.8 (14.5–26.6)	20.7 (17.0–25.8)	0.72
NREM (%)	72.0 (67.3–77.3)	72.1 (64.8–77.5)	71.9 (69.2–77.0)	0.95
REM (%)	18.1 (13.9–21.4)	17.7 (13.3–23.1)	18.3 (14.5–21.0)	0.32
AHI (events/h)	9.8 (7.4–12.9)	9.8 (7.3–12.9)	9.8 (7.6–12.6)	0.83
ODI (events/h)	6.8 (3.9–11.0)	6.6 (3.5–11.7)	6.9 (4.1–10.4)	0.80
T90 (%)	0.3 (0.1–1.9)	0.4 (0.1–1.9)	0.2 (0.1–1.6)	0.84
MSLT				
MSL (min)	9.5 (6.4–13.9)	14.0 (11.8–16.6)	6.5 (5.1–8.1)	3e-24

Statistical significance was calculated with the Mann–Whitney U test (for continuous variables) or the Chi-squared test (for categorical variables). Bolded values were considered significant (*p*-values < 0.01). All parameters are presented as median (IQR). AHI, apnea-hypopnea index; BMI, body mass index, IQR, Interquartile range; MSL, mean sleep latency; MSLT, Multiple sleep latency test; NREM, non-rapid eye movement sleep; ODI, oxygen desaturation index; REM, rapid eye movement sleep; T90%, percent sleep time below 90% oxygen saturation; WASO, Wake after sleep onset.

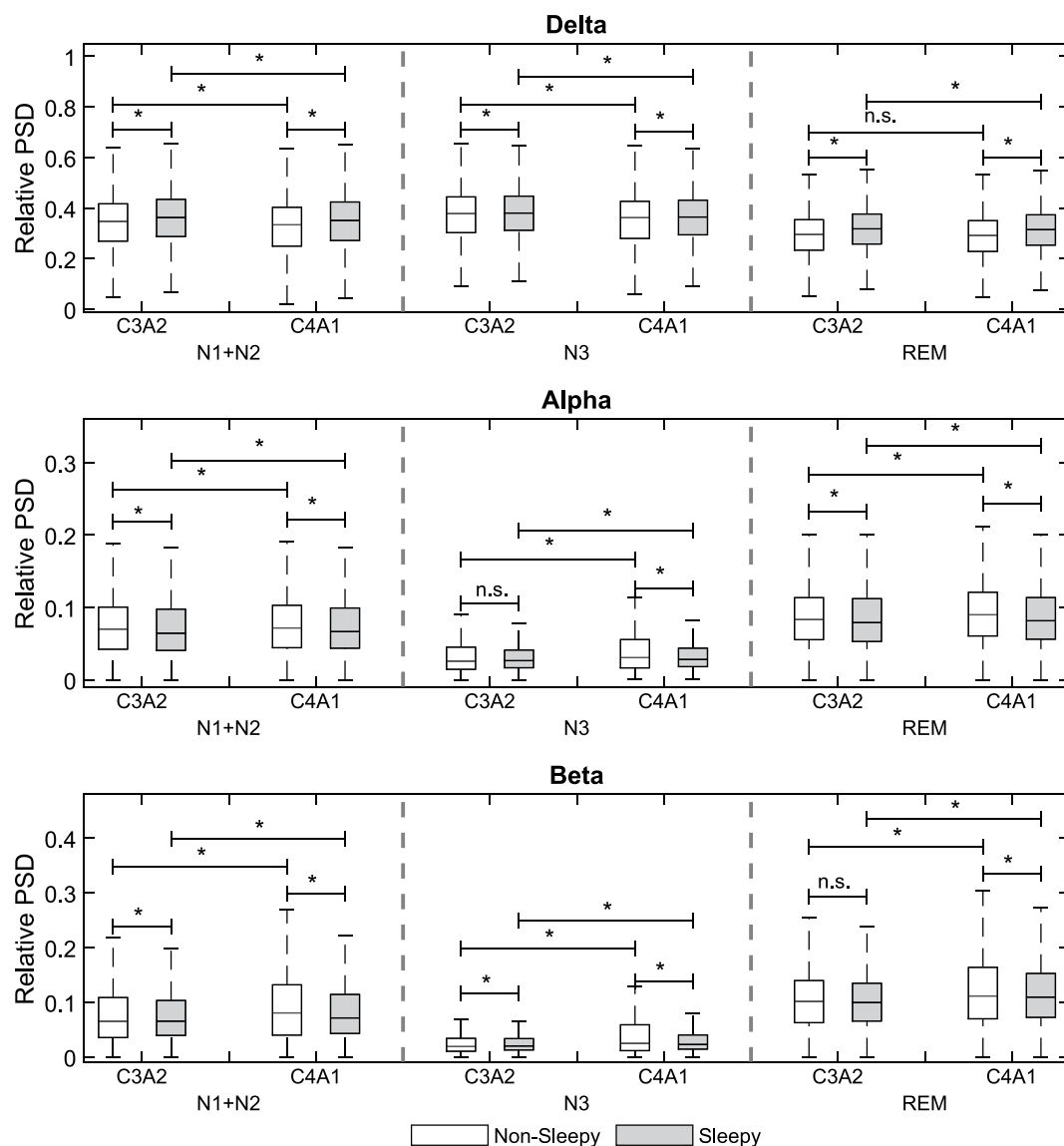


FIGURE 1

Comparison of the relative electroencephalogram power spectral densities (PSD) between sleep and non-sleep groups in N1 + N2, N3, and REM for C3A2 and C4A1 channels. $p < 0.01 = *$.

showed significantly higher delta power, and reduced alpha and beta power, though the reduced alpha was only evident in the C3A2 channel. Among sleepy patients, the C3A2 channel showed significantly higher delta power, and lower alpha and beta power than the C4A1 channel. Among non-sleepy patients however, though the delta power in C3A2 was significantly higher than in the C4A1, the beta power was also significantly greater in C3A2, with no difference in alpha power between channels. Similar results were seen in N3 stage, with sleepy patients showing significantly increased delta, and reduced alpha and beta, though the reduced beta was this time seen only in the C4A1 channel. For both sleepy and non-sleepy patients, delta power was higher in C3A2 compared to C4A1, while alpha and beta powers were lower. In REM stage, sleepy patients had higher delta power, and lower alpha and beta power compared to non-sleepy patients. There was no significant difference in delta power between channels, however alpha and beta power were significantly reduced in the C3A2 channel.

In multivariate binomial regression (adjusted for age, sex, REM, BMI & T90%) relative PSDs at each frequency band showed significant associations with odds for EDS. Increased delta power PSD significantly increased odds of EDS while increased alpha and beta powers significantly decreased the odds for EDS (Tables 2, 3).

The effect size of delta frequency PSDs was significantly stronger in both C3A2 and C4A1 channels than that of either alpha [mean overall difference C3A2 0.824 (95% CI 0.822, 0.827)] or beta (mean overall difference C3A2 0.827 (95% CI 0.824, 0.830)] (Table 4). The effect size of alpha PSD was significantly larger than that of beta overall and in all stages. Furthermore, within the C3A2 channel, for N3 and REM sleep the difference in effect size between alpha and beta was significantly greater than for N1 + N2 stages – however in the C4A1 channel the effect size difference was significantly smaller in N3 compared to N1 + N2 and REM. As well as significant differences in effect sizes between frequencies, there were significant differences in effect sizes between channels within all frequency bands. The effect

TABLE 2 Odds ratios (ORs) of being sleepy based on relative EEG band powers.

Channel	Predictors	Delta		Alpha		Beta	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
C3A2	Age (unit - 1 year)	1.009 (1.008–1.010)	<0.001	1.007 (1.006–1.008)	<0.001	1.008 (1.007–1.009)	<0.001
	BMI (unit - 1 kg/m ²)	1.035 (1.033–1.037)	<0.001	1.030 (1.029–1.032)	<0.001	1.030 (1.028–1.032)	<0.001
	Sex (male)	4.283 (4.142–4.429)	<0.001	4.034 (3.903–4.170)	<0.001	4.134 (3.998–4.274)	<0.001
	REM	1.108 (1.072–1.146)	<0.001	0.967(0.936–0.999)	0.049	1.036 (1.002–1.072)	0.037
	T90% (unit - %)	1.039 (1.037–1.041)	<0.001	1.036 (1.034–1.038)	<0.001	1.035 (1.033–1.037)	<0.001
	Corresponding PSD (unit - 1% in scaled range)	1.025 (1.024–1.026)	<0.001	1.001 (0.998–1.003)	0.594	0.983 (0.981–0.985)	<0.001
C4A1	Age (unit - 1 year)	1.008 (1.007–1.011)	<0.001	1.007 (1.006–1.008)	<0.001	1.008 (1.007–1.009)	<0.001
	BMI (unit - 1 kg/m ²)	1.036 (1.034–1.038)	<0.001	1.032 (1.031–1.034)	<0.001	1.036 (1.033–1.038)	<0.001
	Sex (male)	4.438 (4.291–4.591)	<0.001	4.118 (3.984–4.257)	<0.001	4.481 (4.332–4.634)	<0.001
	REM	1.078 (1.043–1.114)	<0.001	0.987 (0.955–1.021)	0.460	1.093 (1.058–1.131)	<0.001
	T90% (unit - %)	1.041 (1.038–1.043)	<0.001	1.035 (1.033–1.037)	<0.001	1.035 (1.033–1.037)	<0.001
	Corresponding PSD (unit - 100)	1.027 (1.026–1.028)	<0.001	0.989 (0.986–0.992)	<0.001	0.970 (0.968–0.971)	<0.001

Binomial logistic regression analyses were adjusted for age, BMI, sex, REM, and T90%. BMI, body mass index; CI, Confidence interval; OR, odds ratio; PSD, Power spectral density; REM, Rapid eye movement; T90%, percentage of total sleep time under 90% oxygen saturation.

TABLE 3 Odds ratios (ORs) of being sleepy for univariate binomial regression.

Predictors		OR (95% CI)	p-value
Age (unit - 1 year)		1.002 (1.001–1.004)	<0.001
BMI (unit - 1 kg/m ²)		1.015 (1.013–1.016)	<0.001
Sex (male)		2.977 (2.890–3.067)	<0.001
REM		0.960 (0.931–0.991)	0.011
T90% (unit - %)		1.028 (1.026–1.029)	<0.001
Corresponding PSD (unit - 1% in scaled range)	Delta_C3A2	1.016 (1.015–1.017)	<0.001
	Alpha_C3A2	0.994 (0.992–0.996)	<0.001
	Beta_C3A2	0.991 (0.988–0.993)	<0.001
	Delta_C4A1	1.017 (1.016–1.018)	<0.001
	Alpha_C4A1	0.989 (0.987–0.992)	<0.001
	Beta_C4A1	0.979 (0.978–0.981)	<0.001

BMI, body mass index; CI, Confidence interval; OR, odd ratios; PSD, Power spectral density; REM, Rapid eye movement; T90%, percent sleep time below 90% oxygen saturation.

size within the C4A1 channel was significantly smaller than the C3A2 for each frequency. For the beta frequency particularly, the effect size difference between channels was anywhere from two to five-fold greater than for the alpha and delta frequency bands.

Discussion

In this study, among patients with mild OSA, patients with a MSL<10min showed significantly higher relative PSDs in the delta frequency band and significantly lower PSDs in the alpha and beta bands compared to less sleepy patients. These differences in relative PSDs were consistent across sleep stages, with noted hemispherical differences. In multivariate models’ PSDs remained significant, independent predictors for EDS. However, the effect size associated with the delta frequency

band was significantly greater than that of either the alpha or beta frequency bands. We chose to analyse patients with mild OSA, as EDS remains common among these patients despite a lower presence of hypoxia and sleep fragmentation, and therefore other models must be developed to understand and explain the underlying mechanics of EDS (26). Furthermore, previous studies have identified differences in polysomnographic variables among patients with mild OSA between those subjectively assessed as sleepy and non-sleepy (27, 28).

Delta waves are strongly associated with the intensity of sleep and are known to appear with greater power following periods of sleep deprivation, such that they are considered a marker of sleep drive (34, 42–44). As such it is plausible that excessive daytime sleepiness leads to stronger delta wave activity during the night as opposed to causality in the other direction. A previous study identified similar results, among patients with chronic fatigue syndrome, who were shown to have significantly increased relative delta power (45). Although the patients in the previous study were not ‘sleepy’ as those in the current study but rather ‘fatigued’, there is some overlap between fatigue and sleepiness. Morisson et al. (46) and Xirometris et al. (47) also reported significantly greater relative delta power among patients with OSA compared to controls, with Xirometris et al. further reporting a significant positive correlation between relative delta power and ESS score. However, some key differences are noted in the current study – neither of these previous studies found a significant association between OSA/sleepiness and delta power in the central region specifically, whereas our study did so. Furthermore, our study also found significant differences in alpha and beta powers, whereas the previous studies did not. This may be due to differences in patient selection, with the current study recruiting patients with OSA and complaints of daytime sleepiness and comparing between those with an MSL<10min, and those with an MSL≥10min, while the previous studies compared patients with OSA to controls without OSA. Furthermore, all patients in this study were referred on the basis of self-reported sleepiness, and as such our “non-sleepy” patients can only be considered so in this particular population context and are not relatable to “non-sleepy” individuals in the general population, nor to

TABLE 4 Mean differences in effect size within multivariate binomial regression between alpha, beta and delta frequencies for channels C3A2 and C4A1, and between channels for each of alpha, beta, and delta.

Wilcoxon effect size difference (95% CI)				
Channel	Sleep Stages	Delta vs. Alpha	Alpha vs. Beta	Delta vs. Beta
C3A2	N1 + N2	0.859 (0.855–0.863)	0.031 (0.027–0.035)	0.847 (0.84–0.851)
	N3	0.865 (0.859–0.872)	0.374 (0.367–0.380)	0.865 (0.858–0.871)
	REM	0.859 (0.853–0.866)	0.380 (0.373–0.387)	0.836 (0.828–0.843)
	All sleep stages	0.824 (0.822–0.827)	0.033 (0.030–0.036)	0.827 (0.824–0.830)
C4A1	N1 + N2	0.861 (0.857–0.865)	0.232 (0.228–0.236)	0.795 (0.791–0.799)
	N3	0.865 (0.858–0.872)	0.054 (0.047–0.060)	0.821 (0.814–0.827)
	REM	0.858 (0.852–0.865)	0.496 (0.490–0.504)	0.767 (0.761–0.774)
	All sleep stages	0.830 (0.827–0.833)	0.222 (0.219–0.225)	0.774 (0.771–0.777)
C3A2, C4A1	All sleep stages	0.827 (0.825, 0.829)	0.130 (0.128–0.132)	0.801 (0.799–0.803)
		Delta	Alpha	Beta
	N1 + N2	0.108 (0.104–0.113)	0.038 (0.034–0.043)	0.193 (0.188–0.197)
	N3	0.141 (0.135–0.147)	0.124 (0.118–0.131)	0.295 (0.288–0.301)
	REM	0.039 (0.032–0.046)	0.111 (0.104–0.117)	0.256 (0.249–0.263)
	All sleep stages	0.081 (0.078–0.084)	0.051 (0.048–0.054)	0.198 (0.195–0.201)
	All sleep stages	0.043 (0.041–0.044)		

CI, Confidence interval; N1/N2/N3; non-rapid eye movement stage 1/2/3; REM, rapid eye movement.

those perhaps in other studies. This may also be underlying the very small odds ratios noted for all factors other than sex in the multivariate models.

It has been reported that absolute power increases across all frequencies in response to apnoeic events (48), thus one would expect to see differences in absolute band powers between patients with a greater AHI and those with a lower AHI, but differences in relative band powers may not be visible. In the current study however, there was no significant difference in the AHI between sleepy and non-sleepy groups. Additionally, there are inconsistencies within the literature regarding the thresholds to be used for frequency analyses which may vary by up to 2 Hz in either direction from AASM stated thresholds of 4 Hz, 8 Hz & 13 Hz (32, 47, 49–51), which may in part explain differences in significance and effect size of findings.

Hemispheric coherence has previously been reported to be high in EDS patients (52). Yet, in the current study we noted significant differences between the C4A1 & C3A2 channels in both sleepy and non-sleepy patients, and in each of N1 + N2, N3 and REM sleep stages. Delta frequency relative power was lower in C4A1 compared to C3A2, whereas alpha and beta frequency powers were higher in C4A1 compared to C3A2. It has been reported that during sleep onset and at lower levels of arousal the right hemisphere is dominant (53), yet we noted increased delta activity and reduced alpha and beta in the right hemisphere. Furthermore, we noted statistically significant differences in the effect size for predicting EDS between C4A1 and C3A2 channels in each of N1 + N2 & N3, for all frequency bands (Table 4). The differences were relatively small, with a combined sleep stage difference of 0.081 (0.078, 0.084) in the delta frequency and 0.051 (0.048, 0.054) in the alpha frequency. However, the difference in the beta frequency was significantly larger, at 0.198 (0.195, 0.201). Further research is needed to define if hemispheric coherence is an important aspect of EDS.

Differing brain wave patterns have been noted between patients with insomnia, narcolepsy and a variety of other psychiatric disorders

in comparison to controls. A greater beta power density has been noted during NREM among insomnia patients compared to healthy sleepers (35, 54), while patients with narcolepsy show higher alpha power in REM than controls (36). Seemingly in contrast, the results from the current study show increasing alpha and beta power, regardless of sleep stage, are associated with significantly reduced odds of EDS – highlighting a potential difference in the way these disorders manifest on the EEG. This may be due to the use of relative as opposed to absolute PSDs within which the heightened delta power obscures the ‘true power’ of the other frequency bands. However, as alpha power is associated with relaxed wakefulness, and beta power with active wakefulness it stands to reason that these frequencies would be lower among ‘sleepy’ patients. Additionally, among patients with sleep disordered breathing, symptoms of both depression and paranoid ideation have been associated with greater absolute power of slow oscillations (defined in the cited study as 0.5–1 Hz) (55). Previous research has shown a significant association between depression and EDS (15), which may contribute to why in the current study, increasing delta power was associated with increased odds for EDS.

Another novel method of assessing the correlation between EEG signals and EDS is the odds ratio product (ORP) (56, 57). The ORP differs from PSDs in several key ways. First, in PSDs delta frequency range typically used is 0.5–4 Hz, whereas in the ORP the thresholds used for the lower frequencies are 0.33–2.33 Hz and 2.33–6.7 Hz. Secondly the ORP is calculated in 3-s intervals compared to the 30 s epochs of the PSDs. Finally, the ORP is defined against an external reference standard (56 clinical PSGs including patients with a range of sleep disorders) while relative PSDs are normalised within each patient (56). The ORP is overall a more complex measure, showing the relationship of the powers of different EEG frequencies within a single index, while in comparison PSDs show the power of a single frequency range. Given that there are large interindividual differences in power spectra, the relative PSDs will also differ

significantly based on the profile of the population under study (58). As yet however, although the ORP has shown to be significantly associated with ESS scores, no studies have utilised it to compare to following day MSLTs (59). Overall, given the novelty of the ORP, there is little literature testing the association between it and measures of sleepiness.

Limitations

Patients recruited into this study self-reported subjective sleepiness, and thus, although they were divided into two groups based on objectively assessed MSL, there is a significant difference between the 'non-sleepy controls' in this study (who showed a median MSL of 14.5 min), and what may be considered 'non-sleepy/healthy controls' in the general population. Furthermore, we utilised a 10 min MSL cut-off for sleepy/non-sleepy groups, which differs from the 8 min cut-off used in the AASM criteria for narcolepsy, nor did we consider any REM periods during the MSLT. This study excluded patients with moderate or severe OSA, which counted for 82.5% of the patient sample with demographic information, acceptable EEGs and successful MSLTs, and therefore introduced selection bias – thus these results apply only to mild OSA and cannot be generalised to OSA more broadly. The utilised dataset also lacked clinical comorbidity and medication data, which would have significant impacts on EDS and/or EEG activity. Furthermore, we did not have information on whether patients smoked, consumed caffeine, or drank alcohol prior to the sleep study, nor did we have available any measure of subjective sleepiness such as the ESS. Additionally, as was explored above, relative powers were used in the current study, and this may limit generalisability and comparison to other studies which used absolute powers, or other power transformations. Finally, the overnight polysomnography occurred on only the single occasion, and thus may be limited by the first night effect and the patients state of sleep deprivation prior to the sleep study.

Conclusion

These results show that there are significant differences in PSDs between sleepy and non-sleepy patients with mild OSA as measured objectively via MSLT. Sleepy patients with mild OSA show significantly greater intensity of slow waves during the night, and correspondingly lesser intensity of fast waves, even after accounting for sleep stages, and other polysomnographic and demographic parameters. Furthermore, there appear to be hemispherical differences in frequency band powers among patients with EDS compared to less sleepy patients. Further research is needed to corroborate our findings, and to assess both the impact of a greater severity of OSA and the influence of potential confounders such as cardiorespiratory comorbidities on these results.

Data availability statement

The data analysed in this study is subject to the following licenses/restrictions: This manuscript utilises proprietary data. Requests to access these datasets should be directed to Loewenstein Hospital Rehabilitation Centre.

Ethics statement

The studies involving humans were approved by Ethical Committee of the Loewenstein Hospital – Rehabilitation Center (0006-17-LOE). 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

TH: Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. MT: Methodology, Formal analysis, Writing – original draft. Writing – review & editing. TK: Methodology, Software, Supervision, Writing – review & editing, Investigation, Validation, Writing – original draft. MR: Writing – review & editing, Supervision. HP: Writing – review & editing. AO: Writing – review & editing, Data curation, Resources. SN: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2024.1367860/full#supplementary-material>

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Latent profile analysis of depression in US adults with obstructive sleep apnea hypopnea syndrome

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Objective: This study used latent profile analysis to explore the level of depression among US adults with obstructive sleep apnea hypopnea syndrome (OSAHS) symptoms and to identify different latent categories of depression to gain insight into the characteristic differences between these categories.

Methods: The data of this study were obtained from the National Health and Nutrition Examination Survey (NHANES) database, and the subjects with OSAHS symptoms were aged 18 years and older. The latent profile analysis (LPA) method was used to fit the latent depression categories in subjects with OSAHS symptoms. The chi-square test, rank sum test, and binary logistic regression were used to analyze the influencing factors of depression subgroups in subjects with OSAHS symptoms.

Results: Three latent profiles were identified: low-level (83.7%), moderate-level (14.5%) and high-level (1.8%) depression. The scores of 9 items in the high-level depression group were higher than those in the other two groups. Among them, item 4 “feeling tired or lack of energy” had the highest score in all categories.

Conclusion: Depression in subjects with OSAHS symptoms can be divided into low-level, moderate-level and high-level depression. There are significant differences among different levels of depression in gender, marital status, PIR, BMI, smoking, general health condition, sleep duration and OSAHS symptom severity.

KEYWORDS

latent profile analysis, depression, NHANES, obstructive sleep apnea, OSAHS

Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a chronic sleep-disordered breathing disease. It is characterized by recurrent collapse or obstruction of the upper airway during sleep, resulting in intermittent hypoxia (IH) and hypercapnia (1). This situation greatly increases the risk of multiple psychiatric disorders in subjects with OSAHS symptoms (2). According to the current study, the prevalence of OSAHS in the adult population of the United States ranges from approximately 2% to 14%. It is higher, up to 20%, in individuals over the age of 60 years (3). As of 2019, nearly 1 billion people worldwide are affected by OSAHS, and the prevalence in some countries even exceeds 50%. Of those affected, China has the most significant number, followed by the United States, Brazil and India (4). In addition, subjects with OSAHS symptoms may face a range of severe affective disorders, which may lead to cognitive decline and have the potential to trigger permanent brain damage (3).

Depression is one of the most common affective disorders and a major related cause of the global burden of mental illness (5). It is characterized by mental symptoms such as low mood, loss of interest, difficulty sleeping, pessimism, and low sense of worth (6, 7). Depression is particularly prevalent in subjects with OSAHS symptoms. According to Melanie Harris et al., in a sleep clinic sample, the incidence of depression in subjects with OSAHS symptoms ranges from 21% to 41% (8). In addition, a longitudinal study by Chen Yihua et al. also confirmed the causal relationship between OSAHS and depression. That is, OSAHS may lead to the occurrence of depression (9). The mechanism of OSAHS causing depression may involve the initiation or aggravation of the pathological process of cerebral small vessel disease (C-SVD) and blood-brain barrier (BBB) dysfunction, thus inducing the occurrence of depression (10). The occurrence and development of depression can also affect the mental health of subjects with OSAHS symptoms, which may lead to decreased sleep quality and poor mental state, thus aggravating the symptoms of OSAHS.

Previous studies mainly focused on exploring the influence of different factors on depression in subjects with OSAHS symptoms, including age, gender, OSAHS symptom severity, and other related factors (11–14). However, these studies all used depression as a variable to diagnose the presence of depression or to assess the severity of depression by assessing the total score of the scale or by setting a cut-off value. However, this approach does not fully reflect the reality of the situation. It ignores the intrinsic characteristics of individuals, and there may be specific subgroups that have not yet been identified. To better understand, we need to take a person-centered approach, observe the relationship of relevant variables among participants, and identify subgroups of individuals based on their response patterns to a set of variables (15).

Latent profile analysis (LPA) is a human-centered statistical method used to identify potential, unobserved subgroups or latent profiles in the data. It aims to discover potential, relatively unique groups in the data that show different patterns or characteristics on

the observed variables. LPA is often used to study latent types or subgroups in a population to understand the data better and provide personalized intervention or treatment options (16). In healthcare, LPA has been widely used in a variety of studies, one of which includes the field of sleep medicine (17–19). For example, Wan-Ju Cheng et al. analyzed the endotypes of OSAHS symptoms and found three clusters of pathological endotypes in patients with moderate to severe OSAHS, each of which showed different polysomnographic features and clinical symptom characteristics (20). However, to our knowledge, no study has used LPA to investigate depression in subjects with OSAHS symptoms. Therefore, the primary goal of this study was to use the LPA approach for depression subtype identification in subjects with OSAHS symptoms in the United States to address patient heterogeneity. Secondly, the secondary objective was to investigate the influencing factors of different subtypes of depression to gain insight into the characteristics and related factors of depression in subjects with OSAHS symptoms.

Methods

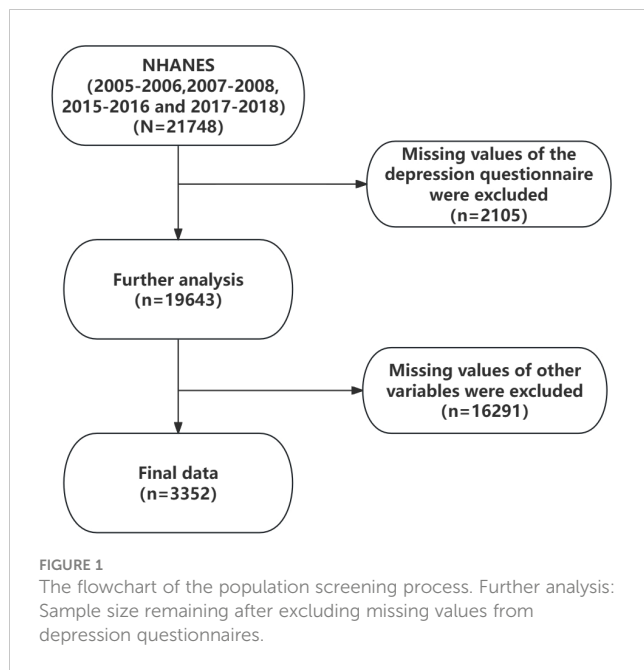
Study participants

The data used in this study were obtained from the US National Health and Nutrition Examination Survey (NHANES) database. Because this study focused only on subjects with OSAHS symptoms, we chose the sleep questionnaire that included the year in which the question was asked: “How often do you snort/stop breathing?” while years in which the question was not mentioned were excluded. Finally, we selected data from the NHANES database for 2005–2006, 2007–2008, 2015–2016, and 2017–2018 as the sample for this study. This study’s original number of participants was 21748, all aged 18 years and older. After excluding missing values for depression scales, the sample size was reduced to 19643. Subsequently, after excluding missing values of other relevant variables, 3352 subjects were finally included. The sample screening procedure is shown in Figure 1. NHANES survey data can be obtained at <https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx>.

Measures

Socio-demographic variables

In this study, we used the ratio of family income to poverty (PIR) as the reference standard to measure family income situation. Those with $PIR \leq 1.3$ were identified as low-income. However, those with $PIR > 1.3$ were considered a non-low-income population. In addition, we used body mass index (BMI) as a measure of obesity, which was divided into four categories: underweight (BMI, < 18.50), normal (18.50 to 24.99), overweight (25.00 to 29.99), and obese (BMI, ≥ 30).



Health behavior variables

Alcohol consumption was categorized into three categories: never, light, and heavy drinking. Never drinking was defined as having a drinking frequency of zero or never drinking in the past 12 months. Light drinking was defined as 1-36 drinks in the previous 12 months, or at least 1-2 drinks per year and up to 2-3 drinks per month. Heavy drinking was defined as drinking more than 37 times in the previous 12 months or drinking at least once a week and up to once a day.

Smoking status was determined based on the subjects' responses to two questions: "Have you ever smoked more than 100 cigarettes in your lifetime?" and "Do you currently smoke?". A response of "no more than 100 cigarettes in his lifetime and no current smoker" was defined as never smoking. A response of "smoking more than 100 cigarettes in a lifetime and not currently smoking" was defined as ever smoking. Answering "smoking more than 100 cigarettes in one's life and now smoking every day, or smoking more than 100 cigarettes in one's life and now smoking on a few days" was defined as current smoking.

Health status variables

The diagnosis of diabetes was based on self-reported judgments of the subject's responses to the following questions: "Ever told by a doctor or health professional that you have diabetes or sugar diabetes?". A response of "yes" was defined as having diabetes, while "no" and "Borderline" were defined as not having diabetes.

General health condition was based on subjects' responses to "I have some general questions about your health" and "Would you say your health in general is?". The responses to these two questions are defined. Excellent, very good, and good were all defined as good health. Fair was defined as general health status. Poor was defined as poor health.

Sleep-related variables

We used seven and nine hours as cut-off points for determining the length of sleep (21, 22). Specifically, sleep duration less than 7 hours was defined as short, sleep duration between 7 and 9 hours was defined as normal, and sleep duration more than 9 hours was defined as long.

OSAHS symptom severity was assessed based on self-report of: "In the past 12 months, how often did you snort, gasp, or stop breathing while you were asleep?". The selection "Rarely" was recorded as "mild OSAHS symptom," "Occasionally," as "moderate OSAHS symptom," and "Frequently" as "severe OSAHS symptom."

Depression

The Patient Health Questionnaire-9 (PHQ-9) is a commonly used self-rating scale to diagnose depression and assess its severity. Each item on the scale was scored using a Likert four-point scale of 0 (not at all), 1 (a few days), 2 (more than half a day), and 3 (almost every day). The total score ranges from 0 to 27, with higher scores indicating more significant depression. At present, the PHQ-9 has been widely validated in multiple domains, and the results show that the scale has good reliability and validity (23–25). In the present study, the Cronbach alpha coefficient of the PHQ-9, a measure of depression, was 0.858. The assignment of each variable is shown in Table 1.

Statistical analysis

Stata 17.0 (StataCorp LLC, USA) software was used to screen, extract, and combine the NHANES data, and Mplus 8.3 (Muthen and Muthen) and SPSS 25.0 (IBM Corp) software were used for statistical analysis. SPSS 25.0 software was used for statistical description and analysis during data analysis. Quantitative data with normal distribution were expressed as mean $\pm$ standard deviation ($M \pm SD$). We used frequency (n) and percentile (%) for representation for qualitative data.

In this study, latent profile analysis of the nine items of the PHQ-9 scale was performed using Mplus 8.3 software. We analyzed latent class by gradually increasing the number of latent classes starting from 1 and simultaneously testing the models' fit index with different classes. We selected the best-fitting model by comparing the fitting indexes of different models. In selecting the best fitting model, we mainly considered the following model fit indicators: sample corrected aBIC (adjusted BIC, aBIC), Lo-Mendell-Rub test (LMRT) and Entropy were used to evaluate the accuracy of classification. Generally, smaller aBIC values indicate a better model fit (26). We evaluated the classification accuracy using Entropy, which ranges from 0 to 1. When the value of Entropy is closer to 1, the classification is more accurate. In general, when Entropy is greater than or equal to 0.8, the classification accuracy is above 90% (27). BLRT is used to test whether the difference between the K category model and the k-1 category model is significant. When their value is less than 0.05, the K category model has a more

TABLE 1 Independent variable assignment.

Predictive factors	Assignment
Gender	"Male" = 1, "Female" = 2
Age	Original value entry
Race	"Mexican American" = 1, "Other Hispanic" = 2, "Non-Hispanic White" = 3, "Non-Hispanic Black" = 4, "Other Race" = 5
Education level	"Less than 9th grade" = 1, "9-11th grade" = 2, "High school graduate" = 3, "Some college or AA degree" = 4, "College graduate or above" = 5
Marital status	"Married" = 1, "Widowed" = 2, "Divorced" = 3, "Separated" = 4, "Never married" = 5, "Living with a partner" = 6
PIR	"Low-income(PIR ≤ 1.3)" = 1, "Non-low-income(PIR > 1.3)" = 2
BMI	"Underweight(BMI<18.50)" = 0, "Normal weight(18.50~24.99)" = 1, "Overweight(25.00~29.99)" = 2, "Obese(BMI≥30)" = 3
Alcohol consumption	"Never (0)" = 0, "Light(1~36/6~10)" = 1, "Heavy(≥37/1~5)" = 2
Smoking	"Never smoked" = 0, "Ever smoked" = 1, "Currently smoked" = 2
Hypertension	"Yes" = 1, "No" = 0
Diabetes	"Yes" = 1, "No" = 0
Asthma	"Yes" = 1, "No" = 0
Coronary disease	"Yes" = 1, "No" = 0
General health condition	"Good(1~3)" = 1, "Fair(4)" = 2, "Poor(5)" = 3
Sleep duration	"Short(<7 hours)" = 1, "Normal(7~9 hours)" = 2, "Long(>9 hours)" = 3
OSAHS symptom severity	"Mild(1 Rarely)" = 1, "Moderate(2 Occasionally)" = 2, "Severe(3 Frequently)" = 3

PIR, ratio of family income to poverty; BMI, body mass index; OSAHS, obstructive sleep apnea hypopnea syndrome.

substantial improvement in fit compared with the k-1 category model (28). In this study, we will make a comprehensive judgment based on the above fitting indicators to determine the best classification model.

We will use the latent category of depression derived using LPA as the dependent variable when performing univariate analyses. We will use the chi-square test and the Kruskal-Wallis H test for categorical variable comparisons for statistical analysis. For continuous variables that follow a normal distribution, we will use one-way ANOVA for statistical analysis. The variables with statistically significant differences were included in multiple logistic regression analyses to analyze the influencing factors of depression categories in subjects with OSAHS symptoms. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The subjects with OSAHS symptoms in this study were mainly male, accounting for 61.4% of the total sample size. Among them, 3352 subjects with OSAHS symptoms ranged from 20 to 85 years, with an average age of 51.0 (SD = 15.942). The primary characteristics of the participants were mainly Non-Hispanic White (44.7%), married (57.3%), obese (50.1%), never smoking (45.2%), and normal sleep duration (58.1%). Most patients had Some college or AA education degree (31.9%), and most had mild OSAHS symptoms (47.0%). Most of the patients were non-low-income people with good income (72.4%), drank alcohol lightly (68.6%), and self-rated general health condition was good (71.0%). Detailed demographic information of the participants is provided in Table 2.

Results of latent profile analysis

In this study, latent profile analysis was performed on the nine items of the PHQ-9 questionnaire, and one to five latent categories were fitted sequentially. The fitting indices of different types of profile models are shown in Table 3. The observations showed that Profiles 4 and 5 had P values of LMRT probability greater than 0.05, indicating that they did not reach the significance level and were therefore excluded. At the same time, the aBIC value of Profile 3 is lower than that of Profile 1 and Profile 2, which is more in line with the optimal criteria. Finally, we also need to consider the entropy value. The entropy value of Profile 3 is closer to 1 than Profile 1 and Profile 2, so Profile 3 has the best classification effect. Taking the above analysis together, it can be concluded that Profile 3 is the optimal model.

In order to verify the reliability of the above latent profile analysis results, we calculated the average attribution probability of the three class samples in each class. The results showed that the correct classification probability of the latent class 1 was 99.2%, the latent class 2 was 96.4%, and the latent class 3 was 100.0%. These probabilities are all greater than 90%, indicating that the results of latent profile analysis in this study are relatively reliable. See Table 4 for details.

Naming of latent profile

According to the LPA results, the mean feature scores of each of the nine items in the PHQ-9 are plotted in Figure 2. Profile 1 scored significantly lower than Profile 2 and 3 on each item. This group comprised 83.7% of the participants, so we named it "low-level depression" based on its score characteristics. In Profile 2, the score of item 9 was similar to that of Profile 1, and the scores of the remaining eight items were between Profile 1 and Profile 3, accounting for 14.5%. Therefore, we named it "moderate-level depression." The scores of all items of Profile 3 were significantly

TABLE 2 Baseline information of depressed patients with OSAHS.

Variable	Total number (N=3352)	Variable	Total number (N=3352)
Gender		Alcohol consumption	
Male	2057 (61.4)	Never	751 (22.4)
Female	1295 (38.6)	Light	2299 (68.6)
Age		Heavy	302 (9.0)
	50.66 ± 15.942	Smoking	
Race		Never smoking	1515 (45.2)
Mexican American	518 (15.5)	Ever smoking	993 (29.6)
Other Hispanic	323 (9.6)	Currently smoking	844 (25.2)
Non-Hispanic White	1497 (44.7)	Hypertension	
Non-Hispanic Black	693 (20.7)	Yes	1459 (43.5)
Other Race	321 (9.6)	No	1893 (56.5)
Education level		Diabetes	
Less than 9th grade	263 (7.8)	Yes	577 (17.2)
9-11th grade	481 (14.3)	No	2775 (82.8)
High school graduate	821 (24.5)	Asthma	
Some college or AA degree	1068 (31.9)	Yes	634 (18.9)
College graduate or above	719 (21.4)	No	2718 (81.1)
Marital status		Coronary heart disease	
Married	1921 (57.3)	Yes	198 (5.9)
Widowed	176 (5.3)	No	3154 (94.1)
Divorced	369 (11.0)	General health condition	
Separated	110 (3.3)	Good	2380 (71.0)
Never married	435 (13.0)	General	751 (22.4)
Living with a partner	341 (10.2)	Poor	221 (6.6)
PIR		Sleep duration	
Low-income	924 (27.6)	Short	1163 (34.7)
Non-low-income	2428 (72.4)	Normal	1948 (58.1)
BMI		Long	241 (7.2)
Underweight	39 (1.2)	OSAHS symptom severity	
Normal weight	594 (17.7)	Mild	1575 (47.0)
Overweight	1039 (31.0)	Moderate	964 (28.8)
Obese	1680 (50.1)	Severe	813 (24.3)

PIR, ratio of family income to poverty; BMI, body mass index; OSAHS, obstructive sleep apnea hypopnea syndrome.

higher than those of Profile 1 and Profile 2, and this group was named as having a “high-level depression.”

Inter-profile characteristic differences

Table 5 compares differences in demographic characteristics between the three underlying depression types. We used the chi-square test, one-way ANOVA, and Kruskal-Wallis H test to compare the differences in the presence of single risk factors among subjects with OSAHS symptoms with different underlying depression categories. The findings revealed statistically significant differences between patients in different underlying depression categories involving multiple factors. These factors included gender, education level, marital status, PIR, BMI, smoking, hypertension, diabetes, asthma, general health condition, sleep duration, and OSAHS symptom severity. For the remaining categorical differences, we did not observe statistically significant differences. This study considered a two-sided p-value of less than 0.05 statistically significant.

In each of the three depression categories, most subjects with OSAHS symptoms were married, obese, and nonlow-income, with good self-reported general health and normal sleep duration. Notably, the proportion of subjects with OSAHS symptoms with low-level depression was higher in men (64.5%) than in women (35.5%). However, the proportion of men with moderate-level and high-level depression decreased (45.2% and 45.8%, respectively). In addition, the smoking rate also increased significantly in people with moderate-level and high-level depression, which were 40.0% and 49.2%, respectively, which were higher than those with low-level depression (22.1%).

Multiple logistic regression of depression profiles

In this study, the classification of profile characteristics of depression was used as the dependent variable, with reference to high-level and low-level depression, and variables statistically significant in the univariate analysis were studied as independent variables. Subsequently, we included these variables in binary logistic regression models to explore the correlation between observed variables and the classification of each profile. The results showed that PIR in depressive traits did not differ significantly between profiles. Compared with “high level of depression,” we found that the following factors had a significant impact on “low level of depression”: gender, marital status, BMI, smoking, general health condition, sleep duration, and OSAHS symptom severity. Specifically, male (OR= 2.215, P= 0.004), underweight (OR=6.538, P < 0.001), never smoking (OR=2.794, P=0.002) or ever smoking (OR=2.695, P= 0.004), P=0.007), good general health condition(OR=6.605, P<0.001) or general health condition(OR=2.711, P=0.010), normal sleep duration (OR=2.460, P=0.030) and mild to moderate OSAHS symptoms (OR=2.711, P=0.010). p=0.002) (OR=2.338, p=0.016) were more likely to be in a

TABLE 3 Classification of potential fitting models.

Profile	k	Likelihood	aBIC	Entropy	LMRT(P)	Proportion
1	18	-34356.574	68802.065			
2	28	-29362.864	58864.045	0.967	0.0000	0.85770/0.14230
3	38	-27374.177	54936.068	0.974	0.0000	0.83711/0.14529/0.01760
4	48	-24314.934	48866.981	0.976	0.2294	0.80907/0.13634/0.03699/0.01760
5	58	-23637.679	47561.870	0.938	0.4858	0.01760/0.05638/0.16766/0.72136/0.03699

aBIC, Adjusted Bayesian Information Criterion; LMRT, Lo-Mendell-Rubin Likelihood Ratio Test.

“low-level” depression state. For “moderate-level” depression, BMI and OSAHS symptom severity had a significant impact on it. Specifically, underweight (OR = 5.439, $P < 0.001$) and mild-to-moderate subjects with OSAHS symptoms (OR = 2.005, $P = 0.035$) (OR = 2.313, $P = 0.021$) were more likely to be in the “moderate-level” of depression. Relative to the “low-level depression,” the “moderate-level” was affected by factors such as gender, PIR, BMI, smoking, general health condition, sleep duration, and OSAHS symptom severity. In particular, people with low-income (OR=1.649, $P<0.001$) were more likely to have a “high-level” of depression. The detailed analysis results of the binary Logistic regression analysis are shown in Table 6.

Discussion

In this study, LPA was used to classify depression in subjects with OSAHS symptoms, and three different characteristics were determined according to the scores of each group, namely “low-level depression” (83.7%), “moderate-level depression” (14.5%) and “high-level depression” (1.8%). Among them, 98.2% of subjects with OSAHS symptoms had a moderate or low level of depression.

The three levels of depression showed higher levels in both item 3, “Difficulty falling asleep or sleeping too much”, and item 4 “, Feeling tired or low in energy”. This indicates that depression subjects with OSAHS symptoms generally have the problem of sleeping too long or too short and often feel tired or lack energy. Combined with the results of this study, we conclude that there is A correlation between short sleep duration and depression, which is consistent with the findings of Michael A. Grandner et al (29). In addition, the study by Tiffany J Braley et al. confirmed that sleep disorders, especially OSAHS, may be responsible for the general fatigue felt by patients (30).

The low-level depression group had the lowest and most balanced scores in the other seven items, accounting for 83.7% of the total subjects with OSAHS symptoms. Such patients may have a low probability of depression. However, special attention should be paid

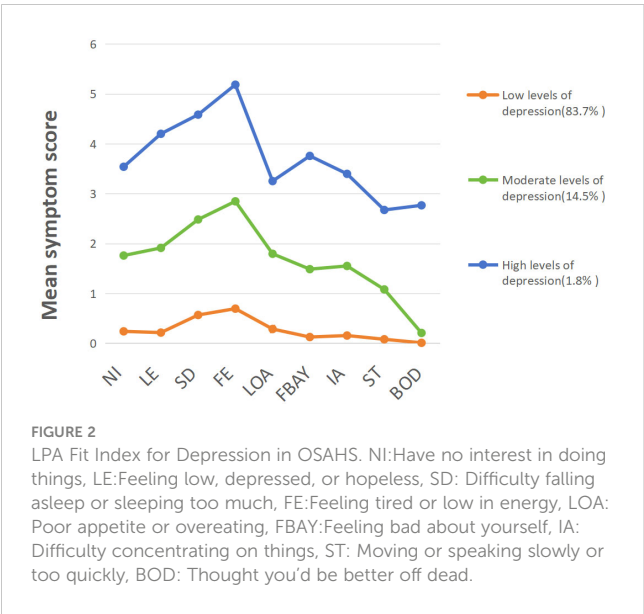
to item 3, “Difficulty falling asleep or sleeping too much”, and item 4 “, Feeling tired or low in energy”. This may be because subjects with OSAHS symptoms have upper airway obstruction during sleep, leading to apnea or hypopnea. This disrupts normal sleep cycles and deep sleep, leading to frequent awakenings, which contribute to short sleep duration (31). subjects with OSAHS symptoms may experience decreased blood oxygen levels due to inadequate oxygen supply during apnea or hypopnea. This further affects the body’s energy metabolism and rest recovery process, resulting in patients feeling tired (22). Combined with the results of this study, we believe that early personalized treatment measures should be carried out for people with low-level depression to reduce the severity and symptoms of OSAHS patients and improve their sleep quality and quality of life to prevent them from becoming moderate or high-level depression. Measures include weight control, smoking cessation, adequate sleep duration, and CPAP therapy.

Among subjects with OSAHS symptoms, 14.5% were classified as moderate-level depression. The most prominent item in this group was item 9, “Thought you would be better off dead”, with a score that coincided with low-level depression and was close to zero. This suggests that the risk of suicide is not high for low-level and moderate-level depression in subjects with OSAHS symptoms (32). This may be because depression caused by OSAHS symptoms usually has milder symptoms. Patients are often more likely to accept and respond positively to treatment, which reduces the probability of suicidality (33). The moderate-level depression group is the category most likely to develop into high-level depression, so the level of depression in patients must be detected early and controlled.

1.8% of subjects with OSAHS symptoms were classified as having high-level depression. The scores of item 6, “Feeling bad about yourself”, and item 7 “, Difficulty concentrating on things”, were significantly higher than those of the other two depression categories. This may be because chronic sleep deprivation and poor sleep quality can also hurt mood, leading to a decrease in patients’ self-perception and ability to focus attention (34, 35). A sleep center physician should perform a thorough history and physical examination to determine the presence of major depressive symptoms. Second, they should cooperate with psychiatrists to jointly develop an individualized treatment plan, including cognitive treatments such as pharmacotherapy and cognitive behavioral therapy (36). In addition, patients can also actively conduct self-management, learn to cope with stress and negative emotions and improve self-management skills (37). These measures help to reduce the level of depression as much as possible.

TABLE 4 Average Posterior Probabilities for Most Likely Latent Class Membership (Row). by Latent Class (Column).

Class	Profile 1	Profile 2	Profile 3
Profile 1	0.992	0.008	0.000
Profile 2	0.036	0.964	0.000
Profile 3	0.000	0.000	1.000



The results of this study showed that gender, marital status, PIR, BMI, smoking, general health condition, sleep duration and OSAHS symptom severity were the influencing factors of depression in OSAHS symptoms patients. Gender plays a crucial role in the development of depression in OSAHS symptoms patients. Due to

the influence of biological, hormonal levels and psychosocial factors related to women, the probability of depression in female OSAHS symptoms patients is generally higher. This conclusion is consistent with the results of multiple studies (38–40). In this study, since the proportion of men with OSAHS symptoms is much more significant than that of women, there may be a higher incidence of depression in men than in women, which is also consistent with the results of Min-hwan Lee et al (41). Therefore, sleep physicians should make a comprehensive treatment plan according to the gender characteristics and needs of patients, including sleep therapy, drug treatment and psychological support.

Recent research suggests that a lack of close, confidence-worthy marital relationships may be a vulnerable factor for depression in women living in disadvantaged circumstances (42). The results of the present study also show that unmarried individuals have higher levels of depression than married individuals, which is consistent with the findings of Akihide Inaba (43). Open and effective communication should be maintained between couples, and subjects with OSAHS symptoms can share their feelings and troubles with their spouse to let the other person understand the situation they have experienced (44). In addition, marriage can provide intimacy and companionship and reduce loneliness in patients. Loneliness is often an essential factor in depression, and marriage can provide the emotional connection and support that patients need (42). Therefore, subjects with OSAHS symptoms

TABLE 5 Demographic characteristics of the different profiles.

Variable	Low-level n = 2806 (83.7%)	Moderate-level n = 487 (14.5%)	High-level n = 59 (1.8%)	χ^2/F	p
	n (%) or M $\pm$ SD	n (%) or M $\pm$ SD	n (%) or M $\pm$ SD		
Gender				71.571	0.000
Male	1810 (64.5)	220 (45.2)	27 (45.8)		
Female	996 (35.5)	267 (54.8)	32 (54.2)		
Age				1.026	0.420
	50.96 $\pm$ 16.140	49.20 $\pm$ 14.677	48.81 $\pm$ 15.949		
Race				14.042	0.081
Mexican American	457 (16.3)	53 (10.9)	8 (13.6)		
Other Hispanic	270 (9.6)	45 (9.2)	8 (13.6)		
Non-Hispanic White	1235 (44.0)	238 (48.9)	24 (40.7)		
Non-Hispanic Black	569 (20.3)	109 (22.4)	15 (25.4)		
Other Race	275 (9.8)	42 (8.6)	4 (6.8)		
Education level				42.885	0.000
Less than 9th grade	208 (7.4)	50 (10.3)	5 (8.5)		
9–11th grade	381 (13.6)	84 (17.2)	16 (27.1)		
High school graduate	671 (23.9)	136 (27.9)	14 (23.7)		
Some college or AA degree	895 (31.9)	157 (32.2)	16 (27.1)		
College graduate or above	651 (23.2)	60 (12.3)	8 (13.6)		

(Continued)

TABLE 5 Continued

Variable	Low-level n = 2806 (83.7%)	Moderate-level n = 487 (14.5%)	High-level n = 59 (1.8%)	χ^2/F	p
	n (%) or M $\pm$ SD	n (%) or M $\pm$ SD	n (%) or M $\pm$ SD		
Marital status				108.185	0.000
Married	1705 (60.8)	195 (40.0)	21 (35.6)		
Widowed	147 (5.2)	26 (5.3)	3 (5.1)		
Divorced	276 (9.8)	82 (16.8)	11 (18.6)		
Separated	78 (2.8)	30 (6.2)	2 (3.4)		
Never married	321 (11.4)	97 (19.9)	17 (28.8)		
Living with a partner	279 (9.9)	57 (11.7)	5 (8.5)		
PIR				139.773	0.000
Low-income	661 (23.6)	238 (48.9)	25 (42.4)		
Non-low-income	2145 (76.4)	249 (51.1)	34 (57.6)		
BMI				29.385	0.000
Underweight	29 (1.0)	10 (2.1)	0 (0)		
Normal weight	526 (18.7)	59 (12.1)	9 (15.3)		
Overweight	890 (31.7)	128 (26.3)	21 (35.6)		
Obese	1361 (48.5)	290 (59.5)	29 (49.2)		
Alcohol consumption				7.098	0.131
Never	607 (21.6)	130 (26.7)	14 (23.7)		
Light	1948 (69.4)	313 (64.3)	38 (64.4)		
Heavy	251 (8.9)	44 (9.0)	7 (11.9)		
Smoking				90.719	0.000
Never smoking	1331 (47.4)	166 (34.1)	18 (30.5)		
Ever smoking	855 (30.5)	126 (25.9)	12 (20.3)		
Currently smoking	620 (22.1)	195 (40.0)	29 (49.2)		
Hypertension				24.273	0.000
Yes	1170 (41.7)	261 (53.6)	28 (47.5)		
No	1636 (58.3)	226 (46.4)	31 (52.5)		
Diabetes				12.558	0.002
Yes	457 (16.3)	103 (21.1)	17 (28.8)		
No	2349 (83.7)	384 (78.9)	42 (71.2)		
Asthma				32.426	0.000
Yes	484 (17.2)	137 (28.1)	13 (22.0)		
No	2322 (82.8)	350 (71.9)	46 (78.0)		
Coronary heart disease				3.855	0.146
Yes	157 (5.6)	35 (7.2)	6 (10.2)		
No	2649 (94.4)	452 (92.8)	53 (89.8)		
General health condition				344.255	0.000
Good	2155 (76.8)	199 (40.9)	26 (44.1)		

(Continued)

TABLE 5 Continued

Variable	Low-level n = 2806 (83.7%)	Moderate-level n = 487 (14.5%)	High-level n = 59 (1.8%)	χ^2/F	p
	n (%) or M $\pm$ SD	n (%) or M $\pm$ SD	n (%) or M $\pm$ SD		
General	541 (19.3)	190 (39.0)	20 (33.9)		
Poor	110 (3.9)	98 (20.1)	13 (22.0)		
Sleep duration				60.022	0.000
Short	930 (33.1)	210 (43.1)	23 (39.0)		
Normal	1704 (60.7)	217 (44.6)	27 (45.8)		
Long	172 (6.1)	60 (12.3)	9 (15.3)		
OSAHS symptom severity				31.190	0.000
Mild	1367 (48.7)	188 (38.6)	20 (33.9)		
Moderate	796 (28.4)	155 (31.8)	13 (22.0)		
Severe	643 (22.9)	144 (29.6)	26 (44.1)		

PIR, ratio of family income to poverty; BMI, body mass index; OSAHS, obstructive sleep apnea hypopnea syndrome.

should be actively involved in sleep therapy as well as other possible treatment methods, such as medication and psychological support.

In this study, we used PIR to indicate household income situation. Income is an essential factor affecting the development of depression in subjects with OSAHS symptoms. This study indicates that people with low income are more likely to suffer from depression than people without low income. This is in line with the findings of Akihide Inaba and Matthew Ridley et al (43, 45). subjects with OSAHS symptoms may need to undergo a range of tests, treatments, and devices, such as sleep monitoring and ventilators. However, the cost of these treatments and devices may be a financial burden for low-income patients. In addition, the level of income may also be associated with the patient’s self-identity and social status. Low income may exacerbate depressive symptoms, leading to feelings of low self-worth and the stress of reduced social status (46). Therefore, it is recommended that low-income groups actively seek appropriate health insurance or social welfare policies to alleviate the financial pressure of treatment and equipment costs.

BMI mainly reflects the weight status of patients. Being overweight or obese is a common risk factor for OSAHS. Excess body weight increases the likelihood of airway obstruction and airway collapse, which leads to an increase in the severity of OSAHS (47). In addition, obesity is associated with chronic inflammation and metabolic disturbances, factors that are thought to be involved in the development of depressive symptoms (48, 49). Therefore, a healthy diet and exercise program is recommended for overweight or obese subjects with OSAHS symptoms with depression in order to lose weight.

In this study, it was found that the order of smoking factors for depression in subjects with OSAHS symptoms was: current smoking greater than former smoking greater than never smoking. This result is consistent with the findings of Tana M. Luger et al (50). Current smokers with OSAHS symptoms may have developed more profound psychological dependence. When faced with stress and anxiety, they were more likely to smoke to relieve their mood. This psychological

dependence may increase the risk of depression (50). Based on the above findings, this study suggests that for patients with comorbid smoking, OSAHS and depression, it is necessary to consider various factors to develop corresponding treatment programs and interventions (51). First, smoking cessation interventions are needed, which can involve medication, counselling, or nicotine replacement therapy to help patients quit (52). Physicians also need to conduct a comprehensive physical and psychological assessment of patients to understand the interplay between smoking, OSAHS, and depression and to develop an individualized treatment plan.

General health condition included physical, mental, social, and lifestyle and chronic disease status (53). Sleep disorders and low oxygen supply may lead to physical fatigue and depression in subjects with OSAHS symptoms, which may affect their physiological health. Long-term poor sleep and hypoxia may negatively affect brain function and increase the risk of depression (54). OSAHS itself is a chronic disease, and chronic disease conditions are also associated with depression, so individuals with OSAHS symptoms have a higher risk of depression (55). Therefore, self-rated health is essential to provide family physicians with a practical and straightforward way to identify patients at risk for long-term adverse depressive outcomes and to inform treatment decisions (56). To understand the patient’s overall health, physicians should perform a comprehensive assessment of the patient, including sleep quality, psychological status, social interactions, lifestyle habits, and chronic disease status.

OSAHS can affect the sleep time and sleep quality of patients and further affect the emotional and mental health of patients (57). The results of this study showed A significant correlation between short sleep duration and OSAHS-related depression, which is consistent with the findings of Michael A. Grandner and Amie C Hayley et al (29, 58). In addition, the study by CAROL J. LANG et al. also noted an increased incidence and severity of depression in men with comorbid OSAHS and insomnia (59). This may be because subjects with OSAHS symptoms may wake up frequently

TABLE 6 The results of multiple logistic regression of depression profiles.

Variables	Low VS Moderate		Low VS High		Moderate VS High	
	OR(95%CI)	<i>p</i>	OR(95%CI)	<i>p</i>	OR(95%CI)	<i>p</i>
Gender						
Male	0.475(0.381, 0.593)	0.000	2.215(1.281, 3.830)	0.004	1.053(0.598, 1.854)	0.858
Marital status						
Married	0.737(0.517, 1.050)	0.091	1.063(0.387, 2.925)	0.905	0.784(0.277, 2.214)	0.645
Widowed	0.645(0.371, 1.120)	0.119	1.128(0.254, 5.007)	0.874	0.727(0.156, 3.379)	0.684
Divorced	1.338(0.883, 2.026)	0.170	0.439(0.147, 1.315)	0.141	0.587(0.191, 1.809)	0.354
Separated	1.347(0.767, 2.366)	0.300	0.880(0.162, 4.780)	0.883	1.186(0.214, 6.585)	0.845
Unmarried	1.414(0.946, 2.113)	0.091	0.323(0.115, 0.909)	0.032	0.457(0.158, 1.321)	0.148
PIR						
Low-income	1.649(1.316, 2.065)	0.000	0.866(0.488, 1.537)	0.624	1.428(0.792, 2.577)	0.237
BMI						
Underweight	1.193(0.516, 2.758)	0.680	6.538(2.776, 12.83)	0.000	5.439(1.228,10.553)	0.000
Normal weight	0.591(0.425, 0.821)	0.002	1.133(0.510, 2.517)	0.759	0.670(0.291, 1.538)	0.345
Overweight	0.921(0.717, 1.182)	0.517	0.621(0.342, 1.129)	0.118	0.572(0.308, 1.062)	0.077
Smoking						
Never smoking	0.500(0.385, 0.650)	0.000	2.794(1.479, 5.279)	0.002	1.398(0.723, 2.701)	0.319
Ever smoking	0.578(0.437, 0.766)	0.000	2.695(1.315, 5.524)	0.007	1.558(0.743, 3.266)	0.240
General health condition						
Good	0.157(0.112, 0.220)	0.000	6.605(3.126, 13.95)	0.000	1.036(0.486, 2.210)	0.926
General	0.447(0.317, 0.629)	0.000	2.711(1.273, 5.774)	0.010	1.211(0.567, 2.585)	0.621
Sleep duration						
Short	0.926(0.639, 1.343)	0.686	1.804(0.788, 4.127)	0.163	1.670(0.715, 3.904)	0.236
Normal	0.567(0.393, 0.818)	0.002	2.460(1.094, 5.532)	0.030	1.396(0.606, 3.214)	0.434
OSAHS symptom severity						
Mild	0.739(0.567, 0.964)	0.026	2.711(1.452, 5.064)	0.002	2.005(1.048, 3.834)	0.035
Moderate	0.989(0.749, 1.307)	0.940	2.338(1.169, 4.678)	0.016	2.313(1.133, 4.724)	0.021

PIR, ratio of family income to poverty; BMI, body mass index; OSAHS, obstructive sleep apnea hypopnea syndrome.

or have apnea during the night, affecting their deep sleep and sleep efficiency, so they may need longer sleep to get adequate rest. However, because sleep quality is affected, they may not get enough quality sleep, which may exacerbate depression (22). Therefore, it is recommended that subjects with OSAHS symptoms depression consult a professional physician or sleep specialist for accurate diagnosis and treatment recommendations.

OSAHS symptom severity is an essential factor affecting the risk of depression. In this study, snoring or apnea frequency was used as a subjective indicator to determine the severity of OSAHS, and the results showed a significant correlation between OSAHS symptom severity and depression. This is consistent with the methodology of Sheikh Shuib et al. and further confirms the conclusions of the present study (60). From the perspective of objective accuracy, it is

more accurate to use the AHI index as an objective criterion to judge the severity of OSAHS, and several studies have fully confirmed the significant correlation between the AHI index and depression (14, 39). OSAHS symptom severity may affect the sleep quality of patients, and severe OSAHS usually leads to frequent apnea and hypoxemia. This decline in sleep quality may cause symptoms such as mood swings, irritability, fatigue, and even induce or worsen depression. In order to maintain mental health, it is recommended that patients relieve stress and improve their emotional state by communicating with relatives and friends, attending support groups, and seeking professional psychological counselling. If a doctor recommends CPAP devices, they should be used on time every night. CPAP devices may reduce episodes of apnea and hypoxemia by providing airflow of positive pressure to maintain airway patency.

Limitations

The selection of the subjects with OSAHS symptoms in the NHANES database only relied on patients' self-reports and did not use professional equipment such as polysomnography (PSG) for diagnosis. This method of data collection may have subjective bias, which in turn affects the objective accuracy of the data. The NHANES database was incomplete, meaning many relevant variables, such as AHI and lowest oxygen saturation, were omitted. Due to the lack of these essential variables, we may not have been able to comprehensively assess their effect on depression in subjects with OSAHS symptoms, which may lead to potential bias.

The effect of menopausal status was not considered in the analysis. Hormonal level changes during menopausal transition may have an impact on the presentation of depression in subjects with OSAHS symptoms. Future studies could take a more comprehensive approach and consider the influence of gender and menopausal status on depression in OSAHS patients to improve the understanding of this complex relationship.

Conclusion

Depression in subjects with OSAHS symptoms has heterogeneity among individuals, which can be divided into three potential categories, namely low-level depression, moderate-level depression, and high-level depression. There were significant differences in gender, marital status, PIR, BMI, smoking, general health condition, sleep duration, and OSAHS symptom severity among different categories of subjects with OSAHS symptoms. According to the individual characteristics of different categories of subjects with OSAHS symptoms, medical staff can pay special attention to people with low-level depression and provide targeted psychological counseling and support and other intervention programs to reduce their depression levels. Such individualized interventions will be more effective in helping patients cope with the challenges of depression and hopefully improve their overall quality of life.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics Statement

The National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB) reviewed and approved the studies

involving human participants. The participants provided their written informed consent to participate in this study.

Author contributions

EL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. FA: Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. CL: Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. QC: Project administration, Validation, Writing – original draft, Writing – review & editing. YZ: Resources, Software, Visualization, Writing – original draft, Writing – review & editing. KX: Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. JK: Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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The relationship between obstructive sleep apnea and osteoarthritis: evidence from an observational and Mendelian randomization study

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Objectives: Obstructive sleep apnea (OSA) and osteoarthritis (OA) are common comorbidities that significantly impact individuals' quality of life. However, the relationship between OSA and OA remains unclear. This study aims to explore the connection between OSA and OA and evaluate causality using Mendelian randomization (MR).

Methods: A total of 12,454 participants from the National Health and Nutrition Examination Survey (2009–2012) were included. OSA participants were identified based on self-reported interviews. The association between OA and OSA was assessed through multivariable logistic regression analysis. A two-sample MR was employed to investigate the relationship between OSA and OA, specifically hip OA and knee OA, utilizing the inverse variance-weighted (IVW) approach.

Results: Based on the observational study, individuals with OSA exhibited a higher risk of OA (OR = 1.67, 95% CI = 1.40–1.98). IVW demonstrated that the risk of OA (OR = 1.13, 95% CI: 1.05–1.21, $p = 0.001$), hip OA (OR = 1.11, 95% CI: 1.04–1.18, $p = 0.002$), and knee OA (OR = 1.08, 95% CI: 1.02–1.14, $p = 0.005$) was significantly associated with OSA. Reverse MR analyses indicated no effect of OA on OSA. Additionally, body mass index (BMI) was found to mediate 36.9% (95% CI, 4.64–73.2%, $p = 0.026$) of the OSA effects on OA risk.

Conclusion: The cross-sectional observational analysis unveiled noteworthy associations between OSA and OA. Meanwhile, findings from the MR study provide support for a causal role.

KEYWORDS

obstructive sleep apnea, osteoarthritis, Mendelian randomization, NHANES (National Health and Nutrition Examination Survey), BMI—body mass index

1 Introduction

OSA is characterized by recurrent upper respiratory tract obstructions during sleep, leading to a reduction or cessation of airflow (1). A total of 936 million individuals are affected by OSA worldwide, with 425 million individuals experiencing moderate-to-severe cases (2). OSA patients endure chronic intermittent hypoxemia and metabolic disorders (3), often accompanied by inflammatory diseases (4). Studies indicate common risk factors associated with OSA and OA patients (5). OA, the most prevalent musculoskeletal disease, affects synovial joints, causing joint pain, decreased mobility, and a diminished quality of life (6). In 2020, the global prevalence of OA affecting approximately 7.6% of the population has been increasing in recent years (7, 8), making OA the fourth leading global cause of disability (9, 10). The medical burden associated with OA is steadily increasing worldwide (11).

Both OSA and OA significantly impact individuals' quality of life. OSA disrupts sleep quality, leading to fragmentation, while OA induces pain and discomfort, particularly during the night. Current drug efficacy for both diseases is limited (5), necessitating urgent and effective treatment strategies. Exploring the correlation and potential mediator between OSA and OA provides valuable insights into disease mechanisms and symptom exacerbation. This understanding can enhance strategies for managing symptoms and finally improve outcomes for patients affected by both OSA and OA.

MR is an innovative epidemiological approach employing genetic variables as instrumental variables (IV) to assess causal effects on outcomes; this approach is less susceptible to biases from confounding factors and reverse causality (12).

This study integrates an observational investigation within the National Health and Nutrition Examination Survey (NHANES) with MR techniques to elucidate the causal relationship between OSA and OA.

2 Methods

2.1 Study population

The NHANES, a comprehensive research initiative evaluating the wellbeing and dietary status of individuals in the United States, comprises five core components: demographic details, dietary data, physical examinations, laboratory discoveries, and questionnaires. Ethical approval for NHANES protocols was duly granted by the National Center for Health Statistics Research Ethics Review Board, and all participants provided informed consent. This research included a total of 39,722 individuals from four NHANES cycles (2005–2006, 2007–2008, 2015–2016, and 2017–2018). The analysis excluded participants with missing OA data ($n = 19,538$) or OSA data ($n = 7$), as well as those with rheumatoid arthritis or other non-osteoarthritis forms ($n = 1,959$). Additionally, participants with missing covariate data were excluded, including family income-to-poverty ratio (PIR) data ($n = 1,447$), educational data ($n = 4$), marital status data ($n = 3$), smoking status data ($n = 6$), alcohol consumption data ($n = 1,713$), BMI data ($n = 91$), chronic kidney disease (CKD) data ($n = 88$), diabetes mellitus (DM) data ($n = 390$), stroke data ($n = 9$), hemoglobin (HB) data ($n = 1,766$), serum alkaline phosphatase (ALP) data ($n = 200$), serum calcium data ($n = 2$), and alanine

aminotransferase (Alt) data ($n = 45$). Consequently, the analysis encompassed a total of 12,454 individuals, as illustrated in Figure 1 through a flow chart.

2.2 Variables

The exposure variable in this study was OSA, while the outcome variable was OA. OSA determination relied on affirmative responses to three yes-or-no questions related to snoring frequency, snorting or cessation of breathing occurrences, and daytime sleepiness. Individuals with positive responses to any of these questions were considered to display symptoms suggestive of OSA (13). OA participants in this study were identified based on self-reported personal interview data on various health conditions.

Demographics, medical conditions, and laboratory examinations were used to classify covariates. During home interviews, data on demographic characteristics, such as age, gender, marital status, educational attainment, PIR, and race, were gathered, along with information on medical conditions such as DM, hypertension, hyperlipidemia, and CKD. As a part of the NHANES laboratory examination, serum samples were collected, including serum calcium, Alt, ALP, creatinine, white blood cell count (WBC), and HB levels.

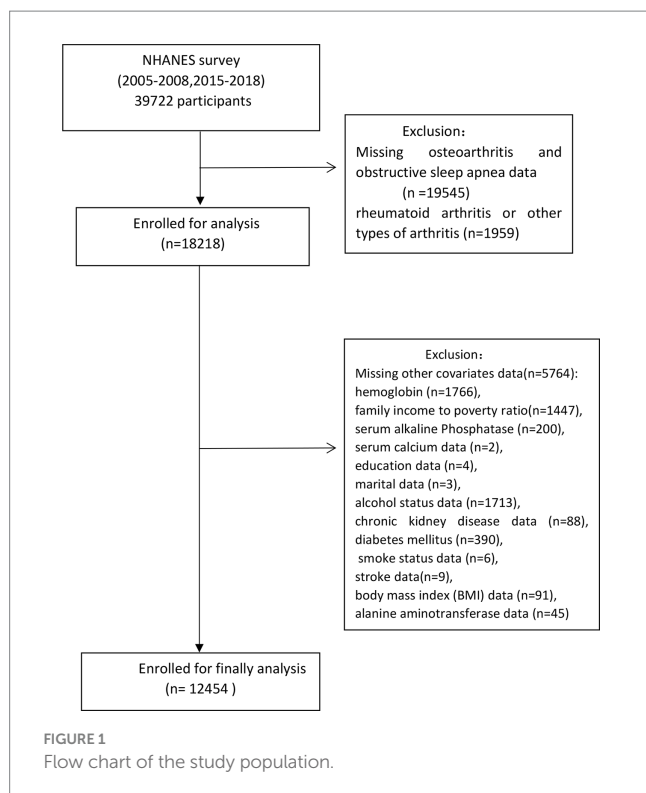
2.3 Mendelian randomization

For this research, we obtained genome-wide association study (GWAS) data on OSA from the Finnegan dataset population, which can be accessed at https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_G6_SLEEPAPNO.gz. The study involved a total of 375,657 individuals, comprising 38,998 individuals with OSA and 336,659 individuals as controls. The GWAS catalog dataset (<https://www.ebi.ac.uk/gwas/downloads/summary-statistics>, ID GCST90044591) provided genetic data associated with OA from Jiang (14), consisting of 8,952 individuals diagnosed with OA and 447,396 control individuals without OA. The GWAS dataset for OA in the knees and hips was acquired from Tachmazidou et al. (15). BMI summary statistics were obtained from MRC-IEU, involving 461,460 samples (IEU GWAS ID ukb-b-19553). To mitigate population stratification bias, only studies including individuals of European descent were used to retrieve all summary data.

All GWAS studies included in this research received approval from the relevant ethical review boards, and participants provided written informed consent. The research adhered to the STROBE MR guideline (16).

2.4 Selection of instrumental variables

We selected instrumental variables (IVs) for OSA, OA, OA of the hip and knee, potential mediator [fasting insulin, Homeostasis Model Assessment of Insulin Resistance, Modified Stumvoll Insulin Sensitivity Index, and Modified Stumvoll Insulin Sensitivity Index (model adjusted for BMI)] GWAS data with a p -value of $< 5 \times 10^{-6}$, ensuring independence ($r^2 < 0.001$, $kb = 10,000$). The IVs for the potential mediator (BMI, waist circumference, hip circumference, waist-to-hip ratio adjusted for BMI, and waist-hip ratio) GWAS data



were chosen based on a p -value of less than 5×10^{-8} , ensuring independence ($r^2 < 0.001$, $k_b = 10,000$). The F statistic for each single nucleotide polymorphism (SNP) was computed using the formula $\text{Beta}^2/\text{SE}^2$.

2.5 Statistical analysis

This study meticulously incorporated intricate sampling designs and weights following the NHANES analytic guidelines, using mobile examination center (MEC) weights for all analyses. Continuous variables are presented as means and standard errors (SEs), while categorical variables are expressed as proportions. The examination of the relationship between OSA and OA involved a multivariate binary logistic regression model to calculate the odds ratio (OR) and 95% confidence intervals (CI). Three models were constructed for statistical inference. Model 1 solely included OSA, while Model 2 expanded to incorporate gender, age, ethnicity, marital status, and educational background. Model 3, an augmented version of Model 2, encompassed additional factors such as creatinine levels, alcohol consumption, BMI, smoking habits, serum calcium, serum ALT, ALP, serum creatinine, WBC, and medical history of hypertension, DM, CKD, stroke, and hyperlipidemia.

Subgroup analyses aimed to explore potential modifications in the impact of OSA on OA. These analyses considered age (<60 , ≥ 60), sex, BMI (<30 , ≥ 30), CKD status (yes, no), hyperlipidemia (yes, no), DM status (yes, no), hypertension (yes, no), and stroke status (yes, no), adjusting for Model 3.

MR analyses included the computation of F statistics to gauge the strength of each instrument. An overview of the MR research design is displayed in Figure 2. The primary method, IVW, assessed the association of genetically predicted OSA and OA. Supplementary MR

models, such as weighted mode, weighted median (WM), MR-Egger, and simple mode, were used. Cochran Q test and MR-Egger intercept were used to examine potential heterogeneity and directional pleiotropy. A leave-one-out analysis identified significant single nucleotide polymorphisms (SNPs) and assessed the robustness of findings.

Furthermore, we used the IEU Open GWAS Project website¹ to explore whether the genetic variants associated with OSA were also connected to other prevalent risk factors that might affect the results obtained from Mendelian randomization, including BMI, arthropathies, bone mineral density (BMD), vitamin D, and smoke (17, 18).

Reverse MR analyses, treating OA as the exposure and OSA as the outcome, were conducted to explore bidirectional causality, using the same GWAS datasets. The IVW examination was duplicated using an alternative osteoarthritis GWAS dataset from IEU GWAS, followed by a meta-analysis to consolidate outcomes.

To determine whether the observed association between OSA and OA was a direct association, we assessed the relationship between genetically previously established risk factors for OA (19) (BMI, waist circumference, hip circumference, waist-to-hip ratio adjusted for BMI, waist-hip ratio, fasting insulin, Homeostasis Model Assessment of Insulin Resistance, Modified Stumvoll Insulin Sensitivity Index, and Modified Stumvoll Insulin Sensitivity Index [model adjusted for BMI]) in MR analyses (GWAS dataset in Supplementary Table S1) (5). For significant associations, potential mediation effects (the exposure-mediator-outcome pathway) may exist. To explore the potential mediator between OSA and OA, a mediator MR analysis was conducted. This involved estimating the overall effect of OSA on OA (α), the effect of the potential mediator on OA (β_2), and the effect of OSA on the potential mediator OA (β_1). The direct impact of OSA on OA was calculated as $\alpha - \beta_1\beta_2$. Statistical analyses were conducted using R Studio 4.2.0 and the R package “Two Sample MR,” with a significance level set at a p -value of <0.05 . Meta-analyses were carried out using RevMan 4.3.

3 Results

3.1 Observational study

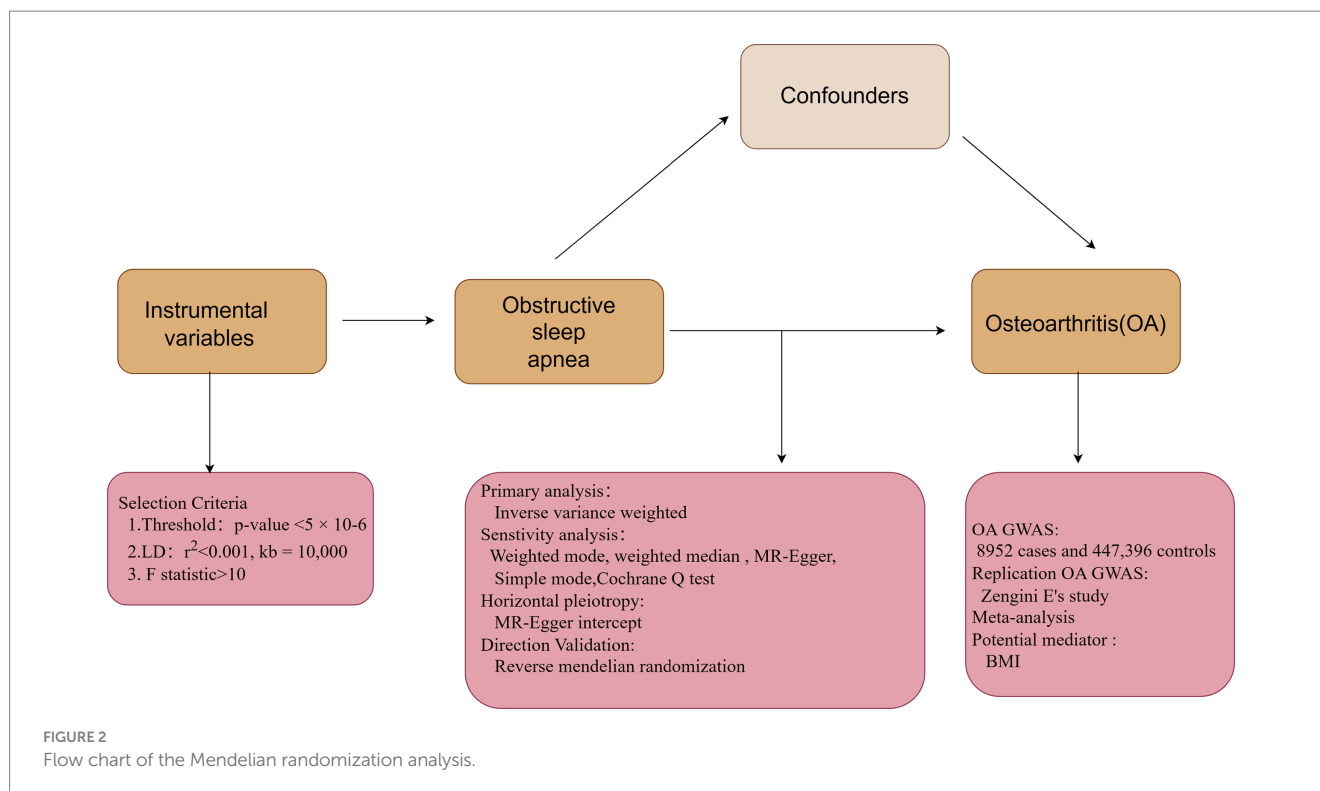
3.1.1 Baseline characteristics

The dataset under scrutiny included 12,454 participants. Table 1 presents the baseline characteristics categorized by OA. Of the participants, 1,560 (5.28%) had OA, and 3,628 (29.53%) had OSA. OSA participants exhibited a higher prevalence of OA (630, 39.84%) than those without OSA (2,998, 27.95%). The OA group was characterized by a higher likelihood of being male, former smokers, and having a history of DM, stroke, CKD, hyperlipidemia, hypertension, elevated serum creatinine, and BMI.

3.1.2 Association between OSA and OA

Table 2 displays the outcomes of logistic regression analyses with multiple adjustments. After meticulous adjustments for various

1 <http://gwas.mrcieu.ac.uk>



factors, Model 1 resulted in $OR = 1.71$, 95% $CI = 1.46\text{--}2.00$, and $p < 0.0001$; Model 2 showed $OR = 1.98$, 95% $CI = 1.67\text{--}2.33$, and $p < 0.0001$; and Model 3 revealed $OR = 1.67$, 95% $CI = 1.40\text{--}1.99$, and $p < 0.0001$.

3.1.3 Subgroup analyses

Subgroup analyses, considering variables such as age, sex, smoking status, history of CKD, hyperlipidemia, DM, hypertension, and stroke, consistently showed results with no significant interaction (all p interaction > 0.05 , Figure 1).

3.2 Mendelian randomization study

3.2.1 MR analyses using primary genetic instruments

The genetic instrument for OSA (Supplementary Table S1) comprised 101 SNPs with F values exceeding 10 (see Supplementary Table S2). Employing the IVW method, the analysis indicated that OSA was associated with an increased likelihood of OA ($OR = 1.13$, 95% $CI = 1.05\text{--}1.21$, $p = 0.001$), hip OA ($OR = 1.11$, 95% $CI = 1.04\text{--}1.18$, $p = 0.002$), and knee OA ($OR = 1.08$, 95% $CI = 1.02\text{--}1.14$, $p = 0.005$). Figure 3 visually represents outcomes from IVW, MR-Egger, weighted mode, weighted median, and simple mode.

The MR-Egger intercept test showed no horizontal pleiotropy regarding the impact of OSA on OA (intercept = 0.00046; $p = 0.915$), hip OA (intercept = 0.0038; $p = 0.500$), and knee OA (intercept = -0.00134 ; $p = 0.861$). The Cochrane Q test revealed no heterogeneity regarding the impact of OSA on OA (IVWQ 83.78, $p = 0.691$) but significant heterogeneity regarding OSA effects on hip OA (IVWQ 143.23, $p = 0.00244$) and knee OA (IVWQ 161.48, $p = 7.45 \times 10^{-5}$). The leave-one-out analysis found no SNP significantly influencing results (Figure 2–4).

After reviewing the IEU Open GWAS Project website, we discovered that 45 SNPs were linked to confounding factors [BMI (28), weight (3), obesity (1), waist circumference (1), arthropathies (6), BMD (2), vitamin D deficiency (2), and smoking (2)]. Then, we removed these 45 SNPs and found that the causality remained the same (OA IVW $OR = 1.151$, 95% $CI = 1.042\text{--}1.273$, $p = 0.006$, knee OA IVW $OR = 1.064$, 95% $CI = 1.002\text{--}1.130$, $p = 0.04146917$, hip OA IVW $OR = 1.086$, 95% $CI = 1.002\text{--}1.178$, $p = 0.043$).

3.2.2 Bidirectional MR, replication, and meta-analysis

Reverse MR analyses indicated no evidence of a causal relationship between OSA and OA. Odds ratios (OR) for OA, knee OA, and hip OA were 1.00 [95% $CI = 0.97\text{--}1.03$, $p = 0.89$], 1.04 (95% $CI = 0.99\text{--}1.09$, $p = 0.08$), and 0.98 (95% $CI = 0.91\text{--}1.06$, $p = 0.67$), respectively. Replication analysis used OA GWAS data from Zengini et al. (20) (IVW $OR = 1.04$, 95% $CI = 0.93\text{--}1.15$, $p = 0.493$), meta-analyses showing increased OA risk with a genetic predisposition for elevated OSA levels ($OR = 1.10$, 95% $CI = 1.03\text{--}1.17$, $p = 0.002$) (Figure 4).

3.2.3 Mediator MR analyses

Given that waist circumference, hip circumference, BMI, and insulin resistance are well-established risk factors for OA, they could potentially mediate the effect of OSA on the risk of developing OA (Supplementary Figure S5 and Supplementary Table S5). Among the three potential mediators, we only identified BMI as a mediator between OSA and OA (Supplementary Table S3).

A total of 458 independent SNPs served as IVs for BMI, all with F statistics > 10 (see Supplementary Table S4). Mediator MR analysis revealed that BMI (IVW: $OR = 1.49$, 95% $CI = 1.35\text{--}1.64$, $p = 3.16 \times 10^{-5}$) was associated with an increased overall risk of OA (indirect effect β_2). An increased BMI risk (indirect effect β_1) was observed in

TABLE 1 Baseline characteristics of study participants based on the OA.

	Total	Non-OA	OA	p-value
Age	45.44 (0.32)	42.98 (0.288)	61.55 (0.45)	<0.0001
Sex				<0.0001
Female	6,101 (50.34)	5,099 (47.87)	1,002 (66.56)	
Male	6,337 (49.66)	5,782 (52.13)	555 (33.44)	
PIR	3.164 (0.04)	3.14 (0.05)	3.30 (0.08)	0.024
Serum ALP	68.81 (0.38)	68.20 (0.36)	72.81 (0.77)	<0.0001
Serum calcium	9.40 (0.01)	9.39 (0.01)	9.41 (0.02)	0.199
Serum ALT	25.43 (0.20)	25.68 (0.22)	23.84 (0.50)	0.001
HB	14.383 (0.04)	14.423 (0.04)	14.12 (0.05)	<0.0001
WBC	7.30 (0.04)	7.30 (0.04)	7.33 (0.07)	0.671
NLR	2.13 (0.02)	2.10 (0.02)	2.28 (0.04)	<0.0001
RWD	13.13 (0.02)	13.09 (0.02)	13.42 (0.05)	<0.0001
BMI	28.82 (0.13)	28.51 (0.13)	30.84 (0.24)	<0.0001
OSA				<0.0001
No	8,818 (70.49)	7,889 (72.06)	929 (60.18)	
Yes	3,620 (29.51)	2,992 (27.94)	628 (39.82)	
Education				0.486
College	6,805 (62.981)	5,918 (62.831)	887 (63.967)	
Non-college	5,633 (37.019)	4,963 (37.169)	670 (36.033)	
Marital status				0.001
Married	6,551 (55.89)	5,680 (55.03)	871 (61.51)	
Non-married	5,887 (44.11)	5,201 (44.97)	686 (38.49)	
Smoke				<0.0001
Former	2,862 (23.78)	2,306 (21.94)	556 (35.89)	
Never	7,039 (56.33)	6,281 (57.42)	758 (49.15)	
Now	2,537 (19.89)	2,294 (20.64)	243 (14.96)	
Stroke				<0.0001
No	12,074 (97.82)	10,644 (98.57)	1,430 (92.90)	
Yes	364 (2.18)	237 (1.43)	127 (7.10)	
DM				<0.0001
No	9,281 (79.36)	8,330 (81.42)	951 (65.86)	
IGT	457 (3.09)	392 (3.02)	65 (3.55)	
IFG	672 (5.46)	555 (5.08)	117 (7.88)	
DM	2,028 (12.10)	1,604 (10.49)	424 (22.71)	
CKD				<0.0001
No	10,483 (87.64)	9,362 (89.22)	1,121 (77.28)	
Yes	1,955 (12.36)	1,519 (10.78)	436 (22.72)	
Alcohol user				<0.0001
Never	1,714 (10.35)	1,496 (10.33)	218 (10.52)	
Former	1,719 (10.96)	1,415 (10.20)	304 (15.99)	
Heavy	2,676 (22.64)	2,516 (24.22)	160 (12.27)	
Mild	4,292 (37.51)	3,639 (36.30)	653 (45.48)	
Moderate	2,037 (18.53)	1,815 (18.96)	222 (15.74)	
Hyperlipidemia				<0.0001

(Continued)

TABLE 1 (Continued)

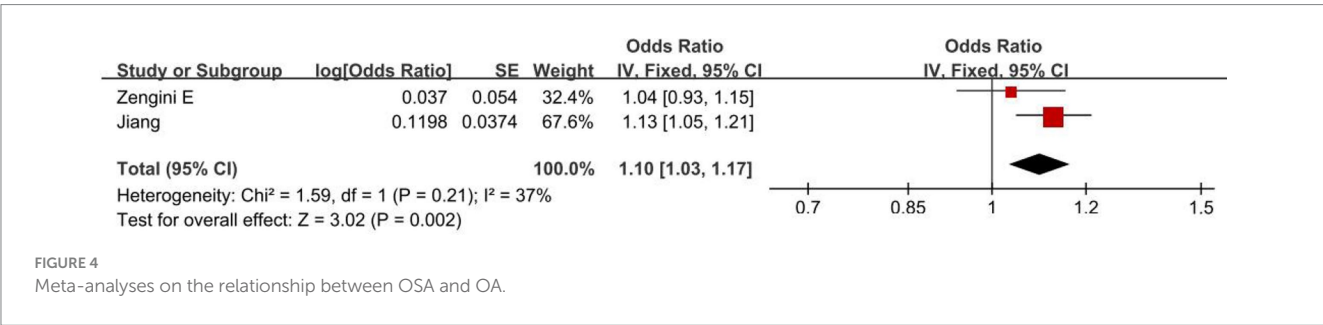
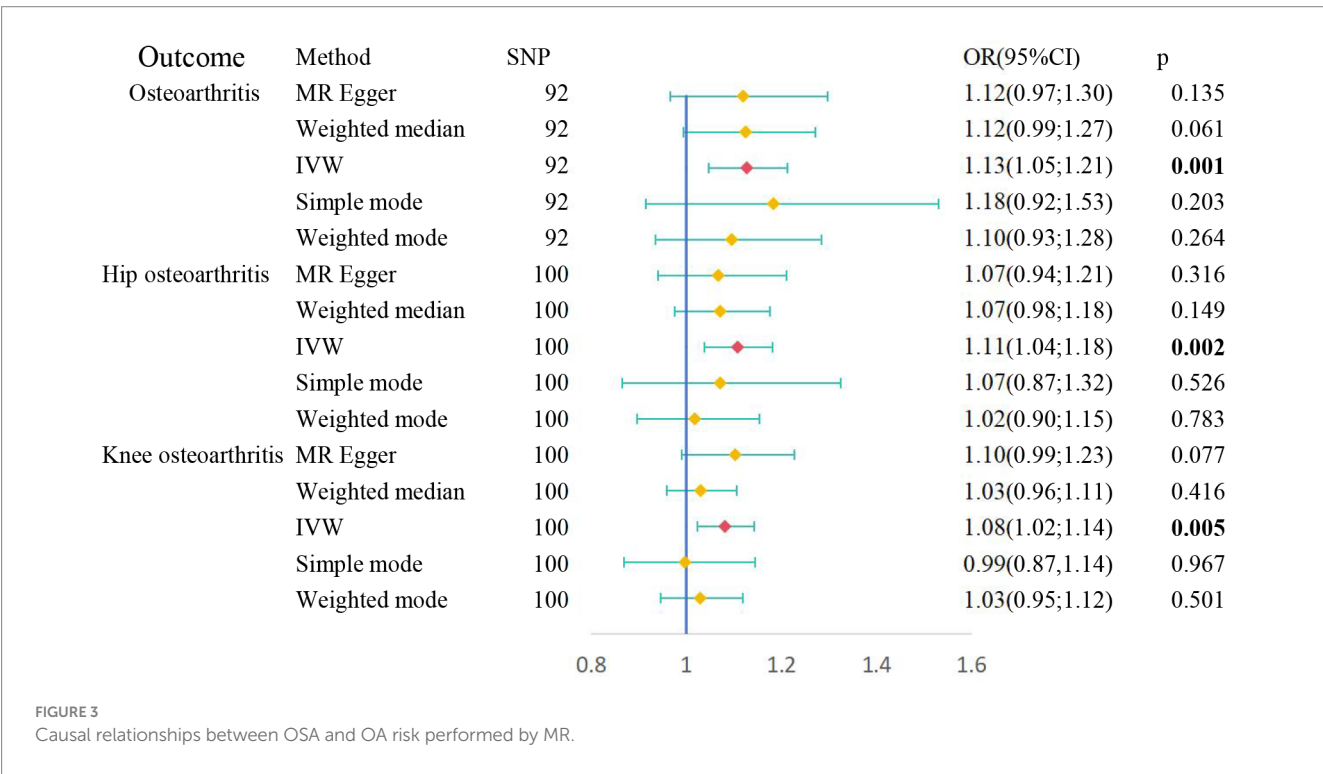
	Total	Non-OA	OA	<i>p</i> -value
No	3,832 (32.09)	3,549 (34.14)	283 (18.64)	
Yes	8,606 (67.91)	7,332 (65.86)	1,274 (81.36)	

Baseline characteristics of study participants. Mean $\pm$ SEs for continuous variables; *p*-value was calculated by weighted student's *t*-test. Number (%) for categorical variables; *p*-value was calculated by weighted chi-square test. BMI, body mass index; DM, diabetes mellitus; IFG, impaired fasting glucose. IGT, impaired glucose tolerance; CKD, chronic kidney disease; RDW, red cell distribution width; HB, hemoglobin; PIR family income-to-poverty ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; OSA, obstructive sleep apnea.

TABLE 2 Independent associations between OSA and OA.

	Multivariable adjusted (OR, 95% CI)					
	Model 1		Model 2		Model 3	
	95% CI	<i>p</i> -value	95% CI	<i>p</i> -value	95% CI	<i>p</i> -value
OSA	1.71 (1.46, 2.00)	<0.0001	1.98 (1.68, 2.33)	<0.0001	1.67 (1.40, 1.99)	<0.0001

Model 1: OSA. Model 2: OSA, age, sex, education, and PIR. Model 3: OSA, age, sex, education, PIR, marriage status, HB, serum calcium, WBC, smoke, stroke, ALP, DM, hyperlipidemia, CKD, alcohol user, RDW, NLR, BMI, and ALT.



relation to OSA (IVW OR 1.12, 95% CI 1.08–1.17, $p=2.46\text{e-}08$). Furthermore, OSA demonstrated a causal association with heightened OA susceptibility (IVW OR=1.13, 95% CI 1.05–1.21, $p=0.001$) (overall effect α). The percentage of the impact of OSA on OA influenced by BMI was 36.9% (95% CI: 4.64–73.2%, $p=0.026$) (Figure 5).

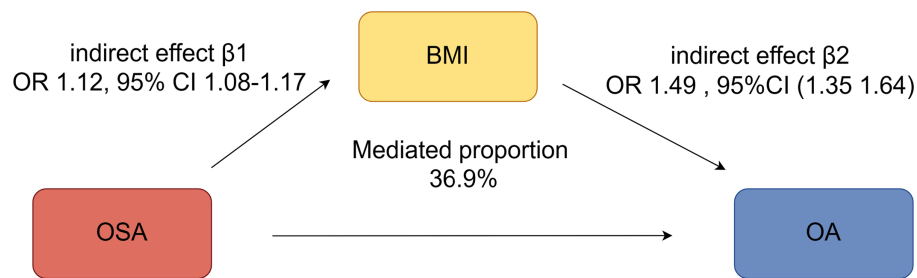


FIGURE 5

Mediation analysis of the effect of OSA on OA via BMI under a two-step Mendelian randomization analysis.

4 Discussion

This study represents the first comprehensive investigation into the relationship between OSA and OA through MR analysis, utilizing large-scale observational study data and genetic datasets. Cross-sectional observational analysis identified significant relationships between OSA and OA, while findings based on the MR study did support a causal role. The analysis of potential mediating factors found that BMI was an important factor between OSA and OA.

OSA and OA are common diseases. Previous studies found that the prevalence of OSA among individuals with OA was significantly higher than that in the general population, with figures standing at 66% versus 17%, respectively (21).

Sleep, as a period of physiological recovery, creates an environment conducive to cell proliferation, migration, and differentiation, with cell division and protein synthesis peaking during sleep (22, 23). OSA causes airway collapse, leading to oxygen deprivation and disruption of sleep rhythm (24–26). Previous studies revealed that OSA can cause increases in inflammatory, oxidative stress, and metabolic abnormalities, such as abnormal blood lipids, uric acid, and blood sugar (22, 23), which may lead to the future development of OA.

In this study, our MR analysis provided evidence of a causal relationship between OSA and OA, substantiated by rigorous examinations of horizontal pleiotropy and heterogeneity. These findings were further reinforced by two-way MR analysis, eliminating the possibility of reverse causality.

Obesity and inflammation are potential pathogenic mechanisms by which OSA leads to OA. Previous studies, through bioinformatics analysis, have found that shared inflammation genes between OSA and OA are significantly enriched in the TNF pathway and the IL-17 pathway (27).

The correlation between OSA and BMI has been a focal point of research for quite some time. The sleep fragmentation due to OSA can result in a state of effective sleep deprivation, which, in turn, can cause daytime drowsiness, a reduction in physical activity, and, consequently, an increase in body weight (28). One key factor contributing to weight gain in individuals with OSA is insulin resistance. Studies have indicated that the development of insulin resistance in the context of sustained intermittent hypoxia is closely tied to the disruption of leptin signaling pathways (28, 29).

In this study, we observed significant mediated effects of BMI on the associations between OSA and OA risk. In particular, other obesity and insulin resistance markers mediated no association between OSA and OA risk, among which the mediated proportion of BMI was 36.9%, consistent with previous research (30). These

findings suggested that OSA may increase obesity and finally aggravate OA.

A high BMI or obesity leads to overloading the joints due to excess weight, which, in turn, leads to the destruction of articular cartilage (31). Others attributed it to excess fat tissue, which secretes hormones and proinflammatory cytokines, contributing to low-grade systemic inflammation (32). Given that BMI is a relatively controllable mediating factor (33), effectively managing BMI in OSA patients could potentially reduce the incidence of OA.

This research integrates a cross-sectional approach with Mendelian randomization, offering a foundational exploration to ascertain preliminary associations. Subsequently, the Mendelian randomization study reinforces these findings by substantiating the underlying causal mechanisms. Moreover, this methodology effectively mitigates the risk of false positives inherent in Mendelian studies, thereby enhancing the credibility of our results (34). The limitations of the study include the identification of OSA based on participants' self-reported interviews. This methodology might have resulted in an inflated estimation of the true incidence of OSA. Furthermore, the absence of granular individual-level data from the GWAS precluded us from discerning whether the condition could introduce any inherent biases into our analysis. Finally, the applicability of our findings to diverse ethnic groups may be constrained, given that our analysis was focused on individuals of European descent, thus limiting the generalizability of our conclusions.

5 Conclusion

The study identified a causal relationship between OSA and OA and uncovered BMI as a mediator, laying a foundation for future research avenues and clinical interventions in the realm of sleep-related musculoskeletal disorders.

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 NCHS Research Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed

consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ZY: Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. TL: Data curation, Methodology, Visualization, Writing – original draft. LJ: Data curation, Supervision, Writing – original draft. XL: Data curation, Methodology, Supervision, Writing – original draft. XZ: Data curation, Methodology, Writing – original draft. XW: Data curation, Methodology, Writing – original draft. LZ: Data curation, Supervision, Validation, Visualization, Writing – original draft. CT: Data curation, Writing – original draft. SC: Data curation, Methodology, Writing – original draft. XY: Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2024.1425327/full#supplementary-material>

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Cardiopulmonary coupling-calculated sleep stability and nocturnal heart rate kinetics as a potential indicator for cardiovascular health: a relationship with blood pressure dipping

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Introduction: High blood pressure (HBP) is an independent, modifiable driver of cardiovascular (CV) morbidity and mortality. Nocturnal hypertension and non-dipping of blood pressure (NdBP) may be early markers of HBP. Similar to patients with NdBP, individuals with non-dipping of heart rate (NdHR) during sleep have an increased risk of CV disease, CV events, and CV-related mortality. The aim of this analysis was to evaluate if cardiopulmonary coupling (CPC) analysis-derived sleep states [stable/unstable non-rapid eye movement (NREM) sleep] and concomitant heart rate (HR) changes can provide information about nocturnal blood pressure (BP).

Method: Plethysmogram (pleth) signals from the HeartBEAT study (NCT01086800) were analyzed for CPC sleep states. Included in the analysis are sleep recordings from participants with acceptable pleth-signal quality at baseline ($n = 302$) and follow-up ($n = 267$), all having confirmed CV disease or CV-disease risk factors. The participants had a high prevalence of obstructive sleep apnea (OSA), 98.4% with moderate-OSA [apnea-hypopnea index (AHI) ≥ 15] and 29.6% severe OSA (AHI ≥ 30). A “heart-rate module” was created to evaluate the utility of identifying patients more likely to have BP dipping during sleep. Patients who did not have a decrease of $\geq 10\%$ in their BP from wake to sleep were defined as NdBP and NdHR if their heart rate during stable-NREM sleep was higher than during unstable-NREM sleep.

Results: The most significant difference in minimum HR (HR_{min}) was observed when comparing BP dippers [56 ± 4 beats per minute (BPM)] and non-BP dippers (59 ± 4 BPM; $p < 0.0001$) during diastolic blood pressure in stable-NREM sleep. Higher HR_{min} were associated with an increased likelihood of being a non-dipper, with the strongest relationship with diastolic BP and stable-NREM sleep. Every increase of 1 BPM during stable-NREM sleep was associated with an $\sim 4.4\%$ increase in the probability of NdBP ($p = 0.001$). Subjects with NdHR have higher mean BP during sleep and wake periods than HR dippers. When continuous positive airway pressure therapy is efficacious, and a dipping pattern is achieved—physical and mental health is improved.

Conclusion: HR analytics in relation to the sleep period and the CPC spectrogram-estimated sleep states can provide novel and potentially clinically useful information on autonomic health. HR dipping (or not) may be a useful screener of BP dipping or non-dipping to identify individuals who may benefit from a formal assessment of 24-h ambulatory BP. Such a stepped approach may enable a more practical and applicable approach to diagnosing HBP.

Clinical Trial Registration: The Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT) study is registered at clinicaltrials.gov/ct2/show/NCT01086800.

KEYWORDS

sleep stability, blood pressure dipping, cardiovascular disease, cardiopulmonary coupling (CPC), heart rate kinetics, heart rate dipping

1 Introduction

High blood pressure (HBP) is a major independent and modifiable driver of cardiovascular (CV) morbidity and mortality globally (Mills et al., 2020). Therefore, early diagnosis and optimal management of HBP are essential (Williams et al., 2018). Hypertension may be overt, with the physician's estimate and multiple home recordings in agreement, or it may be less obvious. The term *masked hypertension* (MH) was first introduced in 2002, describing a hypertension phenotype characterized by normal/not-increased office blood pressure (BP) readings and elevated out-of-office BP (Pickering et al., 2002). Identifying the MH phenotype is of interest for multiple reasons: (a) the prevalence is substantial, estimated at ~10%–30% of individuals attending hypertension clinics (O'Brien et al., 2013; Stergiou et al., 2021); (b) MH increases the risk of CV morbidity, with a meta-analysis comparing normotensive individuals and those with MH finding a 2.09 times increase in experiencing CV events for individuals with MH, while individuals with sustained hypertension have a 2.59 times increase in CV events (Pierdomenico and Cuccurullo, 2011); and (c) MH is more difficult to diagnose, as an out-of-office evaluation is required with 24-h ambulatory BP monitoring (24-ABPM). The availability of classic cuff 24-ABPM may be relatively limited and expensive, and the process is cumbersome and uncomfortable for the user, with cuff inflations and the frequency of measurements possibly causing arousals, disturbing sleep, and affecting the nighttime BP (NBP) measurement, which may not represent the true NBP (Pickering et al., 2006). While novel technologies are in development, including wrist pulse wave analyses, these are not yet fully validated. Moreover, such new technologies enable the collection of a large number of BP readings, which are not readily transferable to intermittent cuff inflation. Thus, disease-related validation remains to be done with more continuous forms of BP recording.

Nocturnal hypertension and non-dipping of BP may be early markers of HBP and MH. Nocturnal BP and night-to-day BP ratio have been identified as significant predictors of adverse CV outcomes (O'Brien et al., 1988; Asayama et al., 2023) and better predictors of fatal and non-fatal CV events and organ damage than daytime BP (Ohkubo et al., 2002; Salles et al., 2016; Staplin et al., 2023). Similar to changes in NBP, individuals with non-dipping of their heart rate (HR) during sleep have an increased

risk of CV disease, CV events, and CV-related mortality (Eguchi et al., 2009; Kabutoya et al., 2010; Tadic et al., 2018; Nelde et al., 2023). For example, obstructive sleep apnea (OSA) is a common disease capable of disrupting normal BP control (Senaratna et al., 2017; Benjafield et al., 2019). A bidirectional relationship exists between OSA and HBP, with OSA patients having an increased risk of developing HBP, and the prevalence of OSA is higher in patients with HBP (Sawatari et al., 2016). However, other causes of sleep disruption such as insomnia and periodic limb movements are also associated with elevated NBP (Palagini et al., 2013).

Current guidelines highlight the importance of accurate diagnosis of HBP. The gold standard for identifying MH is 24-ABPM (Franklin et al., 2017), but still, the diagnosis is largely based on in-office BP measures, and patients with HBP and MH may therefore remain undiagnosed (Stergiou et al., 2021). Somewhat surprisingly, another readily available signal, HR during sleep [from ambulatory recordings and the millions of laboratory polysomnography (PSG) or home polygraphy done yearly], has not been subjected to rigorous analysis. Arousals from sleep are associated with both HR and BP elevations. It is thus plausible that an analysis of HR during sleep may provide a surrogate of BP or at least identify those who should have a formal 24-ABPM performed. HBP in patients with OSA is often predominantly nocturnal, and non-dipping BP is common (Marin et al., 2012). Therefore, alternative, simple, and less invasive measures that may estimate changes related to HR might be of value to identify non-dippers for further evaluation, including 24-ABPM as a tool that might assist in managing patients with OSA, insomnia, or comorbid insomnia and sleep apnea (Sweetman et al., 2019) and HBP (Tadic et al., 2018; Nelde et al., 2023).

This report targeted nocturnal heart rate (NHR) by analyzing photoplethysmogram (PPG) and oximetry information (SpO₂) recorded during a conventional home sleep apnea test (HSAT). The cardiopulmonary coupling (CPC) sleep state and the HR kinetics analysis were computed to estimate alignments of HR with stable- and unstable-NREM sleep (Al Ashry et al., 2021b). It has been noticed that HR profiles across the night can on average drop ("HR dipping"), remain relatively flat ("HR non-dipping"), or even rise ("HR reverse dipping"). HR dipping is maximal during stable-NREM sleep periods [high-frequency coupling (HFC)] but can sometimes rise during such

periods, suggesting increased sympathetic drive when normally NREM3/stable NREM2 should be associated with reduced sympathetic drive. We hypothesized that a simple method for calculating HR changes during stable-NREM sleep can be utilized to estimate dipping, non-dipping, or reverse-dipping HR. To test our hypothesis, we utilized the Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT) study, which was designed to evaluate alternative approaches to reduce the risk of heart diseases. This study included classic cuff ABPM (Gottlieb et al., 2014).

2 Materials and methods

2.1 Study design

The HeartBEAT study (NCT01086800) was a four-site, randomized, parallel-group trial among patients with high CV risk (Gottlieb et al., 2014). At baseline, patients were screened for OSA with the Berlin questionnaire (Netzer et al., 1999), and if they were at risk for OSA, an HSAT was initiated utilizing a portable sleep monitor, including recording PPG-signal and pulse-oximetry (SpO₂) data from a fingertip sensor. Patients with an AHI of ≥ 15 events per hour of sleep were eligible to participate in the study. Patients with an AHI of > 50 and a central index of > 5 were excluded from randomization. The primary outcome of the HeartBEAT study was to evaluate changes in 24-h mean arterial blood pressure (MAP). In addition, nocturnal dipping and non-dipping of BP were reported, with non-dipping BP defined as a mean nocturnal BP higher than 90% of the mean daytime BP value. Participants in the HeartBEAT study were randomly assigned to one of three groups: continuous positive airway pressure (CPAP) therapy, nocturnal oxygen therapy, or healthy lifestyle with sleep education. Institutional review board approval was obtained from each participating institution. For this analysis, a data user agreement was obtained from the National Sleep Research Resource (Dean et al., 2016).

2.2 Participants

Patients aged 45–75 with established coronary heart disease or multiple CV-disease risk factors and well-managed hypertension, were recruited from cardiology practices at four participating medical centers. Patients with an AHI in the range of 15–50 were offered the opportunity to participate in the study. This study is based on a CPC analysis of the data derived from the fingertip PPG-sensor (the pleth waveform and oxygen data), as well as information reported about participants' dipping or non-dipping status.

2.3 Follow-up

A detailed description of the methodology and primary results of the trial's outcome have been reported (Gottlieb et al., 2014). In brief, outcomes were measured at baseline and 12 weeks after randomization. The primary outcome was 24-h MAP (measured using the 90207 Ambulatory Blood Pressure Monitor, Spacelabs

Healthcare). The mean pressure was calculated at each reading as one-third of systolic pressure plus two-thirds of diastolic pressure. The 24-h mean pressure was calculated as a weighted average of the mean pressure during wakefulness and sleep, with the weights determined by the percentage of reported time spent in each state as recorded in a sleep diary. Nocturnal non-dipping blood pressure was defined as the mean nocturnal BP higher than 90% of the mean daytime value.

2.4 Methods

2.4.1 The data set

The HeartBEAT study measured and reported BP dipping and non-dipping. Subjects were stratified into BP dippers and BP non-dippers, where non-dippers did not demonstrate a decrease in BP of $\geq 10\%$ from wake to sleep.

2.4.2 CPC analysis

The CPC method has been described in detail in several prior publications (Thomas et al., 2005; Al Ashry et al., 2021a). Cardiopulmonary sleep spectrograms were first obtained from a single lead electrocardiogram (ECG). ECG-derived respiration (EDR) is obtained either by using R-S wave amplitudes or variations in the QRS complex area. Ectopic beats are identified and removed, normal sinus-normal sinus (NN) intervals are extracted, and outliers are filtered (Thomas et al., 2005). After extracting the NN interval series on ECG and its associated EDR, the signals are then resampled using cubic splines at 2 Hz. The fast Fourier transform is applied to three overlapping 512-sample sub-windows within the 1,024-coherence window. The 1,024-coherence window is then advanced by 256 samples (2.1 min), and the calculation is repeated until the entire NN interval/EDR series is analyzed. Thus, the cross-spectral power and coherence of these two signals are calculated over a 1,024-sample (8.5-min) window. For each 1,024-sample window, the product of the coherence and cross-spectral power is used to calculate the ratio of coherent cross-power in the low-frequency (0.01–0.1 Hz) band to that in the high-frequency (0.1–0.4 Hz) band. The logarithm of the high-to-low-frequency CPC ratio [$\log(\text{HFC/LFC})$] is then computed to yield a continuously varying measure of CPC sleep stability/instability output metrics. While, originally, the ECG signal was used as input, any signal or signal set that encodes respiration and heart rate variability (HRV) may be used to compute the CPC sleep spectrogram; most conveniently, this signal set can be obtained from the peripheral PPG-signal, which is readily available from current generation oximeters. The current embodiment uses a ring- or fingertip-based oximeter to collect the data coupled with a mobile application and Bluetooth to stream the data for automated analysis. The SleepImage system complies with the Health Insurance Portability and Accountability Act (HIPAA), is cleared by the Food and Drug Administration (K182618), and complies with the EU Medical Device Directive (CE-mark 2862) to automatically generate biomarkers, presented numerically and graphically (Figure 1). The analysis is otherwise essentially identical. The outputs of the CPC algorithm include low-frequency

(LFC; 0.01–0.1 Hz), high-frequency (HFC; 0.1–0.4 Hz), and very low-frequency (vLFC; 0.001–0.01 Hz) couplings, and an elevated LFC-broad band (eLFC_{BB}) that is a sleep fragmentation signal biomarker (Thomas et al., 2005). HFC/LFC covary more strongly with an electroencephalographic (EEG) non-cyclic alternating pattern (n-CAP) and CAP, respectively (Thomas et al., 2005), than conventional N3/N2—although most of N3 is HFC, and much of HFC occurs during N2.

Stable-NREM sleep (HFC) is associated with several desirable sleep characteristics, including increased absolute and relative delta power (Thomas et al., 2014), a consolidated NREM sleep <1-Hz slow oscillation, temporally stable breathing, stable arousal thresholds, normal arterial oxygen (O₂) and carbon dioxide (CO₂) concentrations, and BP dipping (Wood et al., 2020). Unstable NREM (LFC) is characterized by features opposite of stable-NREM (HFC), and ineffective (fragmented) REM sleep takes on LFC coupling signatures, while wake or effective REM sleep shows vLFC pattern (Thomas et al., 2005). HFC covaries better with relative than absolute EEG slow-wave power and is thus less constrained by the “loss” of slow-wave sleep (SWS) with age (Thomas et al., 2014). Specific spectrographic signatures of fragmented sleep (elevated LFC narrow band, eLFCNB) are biomarkers of strong chemoreflex effects on sleep respiration (Thomas et al., 2007), identifying areas of sleep with central apneas and periodic breathing. BP dipping occurs only during periods of HFC (Wood et al., 2020), consistent with the demonstration that non-CAP is the EEG correlate of BP dipping (Iellamo et al., 2004). LFC is associated with hypertension and stroke (Thomas et al., 2009), while HFC is reduced in depression (Yang et al., 2011), heart failure (Yeh et al., 2008), and fibromyalgia syndrome (Thomas et al., 2010). HFC is an independent determinant of the glucose disposition index (Pogach et al., 2012). Pre- and posttreatment effects in sleep apnea are captured via changes in HFC/LFC (Lee et al., 2014). An integrated metric, the Sleep Quality Index (SQI), which is heavily weighted by stable-NREM sleep, is associated with desirable directions of metabolic health and blood pressure (Magnusdottir et al., 2020, 2021, 2022).

2.4.3 HR and CPC analysis

The PPG signal from each polygraphy recording in the HeartBEAT data was processed through the SleepImage System algorithms. A software module (“HR module”) was developed for evaluating the HR data collected during the sleep study, which was then intersected with the sleep-state output from the SleepImage System: (a) A 2-sample-per-second resampled NN series was evaluated by cropping the entire series from sleep onset to sleep conclusion. Then, a linear trendline was fitted to generate a slope coefficient, the associated *p*-value, and an *R*² for model fit. While this method may provide insight that some clinical professionals may value, it was not expected to have much explanatory power, as it attempts to describe HR as a linear trend over the course of the sleep period, lumping all sleep states together. The disproportionate effect of sleep stage on BP dynamics has been explained in the literature (Stein and Pu, 2012). (b) HR rate statistics for each CPC sleep state classification were

then calculated using the same 2-sample-per-second resampled NN series.

2.4.4 Primary endpoint

For this analysis, the following variables of interest were extracted from the HeartBEAT data set: (a) MAP non-dipping and dipping, (b) systolic blood pressure (SBP) non-dipping and dipping, and (c) diastolic blood pressure (DBP) non-dipping and dipping, where non-dippers were defined as patients who did not demonstrate a decrease in BP $\geq 10\%$ from wake to sleep. The primary endpoint was to evaluate (a) the relationship between HR during stable and unstable CPC sleep states and BP and (b) if sleep evaluation combined with this HR module can be utilized to stratify patients to identify patients more likely to have non-BP dipping during sleep for further evaluation.

2.5 Statistical analysis

The primary endpoint, questioning if the HR module can be utilized to identify BP dipping during sleep, was evaluated using a logistic regression, regressing HR parameters from the HR module on the dipping and non-dipping variables extracted from the HeartBEAT data, controlling for gender, age, and race to assess the predictive power on BP dipping.

Basic summary statistics, such as counts, are presented, along with means and standard errors (in parentheses) for gender, race, age, and body mass index (BMI). A one-way analysis of covariance was utilized to compare non-dippers and dippers controlling for age, gender, BMI, and site identifier. Means and standard errors for the HR parameters are presented, along with the *p*-values for pairwise comparison between the groups. The analysis was performed using Stata version 15.1.

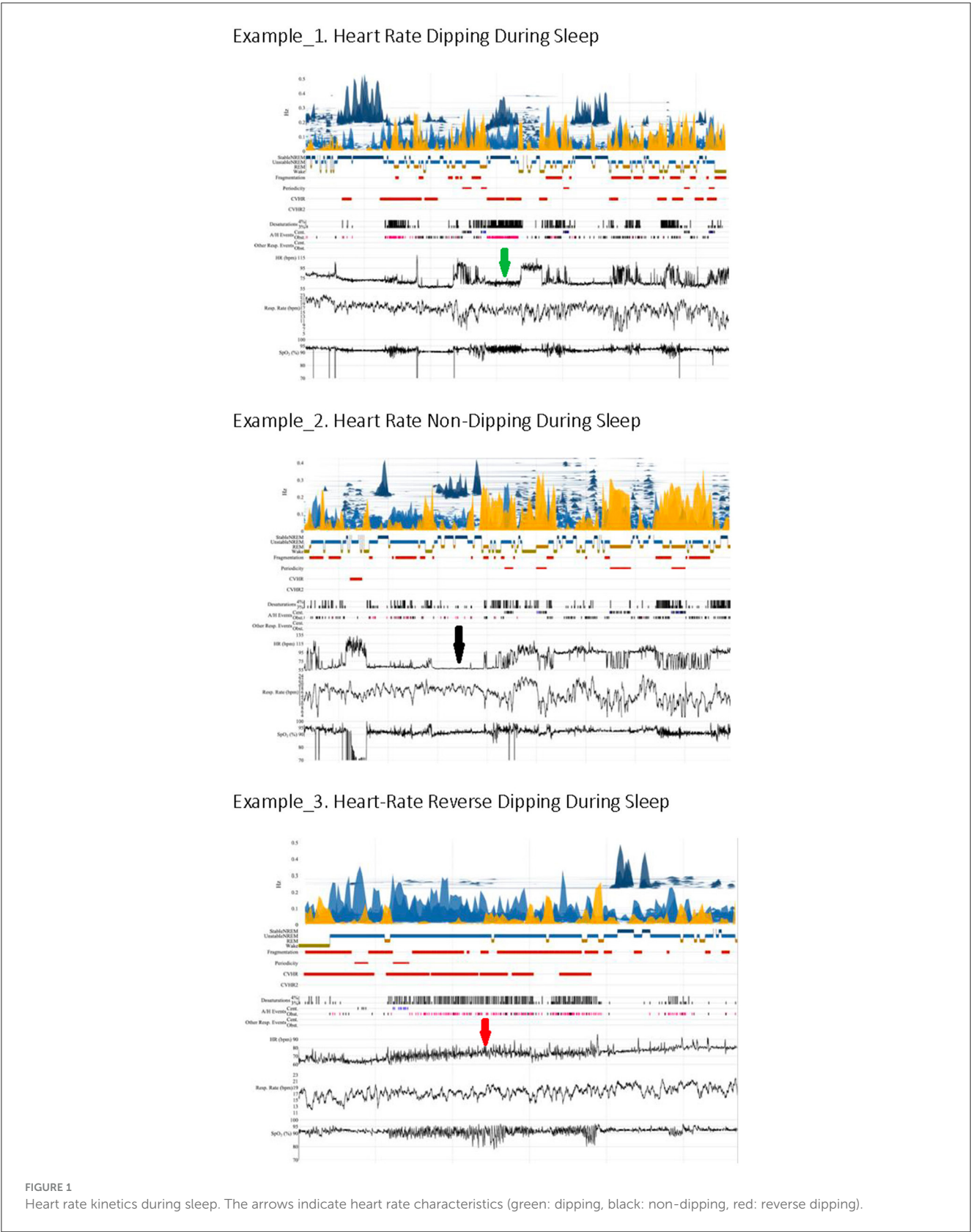
3 Results

3.1 Study population

Included in this analysis of the pleth signal from the HeartBEAT data (Gottlieb et al., 2014) are both baseline and follow-up recordings with signal quality defined as average successful peak detection on the overnight recording of no <70% for analysis to evaluate HR during sleep and on data describing dipping and non-dipping BP status. The data set contained sleep recordings with acceptable pleth-signal quality from 302 patients at baseline and 267 at follow-up, or a total of 569 sleep recordings (Supplementary Table S1).

3.2 Primary outcome measures

First, the relationship between the CPC-sleep-state analysis and the software HR module and dipping or non-dipping status of BP was evaluated (Table 1). The most significant difference in minimum HR (HR_{min}) was observed when



comparing HR for dippers (56 ± 4 BPM) and non-dippers (59 ± 4 BPM) during DBP and stable-NREM sleep ($p < 0.0001$).

Table 2 presents the result from different logit models regressing variables of interest (HR metrics; HR_{min} during sleep and HR_{min} during stable-NREM sleep), controlling for age and race

TABLE 1 Heart rate (HR) software module (“HR parameters”) for dippers and non-dippers, beats per minutes (BPM).

	Average HR (BPM) measured during diastolic blood pressure (mm/Hg)			Average HR (BPM) measured during systolic blood pressure (mm/Hg)			Average HR (BPM) measured during mean arterial blood pressure (mm/Hg)		
	Non-Dip ^a	Dip ^a	p-value ^b	Non-Dip ^a	Dip ^a	p-value ^b	Non-Dip ^a	Dip ^a	p-value ^b
Sleep									
Mean HR	66.4 (±5.5)	64.7 (±5.5)	0.063	66.0 (±5.5)	65.1 (±5.5)	0.301	66.6 (±5.5)	65.1 (±5.5)	0.090
Min HR	55.6 (±2.6)	54.31 (±2.6)	0.003	55.6 (±2.6)	54.6 (±2.6)	0.016	55.8 (±2.6)	54.6 (±2.6)	0.003
Wake									
Mean HR	69.2 (±5.7)	67.8 (±5.6)	0.126	69.1 (±5.7)	68.1 (±5.6)	0.293	69.6 (±5.7)	68.1 (±5.6)	0.100
Min HR	57.5 (±3.0)	55.9 (±3.0)	0.001	57.7 (±3.0)	56.2 (±3.0)	0.003	57.871 (±3.0)	56.3 (±3.0)	0.001
Stable NREM									
Mean HR	67.2 (±7.4)	64.3 (7.3)	0.017	66.1 (±7.4)	64.9 (±7.34)	0.318	66.6 (±7.4)	64.6 (±7.3)	0.150
Min HR	58.6 (±4.1)	56.3 (4.1)	<0.0001	57.6 (±4.2)	56.74 (±4.1)	0.189	58.25 (±4.2)	56.7 (±4.1)	0.022

HR, heart rate; NREM, non-rapid eye movement sleep; BPM, heart beats per minute.

^aValues are mean ± standard deviation.

^bDifference between groups (p-value).

on the indicator variables for diastolic, systolic, and MAP non-dipping. BMI was explored as a control but did not add to the explanatory/predictive power of any of the models. The results are presented as coefficient estimates from the logit regression with *p*-values in parentheses. The strongest associations were observed when including HR_{min} during stable-NREM sleep. Higher HR_{min} were associated with a higher likelihood of being a non-dipper, with an increase of 1 beat per minute in HR_{min} during stable NREM being associated with an approximate 4.4% increase in the probability of being a non-dipper (*p* = 0.001). Being African American and increased age were found to be factors that increased the likelihood of being a non-dipper, while gender did not seem to be a significant predictor. For the sake of brevity, the mean HR in stable-NREM sleep was not included in the results, although it showed a statistically significant effect on diastolic non-dipping, in favor of the minimum, which had a higher coefficient. The variance inflation factor (VIF) was calculated to investigate the presence of collinearity. The average VIF did not exceed 1.08 for any of the models, with the highest calculated VIF of 1.14 for an individual variable. This indicates that multicollinearity is not of concern with the chosen independent variables.

Second, the cohort was stratified based on the “HR parameter” into HR dippers and HR non-dippers (Table 3). At baseline, fewer HR non-dippers used calcium-channel blockers (10.7%, *p* = 0.047) and diuretics (10.9%, *p* = 0.044) than HR-dippers. Additionally, HR non-dippers presented with a higher mean MAP when awake of 2.2 mmHg (*p* = 0.046) than HR-dippers. Comparing HR dippers and non-dippers and focusing on BP, HR non-dippers have significantly higher average DBP (DBP^{ave}; 85.3 vs. 83.8 mmHg, *p* = 0.035); DBP^{sleep} (74.6 vs. 72.7 mmHg, *p* = 0.018); and DBP^{wake} (90.8 vs. 89.0 mmHg, *p* = 0.024). Additionally, they have a higher average MAP (MAP^{ave}; 89.7 vs. 88.1 mmHg, *p* = 0.050); MAP^{sleep} (79.4 vs. 77.4 mmHg, *p* = 0.036); and MAP^{wake} (95.2 vs. 93.3 mmHg, *p* = 0.031), respectively (Table 4).

Finally, the subgroup that received the CPAP therapy was stratified based on dipping status (HR dipper or HR non-dipper)

at baseline and at a 12-week follow-up (Table 5). When comparing participants who were HR non-dippers at baseline and HR dippers at follow-up, significant improvements were observed in depression severity measured using the Patient Health Questionnaire-9, −3.1 (*p* = 0.005), and the health and quality-of-life indicators that were evaluated using the Short Form (36) Health Survey: (a) vitality, 12.8 (*p* = 0.036); (b) physical functioning, 20.1 (*p* = 0.003); and (c) emotional functioning, 16.5 (*p* = 0.005); social functioning, 17.4 (*p* = 0.007); and mental health and emotional wellbeing, 13.9 (*p* = 0.001).

4 Discussion

The analysis of HR across the night in relation to CPC sleep state, HR, and BP showed the following statistically significant results: (a) lower HR_{min} during sleep in participants who demonstrated diastolic, systolic, and MAP dipping when compared to non-dippers; (b) lower HR_{min} during wake *within* the sleep period in participants who demonstrated diastolic-, systolic-, and MAP dipping compared to non-dippers; (c) lower HR_{min} and HR_{mean} during stable-NREM sleep (HFC) in those who demonstrated diastolic dipping compared to non-dippers; (d) the strongest associations were observed when including HR_{min} during stable-NREM sleep (HFC); (e) when utilizing the HR module to stratify the cohort based on HR dipping and non-dipping, participants with non-dipping of HR had significantly higher MAP and DBP when comparing all readings, readings during sleep, and readings during wake; and (f) in the subgroup of participants who received CPAP-therapy, participants with a HR non-dipping pattern at baseline and HR dipping pattern at follow-up (i.e., treatment responders based on heart rate profiles), significantly improved their subjective mental and physical functioning. The results overall suggest that HR dipping in stable-NREM sleep/HFC is a desirable biological characteristic.

TABLE 2 Logistic regression models regressing the HR parameter on diastolic, systolic, and mean arterial blood pressure (MAP) non-dip indicators.

	Diastolic non-dipping blood pressure ^a		Systolic non-dipping blood pressure ^a	MAP non-dipping blood pressure ^a	
Sleep _{min}		0.049 (0.010)	0.041 (0.035)		0.049 (0.010)
Stable NREM _{min}	0.044 (0.001)			0.026 (0.032)	
Male	0.092 (0.674)	0.117 (0.591)	0.030 (0.891)	0.153 (0.483)	0.193 (0.378)
Race					
African American	0.744 (0.009)	0.720 (0.012)	1.013 (0.001)	0.960 (0.001)	0.921 (0.002)
Other	0.086 (0.815)	−0.002 (0.995)	0.007 (0.983)	0.195 (0.592)	0.117 (0.749)
Age	0.019 (0.146)	0.023 (0.073)	0.035 (0.008)	0.026 (0.049)	0.032 (0.016)
Const.	−4.205 (0.000)	−4.572 (0.001)	−4.400 (0.002)	−3.532 (0.002)	−5.010 (0.000)

NREM, non-rapid eye movement sleep; MAP, mean arterial pressure.

^aValues are the logistic regression coefficients with p-values in parenthesis.

HR kinetics during sleep seems to provide indirect information about BP during sleep, an important cardiovascular health variable. HR is readily available through most systems that track sleep oximetry and could allow for risk stratification; individuals with a non-dipping HR pattern could be directed to selectively undergo conventional ABPM. The finding that HR was specifically influenced by stable-NREM sleep (HFC) as estimated through the pleth spectrogram was not surprising. Autonomic physiology presents an important window into sleep; for example, hemodynamics, HRV, and respiration are markedly dependent on the sleep stage, with vagal dominance, stable breathing, and BP reductions (“dipping”) during SWS/N3 (Javaheri and Redline, 2012). Furthermore, standard reporting of EEG-based stages as a percentage of sleep time is an insensitive metric of sleep fragmentation (Bianchi and Thomas, 2013). Most HSATs do not provide EEG stages, although machine learning applied to ECG and respiratory signals can approximate deep sleep. The ability to evaluate HR dynamics in relation to sleep state without the need for extensive PSG has practical advantages.

A reduction in BP during sleep (BP dipping) is considered a BP-related biomarker of healthy sleep (Routledge et al., 2007; Salles et al., 2016). There is a progressive reduction of BP from wake through SWS, with an increase in REM sleep or transiently in association with arousals. The HR profile follows this basic scheme and is the highest in REM sleep and unstable-NREM sleep or during arousals and lowest in conventional N3 (Javaheri and Redline, 2012). In a prior study by our group, we used PSG with beat-to-beat BP monitoring, ECG-derived CPC analysis, and quantified delta power and the rate of occurrence of the <1-Hz slow oscillation. We found that BP dipping occurred only during periods of stable NREM (HFC), concomitant with slow oscillation/delta power-enriched NREM sleep. HR was lowest in N3, but the small sample size of 11 subjects perhaps explained the lack of HR dipping during HFC; however, the current analysis shows the predicted dip in HR. Mechanisms associated with rising slow wave/delta power and a high grade of electrocortical synchrony are likely the drivers of an integrated response of BP, HR, and stable breathing. Even in conditions associated with fragmented sleep, such as sleep apnea, delta power, and vagal HRV dominance tends to ebb and flow in a correlated manner (Jurysta et al., 2006; Wood et al., 2020).

There is substantial variability in sleep quality in individuals with similar severities of sleep apnea. Such differences may be quantified by subjective symptoms e.g., questionnaire such as the Insomnia Severity Index (Bastien et al., 2001); conventional criteria e.g., N1, N3, total sleep time, sleep efficiency; EEG-based methods such as the odds ratio product, which estimates sleep depth continuously (Younes et al., 2015; Younes, 2023); and ECG/PPG CPC spectrograms and the SQI (Thomas et al., 2014; Hilmisson et al., 2019; Magnúsdóttir et al., 2020). BP during sleep is another useful measure, while HR analysis could provide a complementary metric for sleep quality.

There are sleep and circadian influences on BP and HR control. Even in forced desynchrony experiments, both metrics are low in the biological night when body temperature is low and melatonin is high. Thus, there are both sleep and circadian components to BP and HR dipping, and a loss of this pattern can occur from either sleep or circadian factors. Any case of sleep fragmentation can flatten or even reverse BP and HR during the biological night. OSA can affect sleep quality and cause non-dipping BP by autonomic dysfunction, transient surges associated with arousals, the upregulation of neurohumoral systems, oxidative stress, and a general lowering of sleep depth. However, when there is non-dipping of either BP or HR during stable (unfragmented) sleep of which HFC is a good biomarker, it likely reflects abnormal autonomic regulation as many other drivers are less active during this state (e.g., breathing and oxygenation are stable). Profiles of HR may be useful when following treatment of sleep apnea, especially with therapies with residual apnea. While CPAP when used can largely normalize breathing, other increasingly used therapies, such as weight loss, hypoglossal nerve stimulation, and oral appliances, are more likely to have residual apnea. Partial CPAP use will also demonstrate residual apnea. HR profiles could be one way to assess the impact of residual disease as successful therapy could be expected to improve HR dipping and even convert a non-/reverse dipper to a dipper as demonstrated in this analysis when looking at the subgroup treated with CPAP.

This analysis has some limitations, including (a) the study population was selected for presence of CV disease or risk and does not readily generalize to the range of medical backgrounds on which sleep apnea occurs; (b) classic sleep staging was

TABLE 3 Baseline characteristics: heart rate dippers vs. non-dippers.

	Heart rate ^a			
	All ^a (n = 302)	HR dippers ^a (n = 143, 47.4%)	HR non-dippers ^a (n = 159, 52.6%)	HR dippers compared to HR non-dippers (p-values) ^b
Characteristics				
Age (years)	63.0 (±0.410)	63.1 (±0.617)	63.0 (±0.585)	0.910
Body mass index (BMI; kg/m ²)	34.4 (±0.358)	34.9 (±0.539)	33.7 (±0.511)	0.103
Neck circumference (cm)	42.2 (±0.211)	42.3 (±0.313)	42.0 (±0.297)	0.561
Waist/hip ratio	1.0 (±0.004)	1.0 (±0.006)	1.0 (±0.006)	0.091
African American (%)	13.2	13.3	12.6	0.855
Caucasian (%)	79.2	78.3	79.9	0.741
Ever smoked (%)	62.9	6.3	11.3	0.127
Coexisting conditions (%)				
Prior myocardial infarction	22.0	22.3	23.3	0.532
Diabetes mellitus	42.5	44.3	40.9	0.554
Dyslipidemia	77.8	77.8	78.6	0.874
Hypertension	82.8	85.7	80.5	0.233
Obstructive sleep apnea (%)				
Moderate (AHI 15–30)	98.4	97.2	99.3	0.141
Severe (AHI ≥ 30)	29.6	29.4	29.6	0.971
Medication use (%)				
ACE or ARB	69.8	73.4	64.8	0.106
Any beta-blockers	67.3	65.7	66.7	0.865
Calcium-channel blocker	30.1	37.1	26.4	0.047
Medication for diabetes	39.3	42.7	35.8	0.227
Diuretic	37.7	42.7	31.8	0.044
Lipid-lowering medication	89.0	86.0	91.8	0.107
Questionnaires				
Epworth Sleepiness Scale	8.9 (±0.204)	9.1 (±0.304)	8.8 (±0.288)	0.431
Patient Health Questionnaire-9 (PHQ-9)	5.5 (±0.279)	5.5 (±0.420)	5.6 (±0.399)	0.971
PHQ-9 depression severity	0.7 (±0.054)	0.8 (±0.080)	0.7 (±0.076)	0.687
Sleep measures				
Sleep Quality Index (SQI)	41 (±0.910)	41 (±1.324)	40 (±1.255)	0.489
Apnea-Hypopnea Index (AHI)	33 (±0.555)	33 (±0.809)	33 (±0.764)	0.935
Stable sleep (%)	27 (±1.030)	28 (±1.498)	26 (±1.420)	0.352
Unstable sleep (%)	50 (±0.982)	49 (±1.428)	51 (±1.354)	0.476
Fragmentation (eLFC _{BB} : %)	26 (±0.945)	26 (±1.375)	26 (±1.304)	0.925
Periodicity (e-LFC _{NB} : %)	3 (±0.276)	3 (±0.401)	3 (±0.381)	0.910
Blood pressure measures (mm/Hg)				
Average diastolic pressure, all readings	71 (±0.456)	70 (±0.684)	71 (±0.646)	0.101
Average diastolic pressure, sleep	65 (±0.490)	64 (±0.231)	65 (±0.685)	0.184
Average diastolic pressure, wake	73 (±0.742)	72 (±0.742)	74 (±0.701)	0.067
Average systolic pressure, all readings	124 (±0.833)	123 (±1.262)	125 (±1.191)	0.160

(Continued)

TABLE 3 (Continued)

	Heart rate ^a			
	All ^a (n = 302)	HR dippers ^a (n = 143, 47.4%)	HR non-dippers ^a (n = 159, 52.6%)	HR dippers compared to HR non-dippers (p-values) ^b
Average systolic pressure, sleep	116 (±0.943)	115 (±1.415)	117 (±1.330)	0.223
Average systolic pressure, wake	128 (±0.844)	126 (±1.280)	129 (±1.208)	0.102
Average mean arterial pressure, sleep	83 (±0.573)	82 (±0.855)	84 (±0.804)	0.138
Average mean arterial pressure, wake	92 (±0.523)	91 (±0.789)	93 (±0.745)	0.046

HR, heart rate; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.
^aValues are mean ± standard deviation for continuous variables and percentages for categorical variables.
^bDifference between groups (p-value).

TABLE 4 Heart rate dipper vs.. non-dipper: blood pressure and biochemical measures.

	HR-dipper ^a (n = 143, 47.4%)	HR-non-dipper ^a (n = 159, 52.6%)	p-values ^b
Medication use (%)			
ACE or ARB	76	65	0.008
Any beta-blockers	59	56	0.455
Calcium-channel blocker	12	2	0.017
Medication for diabetes	28	19	0.028
Diuretic	26	17	0.031
Lipid-lowering medication	35	35	0.953
Blood pressure measures (mm/Hg)			
Average diastolic blood pressure	84 (±3.183)	85 (±3.164)	0.035
Average diastolic pressure, sleep	73 (±3.459)	75 (±3.436)	0.018
Average diastolic pressure, wake	89 (±3.392)	91 (±3.371)	0.024
Average systolic pressure	106 (±5.723)	108 (±5.688)	0.230
Average systolic pressure, sleep	94 (±6.415)	96 (±6.371)	0.145
Average systolic pressure, wake	112 (±5.854)	114 (±5.818)	0.175
Average mean arterial pressure	88 (±3.568)	90 (±3.546)	0.050
Average mean arterial pressure, sleep	77 (±4.040)	79 (±4.013)	0.036
Average mean arterial pressure, wake	93 (±3.713)	95 (±3.690)	0.031

HR, heart rate; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.
^aValues are mean ± standard deviation for continuous variables and percentages for categorical variables.
^bDifference between groups (p-value).

not available or possible; (c) only one night of recording was available at any given time point; (d) HR can be modified by numerous factors including stress, anxiety, and pain, the impact of which on the type of analysis we performed is unknown; (e) the implications of HR-pattern analysis for disease prognostics, well established for conventional ambulatory blood pressure, are unknown; (f) the impact of drugs such as beta-blockers or antihypertensives in general on the noted patterns need to be established, and it is plausible that both attenuation or amplification of the HR response during sleep may occur based on cardiovascular functional status; and (g) conditions such as heart failure, advanced renal disease, post-cardiac transplant, or advanced autonomic neuropathy are likely to have relatively unchanging HR across the night and may not allow this analysis. Heart rate analysis would be invalidated by atrial fibrillation and

during fixed-rate cardiac pacing for bradyarrhythmias, while other modes of pacing may still allow analysis, but that needs to be directly demonstrated. The parent study design and our current analysis cannot determine if HR is an independent risk factor (beyond nocturnal BP) for cardiovascular outcomes. Additionally, a generalization of its potential usefulness to non-apnea conditions such as insomnia or restless legs and their treatments cannot be determined.

In conclusion, HR analytics in relation to the sleep period and the CPC spectrogram-estimated sleep states can provide novel and potentially clinically useful information on autonomic health. HR dipping (or not) may be a useful screener of BP dipping/non-dipping and identify individuals who may benefit from formal assessment of ambulatory BP and/or evaluate the efficacy of various therapies. Such a stepped approach may

TABLE 5 Heart rate dipper vs. non-dippers: comparison of characteristics.

	Baseline		Follow-Up		<i>p</i> -values ^b			
	I. HR-dipper ^a (<i>n</i> = 45, 45.9%)	II. HR-non-dipper ^a (<i>n</i> = 53, 54.1%)	III. HR-dipper ^a (<i>n</i> = 42, 51.2%)	IV. HR-non-dipper ^a (<i>n</i> = 40, 48.8%)	III vs. I	IV. vs. I	III vs. II	IV vs. II
Characteristics								
Age (years)	63.3 (±1.025)	62.5 (±0.618)	64.0 (±1.074)	62.5 (±1.087)	0.966	0.951	0.729	1.000
Body mass index (BMI; kg/m ²)	33.6 (±0.769)	33.5 (±0.708)	32.5 (±0.815)	33.9 (±0.815)	0.757	0.997	0.795	0.898
Neck circumference (cm)	42.2 (±0.518)	41.5 (±0.478)	41.1 (±0.550)	42.0 (±0.550)	0.477	0.944	0.948	0.906
Waist/hip ratio	1.0 (±0.009)	1.0 (±0.008)	1.0 (±0.009)	1.0 (±0.009)	0.998	1.000	0.848	0.742
African American (%)	8.9	3.8	9.5	2.5	0.999	0.613	0.654	0.994
Caucasian (%)	82.2	86.8	78.6	85.0	0.969	0.986	−0.714	0.996
Coexisting conditions (%)								
Prior myocardial infarction	15.6	18.9	14.3	25.0	0.999	0.680	0.941	0.876
Diabetes mellitus	37.2	43.4	57.1	37.5	0.252	0.975	0.537	0.941
Dyslipidemia	79.1	83.0	78.6	67.5	1.000	0.590	0.955	0.291
Hypertension	72.1	84.9	81.0	67.5	0.765	0.959	0.968	0.200
Medication use (%)								
ACE or ARB	68.9	66.0	78.0	60.0	0.800	0.817	0.604	0.926
Any beta-blockers	57.8	62.3	58.5	57.5	1.000	1.000	0.984	0.968
Calcium-channel blocker	40.0	26.4	26.8	27.5	0.549	0.710	1.000	0.999
Medication for diabetes	35.6	33.9	48.8	25.0	0.575	0.740	0.445	0.807
Diuretic	28.9	30.2	41.5	35.0	0.611	0.934	0.664	0.963
Lipid-lowering medication	93.3	88.7	92.7	85.0	1.000	0.584	0.920	0.938
Questionnaires								
Epworth sleepiness scale score	8.2 (±0.554)	8.1 (±0.511)	8.6 (±0.574)	8.2 (±0.588)	0.972	1.000	0.927	1.000
Patient Health Questionnaire-9 (PHQ-9)	4.8 (±0.658)	5.7 (±0.606)	2.6 (±0.681)	4.6 (±0.698)	0.119	1.000	0.005	0.657
PHQ-9 Depression severity	0.6 (±0.123)	0.8 (±0.113)	0.2 (±0.127)	0.6 (±0.130)	0.233	0.999	0.01	0.746
Short Form (36) Health Survey								
SF-vitality	54.8 (±3.370)	54.1 (±3.105)	66.9 (±3.530)	57.0 (±3.574)	0.067	0.969	0.036	0.928

(Continued)

TABLE 5 (Continued)

	Baseline		Follow-Up		<i>p</i> -values ^b			
	I. HR-dipper ^a (<i>n</i> = 45, 45.9%)	II. HR-non-dipper ^a (<i>n</i> = 53, 54.1%)	III. HR-dipper ^a (<i>n</i> = 42, 51.2%)	IV. HR-non-dipper ^a (<i>n</i> = 40, 48.8%)	III vs. I	IV. vs. I	III vs. II	IV vs. II
SF-physical functioning	74.4 (±4.190)	65.5 (±3.861)	86.1 (±4.390)	65.6 (±4.445)	0.221	0.474	0.003	1.000
SF-general health perceptions	62.6 (±3.345)	56.4 (±3.082)	66.5 (±3.504)	60.9 (±3.548)	0.853	0.984	0.138	0.778
SF-emotional functioning	81.3 (±3.514)	75.6 (±3.238)	92.1 (±3.681)	76.7 (±3.727)	0.152	0.803	0.005	0.997
SF-social functioning	81.1 (±3.797)	73.8 (±3.499)	91.2 (±3.978)	76.6 (±4.027)	0.264	0.844	0.007	0.997
SF-mental health/emotional wellbeing	74.0 (±2.567)	72.2 (±2.365)	86.1 (±2.689)	72.6 (±2.722)	0.007	0.983	0.001	1.000
Sleep measures								
Sleep Quality Index (SQI; 0–100)	41 (±2.538)	40 (±2.339)	42 (±2.627)	41 (±2.692)	0.995	1.000	0.957	0.994
Apnea-Hypopnea Index (AHI)	32 (±1.774)	32 (±1.635)	20 (±1.836)	25 (±1.882)	<0.001	0.042	<0.001	0.013
Blood pressure measures (mm/Hg)								
Average diastolic blood pressure, all readings	73 (±1.117)	71 (±1.028)	69 (±1.157)	70 (±1.187)	0.063	0.382	0.499	0.963
Average diastolic pressure, sleep	68 (±1.236)	66 (±1.135)	63 (±1.282)	65 (±1.315)	0.062	0.534	0.488	0.996
Average diastolic pressure, wake	76 (±1.185)	74 (±1.090)	71 (±1.228)	73 (±1.259)	0.074	0.552	0.461	0.989
Average systolic pressure, all readings	126 (±2.014)	122 (±1.853)	123 (±2.087)	122 (±2.140)	0.816	0.685	0.990	1.000
Average systolic pressure, sleep	118 (±2.378)	115 (±2.184)	115 (±2.466)	115 (±2.530)	0.791	0.858	1.000	1.000
Average systolic pressure, wake	130 (±2.026)	126 (±1.864)	127 (±2.099)	126 (±2.152)	0.745	0.704	0.990	0.995
Average mean arterial pressure, sleep	85 (±1.488)	83 (±1.366)	82 (±1.543)	83 (±1.583)	0.288	0.724	0.860	1.000
Average mean arterial pressure, wake	94 (±1.264)	92 (±1.163)	90 (±1.310)	92 (±1.343)	0.238	0.700	0.859	1.000

HR, heart rate; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

^aValues are mean ± standard deviation for continuous variables and percentages for categorical variables.

^bP-values based on difference between groups at baseline and follow-up.

enable a more practical, cost-effective, and applicable approach to diagnosing MH.

Data availability statement

Publicly available datasets were analyzed in this study. This analysis was made possible by the National Sleep Research Resource, with access to the HeartBEAT-database—<https://www.sleepdata.org/datasets/heartbeat>.

Ethics statement

The studies involving humans were approved by Brigham & Women's Hospital and Case Western Reserve 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.

Author contributions

HH conceptualized and designed the analysis, analyzed the data and conducted the statistical analysis, interpreted the data output, and reviewed, edited, and approved the overall content of the final manuscript. RT and SM wrote the manuscript, interpreted the data, and reviewed, edited, and approved the overall content of the final manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

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Conflict of interest

HH is Director of Research & Development for MyCardio LLC. SleepImage is the brand name of MyCardio LLC, a privately held entity. RT reports patent, license, and royalties from MyCardio LLC; patent, license, and royalties from DeVilbiss-Drive; and general sleep medicine consulting through Guidepoint Global and GLG Councils. SM is Chief Medical Officer for MyCardio LLC and has a partial ownership. SleepImage is the brand name of MyCardio LLC, a privately held entity. MyCardio LLC is a licensee of the Cardiopulmonary coupling (CPC) algorithms, a method to phenotype sleep and sleep apnea, from the Beth Israel Deaconess Medical Center, Boston, MA, USA.

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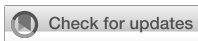
Supplementary material

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Identification and Mendelian randomization validation of pathogenic gene biomarkers in obstructive sleep apnea

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Background: By 2020, obstructive sleep apnea (OSA), a prevalent respiratory disorder, had affected 26.6–43.2% of males and 8.7–27.8% of females worldwide. OSA is associated with conditions such as hypertension, diabetes, and tumor progression; however, the precise underlying pathways remain elusive. This study aims to identify genetic markers and molecular mechanisms of OSA to improve understanding and treatment strategies.

Methods: The GSE135917 dataset related to OSA was obtained from the GEO database. Differentially expressed genes (DEGs) were subsequently identified. Weighted gene co-expression network analysis (WGCNA) was conducted to pinpoint disease-associated genes. The intersection of these data enabled the identification of potential diagnostic DEGs. Further analyses included Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment studies, exploration of protein–protein interactions based on these genes, and an examination of immune infiltration. Mendelian randomization was employed to validate core genes against the Genome-Wide Association Study database.

Results: A total of 194 DEGs were identified in this study. WGCNA network analysis highlighted 2,502 DEGs associated with OSA. By intersecting these datasets, 53 diagnostic DEGs primarily involved in metabolic pathways were identified. Significant alterations were observed in immune cell populations, including memory B cells, plasma cells, naive CD4 T cells, M0 macrophages, and activated dendritic cells. CETN3, EEF1E1, PMM2, GTF2A2, and RRM2 emerged as hub genes implicated in the pathogenesis. A line graph model provides diagnostic insights. Mendelian randomization analysis confirmed a causal link between CETN3 and GTF2A2 with OSA.

Conclusion: Through WGCNA, this analysis uncovered significant genetic foundations of OSA, identifying 2,502 DEGs and 194 genes associated with the disorder. Among these, CETN3 and GTF2A2 were found to have causal relationships with OSA.

KEYWORDS

obstructive sleep apnea, differentially expressed genes, WGCNA, Mendelian randomization, immune infiltration

Introduction

Obstructive sleep apnea (OSA) is a prevalent chronic sleep disorder affecting individuals globally. In the United States, approximately 10% of adults experience mild OSA, with moderate to severe cases ranging from 3.8 to 6.5% (1, 2). The primary symptom of OSA is repetitive upper airway collapse during sleep, largely due to the activity of the genioglossus muscle. This collapse leads to sleep disruptions and intermittent hypoxia, causing daytime fatigue and drowsiness. Moreover, OSA significantly increases the risk of various conditions, including coronary heart disease, diabetes, and cerebrovascular accidents, creating a substantial health and economic burden on individuals and society (3). Polysomnography is the primary diagnostic tool for OSA (4). However, its limited availability in specialized medical institutions and issues with patient discomfort challenge its widespread use (5). OSA often results in chronic intermittent hypoxia, which can lead to alterations in genes associated with hypoxic phenotypes (6). OSA is closely associated with a genetic basis. Studies utilizing allele models have identified 10 genetic variants that are linked to an increased risk of OSA. These variants demonstrate odds ratios ranging from 1.21 to 2.07 in the global population, indicating a significant genetic contribution to the risk of developing OSA (7). Understanding these genetic changes not only provides insights into the mechanisms underlying OSA but may also pave the way for innovative and precise diagnostic methods.

Weighted gene co-expression network analysis (WGCNA) is a specialized statistical tool designed for an in-depth analysis of gene expression data (8). It identifies co-expression patterns among genes or transcripts, groups genes with similar expression traits, and pinpoints gene modules linked to specific biological processes or diseases. Unlike traditional methods, WGCNA uses a weighted network strategy to emphasize significant gene correlations, providing a systematic view of gene interactions and disease mechanisms. Recent research employing WGCNA reveals genetic factors for diseases, yet gaps remain in identifying markers for OSA and understanding their roles (9, 10). The goal of utilizing WGCNA in our study is to identify diagnostic genes associated with OSA (11, 12).

Mendelian randomization (MR) is a genetics-based approach designed to assess causal relationships between exposures and diseases. By leveraging genetic variants, such as SNPs, as instrumental variables, MR evaluates associations between environmental or lifestyle factors and disease risk. One of its inherent strengths is the random allocation of genes at conception, which ensures independence from many confounding factors, thereby facilitating a more unbiased assessment of causality (13, 14). To validate the core diagnostic genes associated with OSA, they were included in an MR analysis, building upon the genes previously identified through WGCNA. This study aims to enhance our understanding of the genetic foundations of OSA through the use of advanced bioinformatics tools like WGCNA and MR analysis. By identifying and validating genetic markers associated with OSA, we seek to develop more accurate diagnostic tools and targeted therapeutic strategies, ultimately reducing the substantial health and economic burdens of this disorder.

Methods

Differentially expressed genes of the OSA gene dataset

In R v4.1.2, the analysis began by loading the “limma” and “pheatmap” packages. Gene expression data were obtained from the GSE135917 dataset available in the GEO database (15). The dataset involved two distinct groups: a control group comprising 8 individuals and an OSA patient group consisting of 34 individuals. The diagnosis of OSA within this cohort was primarily reliant on the respiratory disturbance index (RDI). Following initial data processing, a differentially expressed gene (DEG) analysis was conducted using the “limma” package. A logFC threshold of 0.585, equivalent to a 1.5-fold change, and an adjusted p -value criterion of adjusted p -value < 0.05 were applied to identify statistically significant genes. This threshold selection was based on common practices in other studies, ensuring that the identified gene changes were biologically meaningful and controlling the false positive rate, thereby ensuring the statistical validity and biological relevance of the results (16, 17). Subsequently, an expression heatmap was generated based on these identified genes.

WGCNA analysis of gene expression

Utilizing the WGCNA approach, the normalized expression data were analyzed. Genes with fluctuations below 0.1 were excluded, and sample clustering was performed to eliminate outliers. An optimal soft threshold was determined based on the softPower criteria. Using the TOM algorithm and the specified softPower value, a gene adjacency matrix was constructed. Dynamic cutting was applied with a depth of 2 and a minimum module size of 100, and congruent modules were merged at a cut height of 0.35. Advanced analysis revealed correlations between modules and clinical markers, and core genes were identified by applying set thresholds: gene significance > 0.5 and module association > 0.8. These thresholds were chosen to ensure a high level of confidence in the biological significance of the findings, aligning with established practices in the field as illustrated in similar studies (18, 19).

Diagnostic DEG identification and enrichment analysis

By intersecting datasets, potential diagnostic DEGs were identified. The “clusterProfiler” and “enrichplot” packages were then used to perform Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analyses (12, 13). The GO analysis focused on three dimensions: biological process, cellular component, and molecular function. A p -value < 0.05 was considered statistically significant.

Diagnostic DEG analysis and interaction

The STRING database¹ was used to evaluate diagnostic DEGs. Interactions among these genes were then visualized with Cytoscape

¹ <https://cn.string-db.org/>

v3.9.0. To refine the module's density and significance within the protein–protein interaction networks, the “cytoHub” plug-in in Cytoscape was utilized.

Receiver operating characteristic analysis for hub diagnostic genes diagnostic

The expression data from GSE13597 were meticulously analyzed using the “glmnet” and “pROC” packages. During this process, structured sample categorization was performed, hub diagnostic genes were identified and ranked, and receiver operating characteristic (ROC) curves were generated. These ROC curves provided an intuitive visual representation of the diagnostic capabilities of each core gene, with their performance quantitatively assessed using the area under the curve (AUC) values.

Calibrating hub diagnostic gene model

The “rms” and “rmda” packages were used to extract gene expression data from the GSE135917 dataset and identify key diagnostic genes. Samples were categorized into “high” or “low” based on their expression profiles. To optimize the logistic regression modeling approach, the “datadist” function was employed for data structuring. The “lrm” function was then used to create a logistic regression model, with sample categories as dependent variables and gene expression classifications as predictors. From this model, a nomogram was generated using the “nomogram” function, providing a graphical representation of the “risk of disease” in relation to gene expression levels. Subsequently, a logistic regression analysis yielded a plotted nomogram and a calibration curve, confirming the model's calibration accuracy.

Immune cell infiltration and gene correlation analysis

The “CIBERSORT” method was utilized to evaluate immune cell infiltration within the expression data of the dataset (20). Cells were rigorously filtered based on a significance threshold of $p < 0.05$. For enhanced visualization, the “pheatmap” and “corrplot” packages were employed to generate heatmaps and correlation plots of immune cells, respectively. Subsequently, violin plots were constructed to provide a detailed depiction of the distribution of infiltrated immune cells. Furthermore, the relationship between the expression of the hub diagnostic gene and the abundance of immune cells was elucidated.

MR analysis

An MR study was conducted using the “TwoSampleMR” package to explore potential causal relationships. Exposure data were obtained from various eQTL IDs, including eqtl-a-ENSG00000171848, eqtl-a-ENSG00000140307, eqtl-a-ENSG00000140650, eqtl-a-ENSG00000124802, and eqtl-a-ENSG00000153140. Outcome data were sourced from the ebi-a-GCST90018916 ID (21). Following extraction, datasets were harmonized, and appropriate instrumental

variables for MR were identified. Subsequent MR analyses were performed, and results were converted to estimate odds ratios. Additionally, the heterogeneity and pleiotropy of the instrumental variables were critically assessed. To facilitate visual interpretation of the findings, scatter plots, forest plots, funnel plots, and leave-one-out sensitivity plots were generated, offering a comprehensive overview of the MR results and the robustness of the conclusions.

Results

Integrated analysis reveals the diagnostic genes

A comprehensive DEG analysis was performed on the GSE135917 OSA gene dataset, resulting in the identification of 194 DEGs. These genes, which may play a pivotal role in the progression and manifestation of OSA, were visually represented in a heatmap (Figure 1A). To gain further insights into the interplay and co-expression patterns among these genes, WGCNA analysis was employed. This analysis identified an optimal soft threshold of 12, ensuring a scale-free topology in the gene network, as illustrated in Figures 1B,C. Within this network analysis, the “MEblue” module emerged as a significant player, demonstrating a strong association with OSA. This module alone comprises an extensive set of 2,502 DEGs (Figure 1D). The magnitude and co-expression patterns within this module underscore its critical significance in the development of OSA, suggesting it may harbor genes or pathways central to the molecular mechanisms of the disease.

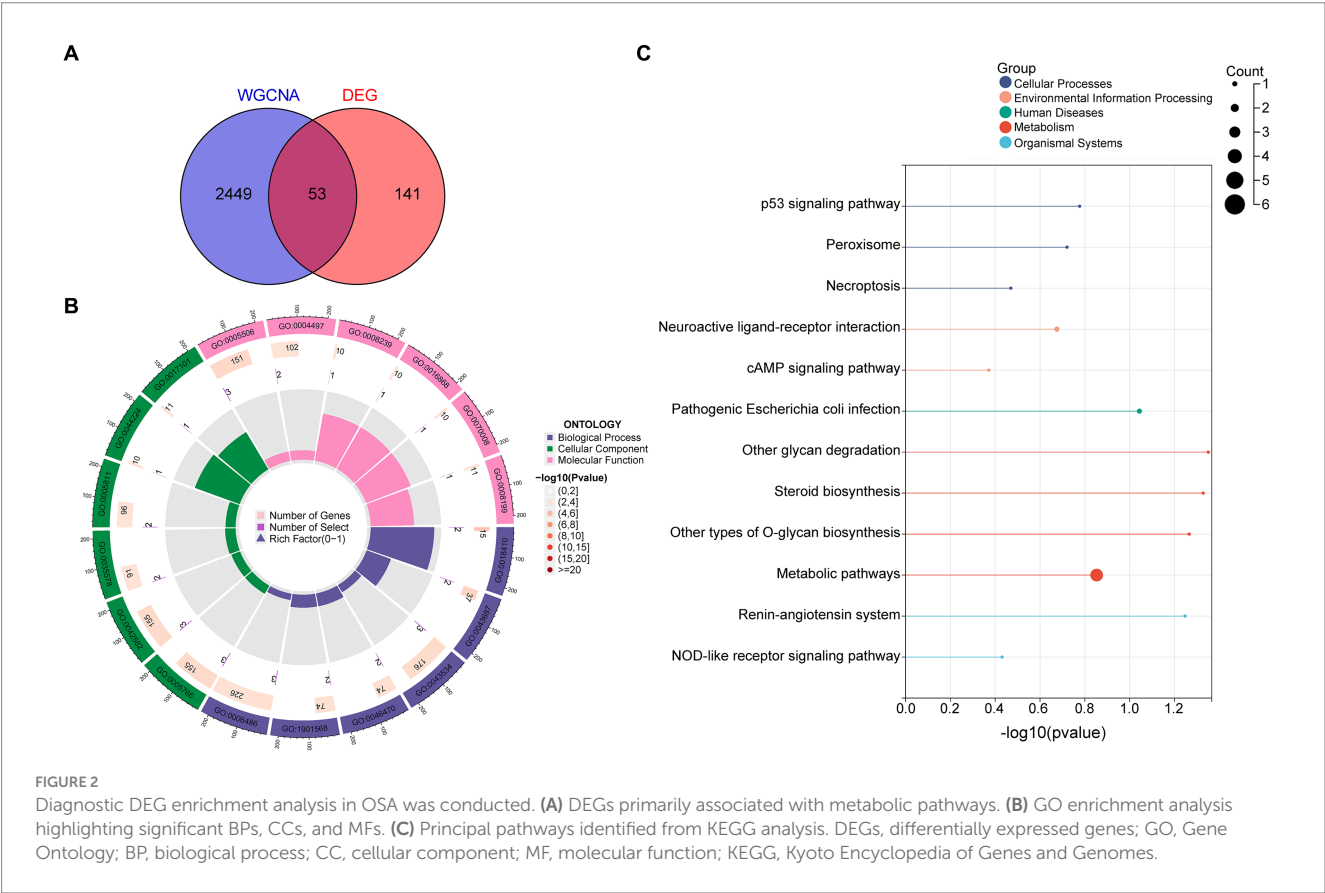
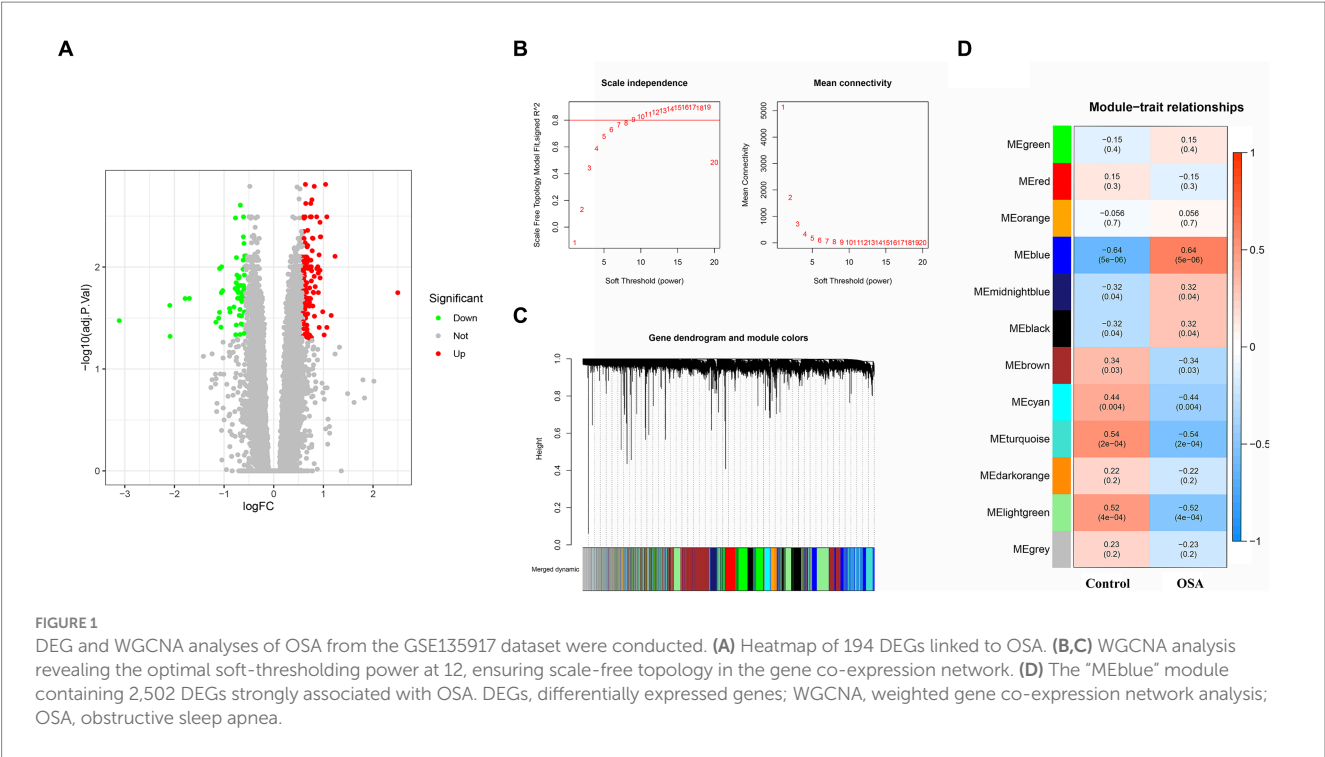
Diagnostic DEG enrichment analysis

By intersecting these datasets, 53 diagnostic DEGs predominantly associated with metabolic pathways were identified (Figure 2A). GO enrichment analysis highlighted key biological processes, including C-terminal protein amino acid modification, post-translational protein modification, blood vessel endothelial cell migration, and fatty acid derivative metabolic processes. In the cellular component category, the primary focus was on the lysosome and azurophil granule, while molecular function emphasized iron ion binding and monooxygenase activity (Figure 2B; Supplementary Figure S1). Additionally, KEGG analysis underscored metabolic pathways, the p53 signaling pathway, the cAMP signaling pathway, necroptosis, and peroxisome (Figure 2C).

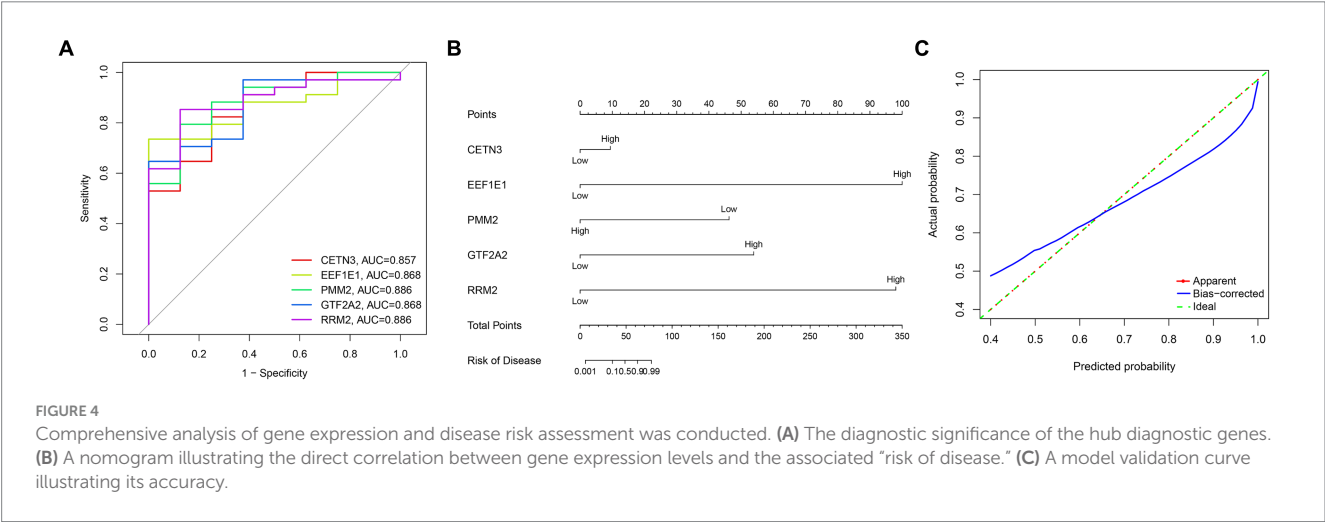
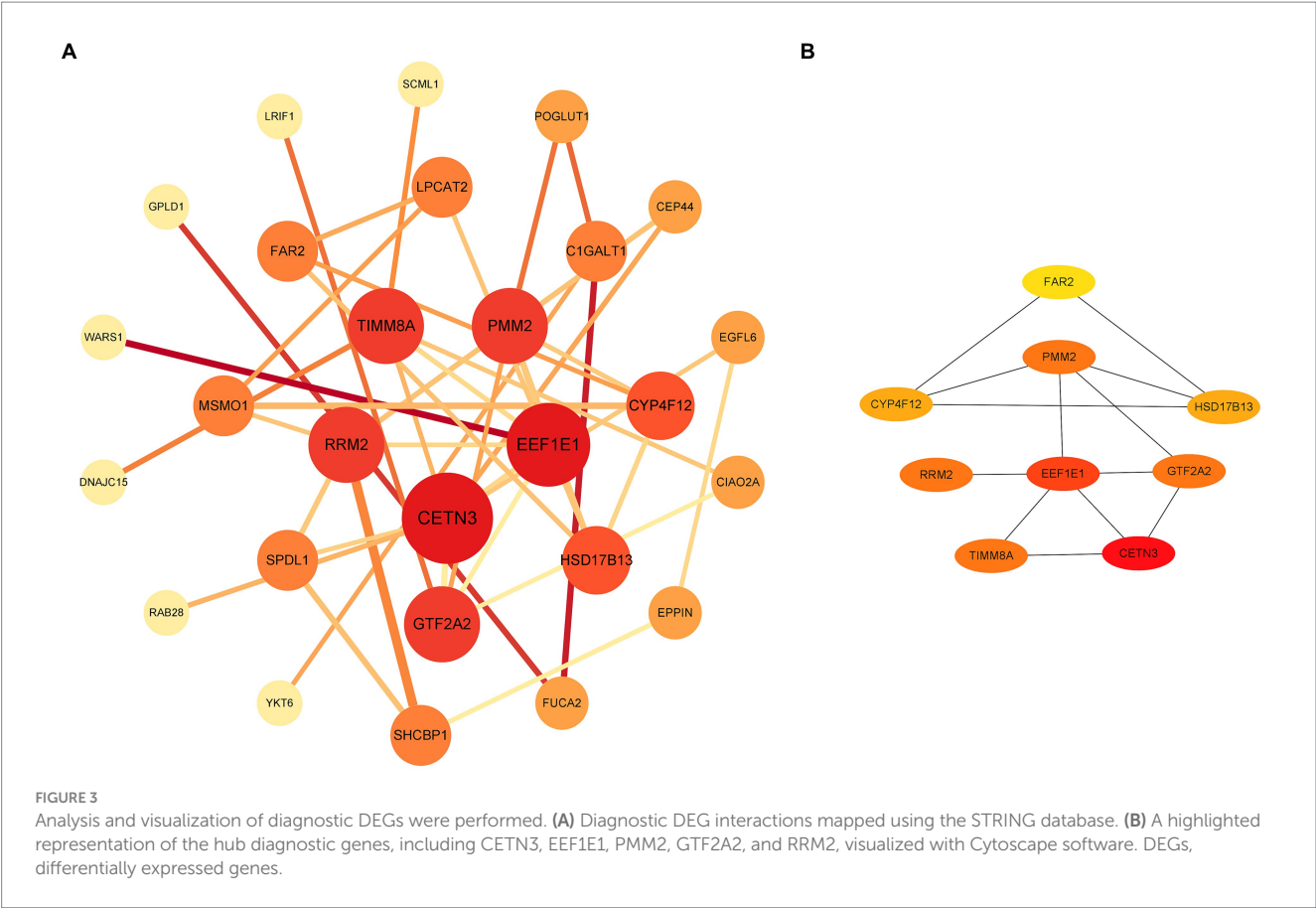
Hub diagnostic genes identification and modelling

Through a comprehensive exploration of the diagnostic DEGs using the STRING database and further visualization in Cytoscape software, essential core genes, including CETN3, EEF1E1, PMM2, GTF2A2, and RRM2, emerged prominently in their relevance (Figures 3A,B). Within the context of the GSE13597 dataset, these genes were identified as potential diagnostic cornerstones. Their diagnostic effectiveness was reinforced by an AUC value exceeding 0.85, demonstrating their strong diagnostic capability (Figure 4A).

Leveraging the predictive potential of key genes, including CETN3, EEF1E1, PMM2, GTF2A2, and RRM2, an advanced model



was meticulously developed to assess disease susceptibility based on gene expression nuances. Using the nomogram function, a detailed nomogram was created, providing a clear visual representation of the direct association between gene expression levels and the “risk of disease” (Figure 4B). Following data collection and processing, a logistic regression was implemented. The resulting analysis produced a comprehensive nomogram that visually elucidates the probability of various outcomes, considering multiple predictors. To validate the accuracy and robustness of the established model, a calibration curve was generated. The remarkable alignment of this curve with the

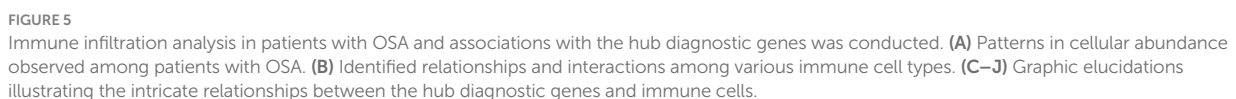


45-degree reference line underscores the high consistency between predicted and observed outcomes, reaffirming the predictive strength of the model in categorizing gene expression levels (Figure 4C).

Immune infiltration in patients with OSA

In an in-depth analysis of immune infiltration within the dataset, specific patterns in cellular abundance were observed

among patients with OSA. Notably, an increased presence of memory B cells and M0 macrophages suggested their potential role in OSA progression or response. Conversely, a noticeable decrease in plasma cells, naive T CD4 cells, and activated dendritic cells hinted at their diminished involvement in the OSA condition (Figures 5A,B). The intricate associations between these core genes and immune cells are visually illustrated in Figures 5C–J, elucidating the potential interactions and interplay between gene expression and immune cell profiles.



Discussion

OSA, a prevalent and severe sleep disorder, disrupts breathing during sleep. Typically, these interruptions last several seconds to a minute and occur when the throat muscles fail to keep the airway open, despite attempts to breathe. This obstruction often causes a decrease in blood oxygen levels and frequent awakenings throughout the night, leading to fragmented and non-restorative sleep (22, 23). The samples derived from GSE135917 originate from the subcutaneous adipose tissue of patients with OSA. This adipose tissue, readily accessible as a fat depot, plays a pivotal role in metabolic regulation.

The analysis included 8 healthy controls from Study Group 1 and 34 patients with OSA from both groups. The GSE135917 OSA gene dataset was thoroughly examined, leading to the identification of 194 DEGs crucial to the progression and manifestation of OSA. Network analysis via WGCNA identified a strong association of the “MEblue” module with OSA, indicating that this module may contain key genes

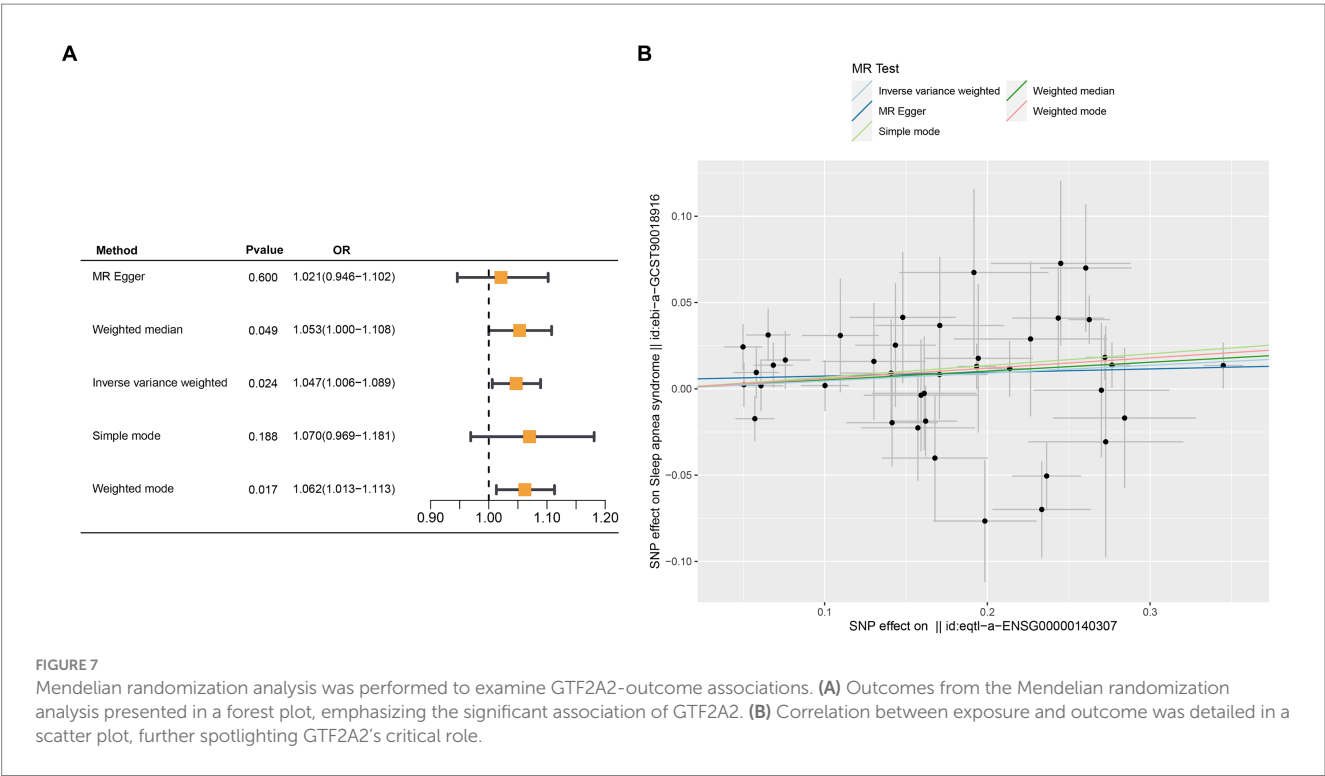
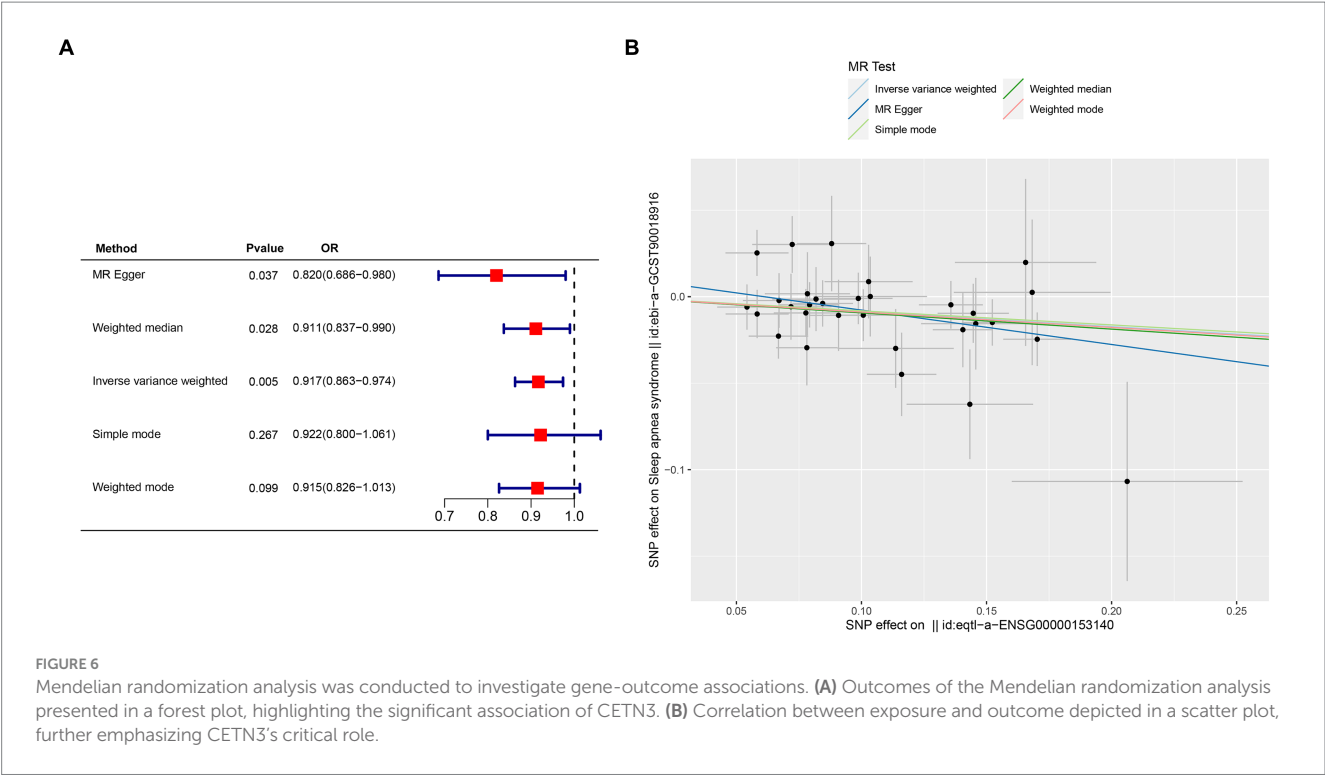


TABLE 1 Heterogeneity and horizontal pleiotropy analyses between CETN3, GTF2A2, and OSA.

Exposure	Outcome	Egger intercept	p-intercept	Cochran’s Q	p-value
CETN3	OSA	0.0121	0.199	24.027	0.728
GTF2A2	OSA	0.0053	0.460	52.804	0.156

or pathways central to the disease's molecular mechanisms. WGCNA has become a prominent tool in OSA research due to its ability to systematically explore the molecular complexities of the disorder (24, 25). Utilizing WGCNA, gene co-expression modules relevant to OSA can be identified, critical driver genes can be discovered, and various data types such as transcriptomics, proteomics, and metabolomics can be integrated, providing a comprehensive understanding of the disease landscape (26, 27).

Through a thorough analysis of datasets, 53 diagnostic DEGs predominantly associated with metabolic pathways were precisely identified. These DEGs provide profound insights into the potential molecular mechanisms underlying OSA, particularly in terms of metabolic regulation. Identified biological processes, such as C-terminal protein amino acid modification, post-translational protein modification, blood vessel endothelial cell migration, and fatty acid derivative metabolic processes, are intriguing. These processes could potentially be linked to metabolic abnormalities, vascular dysfunction, and delayed tissue repair often observed in patients with OSA (28). Regarding cellular components, the prominence of the primary lysosome and azurophil granule suggests an impact of OSA on cellular acidic environments and inflammatory responses. Notably, azurophil granules are associated with inflammatory responses in various ailments (29). Insights into molecular function, highlighting iron ion binding and monooxygenase activity, suggest a potential connection between OSA and red cell functionality and the oxidative stress response at the tissue level (30). The STRING database, combined with Cytoscape software, facilitated a detailed examination of diagnostic DEGs, uncovering the intricate interrelationships among these genes (31). Subsequent ROC curve analyses emphasized the robust diagnostic potential of the identified core genes. Additionally, the established gene model, utilizing logistic regression and model calibration, offers profound insights into the disease and illuminates new avenues for future diagnostic and therapeutic interventions.

The unique dynamics of immune cells in patients with OSA were revealed through an in-depth analysis of immune infiltration. Memory B cells and M0 macrophages showed a significant increase, suggesting their role in mediating inflammatory cascades and subsequent tissue impairments associated with the disease (32). In contrast, plasma cells, naive T CD4 cells, and activated dendritic cells exhibited a reduced prevalence, indicating a diminished regulatory capacity as the disease progresses, likely linked to the chronic hypoxic environment and persistent inflammation inherent in OSA (33). Particularly, the reduction in plasma cells may lead to weakened antibody-mediated immune responses in patients with OSA, diminishing their defense against pathogens (34). The decrease in naive T CD4 cells could affect the regulatory and activation functions of the immune system in OSA patients, weakening their resistance to infections (35). Furthermore, a reduction in activated dendritic cells suggests that OSA may interfere with effective antigen presentation and the initiation of immune responses, impacting overall immune regulation. These insights, combined with the complex interplay between cellular components and key genes, pave the way for a deeper exploration of the molecular and immunological foundations of OSA. Several studies have delved into SNPs and their connection to OSA, highlighting the discovery of rs11691765 in GPR83 and rs35424364 in C6ORF183 within the Hispanic/Latino American population. These genomic-level findings shed new light on the roles of inflammation and hypoxia signaling pathways in sleep apnea (36). OSA demonstrates distinct genetic

disparities among various ethnic groups. In the case of European Americans, genetic variants in CRP and GDNF show a significant association with the AHI. Conversely, in African Americans, the rs9526240 variant within the HTR2A gene is notably correlated with the presence of OSA (37). Our study distinctively emphasized MR analysis within a European population, providing specialized insight into genetic influences. While our findings were primarily based on this demographic, we acknowledged the importance of comparing these results with SNP data reported in Hispanic/Latino and African American populations to understand broader genetic implications. The MR approach revealed pronounced correlations between certain genes and outcomes relevant to OSA. CETN3, in particular, showed distinct associations across various methodologies, underscoring its critical role in the genetic framework of OSA. Similarly, GTF2A2 emerged as another significant contributor within the genetic context of the disease. On the other hand, several genes, including EE1E1, PMM2, and RRM2, did not exhibit robust associations, highlighting the nuanced and multifaceted genetic architecture of OSA.

Investigations into family genetics have shown that in OSA, inherited traits may influence late sleep timing associated with increased IL-6 levels, and a genetic tendency towards more significant social jetlag corresponding with higher IL-1 levels (38). The genetic relationship between OSA and its pathological features is evident, as demonstrated by a twin study from Hungary on OSA. Specifically, the study found a significant shared genetic basis linking serum triglyceride levels with key indicators of OSA severity, such as the oxygen desaturation index and the proportion of sleep time with oxygen saturation below 90% (39). In summary, it is evident that genetic variations significantly contribute to the development and progression of OSA, underlining the importance of genetic factors in understanding and addressing this condition. CETN3, also known as centrin 3, encodes a protein belonging to the EF-hand protein superfamily. As calcium-binding proteins, centrans play a crucial role in centrosome dynamics, particularly in centrosome replication and separation, both essential for cell division (40, 41). Oxidative stress, commonly associated with conditions like OSA, can disrupt the cell cycle by affecting both protein functions and DNA integrity (42). Elevated oxidative stress could, therefore, compromise the functional integrity of CETN3, hindering its primary role in maintaining centrosome dynamics. Studies have shown that disruptions in cell cycle regulation are linked to sleep disturbances and respiratory dysfunction, highlighting the relevance of CETN3 in OSA pathology (43). Similarly, GTF2A2 encodes a critical subunit of the general transcription factor IIA, which is essential for the assembly of the preinitiation complex in gene transcription directed by RNA polymerase II. Composed of two main subunits, GTF2A2 represents one of them (44, 45). Given GTF2A2's central role in transcription initiation, oxidative stress induced by elevated ROS levels, often seen in OSA, might impede its function or expression (46). The potential of ROS to alter transcription regulators and their target genes suggests that the cellular imbalances caused by OSA could indirectly modulate the function of genes such as GTF2A2. This impairment may lead to altered transcriptional regulation, which has been shown to affect cellular function and contribute to the systemic effects observed in OSA patients, such as enhanced inflammatory responses and metabolic dysregulation (47).

Additionally, we recognize that due to limited sample sizes and selection biases, our findings may need to be validated in a broader

population to confirm their generalizability. Variations and potential biases may occur from exclusive reliance on specific datasets and sample origins. Despite strong associations identified with CETN3 and GTF2A2, further investigation is necessary for genes such as EEF1E1, PMM2, and RRM2. It's critical to experimentally validate the causal roles of these genes in OSA. Although the MR approach is robust, it requires cautious interpretation due to its foundational assumptions. Future research should expand to include a wider range of tissues and functional validations to deepen our understanding.

Conclusion

In-depth analysis has identified critical genes, notably CETN3 and GTF2A2, with potential roles in the etiology and progression of OSA. Insights into immune cell dynamics further emphasize the multifaceted nature of the disease. While promising, inherent limitations in the study must be considered, particularly concerning potential biases in the datasets and assumptions in the methodology. These findings offer a foundation for future OSA research, highlighting the need for experimental validation and broader exploration.

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

NG: Conceptualization, Software, Writing – original draft. YT: Conceptualization, Data curation, Visualization, Writing – original

draft. PL: Funding acquisition, Project administration, Validation, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2024.1442835/full#supplementary-material>

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Prevalence and impact of sleep-related breathing disorder in multiple system atrophy patients: a cross-sectional study and meta-analysis

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Objective: Sleep-related breathing disorder (SRBD) is a prevalent non-motor symptom in multiple system atrophy (MSA). However, the reported prevalence of SRBD in MSA from different studies has shown inconsistency. Additionally, only one study has examined the impact of SRBD on both motor and non-motor symptoms in MSA.

Methods: Cross-sectional study of 66 patients with probable MSA from China. SRBD was ascertained with polysomnography (PSG). All the MSA individuals were assessed using the Epworth Sleepiness Scale (ESS), Unified Multiple-System Atrophy Rating Scale (UMSARS), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), the Mini-mental State Examination (MMSE), Non-Motor Symptoms Scale (NMSS), and Pittsburgh Sleep Quality Index (PSQI). Moreover, a meta-analysis was conducted by searching studies related to MSA and SRBD in PubMed, Web of Science, Embase, and Cochrane databases. Data were pooled as necessary to calculate prevalence of SBRD with 95% confidence intervals (CI).

Results: Our study included 66 patients with MSA, 52 of whom had a diagnosis of SRBD (78.8%). There were no significant differences between the MSA with SRBD and without SRBD groups on the age, sex, disease onset, disease duration, UMSARS I, II, and IV, the NMSS, the HAMA, HAMD, the ESS the FSS, the MMSE, and the PSQI scales. However, MSA patients with SRBD having a significant higher obstructive apnea index and percentage of snoring during sleep than MSA patients without SRBD [10.0 (4.1–10.6) vs. 0.1 (0–0.3), and 8.3 (5.1–12.2) vs. 4.2 (0–7.5)]. Also, between the two groups, the mean and minimum oxygen concentrations during sleep were lower in MSA patients with SRBD than in those without SRBD [93.7 (93–95) vs. 95.5 (95.8–97), $p = 0.001$] and [83.9 (81.2–89.0) vs. 90.3 (89.8–93.3), $p = 0.000$]. The primary search strategy identified 701 articles, with 10 meeting the inclusion criteria. The overall prevalence of SRBD in a combined sample of 295 MSA patients was found to be 60.5% (95% CI, 43.2–76.5%). Further analysis revealed that the prevalence of SRBD in MSA patients in Asia was 79.2% (95% CI, 54.7–96.3%), which was higher than that in Europe (41.6, 95% CI, 32–51.5%).

Conclusion: The study found a prevalence of 78.8% of SRBD in MSA patients, with a notably higher prevalence in Asia compared to Europe. The majority of SRBD cases in MSA were attributed to obstructive apnea. Furthermore, the presence of SRBD did not show a significant impact on the motor and non-motor symptoms of MSA patients.

KEYWORDS

multiple system atrophy, sleep related breathing disorder, prevalence, motor symptoms, nonmotor symptoms

Introduction

Multiple system atrophy (MSA) was first proposed by Graham and Oppenheim in 1969 as an alpha-synucleinopathy disease characterized by poor response to levodopa, autonomic dysfunction and/or cerebellar ataxia. It can be classified into two types: MSA-P (predominant Parkinsonism) and MSA-C (predominant cerebellar ataxia), based on the main motor symptoms (1). MSA-P type presents Parkinson's syndrome as the main symptom, while MSA-C type shows cerebellar ataxia disorder as the main symptom. Further research on MSA has revealed that it not only exhibits typical motor symptoms but also numerous non-motor symptoms, such as sleep-related breathing disorders (1).

Sleep-related breathing disorder (SRBD) is a common sleep disorder in patients with neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies, MSA, hereditary ataxia, and amyotrophic lateral sclerosis (ALS) (2). SRBD typically manifests as obstructive sleep apnea (OSA), central sleep apnea (CSA), irregular breathing, apnea, Cheyne-Stokes breathing pattern, and stridor (2). Certain episodes of sleep breathing disorders can impact patient safety, with issues like nocturnal wheezing potentially leading to sudden nocturnal death (3). Wheezing in the early stages of MSA has been identified as an independent risk factor for shorter survival in MSA patients (4). Moreover, central and peripheral respiratory disturbances are common in MSA patients, occurring during both sleep and wakefulness. These disturbances can include intermittent involuntary gasping, periodic or irregular breathing, abnormal hypoxic and hyperventilatory responses, respiratory failure, and stridor (2).

Sleep-related breathing disorder are a common non-motor symptom in patients with MSA. However, current reports on the prevalence of SRBD in MSA show varying results, with previous studies indicating occurrence rates ranging from approximately 24.9–100% among MSA patients (5–14). Research on the impact of SRBD on both motor and non-motor symptoms in MSA is limited. Only one study published in 2017 examining the effects of SRBD on MSA patients revealed that those with SRBD exhibited more severe motor deficits, depressive symptoms, and frontal lobe dysfunction compared to those without SRBD. Additionally, they experienced more daytime sleepiness, sleep deprivation, longer average sleep duration, and OSA (9).

This study aims to further investigate the prevalence of SRBD in MSA and its effects on motor and non-motor symptoms. Furthermore, a meta-analysis of previously published studies on SRBD prevalence in MSA patients will be conducted to discuss the factors contributing to the wide range of reported SRBD prevalence in MSA.

Methods

This cross-sectional study included 66 consecutive patients with probable MSA who were admitted to the Department of Neurology at

West China Hospital and Sichuan Taikang Hospital between 2016 and 2024. Diagnosis was made by neurologists based on second consensus statement on the diagnosis of MSA proposed by Gilman et al. (15). Apnea was defined as a $\geq 90\%$ decrease in the airflow signal from baseline for ≥ 10 s, while hypopneas were diagnosed as a $\geq 30\%$ decrease in airflow lasting ≥ 10 s, associated with either $\geq 3\%$ desaturation from the prevent baseline or an arousal. Irregular breathing was defined as irregular respiratory rhythm, which is characterized by alternating depths or uneven speeds (16). Blood oxygen was defined as the oxygen saturation measured by finger oximetry. Periodic limb movements were defined in the 2007 AASM Manual for the Scoring of Sleep and Associated Events (17). SRBD were identified by an Apnea-Hypopnea Index (AHI) > 5 /h, with severity categorized as mild (AHI: 5–15/h), moderate (AHI: 15–30/h), and severe (AHI > 30 /h) (17). Polysomnography (PSG) was conducted at the Sleep Medicine Center of West China Hospital.

The study was approved by the Ethics Committees of West China Hospital, Sichuan University (2020-842), and all patients provided written consent. Patients meeting the diagnostic criteria for probable MSA, completing relevant questionnaires and PSG, and showing no brain injury on MRI were included. Exclusion criteria were the use of medications affecting sleep, cognitive impairment, acute psychosis, or critical illness.

Demographic and clinical characteristics were recorded for all MSA patients, with “disease onset” defined as the initial motor or autonomic symptom presentation and “disease duration” as the time from symptom onset to study enrollment. Various questionnaires were used to evaluate clinical characteristics in the patients. The Non-Motor Symptoms Scale (NMSS, nine domains) was used to evaluate the severity of non-motor symptoms. The severity of depression and anxiety were assessed, respectively, using the Hamilton Depression Rating Scale (HAMD, 17 items) and Hamilton Anxiety Rating Scale (HAMA). Patients were also evaluated using the Fatigue Severity Scale (FSS) and Epworth Sleepiness Scale (ESS). Severity of motor symptoms was assessed using the Unified Multiple System Atrophy Rating Scale (UMSARS); cognitive function, using the Mini-mental State Examination (MMSE); non-motor symptoms, Non-Motor Symptoms Scale (NMSS); and sleep quality, using the Pittsburgh Sleep Quality Index (PSQI).

Overnight video-PSG

Overnight video-PSG began for each patient at 22:00 every night in a quiet room with appropriate lighting and temperature, and it consisted of continuous recordings by electroencephalography (F4–M1, C4–M1, O2–M1, F3–M2, C3–M2, and O1–M2), electro-oculography (ROC–M1, LOC–M2), submental electromyography, right and left anterior tibialis surface electromyography, and electrocardiography. Overnight PSG was performed with video and audio in the Sleep Medicine Center of West China Hospital at Sichuan University. PSG was used to monitor the following indices: video, audio, electroencephalography, blood oxygen, oral-nasal airflow,

thoracic and abdominal breathing, electrocardiography, eye movement, and mandible and limb electromyography. PSG results were scored by sleep technicians and interpreted by sleep specialists. Sleep staging, respiratory events, arousal, and limb movements were evaluated according to the guidelines for scoring sleep and related events from the American Academy of Sleep Medicine (18).

The following sleep variables were analyzed: sleep latency (SL); REM sleep latency; sleep efficiency (SE); total sleep time; percentage of total time spent in stage N1, N2, and N3 or REM sleep; wake after sleep onset (WASO); apnea-hypopnea index (AHI); Obstructive apnea index; Central apnea index; average/minimum oxygen saturation (SaO₂); and periodic leg movement index (PLMI).

Statistical analysis

Data were analyzed using SPSS 19.0 (IBM, Chicago, IL, United States). Continuous data showing a normal distribution were expressed as mean $\pm$ standard deviation (SD), while continuous skewed data were reported as median (interquartile range). Inter-group differences were assessed for significance using Student's *t* test. Inter-group differences in continuous skewed data were assessed using a Mann-Whitney U test. Differences in categorical data were assessed using the chi-squared test. Logistic regression analysis was used to estimate the odds ratio (OR) and 95% CI after adjusting for potential confounding factors, including quantitative variables (age and disease duration) and categorical variables (sex, smoking, alcohol consumption, and MSA sub-type). Differences associated with $p < 0.05$ were statistically significant.

Meta-analysis methods

Searching strategy

This meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (19). The Cochrane Collaboration definition for systematic review and meta-analysis was strictly followed. Two authors (HW and TZ) independently searched Medline via PubMed, Web of Science, Embase via [embase.com](https://www.embase.com), and Cochrane databases for original published studies on the clinical manifestations of MSA patients with or without SRBD. Inclusion criteria were studies published in English before April 2, 2024. The search string was as follows: "Sleep Apnea Syndromes" OR "Apnea Syndrome, Sleep" OR "Apnea Syndromes, Sleep" OR "Sleep Apnea Syndrome" OR "Sleep Hypopnea" OR "Hypopnea, Sleep" OR "Hypopneas, Sleep" OR "Sleep Hypopneas" OR "Apnea, Sleep" OR "Apneas, Sleep" OR "Sleep Apnea" OR "Sleep Apneas" OR "Sleep Apnea, Mixed Central AND Obstructive" OR "Mixed Central AND Obstructive Sleep Apnea" OR "Sleep Apnea, Mixed" OR "Mixed Sleep Apnea" OR "Mixed Sleep Apneas" OR "Sleep Apneas, Mixed" OR "Hypersomnia with Periodic Respiration" OR "Sleep-Disordered Breathing" OR "Breathing, Sleep-Disordered" OR "Sleep Disordered Breathing" OR "sleep-related breathing disorders" OR "sleep related breathing disorders" OR "Sleep Apnea Syndromes" OR "Sleep Apnea, Obstructive" OR "Apneas, Obstructive Sleep" OR "Obstructive Sleep Apneas" OR "Sleep Apneas, Obstructive" OR "Obstructive Sleep Apnea Syndrome" OR "Obstructive Sleep Apnea" OR "OSAHS" OR "Syndrome, Sleep Apnea, Obstructive" OR "Sleep

Apnea Syndrome, Obstructive" OR "Apnea, Obstructive Sleep" OR "Sleep Apnea Hypopnea Syndrome" OR "Syndrome, Obstructive Sleep Apnea" OR "Upper Airway Resistance Sleep Apnea Syndrome" OR "Syndrome, Upper Airway Resistance, Sleep Apnea" AND "Atrophy, Multiple System" OR "Multiple System Atrophies" OR "Multisystemic Atrophy" OR "Atrophies, Multisystemic" OR "Atrophy, Multisystemic" OR "Multisystemic Atrophies" OR "Multiple System Atrophy Syndrome" OR "Multisystem Atrophy" OR "Atrophies, Multisystem" OR "Atrophy, Multisystem" OR "Multisystem Atrophies."

Study selection criteria

Articles were initially screened based on their titles and abstracts, with full text consulted when necessary. Patients were diagnosed with SRBD according to objective instruments, including polysomnography (PSG), Embletta and Apnea Link sleep monitoring devices. In addition, SRBD was diagnosed in the occurrence of an AHI $> 5/h$ (17). Inclusion criteria were (1): original data on SRBD and clinical symptoms of MSA (2), patients diagnosed with probable MSA, (3) and sufficient data to calculate the prevalence of SRBD in MSA patients and the impact of SRBD on MSA patients.

Exclusion criteria were (1): reviews, editorials, conference abstracts, letter or case reports (2); focus solely on SRBD characteristics, pathogenic mechanisms, or MSA management with SRBD (3); comparisons between MSA and other synucleinopathies (4); insufficient data for meta-analysis (5); non-English articles (6); or studies not involving human subjects. Discrepancies in article inclusion were resolved by a third author (WF).

Data extraction and study quality assessment

The data extracted from the original articles included the surname of the first author, publication year, country, sample size, prevalence of SRBD, mean age of patients, sex, disease onset, disease duration. For longitudinal studies, only baseline data were extracted.

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies, as well as the Agency for Healthcare Research and Quality guideline (AHRQ) for cross-sectional studies (20, 21). Any discrepancies were resolved through consensus among all authors.

Statistical analysis

The STATA software version 16.0 was used for statistical analysis. The primary outcome measure was frequency of SRBD in MSA as reported in prevalence (%). The pooled prevalence of SRBD and 95% confidence intervals were obtained by using a DerSimonian-Laird random-effects model with double arcsine transformation (22). A *p* value equal to or less than 0.05 was considered statistically significant. The heterogeneity across studies was evaluated using Cochrane's *I*² values. *I*² $> 75\%$ was defined as high heterogeneity, $50\% < I^2 < 75\%$ as moderate heterogeneity, $25\% < I^2 < 50\%$ as low heterogeneity, and $I^2 < 25\%$ as homogeneity. The Begg's and Egger's test was created to detect publication biases.

Results

Polysomnography was completed in 66 MSA patients, and these 66 patients were included in this study, of which 52 (78.8%) reached the diagnosis of SRBD (AHI $> 5/h$), including 31 males and 21 females.

TABLE 1 Comparison of motor and non-motor symptoms in MSA patients with and without SRBD.

Characteristics	All MSA patients (n = 66)	With SRBD (n = 52)	Without SRBD (n = 14)	p
Male/Female	40/26	31/21	9/5	0.753
Age(years)	63.05 ± 10.13	63.69 ± 9.60	60.64 ± 11.58	0.325
Disease onset (year)	60.15 ± 10.3	60.74 ± 9.91	57.93 ± 11.01	0.370
Disease duration (year)	2.79 ± 2.78	2.61 ± 1.86	2.84 ± 2.98	0.962
UMSARS I	13.23 ± 5.8	13.06 ± 5.74	13.86 ± 5.99	0.648
UMSARS II	16.52 (12–20.25)	16.33 ± 6.12	17.29 ± 6.23	0.638
UMSARS IV	1.74 ± 0.99	1.65 ± 0.84	2.00 ± 1.36	0.751
NMSS	49.35 ± 26.4	49.79 ± 26.23	47.71 ± 28.16	0.797
HAMA	11.14 ± 7.88	10.84 ± 7.29	12.21 ± 9.64	0.804
HAMD	10.28 ± 6.99	9.78 ± 6.14	12.07 ± 9.23	0.642
ESS	7.11 (2.75–11.00)	7.23 (2.25–11.75)	6.64 (2.75–9.00)	0.571
FSS	21.71 (11–30)	22.98 (11–34)	17 (12.50–21.25)	0.723
MMSE	24.58 (22–29)	24.13 (21.25–28)	26.21 (24.50–29.00)	0.172
PLMS (%)	47 (71.2)	35 (67.3)	12 (85.7)	0.318
PSQI	6.64 (3.0–9.5)	6.90 (3–9)	5.64 (1.75–10.00)	0.194

ESS, Epworth Sleepiness Scales; FSS, Fatigue severity scale; HAMA, Hamilton anxiety scale; HAMD, Hamilton depression scale; MSA, Multiple system atrophy; MMSE, Mini-mental state examination; NMSS, Non-motor symptoms scale; PLMS, Periodic limb movements syndrome; PSQI, Pittsburgh sleep quality index; SRBD, Sleep related breathing disorder; and UMSARS, Unified multiple-system atrophy rating scale.
Values are n (%), mean ± SD or median (interquartile range).

Among the 52 patients with SRBD, 19 patients had mild (AHI: 5–15/h), 15 patients had moderate (AHI: 15–30/h), and 18 patients had severe (AHI: >30/h), and the three types accounted for 36.5, 28.8, and 34.6% of all patients, respectively.

As shown in Table 1, in this study, 66 patients diagnosed with MSA were categorized into two groups based on the presence of SRBD. The analysis focused on comparing motor and non-motor symptoms between these two groups. The study found no statistically significant variances between the groups in terms of motor symptom severity assessed by the UMSARS scale, non-motor symptoms evaluated through the NMSS scale, anxiety and depression levels measured by the HAMA and HAMD scales, somnolence assessed by the ESS scale, fatigue evaluated using the FSS scale, cognitive functioning measured by the MMSE scale, as well as assessments of nocturnal sleep functioning PSQI scales ($p > 0.05$). Notably, 71.2% of MSA patients exhibited periodic leg movements, with 35 of them also displaying SRBD.

As illustrated in Table 2, all 66 patients diagnosed with MSA in this particular study underwent PSG. There were no significant variations observed between MSA patients with SRBD and those without SRBD in terms of various sleep parameters such as total sleep time (TST), sleep efficiency (SE), sleep latency (SL), sleep structure (N1, N2, and N3, and the percentage of REM phase in the entire sleep cycle), arousal index, wake after sleep onset (WASO), central apnea index, and periodic leg movement index (PLMI). However, it was noted that MSA patients with SRBD exhibited a notably higher obstructive apnea and hypopnea index compared to MSA patients without SRBD [10.0 (4.1–10.6) vs. 0.1 (0–0.3) and 14.7(8.5–19.3) vs. 2.3(1.3–2.9), $p = 0.000$]. Furthermore, MSA patients with SRBD displayed a significantly higher occurrence of snoring during sleep in

comparison to those without SRBD [8.3 (5.1–12.2) vs. 4.2(0–7.5), $p = 0.015$]. Additionally, compared with MSA patients without SRBD, MSA patients with SRBD had lower mean and minimum oxygen concentrations and higher oxygen desaturation index during sleep [93.7 (93–95) vs. 95.5 (95.8–97), $p = 0.001$], [83.9 (81.2–89.0) vs. 90.3 (89.8–93.3), $p = 0.000$], and 19.9 (10.9–36.6) vs. 2.5(1.5–4.0)].

Table 3 presents the process of logistic regression analysis. After adjusting for age, sex, disease duration, smoking, alcohol consumption, and MSA subtype, the associations between the presence of SRBD in MSA patients and the UMSARS score, NMSS score, HAMA score, HAMD score, MMSE score, PSQI score, and FSS score remained statistically insignificant ($p > 0.05$). It can be concluded that age, sex, disease duration, smoking, alcohol consumption, and MSA sub-type did not significantly affect the relationship between the independent and dependent variables.

Meta-analysis results

The literature search yielded 701 potentially relevant articles (Figure 1). After eliminating duplicates, 458 records were reviewed and 393 were excluded during the title and abstract screening phase. The remaining 65 full-text articles were assessed for eligibility, and 37 were excluded because they were reviews ($n = 3$), studies about treatment ($n = 4$), studies unrelated MSA ($n = 2$) or SRBD ($n = 12$), case series <5 ($n = 2$), letter ($n = 5$), conference abstract ($n = 9$), and insufficient date ($n = 18$).

In the end, 10 articles were ultimately included in our review, involving a total of 295 MSA patients. Five original researches were performed in Asia, five in Europe.

TABLE 2 Comparison of PSG measurements in MSA patients with and without SRBD.

Variables	All MSA patients (n = 66)	With SRBD (n = 52)	Without SRBD (n = 14)	p
TST	337.0 ± 90.2	334.3 ± 86.4	346.9 ± 106.0	0.647
SE, %	66.0 ± 17.3	65.9 ± 16.9	66.4 ± 19.6	0.920
SL, min	22.9(5–28)	22.8(5.5–26.1)	23.1(2.4–33.9)	0.660
N1, %	32.2(30.6–42.35)	33.8(19.6–43.6)	25.9(14.5–34.6)	0.134
N2, %	48.1 ± 14.6	47.88 ± 15.3	48.89 ± 12.0	0.819
N3, %	1.5(0–0.32)	1.1(0–0.3)	3.0(0–2.7)	0.369
REM sleep, %	18.3 ± 3.8	17.19 ± 6.9	22.21 ± 9.8	0.890
WASO, min	151.1 ± 83.9	150.8 ± 81.2	152.1 ± 96.4	0.962
Arousal index, /h	19.7(13.6–23.6)	20.6(11.5–26.0)	16.3(10.5–21.5)	0.246
OA index, /h	7.6(0–9)	10.0(4.1–10.6)	0.1(0–0.3)	0.000
CA index, /h	0.4(0–0.4)	0.5(0–0.5)	0.1(0–0.1)	0.122
hypopnea index, /h	9.6 (3.4–17.3)	14.7(8.5–19.3)	2.3(1.3–2.9)	0.000
Total OA times	1.0(0–2.0)	1.65(0–2)	1.0(0.0–3.0)	0.363
Total CA times	0(0–2.0)	0.5(0–0.25)	1.0(0–2.0)	0.048
Percentage of snoring, %	5.3(1.2–5.9)	6.6(0.1–5.7)	4.6(0–6.6)	0.447
Average SaO ₂ , %	94.1(93–96)	93.7(93–95)	95.5(95.8–97)	0.001
Minimum SaO ₂ , %	85.4(83–90)	83.9(81.2–89.0)	90.3(89.8–93.3)	0.000
ODI, /h	14.9 (6.1–31.9)	19.9(10.9–36.6)	2.5(1.5–4.0)	0.000
Average snoring time, (min)	7.4(3–10.8)	8.3(5.1–12.2)	4.2(0–7.5)	0.015
PLMI, /h	25.2(4.3–43.5)	25.15(4.8–41.0)	25.3(21.2–44.0)	0.733

CA, Central apnea; MSA, Multiple system atrophy; REM, Rapid eye movement; OA, Obstructive apnea; ODI, Oxygen desaturation index; PLMI, Periodic leg movement during sleep index; SE, Sleep efficiency; SL, Sleep latency; SaO₂, Oxygen saturation; TST, Total sleep time; and WASO, Wake after sleep onset. Values are n (%), mean ± SD or median (interquartile range). Bold values indicate $p < 0.05$, indicating statistically significant differences between the two groups.

TABLE 3 Risk factors of SRBD in patients with MSA.

	OR (95%CI)		
	Model 1	Model 2	Model 3
UMSARS	1.01 (0.97–1.06)*	1.02 (0.97–1.07)*	1.02 (0.97–1.08)*
NMSS	1.00 (0.98–1.02)*	1.00 (0.97–1.02)*	1.00 (0.97–1.03)*
HAMA	1.02 (0.95–1.10)*	1.03 (0.95–1.11)*	1.04 (0.95–1.13)*
HAMD	1.05 (0.97–1.13)*	1.05 (0.95–1.14)*	1.05 (0.96–1.15)*
MMSE	1.09 (0.95–1.26)*	1.10 (0.95–1.28)*	1.10 (0.93–1.29)*
PSQI	0.94 (0.82–1.08)*	0.94 (0.82–1.07)*	0.96 (0.83–1.12)*
FSS	0.94 (0.92–1.01)*	0.97 (0.92–1.02)*	0.96 (0.91–1.01)*

CI, confidence interval; FSS, Fatigue Severity Scale; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; MMSE, Mini-mental State Examination; NMSS, Non-Motor Symptoms Scale. Model 1, Crude model; Model 2, Adjusted for age, sex; Model 3, Adjusted for age, sex, disease duration, smoking, alcohol consumption, and MSA sub-type. * $p > 0.05$.

Prevalence of SRBD

As shown in Table 4 and Figure 2, including the results of the present study, the summary prevalence of SRBD in MSA was 60.5% (95% CI, 43.2–76.5%) in a pooled sample of 295 subjects. This study showed high heterogeneity ($I^2 = 88.1\%$). Sensitivity analysis showed unchanged results (Supplementary Figure 1.4). There was no evidence of publication bias as Begg’s and Egger’s test was not significant (Supplementary Figures 1.1.A,B).

As shown in Figure 3, the summary prevalence of SRBD of MSA in Asia was 79.2% (Figure 3A, 95% CI, 54.7–96.3%), which was higher than that in Europe (Figure 3B, 41.6, 95% CI, 32–51.5%). This study revealed significant heterogeneity in the prevalence of SRBD in patients with MSA in Asia ($I^2 = 90.6\%$), while showing homogeneity in Europe ($I^2 = 19.2\%$). Sensitivity analysis confirmed consistent findings (Supplementary Figure 1.5). There was no evidence of publication bias as Begg’s and Egger’s test was not significant (Supplementary Figures 1.2.A,B, 1.3.A,B).

Discussion

The study results revealed that 78.8% of MSA patients were diagnosed with SRBD (AHI > 5), consistent with findings from previous studies (ranging from 24.9 to 100%) (5–14). Gender prevalence did not show a significant difference, aligning with previous research (23). In terms of SRBD severity, 36.5% were classified as mild, 28.8% as moderate, and 34.6% as severe, with a slightly lower proportion of moderate cases compared to previous studies (23). A meta-analysis of previous studies indicated an overall SRBD prevalence of 60.4% in MSA patients (Table 4; Figure 2), differing from the present study’s 78.8%. Further analysis by region showed a prevalence of 79.2% in Asian MSA patients, matching the current study’s findings. In contrast, European MSA patients had a significantly lower prevalence of 41.6% (Figure 2). However, previous studies have shown that sensitivity analysis revealed a comparable

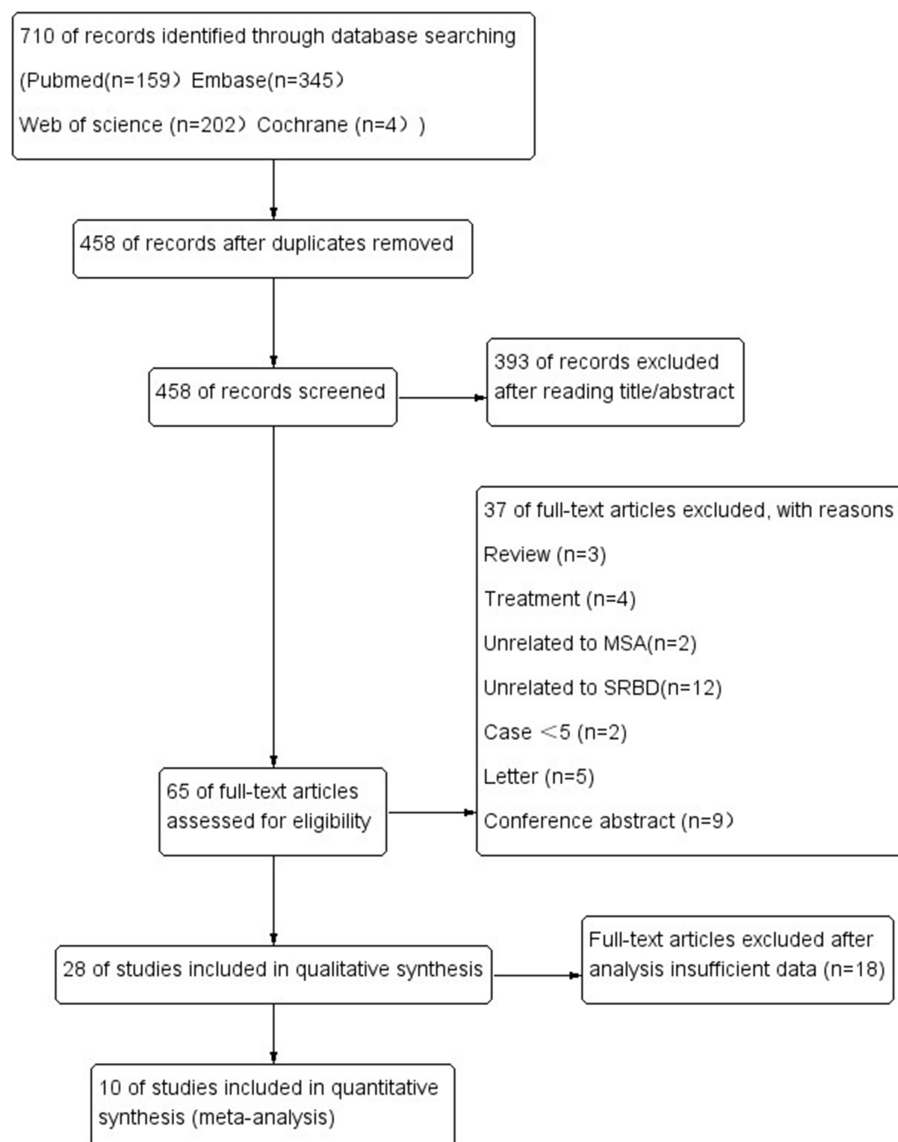


FIGURE 1
Flow diagram of systematic literature searching.

pooled prevalence of SRBD ($AHI > 5$) in Western and Asian populations (24). Therefore, we hypothesized that the variation in SRBD prevalence between MSA patients in Asia and Europe may be attributed to differing impacts of the disease on the respiratory system in different ethnic groups. Further multicenter studies encompassing diverse regions and ethnicities are needed to validate these findings.

In this study, we compared the subjective rating scale scores of motor and non-motor symptoms in MSA patients with and without SRBD. The results indicated no significant differences between the two groups in terms of age, sex, disease onset, disease duration, severity of motor symptoms (UMSARS I, II, IV), severity of non-motor symptoms (NMSS), anxiety and depression levels (HAMA, HAMD), daytime sleepiness (ESS), fatigue (FSS), cognitive functioning (MMSE), and sleep quality (PSQI). These findings suggest that SRBD is not linked to the severity of motor and non-motor symptoms, including cognition, daytime sleepiness, fatigue, and sleep quality in

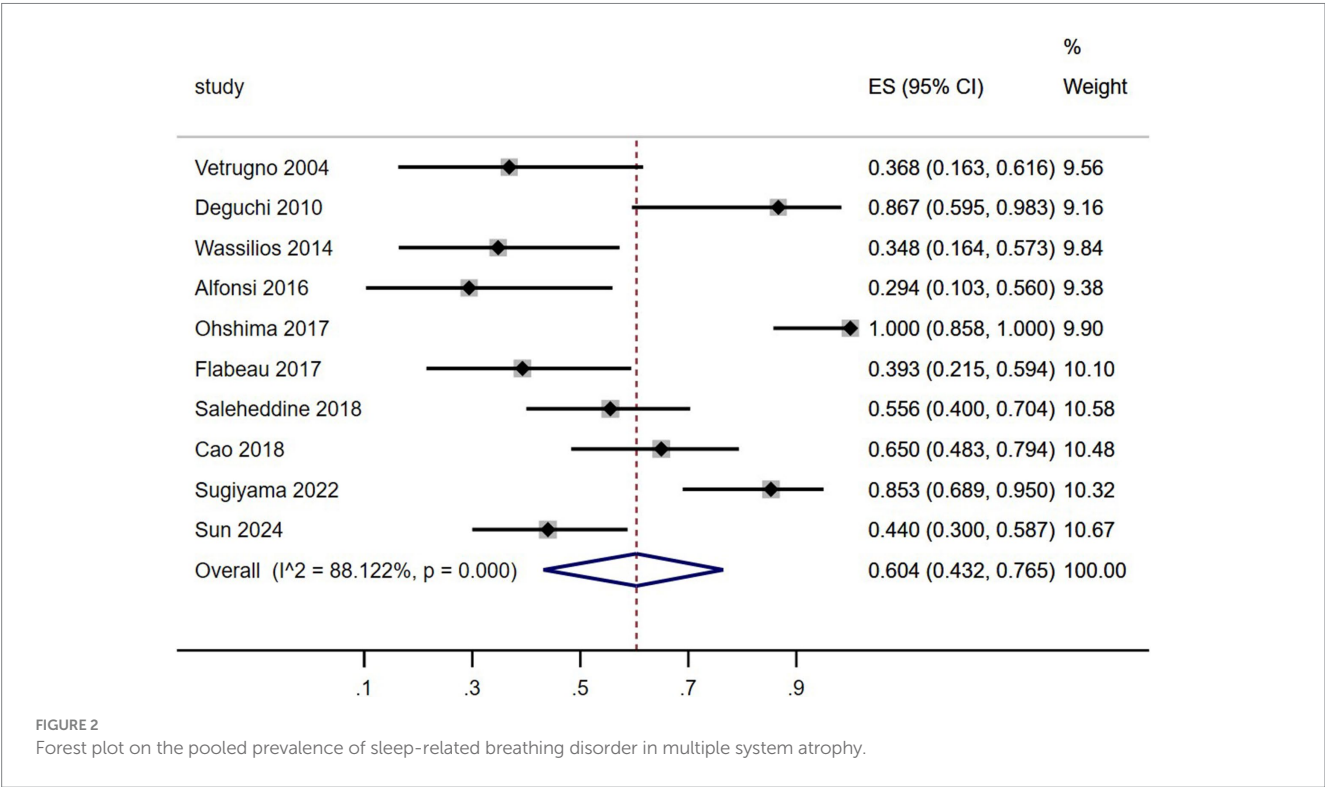
MSA patients. However, previous studies have reported conflicting results, showing that MSA patients with SRBD had higher UMSARS scores and more severe depressive symptoms compared to those without SRBD (9). This discrepancy could be attributed to the limited number of patients ($n = 40$) in the previous study (9), highlighting the need for larger multicenter studies to confirm our conclusions.

In patients with MSA, SRBD encompass obstructive sleep apnea (OSA) and central sleep apnea (CSA). This study revealed that MSA patients with SRBD had a higher frequency and index of obstructive apnea during sleep compared to central apnea. Conversely, MSA patients without SRBD showed similar frequencies and indices of obstructive and central apnea during sleep, aligning with findings from a previous study (9). Furthermore, MSA patients with SRBD exhibited a higher index of obstructive apnea during sleep than those without SRBD, while the index of central apnea did not significantly differ between MSA patients with or without SRBD, consistent with previous research (9). Previous research has linked OSA to abnormal

TABLE 4 Characteristics of studies included in the meta-analyses.

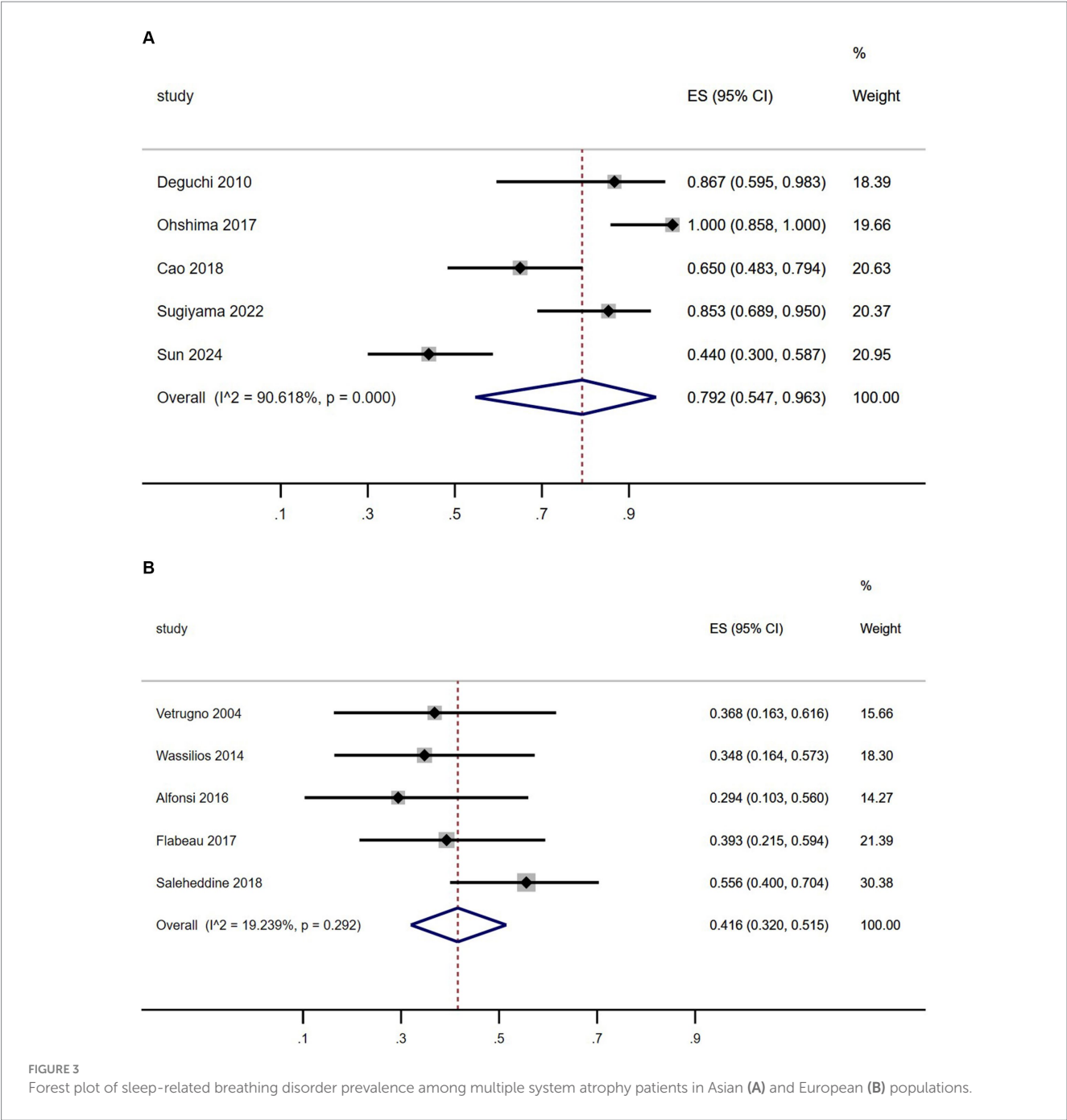
References	First author	Year	Country	Sample size	Diagnostic SRBD method	Proportion of SRBD (%)	AHRQ/ NOS score
(14)	Vetrugno	2004	Italy	19	PSG	37	7
(13)	Deguchi	2010	Japan	15	PSG	86.7	6
(5)	Wassilios	2014	France	23	PSG	34.8	6
(12)	Alfonsi	2016	Italy	17	PSG	29.4	7
(10)	Ohshima	2017	Japan	24	PSG	100	6
(11)	Flabeau	2017	France	28	PSG	39.3	7
(8)	Saleheddine	2018	France	45	PSG	56	7*
(9)	Cao	2018	China	40	PSG	65	7*
(7)	Sugiyama	2022	Japan	34	PSG	85	6*
(6)	Sun	2024	China	50	PSG	44	7
				295	PSG	60.4	

AHRQ, The Agency of Healthcare Research and Quality guideline; PSG, Polysomnography; SRBD, Sleep-related breathing disorder; MSA, Multiple system atrophy; NOS, Newcastle-Ottawa Scale. Details of the Literature Quality Assessment scoring are shown in [Supplementary Tables 1, 2](#). *Evaluating cross-sectional studies quality using NOS.



upper airway anatomy, compromised stability of ventilatory control, and dysfunction in upper airway muscles and their neuromodulation (25). These underlying mechanisms result in hypoventilation during sleep in affected individuals. Our study revealed that MSA patients with SRBD exhibited a higher hypopnea index and a greater percentage of snoring during sleep compared to MSA patients without SRBD. Central apnea in MSA may be linked to the loss of neuronal cells in specific respiratory rhythm-controlling areas of the brain (26). Therefore, SRBD in MSA patients is likely due to

obstructive apnea from abnormal upper airway caused by the disease itself, rather than central apnea from central nervous system atrophy. Our study found no significant differences in total sleep time, sleep efficiency, sleep structure, or subjective sleep quality between MSA patients with and without SRBD, consistent with previous research (9). However, patients with MSA and SRBD exhibited lower mean oxygen saturation and higher oxygen desaturation index during sleep compared to those without SRBD. Previous studies have also indicated a higher prevalence of excessive daytime sleepiness (EDS)



in MSA patients with SRBD (9). This suggests that SRBD may contribute to the development of EDS in these patients. By synthesizing our findings with existing literature, we propose that SRBD does not impact sleep quality or architecture in MSA patients, and that the increased EDS in MSA patients with SRBD may be attributed to the hypoxic nature of SRBD during sleep.

The study's strengths included a larger sample size, low dropout rate, and comprehensive clinical and PSG variables. However, several limitations should be acknowledged. Firstly, the average age of the participants was 60 years, suggesting a potential risk of selection bias. Secondly, neurodegenerative disease diagnosis relied on clinical assessment, potentially leading to diagnostic accuracy

issues. Thirdly, all patients had to meet the diagnostic criteria for probable MSA, introducing a selection bias towards more severe cases. Fourthly, non-motor symptoms were mainly assessed through questionnaires, potentially affecting diagnostic precision. Fifthly, the study was conducted at a single center, highlighting the need for multicenter studies involving diverse populations to determine SRBD prevalence in MSA patients. Sixthly, both our study and existing literature on SRBD effects in MSA patients have primarily originated from Asia, with a lack of studies from Europe and the United States. This geographical bias raises questions about potential ethnic differences in SRBD effects on MSA. Additionally, the criteria used to diagnose probable MSA are those published in

2008, not the most recent criteria published by the Movement Disorder Society in 2022.

Conclusion

The study found a prevalence of 78.8% of SRBD in MSA patients, with a notably higher prevalence in Asia compared to Europe. The majority of SRBD cases in MSA were attributed to obstructive apnea. Furthermore, the presence of SRBD did not show a significant impact on the motor and non-motor symptoms of MSA 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 author.

Ethics statement

The studies involving humans were approved by Biomedical Ethics Review Committee, West China Hospital, Sichuan University, China. The studies were conducted in accordance with the local legislation and institutional requirements. All patients provided written consent.

Author contributions

HW: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. TZ: Formal analysis, Writing – original draft. WF: Writing – review & editing. YX: Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2024.1440932/full#supplementary-material>

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Beyond sleep duration: protocol for a systematic review of multidimensional sleep health in relation to cardiovascular disease and mortality

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Adequate sleep duration has recently been recognized as a major determinant of cardiovascular health by the American Heart Association. This is a significant step toward recognizing sleep as a major lifestyle factor and pillar of health, along with physical activity and nutrition. However, healthy sleep is not only a matter of duration. Other dimensions, such as timing, regularity, efficiency, satisfaction with sleep, and daytime alertness are also deemed important to consider. We have designed a systematic review protocol according to the PRISMA-P guidelines with the objective of determining which sleep dimensions are predictors of all-cause mortality and major adverse cardiovascular events (MACE; cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina requiring hospitalization), and whether or not the use of multiple dimensions of sleep yields superior predictive value to the use of sleep duration alone in predicting the above-mentioned outcomes. We will implement a systematic search strategy in 10 databases with independent manual screening by two reviewers. The aim is to comprehensively identify longitudinal studies which have examined the relationship between sleep duration and at least one other dimension of sleep and mortality or MACE. Meta-analysis will be performed after data extraction to address these objectives quantitatively. We anticipate that several sleep dimensions beyond sleep duration have been studied in relationship to all-cause mortality and MACE, and that a combination of multiple sleep dimensions can better predict these outcomes than sleep duration alone. Such findings would lay important groundwork to establish multidimensional sleep health as a major determinant of cardiovascular health.

KEYWORDS

circadian, lifestyle, longitudinal study, MACE, personalized medicine, preventive medicine, risk factor, sleep disorder

Introduction

Cardiovascular disease (CVD), especially major adverse cardiovascular events (MACE), which include cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina requiring hospitalization (Bosco et al., 2021), is a leading cause of morbidity and mortality worldwide, with 523 million cases, and nearly 19 million deaths in 2019 (Roth et al., 2020). Primary prevention, with a focus on promoting health throughout the life course before manifest disease is a key

strategy to combat the burden of CVD. In 2010, the American Heart Association (AHA) introduced a concept of “Cardiovascular Health” (CVH), which encompassed seven interrelated and modifiable health factors and behaviors, coined “Life’s Simple Seven” (Lloyd-Jones et al., 2010). These were three lifestyle factors: diet, physical activity, and nicotine exposure; and four health factors: blood pressure, blood lipids, body weight, and blood glucose, which can be modified by lifestyle and targeted therapy. High CVH has been associated with lowered risk for not only CVD, but also cancer, end-stage renal disease and dementia, as well as many other benefits such as improved cognitive function and quality of life (Rasmussen-Torvik et al., 2013; Han et al., 2016; Virani et al., 2021).

Sleep was not included in the initial “Life’s Simple Seven”, despite its influence on CVH as well as general health and wellbeing. The AHA updated their concept of CVH in 2022 to include sleep duration as the eighth factor of CVH, now termed “Life’s Essential Eight” (Lloyd-Jones et al., 2022). Sleep duration is indeed a major health factor, demonstrated by evidence that both short and long sleep duration is associated with increased cardiovascular events and all-cause mortality (Wingard and Berkman, 1983; Yin et al., 2017). However, it is far from being the only sleep-related factor that is relevant to health.

Sleep is a physiological and behavioral state characterized by a lack of consciousness and voluntary movement and considered a period of rest and recovery in which humans spend about one third of their lives (Aminoff et al., 2011). It is a physiologically complex state that is essential for wellbeing, health, and even survival, as can be demonstrated by the ultimately lethal effects of sleep deprivation (Everson et al., 1989). Although yet to be fully clarified, sleep is known to be involved in childhood development (Roffwarg et al., 1966; Mirmiran et al., 1983; Zielinski et al., 2016), energy conservation (Benington and Heller, 1995; Scharf et al., 2008; Zielinski et al., 2016), immune modulation (Krueger, 2008; Zielinski and Krueger, 2011; Zielinski et al., 2016), cognitive and physical performance (Walker, 2008; Killgore, 2010; Zielinski et al., 2016; Watson, 2017; Cunha et al., 2023), psychological wellbeing (Scott et al., 2021), and clearance of brain waste (Xie et al., 2013; Zielinski et al., 2016).

There are numerous ways to characterize and evaluate sleep, and many factors are involved in the construct of “healthy sleep”. Polysomnography, for instance, can be used to study sleep architecture and duration, as well as to identify sleep-related disorders such as sleep-disordered breathing, periodic limb movements, and narcolepsy. Actigraphy and sleep diaries used over an extended period of time can be used to identify rest-activity patterns including sleep duration, timing, and regularity as well as environmental factors. Questionnaires and interviews can be used to determine how individuals perceive their sleep, as well as to evaluate daytime symptoms such as fatigue and sleepiness. Neuroimaging with positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) have been used in research to study metabolism, cerebral blood flow, waste build-up, and neurotransmission in sleep (Dang-Vu et al., 2010; Pak et al., 2020). Many of these individual sleep factors, including perceived quality, timing, latency, duration, daytime alertness, napping, and

sleep disorders have been associated with mortality, morbidity and wellbeing, suggesting that it is relevant to consider multiple factors in the assessment of sleep as a component of CVH and a major pillar of healthy lifestyle (Kojima et al., 2000; Newman et al., 2000; Akerstedt et al., 2004; Jennings et al., 2007; Young et al., 2008; Gottlieb et al., 2010; Laugsand et al., 2011; Ohayon et al., 2014; Cubo et al., 2019; Zhang et al., 2019).

There currently exist several tools which measure sleep health as a complex construct, taking multiple dimensions into account. Buysse’s “RU-SATED” scale, for example, rates sleep regularity, sleep satisfaction, daytime alertness, sleep timing, sleep efficiency, and sleep duration to evaluate sleep health (Buysse, 2014). A “healthy sleep scale” (HSS), which combines sleep duration, chronotype, insomnia, snoring, and excessive daytime sleepiness to evaluate sleep health has been developed in the UK biobank cohort, and shown to predict CVD in several studies (Fan et al., 2020; Wang et al., 2022; Nambiema et al., 2023). The National Sleep Foundation has developed a “Sleep Health Index” (SHI) which uses 14 questions to evaluate sleep duration, sleep disorders, and sleep quality (Knutson et al., 2017). “Sleep quality” is a general term which can be considered a composite of several sleep-related factors; in the SHI this refers to feelings of being well-rested, trouble falling asleep and staying asleep, negative impact due to lack of sleep, and unintentional dozing. The “Pittsburgh Sleep Quality Index” (PSQI), also developed by Buysse and colleagues, is one of the most commonly used tools to assess “sleep quality”. The PSQI consists of nine questions evaluating bedtime, time to fall asleep, time one gets out of bed, sleep duration and time in bed, trouble sleeping due to several factors, use of sleep medications, trouble staying awake, enthusiasm to get things done, and a global rating of sleep quality (Buysse et al., 1989). As such, it can also be considered a tool to measure multidimensional sleep health. Yin et al.’s “Sleep Quality Scale” (Yi et al., 2006), Partinen and Gislason’s “Basic Nordic Sleep Questionnaire” (Partinen and Gislason, 1995) are other such questionnaires. Poor sleep health as evaluated by tools measuring multidimensional sleep have been associated with stress (Benham, 2019), CVD (Brindle et al., 2019; Fan et al., 2020; Lee et al., 2022; Wang et al., 2022; Nambiema et al., 2023; Tian et al., 2023), and mortality (Lee et al., 2023).

Current evidence thus suggests that multiple dimensions of sleep health should be considered to achieve optimal health and wellbeing, rather than the AHAs current recommendation of sleep duration alone (Lloyd-Jones et al., 2022). Synthesis of evidence, however, is currently lacking. In this systematic review, we will summarize longitudinal observational studies which have examined the relationship between all-cause mortality and/or MACE and sleep duration in addition to at least one other sleep health factor. Subsequently, we plan to describe which sleep health factors have been studied and associated with the given endpoints. A meta-analysis will be conducted to quantitatively synthesize comparable numerical data (Lisik et al., 2023), in order to determine which factors are most influential in predicting all-cause mortality and/or MACE, if a composite of multiple factors improves predictive capacity of the endpoints, and how many factors should ideally be considered.

Methods

Reporting and protocol registration

This protocol was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (Shamseer et al., 2015). It has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) with the title, *Beyond sleep duration: a systematic review of multidimensional sleep health in relation to cardiovascular disease and mortality* and registration number CRD42024503231. The final report will be written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021), and any deviations from the original protocol will be reported in the final manuscript.

Inclusion/exclusion criteria and outcome measures

This review will include observational longitudinal follow-up studies of adults ≥ 18 years at the start of follow-up. The studies must include an assessment of the participants' sleep duration as well as at least one other sleep dimension (such as sleep timing, regularity, efficiency, daytime alertness and napping, circadian factors, and sleep disorders), as well as MACE and/or death as an endpoint. The outcome measure in this systematic review will be MACE, which in this context will refer to cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina requiring hospitalization, as well as all-cause mortality (Bosco et al., 2021). There will be no exclusion due to language. Google Translate will be used to translate all non-English language reports (Jackson et al., 2019).

Research questions

We aim to answer the following questions:

1. Which sleep health dimensions have been combined with sleep duration to assess MACE and all-cause mortality?
2. Does combining multiple dimensions of sleep provide an added value for predicting MACE and all-cause mortality?
 - a. Which sleep dimensions are predictors of MACE and all-cause mortality?
 - b. Does combination of a greater number of sleep dimensions result in better prediction of the endpoints?

Search strategy

Bibliographic database searches were performed on January 22nd 2024 in 10 databases (CAB Direct, CINAHL, Embase, Google Scholar, PsycINFO, PubMed, Scopus, Web of Science, WHO Global

Index Medicus, and WorldCat Dissertations and Theses), with search queries tailored to each database due to differences in syntax and availability of controlled vocabulary.

Table 1 illustrates the search strategy for PubMed, while search queries for the other databases can be found in the [Supplementary material](#).

The search terms were based on domain knowledge and were refined/extended with pilot searches. Where possible, relevant controlled vocabulary terms were included. Spelling and tense variations were accounted for. This general search strategy was used for nine databases, while it was simplified for Google Scholar due to substantial search limitations in this database.

De-duplication and screening

De-duplication will be conducted in Endnote 21 (Clarivate Analytics, 2023), as previously described by Bramer et al. (2016). Thereafter, an initial screening will be performed based on title, abstract, and keywords. Records which are clearly eligible or for which there is doubt about eligibility will pass to the second step. In the second step, the full text of each record will be retrieved and assessed for eligibility. Both steps of the screening will be performed independently by two reviewers (MKF and DZ), blinded to each other's decisions during each step. Decisions will be unblinded and compared for differences after each step. Disagreements will be resolved through discussion and if needed through arbitration by a third reviewer (DL). Rayyan (rayyan.ai) will be used for screening and documentation of decisions. The main reason for exclusion at the second screening step will be presented in a [Supplementary Table](#) in the final manuscript.

Data extraction

Data to be extracted from the included articles are: surname of first author, study design, country, number of subjects and subject characteristics (age, sex, and comorbidities), sleep duration, other sleep-related parameters, outcome definition, outcome data (point estimates and corresponding 95%CI), and length of follow-up. A standardized Microsoft Excel (Microsoft Corp., 2024) form will be used to extract the data, and corresponding authors will be contacted in order to obtain any missing data. Two reviewers (MKF and DZ) will independently perform all data extraction blinded to the other reviewer's work. Differences will be compared and discussed after completion with arbitration by a third reviewer (DL) where necessary.

Assessment of quality and risk of bias

The Newcastle-Ottawa Quality Rating Scale (NOS) will be used to assess the quality and risk of bias of included articles (Wells et al., 2021). NOS assesses selection of study participants, comparability of cohorts, and the outcome, and is a commonly and easily used quality assessment tool for cohort studies (Deeks et al., 2003; Higgins, 2008; Ma et al., 2020). Two reviewers (MKF and DZ)

TABLE 1 Search strategy for PubMed.

#	Block name	Search terms
1	Sleep duration	(("Sleep Duration"[mh] OR "Sleep Deprivation"[mh] OR "sleep deprivation"[tiab] OR "insufficient sleep"[tiab]) OR ("quantity sleep"[tiab:~2] OR "quantities sleep"[tiab:~2] OR "amount sleep"[tiab:~2] OR "duration sleep"[tiab:~2] OR "length sleep"[tiab:~2] OR "time sleep"[tiab:~2] OR "period sleep"[tiab:~2] OR "hours sleep"[tiab:~2] OR "minutes sleep"[tiab:~2] OR "span sleep"[tiab:~2]) OR ("duration asleep"[tiab:~2] OR "length asleep"[tiab:~2] OR "time asleep"[tiab:~2] OR "period asleep"[tiab:~2] OR "hours asleep"[tiab:~2] OR "minutes asleep"[tiab:~2]) OR ("quantity sleeping"[tiab:~2] OR "quantities sleeping"[tiab:~2] OR "amount sleeping"[tiab:~2] OR "duration sleeping"[tiab:~2] OR "length sleeping"[tiab:~2] OR "time sleeping"[tiab:~2] OR "period sleeping"[tiab:~2] OR "hours sleeping"[tiab:~2] OR "minutes sleeping"[tiab:~2] OR "span sleeping"[tiab:~2]) OR ("short sleep"[tiab:~2] OR "long sleep"[tiab:~2] OR "extended sleep"[tiab:~2]) OR ("short sleeper"[tiab:~2] OR "long sleeper"[tiab:~2] OR "extended sleeper"[tiab:~2]) OR ("short sleepers"[tiab:~2] OR "long sleepers"[tiab:~2] OR "extended sleepers"[tiab:~2]))
2	Sleep components	(("Sleep"[mh] OR "sleep*" [tiab] OR "wake*" [tiab] OR "waking" [tiab] OR "awake" [tiab]) OR ("Polysomnography"[mh] OR "Actigraphy"[mh] OR "actigraph*" [tiab] OR "actimetr*" [tiab] OR "acceleromet*" [tiab] OR "polysomnograph*" [tiab] OR "EEG" [tiab] OR "electroencephalogram" [tiab] OR "MSLT" [tiab] OR "MWT" [tiab] OR "fitbit" [tiab] OR "dreem" [tiab] OR "Oura ring" [tiab] OR "Gen3" [tiab] OR "Fitbit" [tiab] OR "Mi band" [tiab]) OR ("Circadian Clocks"[mh] OR "Circadian Rhythm"[mh] OR "circadian" [tiab] OR "chronotype*" [tiab] OR "chronotherap*" [tiab] OR "eveningness" [tiab] OR "morningness" [tiab] OR "evening type*" [tiab] OR "morning type*" [tiab] OR "bedtime*" [tiab] OR "time to bed" [tiab] OR "time in bed" [tiab] OR "shuteye" [tiab] OR "shut-eye" [tiab] OR "lights off" [tiab] OR "lights on" [tiab] OR "Shift Work Schedule" [mh] OR "shift work*" [tiab] OR "shiftwork*" [tiab] OR "shift schedule" [tiab:~2] OR "shift schedules" [tiab:~2] OR "shift scheduling" [tiab:~2] OR "shifting schedule" [tiab:~2] OR "shifting schedules" [tiab:~2] OR "shifting scheduling" [tiab:~2] OR "working hours" [tiab:~2] OR "work hours" [tiab:~2] OR "work schedule" [tiab:~2] OR "work schedules" [tiab:~2] OR "work scheduling" [tiab:~2] OR "working schedule" [tiab:~2] OR "working schedules" [tiab:~2] OR "jetlag" [tiab] OR "jet-lag" [tiab] OR "light*" [tiab] OR "nois*" [tiab] OR "WASO" [tiab] OR "TIB" [tiab] OR "SE" [tiab]) OR ("Sleepiness" [mh] OR "fatigue*" [tiab] OR "tired*" [tiab] OR "somnolence" [tiab] OR "nap" [tiab] OR "napping" [tiab] OR "alert*" [tiab] OR "ESS" [tiab] OR "KSS" [tiab] OR "EDS" [tiab] OR "day" [tiab] OR "daytime" [tiab] OR "night*" [tiab] OR "drows*" [tiab] OR "siesta" [tiab]) OR ("Sleep Wake Disorders" [mh] OR "insomnia" [tiab] OR "restless legs syndrome" [tiab] OR "restless leg syndrome" [tiab] OR "Willis-Ekbom" [tiab] OR "Wittmaack-Ekbom" [tiab] OR "RLS" [tiab] OR "periodic leg movement*" [tiab] OR "periodic limb movement*" [tiab] OR "Snoring" [mh] OR "snoring" [tiab] OR "snore" [tiab] OR "hypersomnia" [tiab] OR "dysomnia" [tiab] OR "parasomnia" [tiab] OR "narcolepsy" [tiab] OR "night terror" [tiab] OR "nightmare" [tiab] OR "Apnea" [mh] OR "apnea" [tiab] OR "apnoea" [tiab] OR "hypopnea" [tiab] OR "hypopnea" [tiab] OR "OSA" [tiab] OR "OSAHS" [tiab] OR "AHI" [tiab] OR "CSA" [tiab] OR "UARS" [tiab] OR "upper airway resistance syndrome" [tiab]))
3	Multidimensionality	(("Sleep" [mh] OR "sleep*" [tiab]) AND (("RU-SATED" [tiab] OR "RU_SATED" [tiab] OR "PSQI" [tiab]) OR ("score*" [tiab] OR "index" [tiab] OR "indices" [tiab] OR "multidimensional" [tiab] OR "multi-dimensional" [tiab] OR "multi*" [tiab] OR "dimension*" [tiab] OR "component*" [tiab] OR "parameter*" [tiab] OR "metric*" [tiab] OR "composite" [tiab] OR "combination*" [tiab])))
4	Multidimensional sleep health	(#1 AND (#2 OR #3))
5	All-cause outcomes	("Mortality" [mh] OR "mortality" [tiab] OR "death*" [tiab] OR "lethal" [tiab])
6	Specific outcomes of interest	(("Heart Arrest" [mh] OR "SCD" [tiab] OR "cardiopulmonary arrest" [tiab] OR "cardiac arrest" [tiab] OR "heart arrest" [tiab] OR "asystole" [tiab] OR "cardiac event*" [tiab] OR "Myocardial Infarction" [mh] OR "myocardial infarct*" [tiab] OR "Myocardial Ischemia" [mh] OR "myocardial ischemia" [tiab] OR "unstable angina" [tiab] OR "acute coronary syndrome" [tiab] OR "ACS" [tiab] OR "AMI" [tiab] OR "MI" [tiab] OR "Heart Failure" [mh] OR "heart failure" [tiab] OR "cardiac failure" [tiab] OR "myocardial failure" [tiab] OR "heart decompensation" [tiab] OR "ventricular dysfunction" [tiab] OR "CHF" [tiab]) OR ("Stroke" [mh] OR "stroke" [tiab] OR "cerebral infarct*" [tiab] OR "cerebrovascular accident*" [tiab] OR "CVA" [tiab] OR "brain vascular accident*" [tiab] OR "cerebrovascular apoplexy" [tiab] OR "brain ischemia" [tiab] OR "intracranial hemorrhage" [tiab] OR "intracranial hemorrhage" [tiab] OR "cerebral hemorrhage" [tiab] OR "cerebral hemorrhage" [tiab]) OR ("MACE" [tiab] OR "major adverse cardiovascular event*" [tiab] OR "infarct*" [tiab]))

(Continued)

TABLE 1 (Continued)

#	Block name	Search terms
7	Outcomes	(#5 OR #6)
8	Full query	#4 AND #7

mh, search to be made by Medical Subject Headings (MeSH), a controlled vocabulary; tiab, search to be made in title and abstract fields [search terms followed by “:~2” in the field setting denote search terms with a proximity parameter (in which the two words are allowed to occur in any order with up to two words in-between)]. **Clarifications.** (1) **bold font-weight** visually indicates blocks of search terms or parentheses encapsulating these; (2) **green color** denotes blocks of search terms; (3) **dark blue color** denotes search terms with the [tiab] field setting without the proximity parameter; (4) **light blue color** denotes search terms with the [tiab] field setting with the proximity parameter; (5) **purple color** denotes controlled vocabulary search terms.

will independently assess the articles and any disagreement will be resolved by consensus. If needed, a third reviewer (DL) will arbitrate the final rating.

Data synthesis and statistical analysis

Extracted data items will be summarized in a table of characteristics. In addition, relevant aspects will be synthesized narratively. Comparable data (defined here as results from regression analysis with sufficient similarity in study participants, exposure, and outcome, as assessed by MKF and DZ) will be quantitatively synthesized using random-effects meta-analysis with robust variance estimation (RVE) (Hedges et al., 2010). The random-effects model has been chosen as it is expected that the included studies will demonstrate substantial heterogeneity, given different cohorts, exposure definitions/assessment methods, outcome definitions/assessment methods, as well as statistical analysis approaches. The RVE model will be utilized as it relaxes a number of assumptions of conventional methods, such as normal distribution of effect sizes and their estimates. Furthermore, RVE can accommodate non-independent effect sizes (Pustejovsky and Tipton, 2022). As it is expected that some included studies may investigate multiple combinations of sleep health dimensions (and reuse controls), RVE will enable the inclusion of all such effect sizes in more comprehensive meta-analyses. A further strength of RVE is that the precise dependency structure (or degree) does not need to be defined in the model. RVE will be implemented through the *robumeta* R package (Fisher et al., 2015).

A meta-analysis will be performed for each distinct exposure-outcome pair, for which there are at least two studies with comparable numerical data (Ahn and Kang, 2018). Meta-analyses will be performed to assess the predictive value on all-cause mortality and/or MACE of:

- 1) Specific sleep health dimensions (and combinations thereof).
- 2) Quantity of sleep health dimensions.

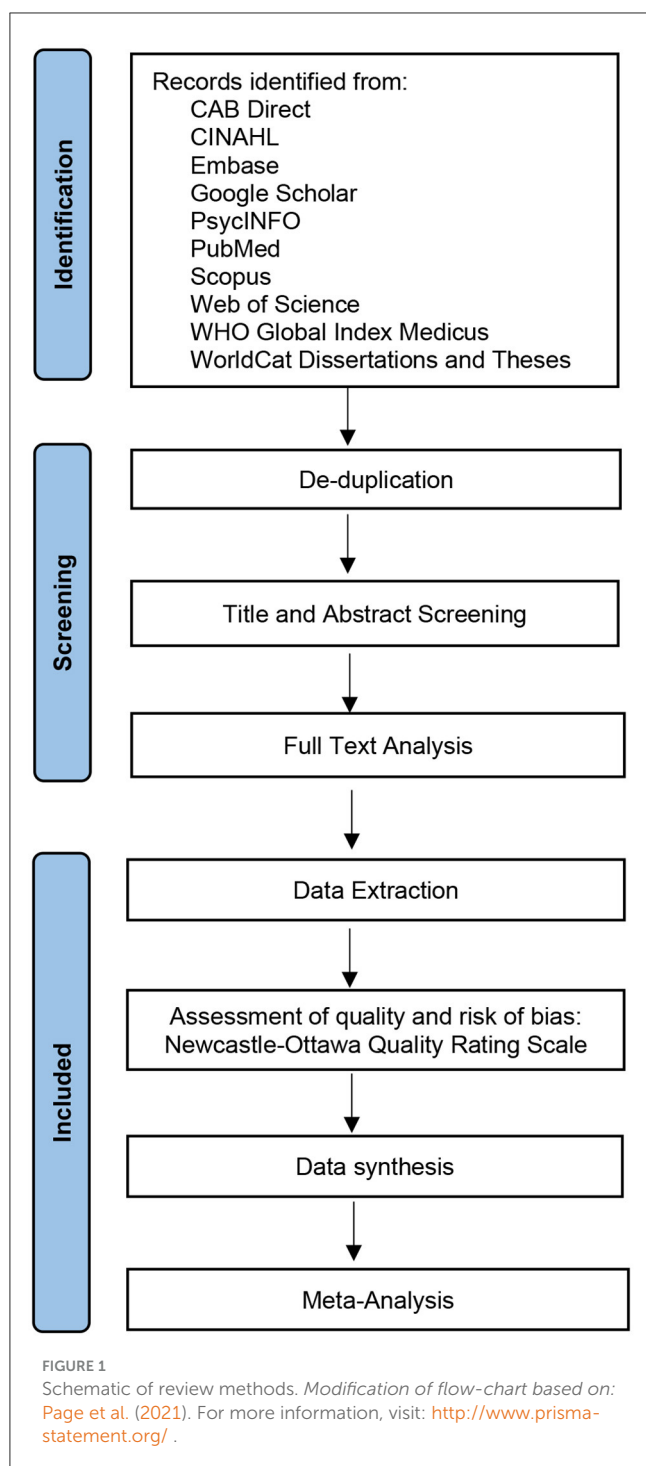
If data allows, meta-regression will be performed to control for relevant confounders such as sex, age, body mass index, hypertension and diabetes.

Depending on the study characteristics (particularly if potential dependency in effect sizes is primarily due to common features of the researchers or assessment tools, or of the subjects), the appropriate weighting model will be chosen (Pustejovsky and Tipton, 2022). All meta-analyses will be performed with small sample adjustment for both the residuals and the degrees of

freedom, as per the general recommendations and in particular given the expectation of relatively small numbers of studies in each meta-analysis (Tipton, 2015). A forest plot will be produced to visualize the results of each meta-analysis, using the *forestploter* R package (Dayimu, 2022). Heterogeneity will be assessed by the I-squared statistic (I^2 ; to quantify the proportion of variation between studies not due to random sampling error) (Higgins et al., 2003) and Tau-squared (τ^2 ; to determine the between-study variance of true effect) (Parr et al., 2019). In meta-analyses with Satterthwaite degrees of freedom (df_s) below 4, the threshold for significant p -value will be 0.01 instead of the default level of 0.05 to reduce the risk of type I error (Tanner-Smith et al., 2016). Publication bias will be assessed in exposure-outcome pairs with ≥ 10 studies (Dalton et al., 2016) through statistical tests (Begg and Mazumdar correlation test and Egger’s regression test, respectively, with p -value of 0.05 as the threshold for significance) and visual inspection of funnel plots. In case of suspected publication bias, we will estimate the number of effect sizes required to return symmetry using the trim-and-fill method. Assessment of publication bias will be undertaken using the *metafor* R package (Viechtbauer, n.d.). A sensitivity analysis excluding studies with a poor overall quality rating will be performed where at least two studies with comparable numerical data remain, to assess the influence of methodological rigor on the pooled results. Other secondary analyses which may be performed include subgroup analyses based on diagnosed sleep disorders, follow-up time, sex and age, if data allows as per above, to discern the stability of the association or potential cause(s) of heterogeneity. Analyses will be performed using the R statistical software (R Core Team, 2024). All data and code will be made available on Open Science Framework or as **Supplementary material**. The methods are outlined graphically in **Figure 1**, based on the PRISMA flow diagram layout (Page et al., 2021).

Discussion

Sleep, an essential and intricate component of human life, is undergoing a transformative reevaluation in the realm of medical science. Traditionally, sleep medicine has centered on diagnosing and treating specific sleep disorders. However, there is a discernible shift toward recognizing sleep health as a comprehensive construct, encompassing various dimensions that collectively influence overall wellbeing (Buysse, 2014). This systematic review aims to explore the intricate relationship between multiple dimensions of sleep and their correlation with mortality and MACE, marking a groundbreaking step in understanding the broader implications of sleep on CVH.

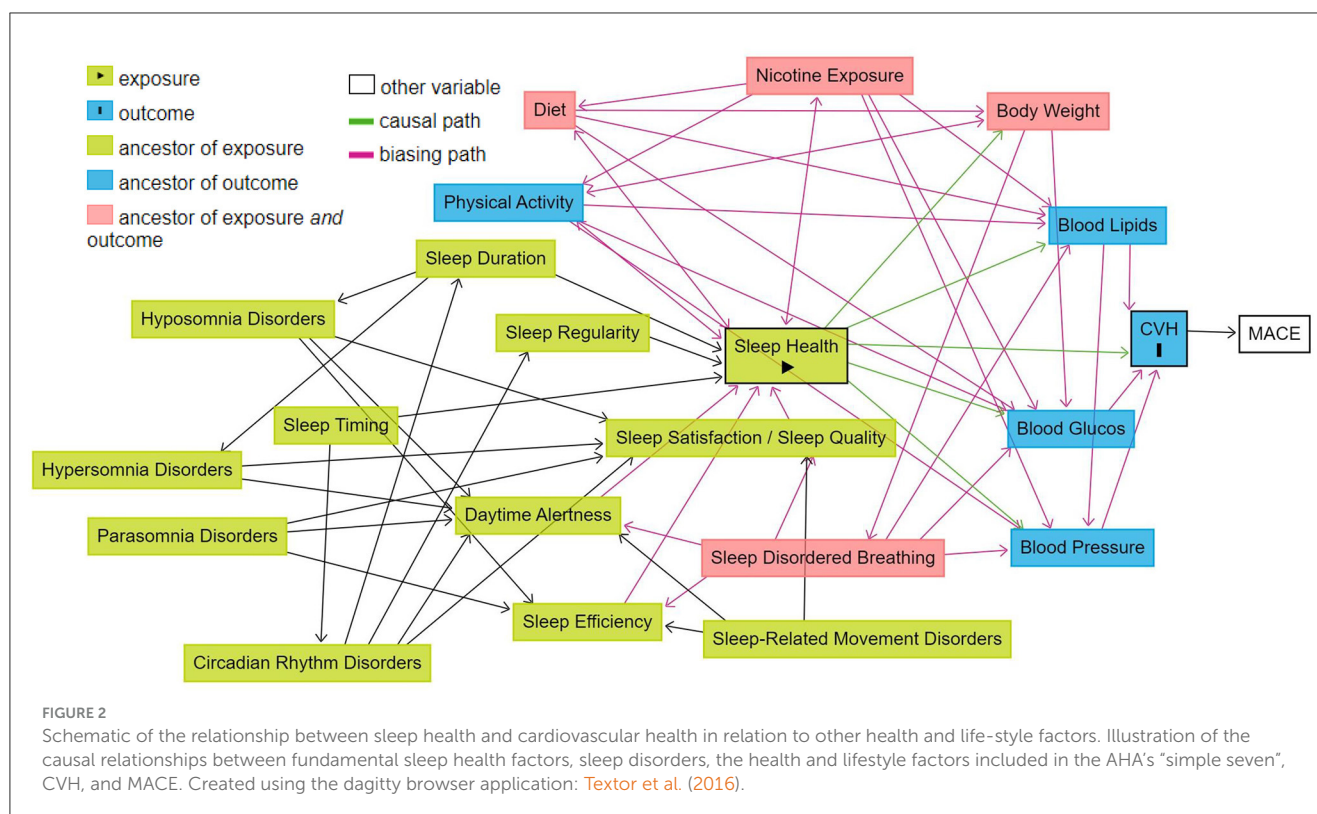


The contemporary societal landscape, characterized by rapid technological advancements and evolving work structures, poses unprecedented challenges to our sleep patterns. Factors such as rigid work schedules, constant exposure to information, and transmeridian travel have become intrinsic disruptors of sleep. Artificial lighting, a product of technological progress, has detached humans from their natural rhythm dictated by the sun, introducing disruptions across various facets of sleep (Zhong et al., 2022). The past decade, marked by a surge in technology, has

exacerbated this phenomenon by introducing devices that emit both light and distractions, further hindering the attainment of optimal sleep.

Temporal aspects of sleep have gained significant attention in recent research. Surprisingly, the timing of sleep initiation, with evidence suggesting that going to bed before 10 pm or after 11 pm is associated with poorer CVH than sleeping between 10 and 11 pm, irrespective of sleep duration, underscores the importance of circadian rhythms (Nikbakhtian et al., 2021). Even subjective factors like dissatisfaction with sleep (Del Brutto et al., 2024) and ease of falling asleep (Li et al., 2021) have shown associations with increased risk of mortality, emphasizing the need to delve beyond mere sleep duration. Recent findings highlight sleep regularity as a more accurate predictor of all-cause mortality than sleep duration alone (Cribb et al., 2023; Windred et al., 2024). This shift in focus toward regularity underscores the intricate interplay of sleep dimensions and their collective impact on health outcomes. Aspects such as consistency in sleep patterns, beyond the conventional consideration of sleep duration, are proving to be pivotal in understanding the complex relationship between sleep and mortality/MACE.

Health, be it sleep health, CVH, or overall general health is a construct that is difficult to define in a straight-forward manner. Rather it, is the result of the complex interplay of multiple social/behavioral, environmental, and biological factors (Grandner and Fernandez, 2021). The impact of lifestyle factors such as physical activity (You, 2024), nutrition (You et al., 2024b), and sleep (You et al., 2024a) on overall health is critical for a holistic understanding of sleep duration. Figure 2 portrays a schematic which illustrates the causal relationships between fundamental sleep health factors, sleep disorders, the health and lifestyle factors included in the AHA's "simple seven" (Lloyd-Jones et al., 2010), CVH, and MACE, created using the DAGitty browser application (Textor et al., 2016). The directed edges (denoting a causal relation between two factors with specified direction) in the schematic have strong support in the literature (Scheer et al., 2009; Calhoun and Harding, 2010; Chennaoui et al., 2015; Visseren et al., 2021; Russell et al., 2023). The schematic also makes apparent one of the principal challenges that accompany the study of something as complex as health; the determination of causation. The studies we will include are observational, thus will limit the ability to assess the extent to which the studied sleep health factors independently cause MACE or mortality, both due to expected limitations in data to perform robust analyses and due to unobserved confounders (as exemplified by the intermediate processes such as hypertension). Moreover, as can be seen in the schematic, sleep disordered breathing has a particular relationship with other factors of cardiovascular health that is not shared with other sleep disorders due to the non-sleep-mediated effects of intermittent hypoxia on the cardiovascular system (Cowie et al., 2021). Such a relationship can further complicate the interpretation of our results, warranting a deeper investigation of the mechanisms linking various sleep factors to MACE, which is beyond the scope of this review. If meta-regression can be performed, this will allow us to determine whether there are underlying cardiovascular risk factors which can also explain the relationship between sleep factors and MACE.



Despite the aforementioned challenges, in an era defined by technological advancements and diverse lifestyles, recognizing and addressing the multifaceted nature of sleep is not only pertinent but may also pave the way for innovative preventive strategies against the growing burden of CVD. Anticipating that various sleep dimensions are intertwined with sleep duration in influencing mortality and MACE, this systematic review intends to contribute to the burgeoning field of multidimensional sleep health. The hypothesis posits that incorporating multiple sleep dimensions in longitudinal studies will yield superior predictive accuracy compared to a singular focus on sleep duration. Should this hypothesis be validated, it could pave the way for a paradigm shift in conceptualizing sleep health as a major determinant of CVH. Recognizing the heterogeneity of contemporary society, the call for a broad perspective on multidimensional sleep health is imperative. Tailoring interventions to individual physiologies and lifestyles becomes crucial in optimizing overall health outcomes. Moreover, since many sleep dimensions, in addition to being modifiable, are easily detectable by self-observation or with the help of readily available tools such as sleep diaries and smartphone applications ([Fino and Mazzetti, 2019](#)) there is a large potential for developing preventative strategies against the burden of CVD. On the individual level, this may be achieved by lifestyle modification to improve sleep health as well as to fine-tune risk prediction to identify individuals in need of more intensive preventive care. Such a strategy would open avenues for personalized interventions that go beyond treating sleep disorders to proactively promoting CVH through holistic sleep management. On the societal level, a deeper understanding of the relationship between sleep health and CVH would be instrumental in guiding work and school policy

to optimize scheduling and environmental conditions. A synthesis of the existing evidence on the relationship between multiple sleep factors and hard cardiovascular endpoints will provide an important steppingstone for the development of ideal lifestyle-related health management strategies.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding author/s.

Author contributions

MK: Conceptualization, Funding acquisition, Methodology, Project administration, Writing – original draft, Writing – review & editing. DL: Conceptualization, Methodology, Writing – review & editing, Data curation. DZ: Conceptualization, Resources, Supervision, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/frsle.2024.1400562/full#supplementary-material>

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Causal effects of obstructive sleep apnea on chronic kidney disease and renal function: a bidirectional Mendelian randomization study

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Background: Observational studies have suggested an association between obstructive sleep apnea (OSA), chronic kidney disease (CKD), and renal function, and vice versa. However, the results from these studies are inconsistent. It remains unclear whether there are causal relationships and in which direction they might exist.

Methods: We used a two-sample Mendelian randomization (MR) method to investigate the bidirectional causal relation between OSA and 7 renal function phenotypes [creatinine-based estimated glomerular filtration rate (eGFR_{crea}), cystatin C-based estimated glomerular filtration rate (eGFR_{cys}), blood urea nitrogen (BUN), rapid progress to CKD, rapid decline of eGFR, urinary albumin to creatinine ratio (UACR) and CKD]. The genome-wide association study (GWAS) summary statistics of OSA were retrieved from FinnGen Consortium. The CKDGen consortium and UK Biobank provided GWAS summary data for renal function phenotypes. Participants in the GWAS were predominantly of European ancestry. Five MR methods, including inverse variance weighted (IVW), MR-Egger, simple mode, weighted median, and weighted mode were used to investigate the causal relationship. The IVW result was considered the primary outcome. Then, Cochran's Q test and MR-Egger were used to detect heterogeneity and pleiotropy. The leave-one-out analysis was used for testing the stability of MR results. RadialMR was used to identify outliers. Bonferroni correction was applied to test the strength of the causal relationships ($p < 3.571 \times 10^{-3}$).

Results: We failed to find any significant causal effect of OSA on renal function phenotypes. Conversely, when we examined the effects of renal function phenotypes on OSA, after removing outliers, we found a significant association between BUN and OSA using IVW method (OR: 2.079, 95% CI: 1.516–2.853; $p = 5.72 \times 10^{-6}$).

Conclusion: This MR study found no causal effect of OSA on renal function in Europeans. However, genetically predicted increased BUN is associated with OSA development. These findings indicate that the relationship between OSA and renal function remains elusive and requires further investigation.

KEYWORDS

obstructive sleep apnea, chronic kidney disease, renal function, Mendelian randomization, causal relationship

1 Introduction

Chronic kidney disease (CKD), distinguished by structural and functional impairments of the kidneys, is generally diagnosed when the Estimated Glomerular Filtration Rate (eGFR) drops below 60 mL/min per 1.73 m² or in instances where kidney damage persists for a minimum of 3 months (1). Being a significant global health issue, CKD affects an estimated 700 million individuals globally (2). It is projected that by 2040, CKD will ascend to become the fifth primary cause of death worldwide (2). There is currently no cure for CKD, and the primary emphasis in treatment and management revolves around modifying risk factors and controlling complications. As CKD progresses, it invariably results in a consistent decline in renal function, frequently necessitating renal replacement therapy for patients suffering from End-Stage Kidney Disease (ESKD) (3, 4). This situation imposes a substantial economic burden on both societal and familial fronts owing to medical expenditures (5). Therefore, there is an exigent requirement to discern treatable risk factors connected with the onset and advancement of CKD.

Obstructive Sleep Apnea (OSA), a condition with high prevalence, is experienced by an estimated 38% of the global adult population in its moderate-to-severe forms (6). OSA is marked by the repeated closure of the upper airway during sleep, consequentially causing sleep fragmentation and intermittent hypoxia (7). Numerous observational studies offer evidence supporting a bidirectional relationship between OSA and CKD (8, 9). OSA may heighten the risk of renal damage, CKD can reciprocally impose a heightened risk of OSA (10–17). Nevertheless, the results derived from observational studies have been inconsistent. For example, in individuals afflicted with Coronary Artery Disease, the severity of OSA was not independently associated with CKD (18). Another study illustrated that OSA alone does not constitute a risk factor for CKD. However, for patients presenting with Metabolic Syndrome, OSA served as an additional burden escalating the risk of CKD (19).

Traditional observational studies are limited in their ability to completely eliminate confounding bias or reverse causality (20). The assessment of causality between OSA and CKD based on the associations observed in observational studies is challenging. Randomized controlled trials are less susceptible to confounding; however, conducting such trials to evaluate the effects of potentially harmful exposures like OSA would be unethical or impractical. Elucidating the causality between OSA and CKD is crucial as it provides insights into the underlying biological mechanisms of the disease and aids in the development of therapeutic strategies for improving CKD prevention. The Mendelian Randomization (MR) design serves as a valuable technique in epidemiological studies for assessing causal inference by employing genetic variants as instrumental variables (21). The strength of MR lies in the random assignment of genetic variants from parents to offspring, which are impervious to self-selective behavior—this can fortify the causal inference by mitigating potential unmeasured residual confounding and precluding reverse causality (22). MR analysis capitalizes on genetic variations as Instrumental Variables (IVs) to corroborate causal associations, taking advantage of their diminished susceptibility to measurement errors or biases. Two-sample MR (TSMR) is commonly applied to link exposure and outcome data sourced from distinct Genome-Wide Association Study (GWAS) datasets (23). For this project, bidirectional MR analyses were employed to surmount

the limitations intrinsic to observational studies and to probe into the relationship between OSA, and CKD, renal function.

2 Methods

2.1 Study design

A TSMR approach was utilized employing summary statistics from distinct GWAS for OSA and CKD. Initially, a forward MR analysis was undertaken to explore the associations between genetically predisposed OSA and both CKD and renal function. Subsequently, given the potential influence of impaired renal function on OSA, a reverse MR analysis was executed to scrutinize the associations between genetically influenced renal function and OSA. A robust MR framework adheres to three critical assumptions: (1) instrumental variables (IVs) are strongly associated with the exposure; (2) IVs are not related to any confounders influencing both exposure and outcome; and (3) the influence of IVs on outcomes is only via their effect on exposure rather than any other causal pathways (24). This article solely employed summary data. The original studies have obtained the necessary ethical approval and informed consent from patients.

2.2 Genetic associations with OSA

The full GWAS summary statistics pertaining to OSA were extracted from the most recent published data in the FinnGen database, which included 375,657 participants—38,998 patients and 336,659 controls (25). The diagnosis of OSA was made based on the International Classification of Diseases, Tenth Revision (ICD-10) and Ninth Revision (ICD-9) codes (ICD-10: G47.3, ICD-9: 3472). These were acquired from the Finnish National Hospital Discharge Registry and the Causes of Death Registry. This diagnosis was established on the basis of subjective symptoms, clinical examination, and sleep registration applying an apnea-hypopnea index ≥ 5 events·h⁻¹ or a respiratory event index ≥ 5 events·h⁻¹. By amalgamating ICD codes from various registries, we constituted disease endpoints. In the fifth round of data from FinnGen, the prevalence of OSA was 7.69%, with 63% of OSA patients being male. The average age of the OSA group was 58.9 ± 13.3 years, with a BMI of 31.72 ± 6.74 kg/m². The age at OSA diagnosis was 55.3 ± 11.9 years. In contrast, the average age in the non-OSA group was 51.8 ± 17.7 years, with a BMI of 26.87 ± 5.02 kg/m², while the overall average BMI was 27.25 ± 5.34 kg/m². Compared with the non-OSA group, the OSA group had a higher prevalence of diseases such as type 2 diabetes, hypertension, and coronary heart disease. Age, sex, and the 10 first principal components were adjusted as covariates in the original GWAS study (26).

2.3 Genetic associations with CKD and renal function

There are seven phenotypes included, and they are primarily from Chronic Kidney Disease Genetics (CKDGen) Consortium and UK Biobank: creatinine-based estimated glomerular filtration rate (eGFR_{crea}), cystatinC-based estimated glomerular filtration rate

(eGFRcys), blood urea nitrogen (BUN), urine albumin to creatinine ratio (UACR), CKD (defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m²), rapid decline of eGFR (Rapid3) (the eGFR decreases by more than 3 mL/min/1.73 m² per year), and rapid progress to CKD (CKDi25) (defined as the decrease of eGFR ≥25% of baseline accompanied by the progression from no CKD to CKD). Instrument variable summary statistics for CKD were sourced from a meta-analysis conducted by the CKDGen Consortium, which incorporated 23 European ancestry cohorts ($n = 480,698$; 41,395 patients and 439,303 controls) (27). Individuals of European ancestry in the CKDGen dataset had a mean age of 54 years old, and 50% of them were male, with a median eGFR of 91.4 mL/min/1.73 m² and a prevalence of CKD of 9%. All genetic associations were adjusted for sex, age, study site, genetic principal components, relatedness, and other study-specific features. The GWAS summary statistics for eGFRcrea, eGFRcys, and BUN were sourced from a meta-analysis that included data from the CKDGen Consortium and the UK Biobank, encompassing 1,201,909 participants (28). The UACR data were derived from a separate meta-analysis, which documented the summary data from both trans-ethnic ($n = 564,257$) and European-ancestry populations ($n = 547,361$) (29). Summary statistics for Rapid3 (comprising 34,874 cases and 107,090 controls) and CKDi25 (encompassing 19,901 cases and 175,244 controls) were obtained from a meta-analysis of 42 GWAS studies from the CKDGen Consortium and the UK Biobank (30). For detailed diagnostic criteria and inclusion procedures, please refer to the original literature. The datasets for CKD, eGFR, UACR, Rapid3, and CKDi25 are accessible at <http://ckdgen.imbi.uni-freiburg.de/>. Detailed information about each dataset can be found in [Supplementary Table S1](#).

2.4 Selection of instrumental variables (IVs)

First, we procured Single Nucleotide Polymorphisms (SNPs) that were strongly associated (p value $< 5 \times 10^{-8}$) with exposures in each MR analysis. For CKDi25 and Rapid3, where only a few significant SNPs were found using the $p < 5 \times 10^{-8}$ threshold, SNPs were selected as IVs at $p < 5 \times 10^{-6}$. Second, it is crucial to ensure the chosen IVs satisfy the independence criterion. To evaluate the independence of these variables and account for potential linkage disequilibrium effects, a linkage disequilibrium parameter (R^2) threshold of 0.001 and a genetic distance cutoff of 10,000 kb were implemented. Additionally, during the reverse MR analysis, duplicate values from the seven renal function phenotype IVs were eliminated. Third, Phenoscanner (31) was employed to check potential confounding factors (such as hypertension, obesity, overweight, diabetes, among others) that might be related to the IVs, thus preventing such factors from interfering with the impact of exposure on outcomes. Moreover, IVs associated with the outcomes at a significance level of $p < 5 \times 10^{-8}$ were excluded. We harmonized the effect alleles of outcome-associated SNPs to ensure consistency with those of exposure-associated SNPs, taking into account allele letters and frequencies. Also, palindromic SNPs were excluded from the analysis. To further bolster the reliability of our research results, we applied Steiger filtering to remove SNPs that exhibited a stronger correlation with the outcomes than with the exposures (32). The meticulous selection process for IVs as described above significantly enhances the credibility of our findings. Furthermore, to eliminate bias induced by weak IVs in the results,

we computed the F statistic. The F statistic is calculated using the formula $F = R^2 (n-k-1) / [k (1-R^2)]$, where R^2 signifies the extent to which the IVs explain the exposure.

2.5 Mendelian randomization analysis

To investigate the causal relationship between exposure and outcome, several methods were utilized, including Inverse Variance Weighted (IVW), MR-Egger, Weighted Median, Simple Mode, and Weighted Mode. The point estimates obtained through IVW correspond to a weighted linear regression of SNP-outcome associations against SNP-exposure associations, with no regard to intercept. It is imperative when using the IVW method to ensure the absence of pleiotropy among SNPs, as this can significantly bias the results (33). In contrast, the MR-Egger method assumes the Instrument Strength Independent of Direct Effect (InSIDE) assumption and primarily examines the dose-response relationship between IVs and outcomes (34). This method takes into account the presence of pleiotropy to a certain extent. Even if most IVs have pleiotropy, MR-Egger can provide effective estimates (34).

The weighted median method is effective in mitigating the impact of using invalid IVs and can provide consistent estimates of causal effects, even when up to 50% of the information is derived from genetic variations in invalid instruments (35). In contrast, weighted mode methods exhibit lower capability in detecting causal effects but are associated with fewer biases (36). If there is no pleiotropy, we chose IVW as the primary method for conducting our MR analysis. If pleiotropy exists, MR-Egger will be employed as the main method, along with the direction of effect size in four MR methods.

2.6 Sensitivity analysis

In our study, we utilized Cochran's Q test to evaluate heterogeneity. Specifically, the inter-instrument Q-test was applied to probe heterogeneity arising from multiplicity or other factors (37). To identify pleiotropy, we conducted the MR-Egger regression test. A significant deviation of the intercept term from zero indicates the presence of horizontal pleiotropy (34). In instances where heterogeneity or horizontal pleiotropy was detected, estimates were recalculated using IVW, MR-Egger, and other methods after the removal of outlier SNPs identified through Radial MR analysis (38). Additionally, a leave-one-out analysis was performed, whereby SNPs were systematically removed one at a time, and the effect was recomputed.

2.7 Statistical analysis

All statistical analyses were conducted using R (version 4.2.3, R Foundation for Statistical Computing, Vienna, Austria). MR analyses were carried out using the "TwoSampleMR" and "RadialMR" packages. To control the type I error rate in the multiple testing, we utilized the Bonferroni correction method. This procedure involves dividing the critical significance level by the number of tests conducted, providing a simple yet effective way to manage multiple comparisons. However, it's worth noting that such correction methods

can become overly conservative when a large number of tests are performed (39). In our study, Bonferroni correction was applied to account for multiple testing of the associations between OSA and 7 renal function outcomes (i.e., eGFRcrea, eGFRcys, BUN, UACR, Rapid3, CKDi25, and CKD) with 5 methods. A two-sided p -value of $<3.571 \times 10^{-3}$ [$0.05/(1 \times 2 \times 7)$] was considered significant.

3 Results

3.1 Forward MR analysis

The number of independent SNPs selected as IVs for OSA was 14 for the analysis of association with eGFRcrea, 15 with eGFRcys, 15 with BUN, 16 with UACR, 15 with Rapid3, 15 with CKDi25, and 16 for CKD. We employed a more stringent p -value criterion in our analysis. A two-sided p value of $<3.571 \times 10^{-3}$ was considered significant. The primary two-sample MR analysis showed no significant association between genetically determined OSA and renal function phenotypes. These results were reproduced in the other analysis methods (Figure 1). Heterogeneity was suspected regarding the association between OSA and eGFRcrea, eGFRcys, BUN, CKD. The MR-Egger intercept, which is an indicator of genetic pleiotropy, was statistically significant for OSA between BUN (Supplementary Table S2). The scatter plots were shown in Supplementary Figures S1–S2. The results of leave-one-out sensitivity and single SNP risk analysis were shown in Supplementary Figures S3–S6. The heterogeneity or horizontal pleiotropy was noted in OSA between eGFRcrea, eGFRcys, BUN, CKD, we recomputed IVW, MR-Egger and other methods estimates after removing the outlier SNPs identified by Radial MR. The MR analysis showed no significant association between genetically determined OSA and eGFRcrea, eGFRcys, BUN, CKD (Figure 1). There was no evidence of significant heterogeneity. There was still pleiotropy between OSA and BUN (Supplementary Table S3). At this point, we selected MR-Egger as the primary analysis method and, combined with the direction of effect sizes from other methods, we did not find a significant association between OSA and BUN.

3.2 Reverse MR analysis

A total of 304, 147, 143, 44, 13, 13, and 15 independent SNPs were selected as IVs for the MR analysis investigating the associations of eGFRcrea, eGFRcys, BUN, UACR, Rapid3, CKDi25, and CKD with OSA, respectively. The IVW method was employed, revealing suggestive evidence of a potential causal association between BUN and the risk of OSA ($p=0.004$) (Figure 2). Heterogeneity was observed in the associations between eGFRcrea, eGFRcys, BUN, UACR, CKD, and OSA. Additionally, horizontal pleiotropy was detected in the relationships between eGFRcys and OSA (Supplementary Table S2). At this point, using the MR-Egger method as the primary analysis method, we did not find a significant association between eGFRcys and OSA. This result was also supported by four other methods. The scatter plots were shown in Supplementary Figures S7–S8. The results of leave-one-out sensitivity and single SNP risk analysis were shown in Supplementary Figures S9–S16. After excluding outlier SNPs,

we recalculated the estimates using IVW, MR-Egger, and other methods. We discovered a significant association between BUN and OSA using the IVW method (OR: 2.079; 95% CI: 1.516–2.853; $p=5.72 \times 10^{-6}$) (Figure 2). Importantly, there was no evidence of significant heterogeneity or pleiotropy in the associations (Supplementary Table S3).

4 Discussion

Our findings indicated that OSA did not directly lead to CKD, which contradicts prior observational studies. Furthermore, the lack of a genetic correlation between OSA and different renal function phenotypes supported this result. However, in our reverse MR analysis, we observed a positive correlation between BUN and OSA. Based on our findings, an elevation in BUN levels could be associated with an increased risk of OSA.

Contrary to our study results, recent epidemiological research has established a link between OSA and CKD. For instance, a cohort study involving more than 3 million US veterans—predominantly males with a mean age of 60.5 years—indicated that an onset diagnosis of OSA was associated with a higher incidence of CKD and a more rapid decline in kidney function over time as compared to those without OSA (40). In a retrospective and longitudinal population-based cohort study leveraging the Taiwan Longitudinal Health Insurance Database 2000, it was observed that individuals with OSA demonstrated an elevated risk of developing CKD, even after excluding those with hypertension and diabetes. The adjusted OR for this association was 1.37. A subgroup analysis further revealed a higher incidence of CKD among women with OSA. However, no significant correlation was found between OSA and CKD development in men (41). A study involving older participants aged 65 years and above, recruited from the general population, involved overnight polysomnography for 277 individuals. The results indicated an increased risk of rapid kidney function decline over an 11-year follow-up period among those with an Apnea-Hypopnoea Index (AHI) of 30 or higher. These findings remained statistically significant even when adjusted for various factors, such as age, sex, BMI, smoking status, diabetes mellitus, hypertension, and history of cardiovascular disease. Thus, it can be inferred that AHI serves as an independent risk factor for glomerular kidney function decline (42). Yayan et al. (43) concluded that CKD is more prevalent in patients with OSA compared to those without OSA, and the frequency of CKD escalates as the severity of OSA intensifies. Moreover, Marrone suggested that severe hypoxia, even if experienced for a limited duration during the night, may pose a greater risk factor for renal damage in patients with OSA than average SpO₂ levels and/or frequency of apnea events (15). Chang et al. (16) reported that severe OSA independently increases the risk of CKD. Additionally, a study conducted by Adams et al. disclosed a correlation between OSA and stages 1–3 of CKD (17). A cross-sectional study further highlighted the prevalence of OSA in non-dialysis CKD patients to be 28%, with an incidence rate of 88%. The study also demonstrated a rise in the risk and severity of OSA as CKD stages progressed (14). The available real-world data indicates a reciprocal relationship between OSA and CKD. It suggests that individuals with OSA may have an increased

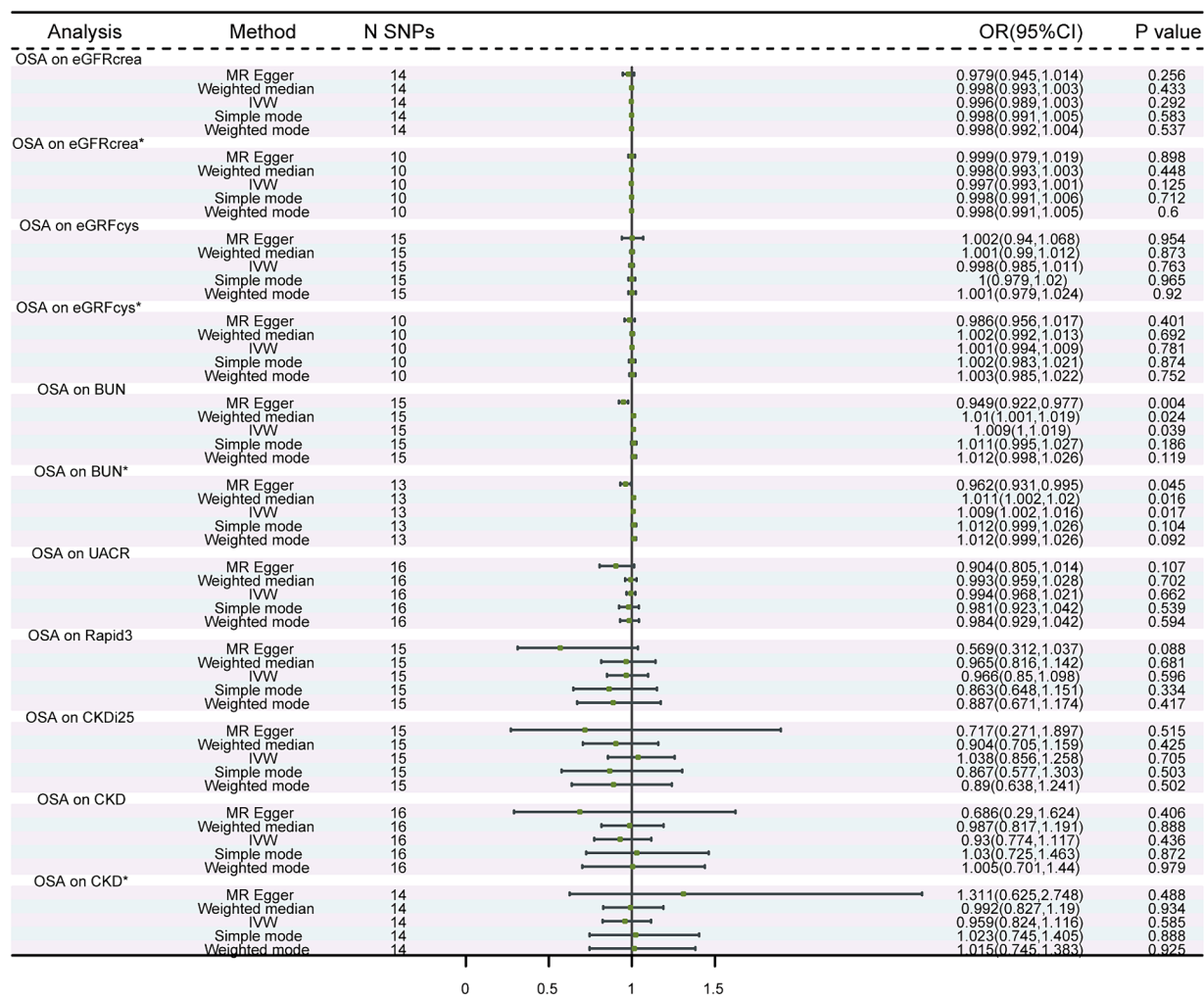


FIGURE 1 MR analysis of the causality of OSA on renal function. OSA, obstructive sleep apnea; eGFRcrea, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatinC-based estimated glomerular filtration rate; BUN, blood urea nitrogen; UACR, urine albumin to creatinine ratio; Rapid3, rapid decline of eGFR; CKDi25, rapid progress to CKD; CKD, chronic kidney diseases. IVW, Inverse Variance Weighted; *The results of after removing the outlier SNPs.

likelihood of developing CKD and experiencing a decline in kidney function. Conversely, patients with CKD are more vulnerable to developing OSA. However, it is essential to acknowledge that these observational studies have inherent limitations, including methodological shortcomings, small sample sizes, selection bias, and inadequate adjustment for confounding factors, which prevent the establishment of a definitive causal link.

However, it's worth noting that not all observational studies found a definitive significant link between OSA, CKD, and renal function. For instance, a retrospective cohort sub-study of the Wisconsin Sleep Cohort Study did not identify any association between the severity of sleep apnea and the decline in renal function (44). Lee et al. (19) suggested that OSA alone does not pose a risk factor for CKD, but in patients with metabolic syndrome, OSA was an additional burden escalating the risk of CKD. Also, Fernandes et al. (45) found a high prevalence—approximately 67%—of OSA in patients with stages 3b-4 CKD. However, intriguingly, the AHI was very similar between these two groups of patients, and no

significant association was discerned between AHI and the eGFR. The retrospective study conducted by Uyar et al. (46) assessed patients diagnosed with OSA, excluding those with a previous diagnosis of CKD. The results showed no difference between OSA patients and the control group when evaluated concerning an estimated eGFR of less than 60 mL/min/1.73m². Moreover, no correlation was observed between eGFR and the desaturation index. The study conducted by Canales et al. did not establish a significant relationship between renal function and sleep-disordered breathing (47). Furthermore, OSA was not found to be an identifying factor for patients at risk of CKD (48).

Due to the limitations of association studies in addressing causality, it remains challenging to definitively establish the causal relationship between OSA and CKD based solely on observational studies. Therefore, it is important to interpret the aforementioned findings with caution. Contrary to the majority of observational studies, our investigation did not uncover any causal link between OSA and CKD. In the reverse MR analysis, the results indicated

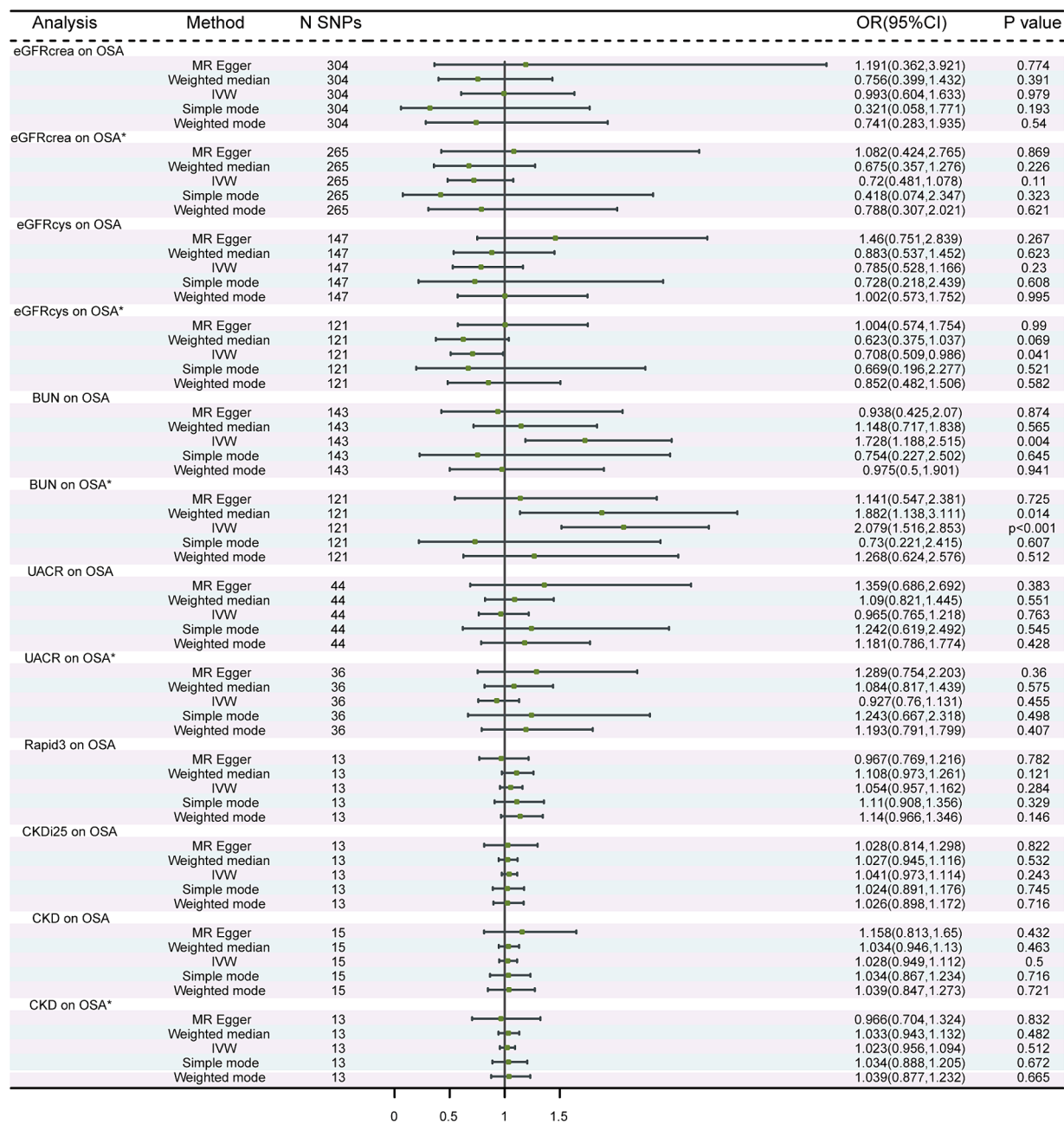


FIGURE 2 MR analysis of the causality of renal function on OSA. OSA, obstructive sleep apnea; eGFRcrea, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatinC-based estimated glomerular filtration rate; BUN, blood urea nitrogen; UACR, urine albumin to creatinine ratio; Rapid3, rapid decline of eGFR; CKDi25, rapid progress to CKD; CKD, chronic kidney diseases. IVW, Inverse Variance Weighted; * The results of after removing the outlier SNPs.

that BUN has a causal relationship with OSA. However, there was no evidence of a causal relationship between CKD, as well as other renal function phenotypes, and OSA. There are a couple of possible reasons that may contribute to the association between OSA, CKD and renal function in observational studies. There are several potential factors that could contribute to the observed association between OSA and CKD in observational studies. Age, sex, diabetes, hypertension, glomerulonephritis, cholesterol and cigarette smoking are established risk factors for CKD (49). CKD

patients with cardiovascular disease, diabetes, smoking habit and higher serum phosphorus have a higher risk of kidney damage (50). And in patients with non-dialysis CKD, the cardiovascular risk increases linearly with the higher levels of LDL cholesterol (51). OSA is also a recognized risk factor for cardiovascular disease. Patients with OSA often exhibit comorbidities such as hypertension, diabetes, obesity, and cardiovascular disease (52–54). OSA may be linked to CKD through shared conditions like obesity, hypertension, and diabetes, but the exact influence of

each condition is difficult to determine (55–57). In the reverse MR analysis, we found an association between BUN and OSA. The increase in BUN usually occurs when the glomerular filtration rate decreases by more than 50%, which means that in CKD patients, an increase in BUN often represents the disease progressing to a later stage. Contemporary research elucidates that in patients undergoing hemodialysis, BUN exhibits a significant correlation with OSA (58–61). Moreover, multiple studies have demonstrated that optimized dialysis therapy can mitigate the severity of sleep apnea in patients afflicted with End-Stage Renal Disease (ESRD) (62–64). This implies that ESRD may elevate the risk of OSA. Present-day research has suggested various pathophysiological mechanisms through which ESRD could precipitate OSA, encompassing neuropathy or myopathy induced by uremia and hypervolemia. Diminished sensory function and denervation of the Upper Airway (UA) dilator muscle have been demonstrated to contribute to the pathogenesis of UA obstruction in patients diagnosed with OSA (65). In ESRD, uremic neuropathy is prevalent and may impinge on the sensory function of the UA, thereby augmenting UA collapsibility (66). Moreover, uremic myopathy, known to exacerbate the fatigability of the respiratory muscles (67), could potentially result in decreased tone of the UA dilator muscles, leading to an ensuing increase in UA collapsibility during sleep. On the other hand, there exists a substantial and well-established body of evidence underscoring the role of fluid overload in the pathogenesis of sleep apnea, particularly in conditions typified by fluid overload such as heart failure and End-Stage Renal Disease (ESRD) (68, 69). Hypervolemia and the rostral fluid shift from the legs overnight can both contribute to subsequent fluid accumulation in the neck. This accumulation can result in a reduction in the cross-sectional area of the UA and an increased collapsibility, thereby predisposing individuals to OSA (68). It is also plausible that fluid overload contributes to OSA not merely through its impact on UA collapsibility, but also potentially by influencing ventilatory instability (70). Other research has suggested a direct and independent correlation between the degree of fluid overload and the severity of OSA in ESRD (71–73).

Our MR study offers several key advantages. Firstly, to the best of our knowledge, it is the first study to assess the causal relationship between OSA and CKD, as well as renal function, using a two-sample MR analysis. Second, we utilized GWAS datasets predominantly from populations of European ancestry to mitigate the effects of population stratification. Third, different estimation models and rigorous sensitivity analysis were used to ensure the reliability and robustness of the results. However, our study has certain limitations. Firstly, the exclusive inclusion of participants with European ancestry in our dataset introduces potential participant overlap, and the generalizability of the results to the entire population needs further verification. Secondly, despite implementing a rigorous process to identify outlier variants and mitigate horizontal pleiotropy, complete elimination of its impact was unattainable due to the complex and uncertain biological functions of numerous genetic variants. Thirdly, larger sample sizes and more advanced methodologies are required to confirm the findings and comprehensively demonstrate statistical power. Finally, our study did not conduct subgroup analyses. In our analysis, the definitions of OSA and CKD were based on

binary variables (i.e., the presence or absence of the disease) without considering the severity of these conditions. This could lead to an incomplete understanding of the relationship between OSA and CKD. For instance, if only severe OSA significantly increases the risk of CKD, while mild or moderate OSA has a lesser or no impact, our analysis may fail to capture this distinction. Additionally, the stages of CKD progression could also affect its association with OSA, but due to the lack of data, we were unable to assess this variation.

In conclusion, our MR analysis indicates that genetically predicted OSA does not have a causal impact on CKD and renal function phenotypes. This finding contradicts the results of most observational studies. Additionally, in the reverse MR analysis, only BUN was found to be statistically associated with OSA. To ensure the accuracy of our results, future research should rely on higher quality GWAS data and utilize more advanced methods. Furthermore, this study emphasizes the importance of further investigating the underlying mechanism linking OSA and CKD.

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

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

YH: Writing – original draft, Writing – review & editing. YL: Writing – review & editing. ZX: Supervision, Writing – review & editing. ZW: Supervision, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2024.1323928/full#supplementary-material>

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