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

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

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Table of contents

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

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Editorial on the Research Topic
Novel technologies in the diagnosis and management of sleep-disordered breathing

The year 2023 is a memorable one in the history of sleep-disordered breathing (SDB). Obstructive sleep apnea (OSA) was first described as a new disease 50 years prior in 1973 (Guilleminault et al., 1973). After these 50 years of continuous development, nocturnal SDB has become one of the most active fields in sleep medicine, forming a platform for multidisciplinary collaboration.

Sleep-disordered breathing diagnosis and management—Where are we now?

SDB encompasses a wide spectrum of conditions, from habitual snoring to severe cases of OSA, and affects a vast segment of the population worldwide (Benjafield et al., 2019). These conditions not only disrupt sleep but also lead to a range of negative health consequences such as excessive daytime sleepiness, cognitive impairments, and increased risk of cardiometabolic diseases. Traditional diagnostic methods, including in-lab polysomnography, often necessitate specialized sleep centers, are labor-intensive, and are not readily available. The current diagnostic methods also fall short in forecasting long-term health implications, underscoring an urgent need for innovation in diagnostic approaches and metrics for tailored disease management. Likewise, the management of SDB also stands at a transformative juncture in the rapidly advancing field of sleep medicine. While continuous positive airway pressure (CPAP) therapy remains the cornerstone of SDB treatment, its effectiveness in addressing the broader spectrum of SDB-related health issues is limited (Patil et al., 2024). This scenario underscores the critical need for alternative treatment modalities. The integration of machine learning, advanced diagnostic technologies, and novel therapeutic strategies heralds a move toward more personalized care and improved outcomes for patients (Korkalainen et al., 2024).

This Research Topic delves into the forefront of innovation in the diagnosis and management of SDB, highlighting a shift toward diagnostic tools and treatment methods that promise greater accuracy, efficiency, and patient-centric care. By exploring the latest in diagnostic technologies—ranging from portable devices capable of capturing detailed sleep data outside conventional lab settings to computational techniques designed to automate and enhance data analysis—this Research Topic underscores the move toward more accessible and comprehensive sleep assessments. In addition, the Research Topic examines cutting-edge approaches in the development of disease management, such as advanced physiological modeling and phenotyping, which aim to unravel the complexities of individual disease patterns, symptoms, and associated conditions. These insights are pivotal for developing personalized management strategies that address the nuanced needs of those affected by SDB. Together, the articles presented in this Research Topic offer a glimpse into the evolving landscape of SDB care, highlighting both the current hurdles and promising avenues for future interventions.

At-home recordings for more affordable and available diagnostics

Accurate diagnosis is the cornerstone for assessing the severity of sleep disorders as well as for designing optimal disease management. New more affordable and simpler solutions are required due to the shortcomings of polysomnography. This can be made possible by technological advances as well as advanced analytical pathways, machine learning, and deep learning methodologies. Zou et al. discuss advancements in home sleep apnea testing that utilize technology based on peripheral arterial tone and photoplethysmography to detect respiratory events and their potential to act as a non-invasive, cost-effective, and accessible solution for multi-night sleep monitoring. Concurrently, Campbell and Sulaiman review the diagnostic potential of the WatchPAT device, which utilizes peripheral arterial tomography in conjunction with heart rate, oximetry, actigraphy, and respiratory movements for a minimally intrusive home diagnosis of OSA. This device exemplifies the trend toward integrating multiple physiological signals to refine diagnostic accuracy outside traditional laboratory environments. Teplitzky et al. contribute to this dialogue by reviewing alternative diagnostic methods to polysomnography that could increase the efficiency and accessibility of pediatric OSA diagnosis, highlighting the urgent need for adaptable diagnostic tools in younger populations. Finally, Zhu et al. introduce a novel approach using triboelectric nanogenerators embedded in wearable devices. This method has the potential for real-time, non-invasive sleep monitoring through analysis of respiratory rates and body movements.

Leveraging machine learning to improve diagnostics

Artificial intelligence, driven by advancements in machine learning and deep learning methodologies further holds the potential to transform diagnostics. Overall, these approaches have shown promising results in automating the analysis of overnight recordings as seen in Somaskandhan et al.. This research shows the capability of a deep learning-based method to automatically score sleep stages in preadolescent populations, a population that often necessitates in-laboratory polysomnography. Their results already illustrate accuracy on par with inter-rater reliability between expert scorers. Meanwhile, Piccini et al. explore the application of machine learning to identify sleep stages and diagnose OSA using electrodermal activity signals. Their work suggests that wearable devices could significantly reduce reliance on polysomnography by providing a more patient-friendly approach to sleep diagnostics. In addition to automating the scoring or simplifying the recordings, deep learning and machine learning methods hold the potential to gain deeper insights from the recordings. This is supported by a review by Anderer et al. on the utilization of artificial intelligence to provide consistent and reliable scoring of sleep stages based on neurological and cardiorespiratory signals, especially the utilization of hypnodensity as a method to quantify sleep stage ambiguity and stability. These works offer a novel perspective on the assessment of SDB.

Novel diagnostic metrics and measurement techniques

To unravel the complexities of sleep disorders, it is crucial to delve beyond traditional analyses by employing innovative methods that offer a more nuanced understanding of sleep dynamics and pathophysiological underpinnings. Traditional sleep stage classification, with its discrete five-stage system, while useful, often falls short in capturing the intricate patterns of sleep fragmentation seen in disorders like OSA. Recognizing this limitation, alternative analytical approaches have been developed to provide deeper insights into sleep quality and architecture. One of these methods is odds ratio product (ORP), a continuous metric for sleep depth that can help identify differences in sleep depth between and within individuals even when the changes are not discernible by conventional sleep staging. Younes, the developer of ORP, provides a comprehensive overview of ORP's measurement, validation, and application, underscoring its potential in identifying distinct phenotypes of sleep disorders. ORP thereby facilitates more personalized and effective management strategies for conditions such as SDB, insomnia, and idiopathic hypersomnia.

Innovative diagnostic tools such as mandibular jaw movements (MJM) and electrical impedance tomography can provide additional detailed and non-invasive information on sleep disorders. Martinot and Pépin review the use of MJM as a novel, non-invasive method for assessing respiratory effort in SDB. This approach utilizes a single point-of-contact sensor placed on the patient's chin to capture MJM, which is then analyzed using machine learning algorithms to provide diagnostic information. The article highlights the potential of MJM monitoring as a reliable, patient-friendly alternative to traditional, more invasive methods for measuring respiratory effort, such as esophageal pressure monitoring. Similarly, Piccin et al.'s exploration of neck electrical impedance tomography for monitoring upper airway patency during sleep offers real-time insights into airway obstruction

dynamics, showcasing the potential of these methodologies in enhancing our diagnostic capabilities and ultimately improving patient care. Exploring the multifaceted relationship between sleep disorders and other physiological disturbances can further enrich our understanding. For instance, Ji et al.'s study on gastrointestinal electrophysiological signals reveals a promising avenue for predicting sleep disturbances, highlighting the interconnected nature of physiological systems and their impact on sleep health. Together, these advancements signal a shift toward a more comprehensive and nuanced approach to diagnosing and understanding sleep disorders, paving the way for innovative treatment modalities and improved patient outcomes.

Pathophysiological factors, endotyping, and phenotyping to guide treatment

The intricate nature of SDB necessitates a nuanced understanding of its pathophysiology for the development of personalized treatment modalities. The comprehensive phenotyping and endotyping of OSA, leveraging a wealth of data from patient characteristics and diagnostic recordings, is pivotal to tailoring treatments to address specific disease traits, and can potentially lead to enhanced treatment adherence. McNicholas and Korkalainen discuss the complex pathophysiology and phenotypes of OSA as well as the translation to personalized treatment strategies. Novel diagnostic approaches are needed to gain a deeper insight into endotypical and phenotypical factors and to gauge the systemic effects of OSA. This likely requires adaptation to facilitate ambulatory and multi-night diagnostic studies, as well as simplification of recordings and the development of more detailed analyses. As a potential solution, Finnsson et al. provide an overview of the Endo-Phenotyping Using Polysomnography (PUP) method, a model-based tool for estimating endotypic traits from standard polysomnography. This method represents a significant step forward in the pursuit of precision medicine for OSA, offering a pathway to targeted treatments based on individual patient profiles. However, the authors also acknowledge the challenges that must be overcome to translate the PUP algorithm into clinical practice, indicating that further research and development are essential for realizing the full potential of the technology in the context of personalized medicine in OSA. Moreover, the upper airway muscles have no bony or cartilaginous support and are prone to collapse during sleep and the role of neuromuscular function in the pathogenesis and management of OSA is summarized by a group of experts led by Mehra et al.. In their consensus, a point-of-care model using novel electrodiagnostic technology for upper airway assessment is proposed. These discussions illuminate the path toward understanding the underlying pathophysiology of SDB and the importance of detailed phenotyping and endotyping in developing personalized treatment plans. Such an approach not only promises to address the specific characteristics of the disease but also to improve patient outcomes through higher adherence to tailored treatment strategies.

The analysis of pathophysiological factors, endotypes, and phenotypes could guide the optimal treatment, as discussed extensively in Gruenberg et al. who highlight the potential benefits and limitations of various non-CPAP therapeutic modalities including myofunctional therapy, upper airway training, and several forms of electrical stimulation of the upper airway muscles and nerves. For SDB patients exhibiting high loop gain, CPAP may not suffice, prompting the need for alternative treatments such as the enhanced expiratory rebreathing space (EERS), reviewed by Quinn et al. EERS modifies the dead space of CPAP devices to mitigate CO_2 loss during sleep arousals, thus stabilizing breathing patterns and addressing central sleep events triggered by hypocapnia. This approach provides an alternative for patients who are unresponsive to traditional CPAP therapy. Finally, Gentina et al. present the study protocol and baseline data for a prospective study (Self-Efficacy Measure for Sleep Apnea study; SEMSAS) underscoring the importance of health literacy, self-efficacy, and socio-economic factors in predicting CPAP adherence. This ongoing study promises to elucidate the multifaceted influences on CPAP compliance, offering a foundation for identifying patients most likely to benefit from CPAP and refining treatment approaches in the long term.

Treatment innovations

Patients with central sleep apnea (CSA) are often multi-morbid and difficult to treat. Javaheri et al. evaluate the efficacy of phrenic nerve stimulation as a treatment alternative. Their findings suggest phrenic nerve stimulation is a safe and effective treatment modality, capable of reducing the apnea-hypopnea index (AHI) and enhancing sleep quality, marking it as a viable option for CSA management. Pediatric populations, particularly those with Down syndrome, also present unique challenges in OSA management. Liu et al.'s systematic review and meta-analysis of hypoglossal nerve stimulation highlights its potential selected patients, addressing the low CPAP adherence rates and the need for additional interventions post-surgery in this demographic. Additionally, advancements in mandibular advancement splint (MAS) therapy, as reviewed by Mohammadieh et al., showcase a new generation of MAS devices that integrate digital technologies and machine learning to improve treatment efficacy, patient selection, and compliance monitoring. Emphasizing the role of customization and technological integration in enhancing therapeutic outcomes, it is anticipated that MAS therapy will play a more important role in OSA management.

There is no pharmacological treatment for OSA in clinical practice. The combination of noradrenergic and antimuscarinic drugs discussed by Taranto-Montemurro et al. may open new avenues for management strategies. Despite the promise of these treatments, challenges remain in assessing disease severity and pinpointing specific treatment targets, underscoring the need for continued research and development in pharmacotherapy for OSA (Hedner and Zou, 2022). Together, these recent developments represent a shift toward personalized and diversified treatment strategies for OSA, addressing the limitations of CPAP therapy and expanding the therapeutic landscape to accommodate patient-specific needs and preferences.

Conclusion

This is an exciting era in sleep medicine and sleep research with new concepts and innovations. As we stand on the precipice of transformative advancements in the diagnosis and management of SDB, the horizon is both promising and fraught with challenges. The integration of machine learning, advanced diagnostic modalities, and innovative treatment approaches heralds a new chapter of personalized medicine, tailored to meet the unique needs of individuals. The shift from "AHI medicine" and "one size fits all" concepts toward precision medicine is poised to revolutionize patient care, offering more accurate diagnoses, enhanced treatment efficacy, and improved patient adherence (Arnardottir et al., 2022). The successful translation of these advancements from research to clinical practice requires not only further validation through large-scale studies but also a reevaluation of existing healthcare models to ensure accessibility. Moreover, the adoption of new technologies necessitates comprehensive training for healthcare professionals to maximize the benefits of these tools. Interdisciplinary collaboration will be crucial in overcoming these barriers, uniting experts from fields such as sleep medicine, respirology, neurology, cardiology, otolaryngology, odontology, biomedical engineering, and data science to address the complex challenges ahead. As we navigate these uncharted waters, the collective efforts of the scientific and medical communities will be paramount in realizing the full potential of these innovations, ultimately improving the lives of millions suffering from SDB.

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Conflict of interest

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Hypoglossal nerve stimulation in adolescents with down syndrome and obstructive sleep apnea: A systematic review and meta-analysis

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Objective: To evaluate the efficacy and adverse effects of hypoglossal nerve stimulation in adolescents with down syndrome and obstructive sleep apnea.

Methods: A systematic search was conducted using PubMed, Web of Science, Embase, and Scopus databases. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive search strategy used a combination of Medical Subject Headings and free words with "OR" and "AND." Articles were screened to extract data reporting apnea-hypopnea index, quality of life, voltage, follow-up duration, and complications. All included participants were adolescents with down syndrome and obstructive sleep apnea.

Results: A total of 92 articles were identified, of which 9 articles met the inclusion criteria. A total of 106 patients were included. All the studies showed that patients receiving hypoglossal nerve stimulation experienced a significant decrease in apnea-hypopnea index (at least 50%). The pooled AHI was significantly lower in patients following treatment (mean AHI reduction 17.43 events/h, 95% confidence interval 13.98–20.88 events/h, $P < 0.001$) after 2 case reports were excluded. The pooled OSA-18 were significantly decreased in 88 patients after treatment (mean OSA-18 reduction 1.67, 95% confidence interval 1.27–2.08, $P < 0.001$) after excluding 5 studies. Four investigations examined the necessity to optimize stimulation voltage for arousal during treatment. The most common complication was pain or discomfort in the tongue or mouth. Most studies had relatively short patient follow-up periods, with the most extended follow-up being 44–58 months.

Conclusion: Hypoglossal nerve stimulation significantly reduces apnea-hypopnea index and improves the quality of life; and thus, could be a potential alternative therapy for obstructive sleep apnea in adolescents with down syndrome. The adolescent's age, potential complications,

adverse events, long-term efficacy, and comfort, needs to be considered while performing hypoglossal nerve stimulation.

KEYWORDS

hypoglossal nerve stimulation, down syndrome, obstructive sleep apnea, adolescents, apnea-hypopnea index

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that causes hypoxia and fragmented sleep, because of repeated airway obstruction or collapse (1). OSA affects approximately 5% of healthy children globally and is associated with concomitant behavioral issues, such as inattention, hyperactivity, and/or cognitive decline in the pediatric population (2). Obesity and craniofacial deformities are the most common causes of airway obstruction (3).

Down syndrome (DS), trisomy 21, or redundancy of chromosome 21, is one of the most complex human congenital diseases (4). Adolescents with DS show several unique characteristics, such as generalized hypotonia, macroglossia, facial hypoplasia, small tracheal caliber, and lingual tonsillar hypertrophy (5). Up to 80% of children with DS have OSA, which is thought to be caused by these unique characteristics (6).

Untreated OSA can affect a child's development, including reduced learning abilities, speech and language delays, and impaired cognitive flexibility and memory (7). Currently, upper airway surgery and continuous positive airway pressure (CPAP) are the commonly used treatments for OSA (8). Although for most individuals OSA improves after treatment, the incidence of residual airway obstruction remains high (9). Following upper airway surgery, residual airway obstruction can cause up to 75% of children to require breathing support (10). Furthermore, compliance with CPAP is not good enough to meet treatment needs due to discomfort, inconvenience, and cognitive delay (11).

Since 2014, hypoglossal nerve stimulation (HNS) has been approved by the US Food and Drug Administration (FDA) for treating OSA in adults (12). HNS improves breathing while sleeping, by stimulating the muscles in the upper airway and by hardening the tongue and soft tissues (13). Studies have shown that HNS is more tolerable and less irritating than CPAP and upper airway surgery, and it is an effective treatment for moderate-to-severe OSA in adolescent patients (14).

However, there is no consensus about reducing OSA in adolescents with DS using HNS. In 2016, the first case of HNS for OSA in adolescents with DS was reported (15). Although most research in recent years have shown that HNS is a better option, these studies have limitations in terms of sample size, in follow-up duration, and in documentation of complications (16).

To the best of our knowledge, this is the first review of HNS for treating OSA in adolescents with DS based on the existing research. We sought to evaluate the efficacy and adverse effects of HNS in adolescents with DS and OSA and to clarify the underlying processes of HNS for treating OSA.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (17). Ethical approval is not required for this review.

Search strategy

A systematic search was carried out through PubMed, Web of Science, Embase, and Scopus databases. The search strategy used a combination of Medical Subject Headings (MeSH) and free words with "OR" and "AND." Retrieval words included "DS," "Trisomy 21," "OSA," "sleep apnea syndromes," "HNS," and "upper airway stimulation." The detailed retrieval strategy is available in Supplementary material. The final literature search was completed on June 25, 2022. Two reviewers (WK and KZ) independently qualified the studies and extracted the data. Differences were resolved through discussion between the two reviewers.

Inclusion and exclusion criteria for study selection

The requirements for studies to be included were as follows: (I) Types of participants – adolescents (the age ranges from 10 to 21 years) (18) with DS and OSA; (II) type of intervention - HNS; and (III) type of language - English. The exclusion criteria included relevant publications, reporting of only surgeries, cell experiments, comments, no outcomes, not adolescents, and repeat investigations.

TABLE 1 A summary of studies on hypoglossal nerve stimulation for adolescents who had down syndrome and OSA.

References	Study design	Cases (*n*)	Age	Treatment assessment	Intervention time (h)	Voltage titration (v)	Follow-up duration (months)	Main results	Adverse events	Conclusions	Risk of bias
Yu et al. (18)	Prospective single-group multicenter cohort study	42	15.1 ± 3.0	PSG, ESS, OSA-18	9.0 ± 1.8/night	Changed but no more than 1.0	12	AHI was decrease ($P < 0.05$); OSA-18 and ESS score was improved ($P < 0.05$); the most common complication was temporary oral discomfort (11.9%).	Yes	HNS is able to be safely performed.	Good
Kay et al. (20)	Case report	1	13	HSAT, PSG, CAI, CO2%	10.5/night	1.6,1.9,2.0	8	8 months after surgery: sleep efficiency improved; AHI decreased from 44.9 to 12.2; min CO2%:90%.	No	HNS is effective in reducing OSA burden.	Poor
Yu et al. (21)	Prospective longitudinal, multicenter single-arm trial	20	15.5	PSG, OSA-18,ESS	NA	Unclear	12	The mean decrease in AHI was15.1 ($P < 0.001$); OSA-18 and the ESS score was lower.	No	HNS treatment is safe and effective	Good
Grieco et al. (22)	Prospective study	9	15.2±3.4	PSG; Neurocognitive and behavioral testing	Unclear	Unclear	6.5	There was a significant mean decrease in AHI by 11.0 ($P < 0.05$); all neurocognitive and behavioral testing scores are improved.	No	The benefits are reduced AHI and improved some neurocognitive and behavioral outcomes.	Fair
Stenerson et al. (23)	Case series	4	10–13	PSG; OSA-18	Unclear	1.5, 1.8, 1.9, 2.1,2.2, 2.8	44–58	AHI decreased by at least 50% in all participants; OSA-18 scores improved in 3 participants; but 2 participants exhibited severe OSA when the device was turned off.	No	HNS effectively controls their OSA, but their underlying untitrated OSA appears to persist into adulthood.	Good
Karlik et al. (24)	Case series	3	10–19	PSG; Anesthetic and medications	Unclear	No	Unclear	The average AHI change was 87.4%; tailored anesthesia protocols improve patient outcomes.	No	HNS combined with individualized perioperative management can improve OSA symptoms in patients	Good
Caloway et al. (25)	Case series	20	The median 13.75–17.25	PSG, OSA-18	The median 9.21/night	Unclear	2	Median percent reduction in AHI of 85%; The median OSA-18 score	Yes	HNS treatment effectively reduced	Good

(Continued)

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TABLE 1 (Continued)

References	Study design	Cases (*n*)	Age	Treatment assessment	Intervention time (h)	Voltage titration (v)	Follow-up duration (months)	Main results	Adverse events	Conclusions	Risk of bias
								reduction was 1.15		the patient's AHI score and improved quality of life.	
Diercks et al. (26)	Case report	6	12–18	PSG; OSA-18	5.6–10/night	No	6–12	Demonstrated a 56% to 85% reduction in AHI; the total score for OSA-18 improved (1.5±0.6).	Yes	HNS is a potential therapeutic option.	Good
Diercks et al. (15)	Case report	1	14	PSG	8–9/night	1.3,1.4,1.5	5	Baseline of AHI was 48.5; with increasing stimulation voltage (1.1–1.5v), AHI decreased (10.6–3.4 events/h).	No	HNS is well tolerated and significantly improved OSA.	Fair

HGS, Hypoglossal nerve stimulation; AHI, Apnea-hypopnea index; PSG, Polysomnographic; ESS, Epworth Sleepiness Scale; OSA-18, A validated, disease-specific quality of life instrument for OSA; HSAT, Wrist-based home sleep apnea test; CAI, central apnea index; CO2%, Oxygen saturation; ODI, Oxygen desaturation index.

Data extraction

Two reviewers (WK and KZ) extracted data using Excel (Microsoft Inc., USA) spreadsheet. The data included were as follows: authors, year of publication, study design, voltage titration, sample size, age, treatment assessment, intervention time, follow-up duration, main results, adverse events, and conclusions.

Assessment of risk of bias

Two reviewers (WK and KZ) independently evaluated the selected articles. The quality of the articles included in this review was assessed using the National Institutes of Health quality assessment tools (observational cohort studies and cross-sectional studies) (19). The quality of each article was rated as "good," "fair," or "poor" according to its overall quality score. Any disagreement was resolved by consensus through discussions between the two reviewers.

Statistical analysis

Mean differences (MD) were calculated to create forest plots of continuous data to analyze the variations in the apnea-hypopnea index (AHI) and A validated, disease-specific quality of life instrument for OSA (OSA-18) between HNS and non-HNS. We merged data using Review Manager 5.3 software. The test was regarded as statistically significant when the P value was <0.05 and 95% confidence intervals (CIs) were given. The Q statistic, with a significance level of $P < 0.10$, was used to investigate the heterogeneity of Mean differences. The study was divided into two groups according to whether the number of cases was >10, and a subgroup analysis was conducted. The random-effects model was employed throughout the analysis.

Results

Search outcome

A total of 92 articles were obtained from the 4 databases, out of which 41 articles remained after excluding the duplicate ones. The literature was then further screened using the article titles and abstracts and 20 irrelevant articles were excluded. Next, two abstracts without full text, one surgical procedure study, one with cellular experimental study, four review articles, one no result article, and three non-adolescent studies, were also excluded by full-text literature identification. Ultimately, 9 studies met the inclusion criteria for this systematic review.

A total of 106 patients were included in all investigations; three articles had a sample size with more than 10, while 6

articles had a sample size of no more than 10 cases. The first related publication was published in 2016. Further, an article was published each, in 2017, 2019, and 2020 years. Because of the rising interest in this topic, four relevant articles were published in 2021. Table 1 summarizes the studies included in the review. The flow chart of the literature search is shown in Figure 1.

Treatment outcomes

AHI

All the studies showed that patients receiving HNS experienced a significant decrease in AHI, based on the Polysomnography (PSG) results. Diercks et al. reported the first case of HNS treatment for a 14-year-old boy, whose AHI dropped from 48.5 to 3.4 events/h (15). Yu et al. followed 42 patients for a year; the findings revealed that the average AHI decreased by 12.9 ± 13.2 events/h, 65.9% of the patients experienced a 50% decrease in AHI, and 73.2% of the patients had an AHI of <10 events/h (18). After excluding 2 case reports, a total of 104 patients were included in the analysis; pooled data revealed significantly lower AHI in patients after HNS (mean AHI reduction 17.43 events/h, 95% CI 13.98–20.88 events/h, $P < 0.001$); however, there was moderate heterogeneity between the studies ($I^2 = 42\%$, $P = 0.11$). The forest plot of studies investigating AHI is shown in Figure 2.

Quality of life

Five studies used the OSA-18 (a validated, disease-specific quality of life instrument for OSA) and Epworth Sleepiness Scale (ESS) questionnaires, to examine the improvements in treatment durations (18, 21, 23, 25, 26). As a result, it improved their sleep quality and subjective feelings. Kay et al. found that

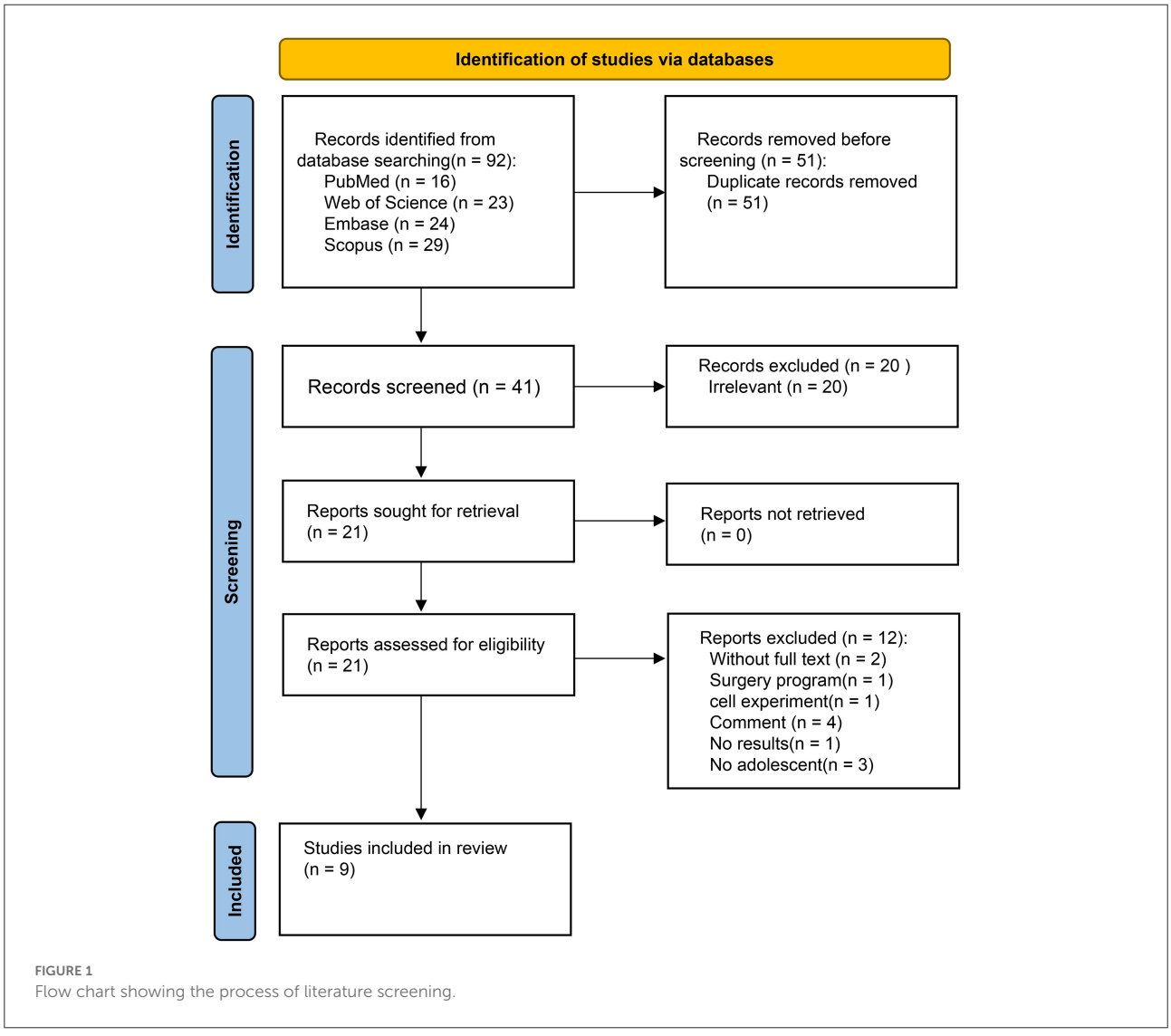

FIGURE 1
Flow chart showing the process of literature screening.

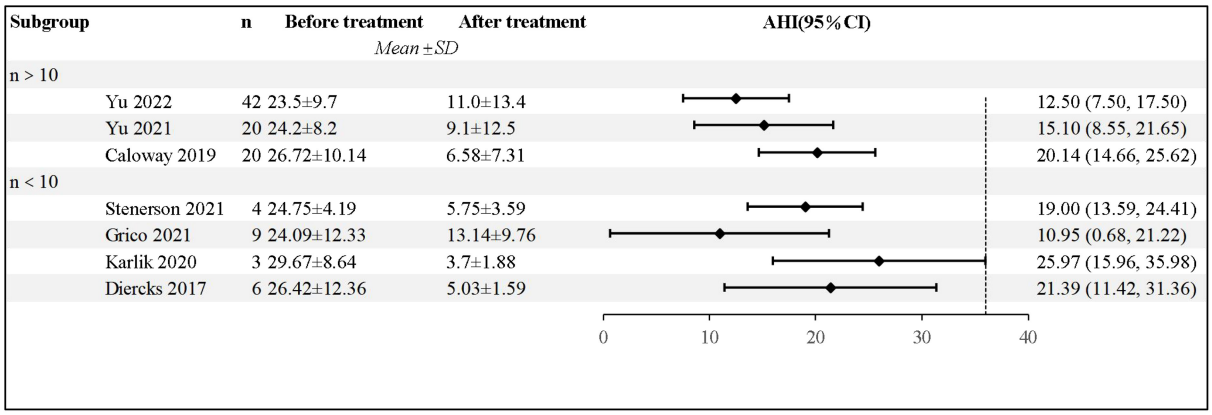

FIGURE 2
The forest plot of studies investigating AHI.

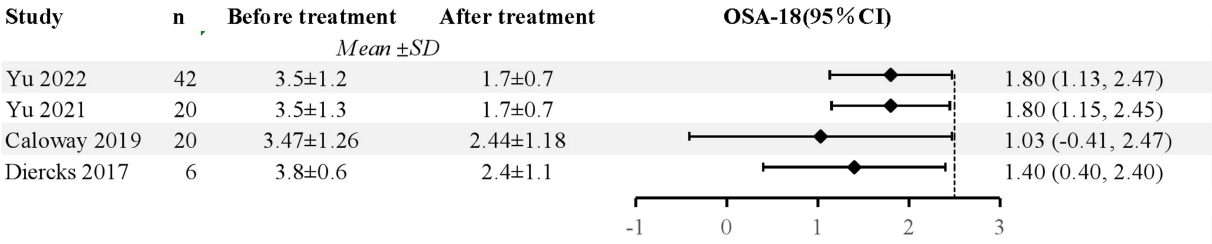

FIGURE 3
The forest plot of studies investigating OSA-18.

snoring, daytime sleepiness, behavioral problems, and supine sleeping improved in these patients (20). According to two studies, HNS can decrease patients' ESS scores in terms of sleep quality (18, 21). In addition, Greco et al. found that participants' neurocognitive and behavioral outcomes were also amended (22). A total of 88 patients were included after 5 studies were excluded, and the pooled data revealed significantly decreased OSA-18 in patients following HNS (mean OSA-18 reduction 1.67, 95% CI 1.27 to 2.08, $P < 0.001$), and there was no evidence of study heterogeneity ($I^2 = 0\%$, $P = 0.43$). The forest plot of studies investigating OSA-18 is shown in Figure 3.

Voltage

Four investigations examined the necessity to optimize stimulation voltage for arousal during treatment (15, 18, 20, 23). According to research, AHI decreases as stimulation voltage increases, with 21.1 events/h at 1.3 V, 3.7 at 1.4 V, and 3.4 at 1.5 V (15). The remaining five investigations, however, did not specifically record any information regarding the titration voltage (21, 22, 24–26).

Follow-up duration

Most researchers followed patients with DS and OSA for a short duration. Only one study had a follow-up duration of 44 to 58 months (23), two studies had <6 months (15, 25), five studies had 6 to 12 months (18, 20–22, 26), and one study provided no details regarding follow-up duration (24). Noticeably, two participants had a persistently moderate OSA after 44–58 months of follow-up, postoperatively (23).

BMI

Eight studies stated that HNS treatment should consider the influence of body mass index (BMI) factors (15, 18, 20, 21, 23–26), and five advised that patients should have a BMI of <32 kg/m^2 (15, 18, 21, 23, 26). However, only two studies performed BMI data analysis. There were 11 patients with BMI in the 85th percentile or greater. Five (45.5%) of these 11 patients responded to therapy, compared to 44.4% of patients with a BMI under the 85th percentile ($P = 0.96$) (21). Age- and sex-adjusted BMIs ranged from 19.2 to 24.6 kg/m^2 at baseline, and from 19.8 to 34.6 kg/m^2, and BMI percentiles increased for 3 of the four patients (23).

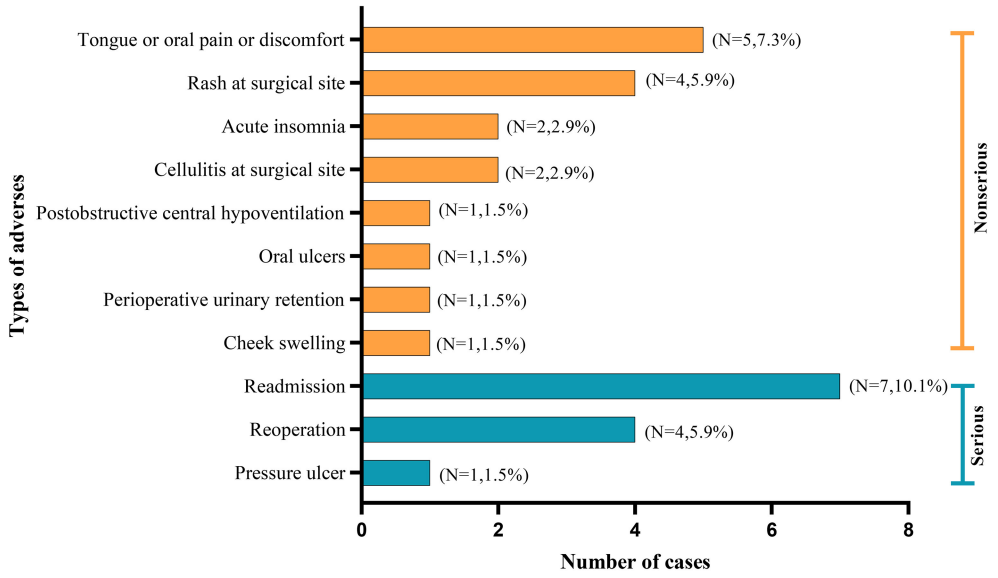

FIGURE 4
The distribution of complications of studies included in the systematic review.

Complications

Pain or discomfort in the tongue or oral cavity, were the most common complications. Notably, three studies documented the occurrence of serious adverse events, such as the incidences of reading and reoperations (18, 25, 26). The distribution of complications is shown in Figure 4.

Discussion

In this review, we investigated the therapeutic effects of HNS for OSA in adolescents with DS, the enhancement of participants' quality of life, and the benefits of the intervention, based on the current literature. In addition, we discussed its potential therapeutic mechanism. After receiving HNS therapy, all participants experienced a significant reduction in AHI. Participant's OSA-18 and ESS scores also indicated noticeable improvements in some studies. Therefore, HNS can be considered as an effective treatment for OSA in adolescents with DS and is a better tolerated option than CPAP or equally well tolerated option than CPAP.

OSA is a complex condition that demands a multimodal treatment strategy, particularly for adolescents with DS, due to the abnormalities in their airway structure (27). Nowadays, tonsillectomy, adenoidectomy, and CPAP are reliable options used to alleviate OSA (28). However, even after surgery or after CPAP use is discontinued, the condition can persist (29). Previous studies have proven that HNS is an effective treatment option for OSA in adults, particularly for those who cannot tolerate CPAP therapy (30). According to a single-center study, the mean AHI for patients with OSA who were treated with HNS decreased from 38.9 ± 12.5 to 4.5 ± 4.8, whereas the mean AHI for those who underwent uvulopalatopharyngoplasty surgery decreased from 40.3 ± 12.4 to 28.8 ± 25.4 (31). Consequently, HNS appears to have a more favorable therapeutic outcome than uvulopalatopharyngoplasty surgery for patients with OSA.

With the advancement of medical technology, electrical stimulation devices have shown numerous benefits in treating OSA. According to research, the loss of genioglossal muscle tone is strongly correlated with airway collapse (32). A hypoglossal nerve stimulator comprises of an implantable pulse generator (IPG), a pressure sensor to detect breathing, and a stimulation lead connected to the sublingual nerve (33). The pressure sensor monitors chest wall motion, allowing the IPG to signal the end of expiration and the beginning of inspiration. The stimulation is subsequently delivered to the hypoglossal nerve through the IPG, and the stimulation leads can specifically activate certain branches of the hypoglossal nerve, which enhances the stiffness and protrusion of the tongue (34). Tongue protrusion expands the cross-sectional dimensions of the airway, consequently facilitating the patient's airway; and thus, preventing airway collapse (35).

The degree of AHI reduction and quality of life improvement, are the essential measures to monitor the effectiveness of therapeutic modalities for treating OSA. All the adolescents included in this systematic review had used CPAP before receiving HNS therapy, but none of them was able to tolerate it. The PSG of all the participants showed a significantly lower AHI score during the HNS therapy, than that before receiving it. This result is comparable to that obtained using

typical pediatric CPAP treatment. According to King et al., CPAP therapy decreased the AHI of pediatric patients from 9.8 (5.7–46.0) to 3.3 (0.4–2.2) (36). Interestingly, one study found that discontinuing HNS did not immediately revert patients to their initial AHI level (23). In addition, employing the ESS and OSA-18 questionnaires, it was determined that the quality of life of these patients improved after receiving HNS treatment (18, 21, 23, 25, 26).

Although there are positive findings on the efficacy of HNS in adults, the data are inconsistent. Zhu et al. followed 82 patients with moderate-to-severe OSA for 4 years and found that the stimulation threshold of the hypoglossal nerve remained constant (37). Further studies are needed to determine if this phenomenon occurs during the treatment of adolescents.

The voltage threshold of HNS is also an important factor to consider and to investigate. In adolescents, the voltage threshold for HNS may differ from that of adults. Since adolescents with DS are going through a particular stage of rapid physical growth, the efficacy and safety of HNS treatment should be focused on. While four studies have been examined at titrating stimulation voltage, none have precisely investigated how variations in voltage stimulation intensity affect the efficacy of the HNS treatment. Diercks et al. observed that increasing stimulation voltage during HNS treatment significantly reduced the AHI of patients (15). The threshold of voltage stimulation required for adolescents did not seem to change with age.

So far, it is unknown whether higher voltage stimulation is necessary during HNS therapy to obtain improved efficacy. According to certain studies, HNS can effectively control OSA in adolescents with DS, but the underlying OSA is likely to continue until adulthood (23). Therefore, a longer period of follow-up is required to evaluate the long-term effectiveness of HNS for adolescents with DS and OSA.

It is well recognized that adolescents with DS suffer from cognitive impairment and that prolonged sleep hypopnea might worsen this impairment (38). Furthermore, adolescents are still in a crucial stage of intellectual and cognitive development; and thus, they may benefit from early OSA treatment. A study of neurocognition and behavior in nine adolescents treated with HNS found that these participants had better neurocognitive and behavioral scores after 6.5 months of treatment for an average of 15.2 $\pm$ 3.4 h per day (22). The actual treatment of adolescents requires more effort from their families daily. Nevertheless, HNS therapy can effectively reduce the burden on families.

BMI may have a significant impact on HNS treatment outcomes. The Food and Drug Administration (FDA) has recommended HNS for treating OSA in neurotypical adults with an AHI $<$50 events/h, a BMI $<$32 kg/m^2, and no circumferential airway collapse at the level of the velopharynx (12, 39). Adolescents with DS are still in a crucial stage of BMI (40). According to one study, increased BMI during treatment may explain the necessity for voltage titration (23). Currently, no more data exists to determine how the BMI of Adolescents with DS affects the therapeutic effect of HNS.

Adolescents with DS who were treated with HNS may experience complications or adverse events. Therefore, understanding the reasons behind adverse occurrences and their consequences can help improve therapeutic outcomes. Three studies reported adverse events, such as tongue or mouth pain, rash, tissue inflammation, cheek swelling, irritation-related discomfort, insomnia, pneumothorax, and swallowing or speech-related problems. These adverse events were primarily caused by device displacement, infection, device migration, and poor postoperative pain control. If the patient has a small chest, the stimulator could become squeezed by the beating heart (41). As the patient ages and their body size increases, it is vital to evaluate whether the length of the device wires is sufficient. Therefore, we could reduce complications by selecting an appropriate surgical site and a matched electrical stimulation device, avoiding migration of the device and lead requires adequate anchoring and limited sac dissection during device placement, and reducing oral discomfort or pain by titrating the voltage. Fortunately, no permanent injuries, life-threatening illnesses, or deaths have been reported in the literature.

This review has some limitations. First, the sample sizes of the included studies were limited, and several were case reports. Also, none of these studies had a control group. Thus, these investigations might be affected by research bias. Second, the safety of HNS therapy and the reasons behind some adverse events, including some severe ones, weren't fully understood by these investigations. Additionally, there was no record of adolescent tolerance to electrical stimulation in these investigations. It is important to consider the safety of HNS therapy and guard against adverse outcomes. Third, the follow-up duration of these participants was typically limited, and the long-term consequences of HNS on adolescents with DS and OSA remains unknown. Therefore, large-scale, prospective, randomized controlled, multicenter studies, are required in the future.

Conclusions

In conclusion, HNS can significantly reduce the AHI and improve the quality of life of adolescents with DS, and can be considered as a potential alternative treatment for OSA. As adolescents get older, more studies are required to fully demonstrate the effectiveness of HNS, with a greater focus on potential complications, adverse events, long-term efficacy, comfort, and cost-effectiveness throughout HNS treatment. Comprehensive therapy protocols incorporating two or more therapeutic techniques, including CPAP, upper airway surgery, and HNS, are also worthy of investigation. Currently, HNS has not yet received FDA approval for pediatric patients, which has restricted its widespread clinical application.

Data availability statement

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

Author contributions

PL: conceptualization, methodology, writing, review and editing, and approval for final version. WK and KZ: investigation, data curation, formal analysis, and approval for final version. CF: investigation, data curation, software, and approval for final version. XD: methodology, writing—review and editing, and approval for final version. XM: conceptualization, writing, review and editing, and approval for final version. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1037926/full#supplementary-material

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The role of neuromuscular function in sleep apnea pathogenesis and management: A consensus of experts

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Study objectives: Although the importance of upper airway assessment in the consideration of obstructive sleep apnea (OSA) is recognized, there are current limitations in our approach to assessment.

Methods: We convened a group of experts in upper airway neuromuscular physiology and anatomy, sleep apnea endophenotypes, novel therapeutics and sleep epidemiology to summarize existing literature and delineate future opportunities to utilize and incorporate innovative and less invasive techniques focused on upper airway neuromuscular physiology to assess and manage OSA.

Results: In OSA, genioglossus electromyogram (EMG) activity is reduced during sleep onset with higher levels observed during wakefulness compared to controls. Surface EMG recordings are limited due to distance from the actual muscle and while needle EMG offers more direct assessment, this approach is more invasive. Novel alternatives overcoming these limitations to assess upper airway neuromuscular physiology in OSA may therefore prove beneficial. Specifically, such an approach would facilitate identification of upstream prognostic biomarkers of OSA clinical trajectory and offer more informative mechanistic data. Novel approaches to neuromuscular assessment in OSA would enhance phenotyping to predict better tolerance to positive airway pressure therapy and set the stage to target neuromuscular function and upper airway anatomy. A quantifiable and repeatable neuromuscular physiologic metric has potential to facilitate a precision medicine strategy and personalize treatment, including measuring treatment response to neurophysiologic-focused interventions including hypoglossal nerve stimulation (HGNS), myofunctional therapy and neuromuscular electrical stimulation. A key area for future investigation is whether observed neuromuscular changes can identify patients at future risk of OSA, facilitating early intervention or prevention strategies.

Conclusions: Overall, recognizing the critical contributions of abnormalities of upper airway neuromuscular function to the pathophysiology of OSA, it may be important to find accurate and reproducible neurophysiological assessments to address existing knowledge gaps in OSA assessment and management.

KEYWORDS

obstructive sleep apnea, neuromuscular function, polysomnography, pathogenesis, upper airway

Introduction

Obstructive sleep apnea (OSA) is a common disease with major neurocognitive and cardiometabolic sequelae (Jenkinson et al., 1999; Gottlieb and Punjabi, 2020). OSA is estimated to affect up to 1 billion people worldwide with the majority of disease remaining undiagnosed and untreated (Benjafield et al., 2019). Diagnostic strategies for OSA have evolved over time from gold standard polysomnography (PSG), which is often regarded as cumbersome and expensive to home sleep apnea testing (HSAT) which provides adequate diagnostic accuracy albeit imperfect (Kuna et al., 2011; Rosen et al., 2012). Despite ongoing efforts, the mechanistic insights which are derived from sleep diagnostics are currently minimal, suggesting a need for more advanced approaches.

OSA pathogenesis is recognized to involve a complex interplay of soft tissue/craniofacial structure, neuromuscular dysfunction, arousal threshold and control of breathing abnormalities (Younes, 2003, 2004; Jordan et al., 2014). Many patients develop OSA primarily due to anatomical abnormalities including increased size of the upper airway soft tissue structures (tongue, soft palate, lateral pharyngeal walls, tonsils, etc.) or small bony craniofacial structures (e.g., retrognathia, micrognathia), while in other patients abnormalities in upper airway dilator muscle function, control of breathing, or arousal threshold play a more prominent role (Edwards et al., 2014). Some patients have combinations of abnormalities that contribute to OSA (Edwards et al., 2016). These underlying mechanisms or endotypes may be important to guide personalized therapeutic interventions and may facilitate mitigation of apnea-related complications if adequately addressed (Malhotra et al., 2020).

At present, the gold standard for OSA diagnosis remains PSG, but this test is relatively cumbersome and expensive and not readily available for large portions of the population (Mulgrew et al., 2007; Kuna et al., 2011). HSAT is increasingly accepted as an alternative approach given less burden and expense. However, both PSG and HSAT generally fail to discriminate among the various mechanistic subtypes of OSA that might inform the personalized therapeutic decisions. Moreover, neither HSAT nor PSG is sufficiently accessible within existing medical insurer coverage paradigms to allow repeated administration as a means of serial testing e.g., in response to therapy. In addition, neither test can be administered in the clinic to provide straightforward assessment at the point of care. While deriving endophenotypes from PSG data is an area of active research (Sands et al., 2018a), the increasing reliance on HSATs, which provide less data than PSG, may hinder the widespread implementation of precision medicine approaches that are dependent on PSG data. Moreover, there is no currently available diagnostic tool that is predictive of the future development of OSA in at-risk individuals or progression of OSA in those with mild disease.

The ideal diagnostic test for OSA would provide reliable and reproducible information in terms of identifying patients who will benefit from interventions. It would be inexpensive, easy to use and non-invasive to allow widespread use of the technology and have high sensitivity and specificity for OSA. It would also be readily accessible in the clinic to allow straightforward assessment at the point-of-care (Montesi et al., 2012). The approach would ideally integrate characterization of mechanistic aspects of OSA. In addition, the ability to make serial assessments of OSA severity and provide information regarding underlying mechanisms longitudinally with ease and minimal burden to patients would provide an opportunity to use the technique to guide therapy and to gauge therapeutic response, e.g., to titrate medications or neuromuscular training/stimulation. As a point of emphasis, a technique to assess OSA severity may be useful diagnostically whereas another technique to allow determination of OSA mechanisms may provide therapeutic guidance. In theory, one method could inform both diagnostics and therapeutics although these two distinct goals need to be considered when validating and implementing new methods. Taking into consideration patient preference is also critical to ensure patient receptivity with implications on engagement in the diagnostic process as well as ultimately treatment adherence as indicated (Table 1).

Given the impact of OSA and limitations of current diagnostic and management approaches, we convened a panel with expertise inclusive of upper airway neuromuscular physiology and anatomy, sleep apnea endophenotypes, novel therapeutics and sleep epidemiology to discuss the potential of neuromuscular function measurement in the assessment of OSA. Our objectives included summarizing the current literature and identifying opportunities for future research and product development. The session was sponsored by Powell Mansfield, Inc., but the sponsor had no role in the academic content or in drafting the manuscript. Mansfield, Inc. is a parent company with subsidiaries of OSA diagnostic companies including Powell Mansfield.

Unmet needs in OSA evaluation and diagnostics

The current practice of sleep medicine relies on diagnosis of established OSA; however, there may be antecedent abnormalities which could identify people destined to develop OSA in the future or who may have transient risk of OSA, for example in pregnancy and during procedural anesthesia and sedation. Although at present, we do not have robust preventative strategies for OSA beyond the general health measures of diet and exercise (Awad et al., 2012; Carneiro-Barrera et al., 2022), a technique that allowed early identification of a high-risk population could facilitate development and testing of novel preventive approaches, and also facilitate targeting of intensive

TABLE 1 Ideal obstructive sleep apnea-specific diagnostic challenges characteristics of potential solutions.

Obstructive sleep apnea-specific diagnostic challenges to address	Attributes	Benefits
Neurophysiologic-focused endophenotypes	Provides mechanistic data	Facilitates precision medicine approach
Large, global disease burden	Sensitive for disease	Screening and diagnostic utility
Expense of diagnostics	Specific for disease	Avoid unnecessary additional testing
Apnea hypopnea index imperfect	Correlates with disease severity	Quantify disease burden, prioritize therapy
Currently a one-size-fits all approach	Treatment responsive	Measure and monitor treatment response
Polysomnography not readily available and cumbersome	Point-of-Care	Efficiency, accessibility, scalability
Expense of diagnostics	Inexpensive	Accessibility, scalability, cost-savings
Polysomnography is cumbersome and inconvenient	Non-invasive	Patient satisfaction and ease of use
Manual scoring is labor-intensive	Easily measured	Does not require major expertise to assess
Current standard is single night testing	Quantitative metric	Serial assessment
Patient-centered decision making	Consideration of patient receptivity and preference	Enhanced adherence and patient satisfaction

lifestyle intervention to those most likely to benefit. One situation where prognostication would have immediate value would be in the perioperative setting (Ayas et al., 2018). Patients without OSA may manifest OSA postoperatively in the context of benzodiazepine and opioid administration (Robinson et al., 1985, 1987; Ayas et al., 2018). Such patients are likely at risk for OSA pre-operatively, but are only identified postoperatively in the face of perturbations. Although questionnaire-based approaches have been shown to have value in OSA screening in the post-operative setting (Chung et al., 2008), approaches with higher accuracy and integrating direct neuromuscular upper airway physiology may improve efficiency of OSA diagnostic paradigms in the post-operative setting with the potential to improve outcomes.

Several practical challenges exist with the current diagnostic paradigm in OSA such as cost, efficiency, accessibility, and scalability. The gold standard PSG is a time-consuming and costly test with limited availability for large portions of the population, involves multiple clinical steps and is performed under atypical sleeping conditions in a sleep lab. The emergence of HSAT has clear value as it has enhanced accessibility and facilitated the diagnosis of OSA without the need for in-laboratory PSG for many patients. However, HSAT has its own limitations, including lack of a sleep assessment for many devices (Malhotra and Ayas, 2020). Although clinical experience suggests utility in the context of patients with major comorbidities, data validating its use in this context are relatively weak. HSAT often involves Level 3 testing without electroencephalogram, thereby limiting accuracy of sleep apnea severity assessment as monitoring time rather than sleep time is used in the calculation of the apnea hypopnea index (AHI) and electroencephalographic (EEG) arousals are not considered with the scoring of hypopnea events (Berry et al., 2022). This situation results in increased likelihood of false negative results, particularly in those with more mild or subtle sleep-disordered breathing. The multi-faceted aspects of the ideal diagnostic test for OSA have been described, and would provide informative mechanistic data with ease and little burden while generating sensitive and specific measures of OSA that track with disease severity and treatment responsiveness (Montesi et al., 2012).

In addition to the practical challenges, current diagnostic approaches frequently fail to provide mechanistic insight into the pathophysiology of OSA in an individual patient. Several investigators have attempted to improve mechanistic insights gleaned from PSG using sophisticated signal processing algorithms (Orr et al., 2018; Sands et al., 2018a), although the clinical utility of these methods has yet to be validated. While these efforts are ongoing with respect to both HSAT and PSG, given the importance of upper airway neuromuscular function to OSA pathogenesis (discussed below), direct measurement of neuromuscular function offers a promising approach that may provide valuable mechanistic information to the more routinely available HSAT and PSG metrics. While traditional methods of neuromuscular assessment are invasive and impractical for routine clinical use, newer non-invasive techniques may be more widely applicable. That said, in this context, an important nuance that bears mention is the difference between OSA endotype (which provides mechanistic information about the mechanisms underlying OSA) versus phenotypes (clinical expression of disease ranging from asymptomatic to severe sleepiness).

Unmet needs in OSA therapeutics and management

The current gold standard for OSA treatment is continuous positive airway pressure (CPAP). CPAP is highly efficacious for control of OSA in most patients and may have transformative benefits for patients who use it consistently, as it can produce major improvement in symptoms and associated improvement in blood pressure, snoring and perhaps cardiovascular risk (Pepperell et al., 2002; Marin et al., 2005). Despite its efficacy, CPAP is not always well tolerated, thus limiting its effectiveness (Schwab et al., 2013). Efforts to improve CPAP adherence are ongoing using intensive education and support, modern technology allowing patient engagement, innovative sleep scoring of the diagnostic PSG to identify patients who are more likely to use CPAP and efforts to improve the patient experience *via* mask fitting, facilitating nasal patency (Hoy et al., 1999; Malhotra et al., 2018; Benjafield et al., 2021; Younes et al., 2022),

etc. Enhanced OSA phenotyping represents an opportunity area that may allow for ability to predict better tolerance or intolerance to CPAP therapy. However, intolerance or suboptimal adherence to CPAP are likely to continue to limit its effectiveness in many patients.

Therefore, the field of sleep medicine is moving beyond the one-size-fits all approach to treatment (Mazzotti et al., 2019) with CPAP therapy. Alternative therapies exist that target either upper airway anatomy (e.g., mandibular repositioning devices and surgical modification of the upper airway) or neuromuscular function (e.g., hypoglossal nerve stimulation (HGNS), myofunctional therapy, neuromuscular electrical stimulation) (Guimaraes et al., 2009; Maghsoudipour et al., 2021; Nokes et al., 2022a,b). These alternative therapies are individually less efficacious than CPAP, however, underscoring the need for accurate and reliable endotypic and phenotypic measures to identify patients likely to benefit from these different interventions. Specific endotypes such as arousal threshold and high loop gain have been derived as endo-phenotyping using polysomnography (PUP) with clinically meaningful applications (Sands et al., 2018b). Neuromuscular physiologic mechanistic data independent of (or complementing) diagnostic HSAT or PSG data may be valuable in identifying specific OSA endotypes that would guide a more personalized approach to disease management. Integration of point of care already described endotypic measures such as breath-hold responses for loop gain (Messineo et al., 2018) or blood sample testing [e.g., bicarbonate levels (Zou et al., 2023)] combined with novel approaches to ascertain upper airway neuromuscular function has potential to considerably advance and optimize current clinical approaches. If a quantifiable and repeatable metric could be developed, it could facilitate a precision medicine strategy and personalize treatment, including measuring treatment response.

As one example, HGNS is FDA approved and while there are data to suggest individual characteristics which predict response to therapy, there is a need for further refinement to identify *a priori* patients who are likely to respond to (or fail) the intervention (Bachour et al., 2021). Some data suggest that age, gender, body mass index may have predictive value (Heiser et al., 2019; Pascoe et al., 2022), but a rigorous evaluation of neuromuscular function may offer biologically relevant insights to predict treatment response. The use of drug-induced sleep endoscopy (DISE) is typically used to stratify the candidates for HGNS based upon type of anatomical collapse, but this approach is invasive, and expensive and may have issues around reproducibility of collapse type (intra and inter-observer on repeated measures). Thus, there is an opportunity to investigate and develop alternative methods to risk stratify patients prior to HGNS to improve treatment response and clinical outcomes.

An increasing body of evidence indicates that myofunctional therapy targeting the upper airway muscles during wakefulness may improve OSA severity and symptoms in mild-to-moderate OSA (de Felicio et al., 2018; Hsu et al., 2020; O'Connor-Reina et al., 2020; Rueda et al., 2020; Carrasco-Llatas et al., 2021). Standardized approaches to assess the evaluation of the stomatognathic system have been validated using the orofacial myofunctional evaluation (OMES) protocol which has facilitated ability to diagnose orofacial myofunctional disorders (de Felicio et al., 2010). Approaches involving soft palate elevation, tongue and buccofacial exercises (de Felicio et al., 2018) applied several times per week have led to significant improvements in AHI and Epworth Sleepiness Scale scores in OSA patients compared with controls (Hsu et al., 2020; Rueda et al., 2020). However, the factors– including neuromuscular physiology– determining which patients are most likely to respond, as well as optimal approaches to therapy, remain unclear and require further investigation.

Another area of interest is the use of neuromuscular electrical stimulation to activate and train upper airway muscles (Guimaraes et al., 2009; Nokes et al., 2022a,b). While randomized studies have not yet been reported, studies with a daytime oropharyngeal stimulation intervention have shown improvement in snoring and mild sleep apnea with this intervention (Guimaraes et al., 2009; Nokes et al., 2022a,b). However, at present, we lack an ability to predict a priori who may respond to this intervention, perhaps suggesting that an assessment of neuromuscular function may have value in distinguishing responders and non-responders. Of note, prior physiological studies in OSA have shown increased strength of the genioglossus on a tongue protrusion task, but with reduced endurance compared to controls (Eckert et al., 2011). Neuromuscular electrical stimulation has been shown to improve endurance in physiological studies, although research is ongoing in this area (Nokes et al., 2022b). *In vitro* studies have similarly demonstrated increased fatigability of human genioglossus samples from non-obese OSA patients compared with controls or CPAP-treated OSA patients (Carrera et al., 2004). These findings suggest a potentially modifiable aspect of upper airway neuromuscular function, although further data are clearly required.

Thus, at present, our ability to identify which patients are likely to respond to HGNS, myofunctional therapy or neuromuscular electrical stimulation remains unclear. A reliable technique utilized during sleep or wakefulness assessing neuromuscular function may therefore be helpful in guiding appropriate therapy. In theory, some patients who are amenable to these interventions could be identified and prioritized for daytime neuromuscular therapy, whereas patients unlikely to respond to daytime measures may be directed to alternative interventions.

Neuromuscular function in OSA

Considerable research has been performed regarding upper airway neuromuscular function in OSA (Kimoff et al., 2001; Nguyen et al., 2005; Kimoff, 2007). Several conclusions have been suggested, although debate is ongoing in this context. First, some evidence of sensory impairment has been observed in the upper airway although the pathophysiological relevance of these findings is unclear (Wallace et al., 2022). Second, regarding motor function, the genioglossus has been shown to have increased strength but reduced endurance in OSA compared to controls (Eckert et al., 2011). Third, a negative pressure reflex has been described whereby the genioglossus and other muscles in the upper airway will activate in response to a negative (sub-atmospheric, collapsing) pressure stimulus (Mathew, 1984). The negative pressure reflex has been shown to be increased not decreased in OSA compared to controls (Berry et al., 2003). Fourth, histological studies have been performed in biopsy specimens from patients with OSA (Series et al., 1995). Series et al. showed a highly trained upper airway muscle in OSA based on fiber type distributions (red, type 1, slow twitch fibers) compared to non-OSA controls (Series et al., 1995). Fifth, some authors have suggested that the mechanical output of the upper airway muscles may be impaired even with adequate neural stimulation (Patil et al., 2004; Jordan et al.,

2007). So-called "neuromechanical uncoupling" has been postulated although direct evidence has been more controversial. In aggregate the data suggest that upper airway neuromuscular function may be important for some but not all OSA patients.

The heterogeneity of the underlying pathophysiologic contributions to OSA has been recognized such that four main endophenotypic traits have been identified, i.e., (1) pharyngeal anatomy/collapsibility, (2) ventilatory control system gain (loop gain), (3) the ability of the upper airway to dilate/stiffen in response to an increase in ventilatory drive, and (4) arousal threshold (Jordan et al., 2014). Intersection with upper airway neuromuscular physiology can be influenced by and can influence these OSA pathophysiologic traits directly and/or indirectly. It has been speculated that upper airway sensory dysfunction in OSA may reflect an OSA-related neuropathic process which may also impact motor innervation (Saboisky et al., 2012a; Wallace et al., 2022). Indeed, several lines of evidence point to upper airway muscle denervation-reinnervation in OSA. Histopathologic studies of OSA upper airway tissue demonstrate fiber type grouping (Lindman and Stal, 2002), myocyte expression of neurotrophic factors (Boyd et al., 2004) as well as pathologic axonal and Schwann cell changes (Shah et al., 2018). In addition, conventional genioglossus intra-muscular electrode recordings by several groups have demonstrated classical denervation potentials (Svanborg, 2005; Saboisky et al., 2012a) in some OSA patients vs. controls. Vibration injury– perhaps in combination with hypoxia– has been suggested to contribute to the observed neuromuscular abnormalities in OSA (Saboisky et al., 2012b). While these changes clearly have the potential to impact upper airway motor function, their prevalence and pathophysiologic significance remain poorly understood. Further study will be required to determine if the observed neuromuscular changes can identify patients at future risk of OSA, facilitating early intervention or prevention strategies.

Assessment of neuromuscular function in OSA

A reliable technique for direct measurement of neuromuscular function has the potential to fill some of the unmet needs in OSA diagnosis and management. However, the sleep medicine field has faced multiple challenges with regards to assessing upper airway neuromuscular physiology. Sensory testing is notoriously subjective and cannot easily be performed during sleep (Nguyen et al., 2005). Upper airway muscle biopsies are invasive with attendant risk of bleeding and infection. Intramuscular EMG can be painful and also has modest risk (e.g., bleeding, infection), and cannot easily be applied to multiple locations within a muscle without repeated instrumentation (Malhotra et al., 2000a). Cost and accessibility have also limited the ability to assess neuromuscular function of the upper airway muscles. For example, intramuscular EMG requires costly specialized equipment that is not readily available. In addition, diagnostic interpretation of intramuscular electromyogram (EMG) recordings requires specialized training and expertise in the field of neurophysiology, making testing hard to standardize between patients and within patients on repeated measurements between physicians. Thus, efforts to optimize accuracy of these measurements are ongoing. Novel approaches to implement point-of-care neuromuscular physiological assessments of the upper airway in OSA are worth pursuing. For example, a protocol-based challenge involving sustained negative pressure through a mask or device to evoke neuromuscular output, i.e., an awake neuromuscular stress test can be considered.

The genioglossus is the best studied of the upper airway dilator muscles, although there are 23 pairs of muscles that are thought to be important in upper airway patency (Horner et al., 1991; Mezzanotte et al., 1992; Horner, 2000). The genioglossus is accessible and thus potentially the easiest muscle to study. In addition, it is a large muscle thought to have important mechanical influences on pharyngeal airway patency (Innes et al., 1995). The genioglossus is a phasic muscle (bursts with inspiration) and is state dependent (changes firing pattern from wakefulness to sleep) (Horner, 1996). At present the gold standard to assess genioglossus activity is intramuscular electromyography using needle or fine wire electrodes (Malhotra et al., 2000b), although it is best used for low-level short contractions and tends to be sensitive to the movement of the electrodes, and as noted above has the disadvantage of being invasive by nature (O'Connor et al., 2007). A simplified, non-invasive technique is therefore desirable for several reasons: to reduce patient discomfort; to reduce cost; to allow assessment of multiple muscles, providing a more thorough evaluation of upper airway neuromuscular function rather than relying on the assumption that genioglossus activity is representative of all the muscles in the upper airway; and to facilitate repeated measurements over time.

Recently, a new electrodiagnostic technology called transmembranous EMG has been developed that addresses some of these challenges (Menon et al., 2022). The technology uses a novel sensor and probe that allows a diagnostic assessment of the neuromuscular function of upper airway muscles without the need for intramuscular electrodes. The transmembranous EMG signal allows measurement of muscle activity but also provides diagnostic information regarding underlying pathologies e.g., myopathy, neuropathy, etc. Due to its minimally invasive nature, multiple muscles can be examined at many different locations without undue burden. Although muscle physiology assessments may have value if they allow the assessment of neuromuscular upper airway pathophysiology to become more accessible, there is need for foundational reproducibility studies and enhanced understanding of how collection of these daytime measures relate to sleep-specific OSA pathophysiology. Further validation of the method will be required and how best to integrate this approach clinically and in the research setting is still to be determined. Of note, additional potential value in use of the transmembranous EMG is to facilitate the assessment of active perception and tongue movement, not only passive, neuromuscular measurements (Guilleminault et al., 2019). One potential advantage of a neuromuscular assessment during wakefulness would be related to feasibility; however, its ability to predict behavior/function during sleep will need further investigation.

Future directions

Although the expert panel agreed on the importance of upper airway assessment in the consideration of OSA, there was also consensus about the need for further validation of newer techniques such as transmembranous EMG and demonstration of its utility in both research and clinical settings. Hence, there was discussion

TABLE 2 Consensus regarding opportunities for innovations in upper airway neuromuscular physiologic assessments in the diagnosis and management of obstructive sleep apnea.

Domain	Statements
Mechanistic	• Investigation of whether noninvasive upper airway neurophysiologic measurements and related endophenotypes also provide insight into disease mechanisms. Moreover, the addition of mechanistic insight may help in terms of patient management. • Clarifying prevalence of denervation or myopathic changes among OSA vs. non-OSA patients including the extent that these changes relate to symptoms, disease severity and disease progression. • Understanding how neurophysiologic measurements can be used to assess responses to targeted therapy. • Evaluating neurophysiologic differences across age, sex, race and other important OSA subgroups.
Diagnostic	• In theory, if a point-of-care inexpensive test were available in a clinical setting, a screen for OSA could be conducted on a large scale. A point of care test would have value if highly sensitive (help to rule out disease) or highly specific (help to rule in disease). One approach could be used to enhance existing screening methods such as questionnaires (STOP-BANG, MAP, Berlin) assuming it provided additional predictive value (Netzer et al., 1999; Chung et al., 2008).
Usability	• Ease of use of the neuromuscular test at the point of care and cross-disciplinary use from clinicians of different specialty type without specialized training to conduct the test and obtain a diagnostic interpretation is a key consideration.
Prognostic	• At present we do not have robust methods to prevent OSA beyond diet and exercise for weight management. However, patients may have high risk of developing future OSA based on neurogenic abnormalities. The appropriate treatment of these patients is unclear, but clinical studies could certainly target these high risk patients to prevent incident OSA and mitigate downstream consequences (symptom-based and adverse clinical outcomes) of untreated OSA if effective interventions were available.
Therapeutic	• Given that a number of interventions are now available to treat snoring and OSA targeting upper airway muscle physiology, a useful approach may be to follow these patients serially over time. In theory, hypoglossal nerve stimulation or daytime neuromuscular stimulation or training could be titrated to daytime neuromuscular pathophysiological assessments which might allow optimization of therapy. In addition, such findings may motivate patient behavior e.g., in the context of weight loss patients may be motivated to pursue and sustain diet and exercise interventions if they received supportive feedback regarding the efficacy of their interventions. • Therapeutic guidance could also be provided to patients averse to CPAP if pathophysiological data were helpful in determining the optimal non-CPAP intervention. • In pharmacotherapeutic approaches for OSA, optimal dosing of medications could potentially be facilitated by measurement of upper airway neuromuscular function assuming the mechanism of action of these medications is *via* enhanced hypoglossal motor output. For example, in the case of atomoxetine plus oxybutynin, the serial measurement of upper airway muscle dilator activity may have therapeutic value.

regarding potential future use cases for innovative and less invasive techniques spanning across OSA mechanistic, diagnostic, usability, prognostic, and therapeutic guidance domains (Table 2).

OSA is now recognized to be a heterogenous disease from the perspective of underlying pathophysiological mechanisms (endotypes) as well as in terms of varying clinical expression (phenotype). The mechanisms underlying OSA include collapsible pharyngeal anatomy, dysfunction in upper airway dilator muscles, low arousal threshold, and unstable ventilatory control as well as other factors. In theory, knowledge of underlying mechanism may guide therapeutic interventions, although rigorous outcome data are lacking regarding this approach. Oxygen or acetazolamide would be predicted to improve patients with unstable control of breathing (Edwards et al., 2012), whereas hypoglossal nerve stimulation or muscle training exercise may help preferentially those patients with upper airway dilator muscle dysfunction. Regarding phenotypes, the data suggest various clusters in which some OSA patients are asymptomatic, some have comorbid insomnia and some have daytime sleepiness (Ye et al., 2014). Of note, OSA patients with hypersomnia as well as comorbid insomnia (Lechat et al., 2022) are thought to be at cardiovascular risk, suggesting that only a subset of OSA patients may experience improvements in cardiovascular risk when treated for OSA. Therefore, recognition of OSA endophenotypes is challenging the "one-size-fits-all" approach of giving nasal CPAP to all OSA patients regardless of mechanism or symptoms (Bosi et al., 2017; Malhotra et al., 2020). Furthermore, as investigated in prior work (Overby et al., 2022), there is also a role for clinical decision-making tools based upon patient interactive physiologic assessments and endophenotypic risk for more personalized approaches to OSA diagnosis and management.

Overall, recognizing the critical contributions of abnormalities of upper airway neuromuscular function to the pathophysiology of OSA (Mazzotti et al., 2019) may be important to find accurate and reproducible neurophysiological assessments to fill existing gaps not only in refinement of our understanding of underlying mechanisms, but also to aid in identification of novel endophenotypes and to enhance management efficiencies in OSA clinical pathways.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

RM reports receiving honorarium from the American Academy of Sleep Medicine, funds for service on the American Board of Internal Medicine and Associate Editor for the American Journal of Respiratory and Critical Care Medicine, NIH funding, investigator initiated research funds to her institution from Resmed, Inspire, Sommetrics and royalties from UpToDate. RS was funded through the NIH. He also gets research funding from Resmed, Inspire, CryOSA; he is a research consultant for Eli Lilly; he is on the Medical Advisory Board for eXciteOSA; he gets royalties from UpToDate and Merck Manual. RK was funded by CIHR and holds research operating funds from Signifier Medical. He reports income from advisory board membership from Bresotec Inc., Powell Mansfield Inc., and Eisai Ltd. NS has grant funding through the NIH and the ASMF. She receives consulting fees from Respicardia, Powell Mansfield and Sunrise. Additionally, she is on the advisory board for Wesper Scientific and Bresotec. DG receives funding from the Department of Veterans Affairs and the NIH, and reports income from advisory boards for Signifier Medical Technologies, Powell Mansfield, Inc., and Wesper,

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Publisher's note

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Using the electrodermal activity signal and machine learning for diagnosing sleep

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Introduction: The use of the electrodermal activity (EDA) signal for health diagnostics is becoming increasingly popular. The increase is due to advances in computational methods such as machine learning (ML) and the availability of wearable devices capable of better measuring EDA signals. One field where work on EDA has significantly increased is sleep research, as changes in EDA are related to different aspects of sleep and sleep health such as sleep stages and sleep-disordered breathing; for example, obstructive sleep apnoea (OSA).

Methods: In this work, we used supervised machine learning, particularly the extreme gradient boosting (XGBoost) algorithm, to develop models for detecting sleep stages and OSA. We considered clinical knowledge of EDA during particular sleep stages and OSA occurrences, complementing a standard statistical feature set with EDA-specific variables.

Results: We obtained an average macro F1-score of 57.5% and 66.6%, depending on whether we considered five or four sleep stages, respectively. When detecting OSA, regardless of the severity, the model reached an accuracy of 83.7% or 78.4%, depending on the measure used to classify the participant's sleep health status.

Conclusion: The research work presented here provides further evidence that, in the future, most sleep health diagnostics might well do without complete polysomnography (PSG) studies, as wearables can detect well the EDA signal.

KEYWORDS

sleep, electrodermal activity, sleep stages, obstructive sleep apnea, machine learning

1. Introduction

Electrodermal activity (EDA) is one of the longest-known and most accessible physiological signals (Boucsein, 2012). Electrodermal activity reflects changes in skin potential due to sweating, which, during sleep, has a thermoregulatory function. Eccrine sweat glands, the sweat glands that are activated during sleep (Boucsein, 2012), are innervated by the sympathetic nervous system (SNS) only, with no parasympathetic input (Baker, 2019). Despite this direct connection between EDA and the SNS during the night, the signal has been so far mostly used in studies of diurnal phenomena. For instance, it has been used for detecting stress (Zontone et al., 2019), epileptic seizures (Poh et al., 2010), and students' emotional engagement in classrooms (Di Lascio et al., 2018).

One of the main reasons for neglecting EDA in sleep studies is the complexity of the recorded signals. Long-term EDA recordings are susceptible to noise from various sources

that cause artifacts in the signals, that is, sudden out-of-scale spikes; the most prominent sources of noise are body movements and poor skin-to-electrode connection. While in laboratory-controlled settings it is possible to log the patient's movements and to discard those signal segments when analyzing data, in free-living conditions, it is more difficult to do so. Because removing artifacts is important, much of the research on EDA signals has focused on automating their detection. Various methods have been proposed, often using supervised or unsupervised machine learning (ML) algorithms (Taylor et al., 2015; Hossain et al., 2022; Subramanian et al., 2022). Electrodermal activity has been only scarcely and only recently used for sleep staging or to infer sleep quality (Anusha et al., 2022; Gashi et al., 2022).

Abnormal sweating patterns may indicate the presence of various sleep disorders (Broman and Hetta, 1994; Idiaquez et al., 2022). In this work, we focused on sleep-breathing disorders, particularly obstructive sleep apnoea (OSA) (Jordan et al., 2014). Obstructive sleep apnoea causes unexpected SNS activity, resulting in frequent nocturnal sweating (Arnardottir et al., 2013). Despite the relationships between EDA and OSA has been studied (Lajos, 2004; Arnardottir et al., 2010), there is still a need for a quantitative model relating EDA and OSA.

In this paper, we applied supervised ML to EDA data to predict sleep stages and the presence of OSA. Currently, diagnosing it requires performing a full polysomnography (PSG) study in a laboratory setting, followed by manual scoring of the recordings. This procedure is time-consuming and can lead to atypical sleep patterns because of the differences between sleeping in a controlled environment, such as a sleep lab, and sleeping at home (Arnardóttir et al., 2021). We present an ML-based approach that uses features extracted from the EDA signal, recorded in a home-setting, to automatically detect sleep stages and OSA.

TABLE 1 Dataset content according to the apnoea-hypopnoea index (AHI) or the oxygen desaturation index (ODI).

	Non-OSA	Mild OSA	Moderate to severe OSA
Number of participants (AHI)	19	24	17
Female participants (AHI)	47.4%	67.0%	29.4%
AHI	2.8 ± 1.3	10.0 ± 2.8	24.9 ± 10.5
BMI	25.8 ± 3.6	26.0 ± 3.6	25.8 ± 3.8
Age	36.2 ± 10.4	49.6 ± 14.7	52.0 ± 14.4
Percentage of epochs (AHI)	32.1%	39.0%	28.9%
Number of participants (ODI)	21	26	13
Female participants (ODI)	42.9%	61.5%	38.5%
ODI	1.5 ± 2.5	9.0 ± 2.5	24.1 ± 7.7
BMI	25.8 ± 3.8	27.7 ± 4.5	29.2 ± 2.8
Age	38.4 ± 12.4	48.2 ± 14.8	53.9 ± 14.0
Percentage of epochs (ODI)	33.9%	44.7%	21.4%

TABLE 2 Distribution of sleep stages for 4 and 5 stages architectures.

Wake	N1	N2	N3	REM
12.2% ± 0.1	16.5% ± 0.1	32.5% ± 0.1	18.2% ± 0.1	20.6% ± 0.1
Wake	Light		Deep	REM
12.2% ± 0.1	49.0% ± 0.1		18.2% ± 0.1	20.6% ± 0.1

We report mean values and standard deviations.

2. Materials and methods

We used a set of 60 full-night PSG recordings from participants in the Sleep Revolution Project (Arnardottir et al., 2022). We describe the cohort in detail in Table 1. The consent of the National Bioethics Committee and the Data Protection Authority of Iceland was granted for this study (VSN-21-070). All participants received and signed an informed consent for study participation.

2.1. Instrumentation

Polysomnography (PSG) studies were recorded using A1 devices from Nox Medical (Reykjavik, Iceland). As the traditional PSG setup does not include EDA recordings, we added a channel for the EDA signal. A1 devices measured EDA at a sampling frequency of 200 Hz. For the measurement of the EDA signal, we used the same technique as in Arnardottir et al. (2010).

2.2. Sleep stage labeling

Sleep experts manually scored the electroencephalogram (EEG) and determined the sleep stage: wake (W), rapid eye movement (REM) sleep, sleep stage 1 (N1), sleep stage 2 (N2), and sleep stage 3 (N3). The scoring procedure was performed according to the American Academy of Sleep Medicine guidelines (Berry et al., 2020), using the Noxturnal software (Nox Medical, Reykjavik, Iceland). In this work, for detection, we considered both the above mentioned five stages or only four stages, by merging the N1 and N2 stages and relabeling them as light sleep. Additionally, we relabeled the N3 stage as deep sleep. The stages that we considered are then W, light sleep, deep sleep, and REM sleep, as is often done in the literature (Genzel et al., 2014). We report the distribution of sleep stages in Table 2.

2.3. Obstructive sleep apnoea labeling

Currently, OSA detection requires either manual scoring of a full PSG study or a home sleep apnoea testing, and the evaluation of two parameters: the apnoea–hypopnoea index (AHI) and the oxygen desaturation index (ODI) per hour of sleep (Berry et al., 2020). A shortcoming of the AHI is that it does not quantify one of the main consequences of OSA, which is oxygen desaturation. For this reason, sleep experts have defined the ODI value as the number of oxygen desaturation events ≥3%

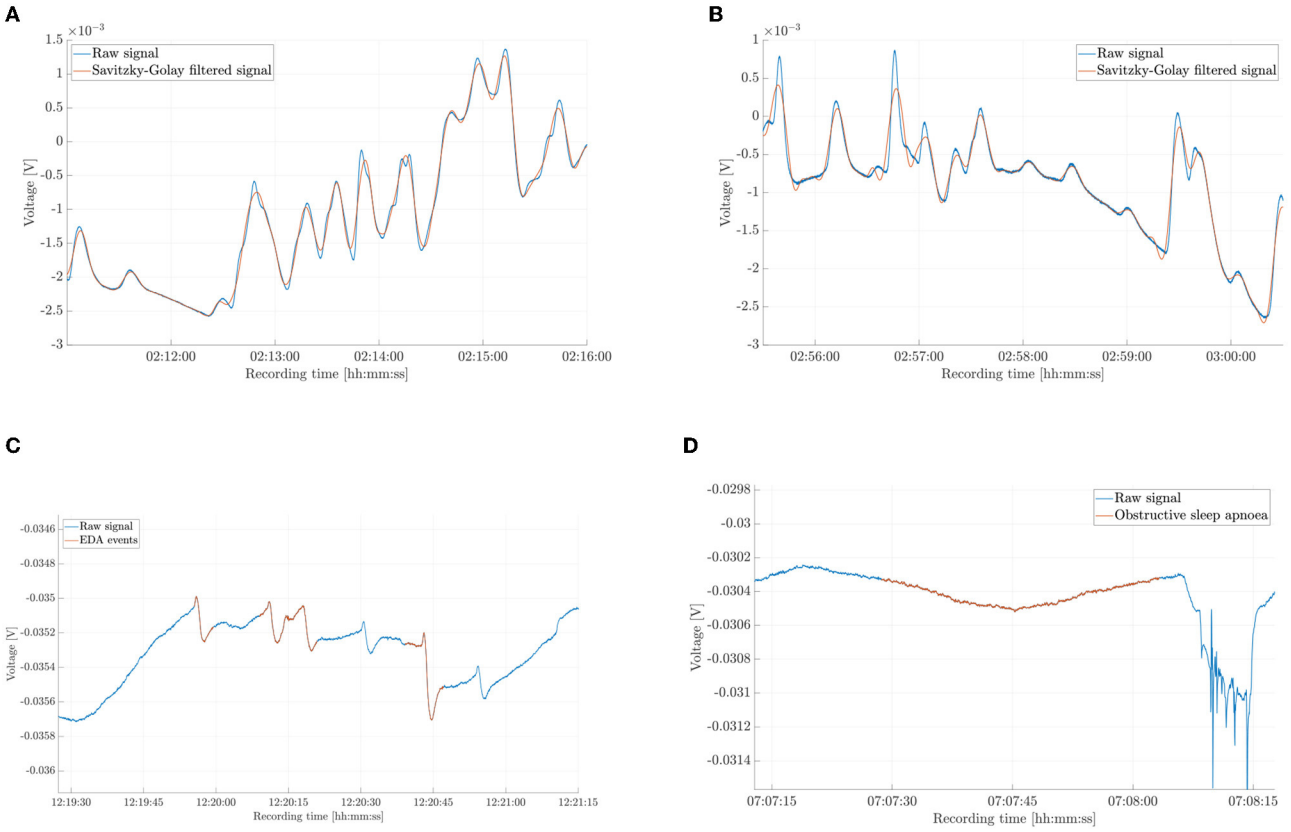

FIGURE 1
Different segments of the electrodermal activity (EDA) signal and of the Savitzky-Golay filtered signal from key phases of sleep. **(A)** Five minutes of raw and filtered signal during sleep stage 3 (N3). **(B)** Five minutes of raw and filtered signal during rapid eye movement sleep (REM). **(C)** EDA events (raw signal). **(D)** EDA during an obstructive sleep apnoea occurrence.

or ≥4% divided by the total sleep time (Chung et al., 2012; Berry et al., 2020). In this work, the sleep experts used 3% as threshold value.

We obtained a participant's OSA status from the manual scoring of PSG. We merged the moderate and severe OSA conditions to obtain three classes. To define them, we used the following modified version of the standard guidelines (AASM, 1999):

- Non-OSA: AHI <5,
- Mild OSA: 5≤ AHI <15,
- Moderate to severe OSA: AHI ≥15.

We also classified the samples based on the ODI and computed the correlation between the two indexes and the EDA signal. Note that the ranges used for the ODI-based classification are the same as the ones for the AHI classification (Chung et al., 2012). Each epoch in an individual's data sample was labeled as either belonging to a non-OSA participant, one with mild OSA, or one with moderate to severe OSA. By epoch, we refer to a 30 s signal window. We adopted this time length to be consistent with the epochs' length used by sleep experts during manual scoring. Note that only seven samples were classified differently depending on whether we used the AHI or the ODI. Finally, we present the distribution of non-OSA, mild OSA, and moderate to severe OSA epochs in Table 1.

2.4. Signal pre-processing

From the Noxturnal software environment, we exported EDA signals using the EDF file format and imported them in MATLAB® (MATLAB, 2022) for pre-processing and feature extraction. We down-sampled the original signal from 200 to 35 Hz to reduce the computational burden, following the guidelines presented in Braithwaite et al. (2013). We then pre-processed the original signal to obtain different kinds of data required by our detection algorithm.

First, because individual sweating patterns lead to significantly different-looking EDA signals (Boucsein, 2012), we computed the second-order polynomial best approximating the raw signal and subtracted it from the raw signal. Second, we applied a seventh-order Savitzky-Golay filter (Schafer, 2011) to the original signal to eliminate high-frequency contributions. We also applied a discrete wavelet transform (DWT) to the original signal. We computed the approximate and detailed discrete wavelet coefficients and soft thresholded the detail coefficients to remove possible recording noise (Coifman and Donoho, 1995). We then subtracted the Savitzky-Golay filtered signal from the discrete wavelet filtered signal; we referred to it as diffEDA.

Third, we computed the first and second-order derivatives of previously described three signals using a differentiator finite impulse response (FIR) filter. We used this method rather

TABLE 3 Set of variables extracted from the electrodermal activity (EDA) signal.

Index	Signal	Computed features
1–18	EDA detEDA	Mode, median, maximum of absolute value, line length, 10th quantile, 75th quantile, singular value decomposition (SVD) entropy, non-linear energy, Shannon entropy
19–34	∂_tEDA, ∂_t^2EDA ∂_tdetEDA, ∂_t^2detEDA	Mean value, variance, median value, numbers above zero
35–40	EDA detEDA	Maximum power spectral density (PSD) estimate, frequency of the maximum PSD estimate, Fisher's g (Posada-Quintero et al., 2016)
41–64	EDA detail coefficients decomposition levels (DL) 1—4	Maximum, mean, standard deviation, median, Euclidian norm, normalized numbers above zero
65–70	EDA detEDA	Lyapunov exponent, maximum value of the upper envelope, minimum value of the lower envelope
71–72	diffEDA	Sum of cross-correlation, maximum convolution value
73–76	EDA	Normalized number of event samples, normalized event energy, normalized number of storm samples, normalized storm energy
77	Individual	Sex

than a finite-differences scheme to prevent noise propagation. Particularly, we used a 50th-order filter with a passband frequency of 10 Hz and a stop-band frequency of 12.5 Hz. We disregarded the transient to avoid including artificial oscillations caused by applying the filter by discarding $N = 50$ samples. Note that, we denoted time derivatives by placing ∂_t or ∂_t^2 before the signal of interest; for example, we referred to the second time derivative of the de-trended signal as ∂_t^2detEDA.

Figure 1 shows the complexity of the EDA signal. We show 5-min time windows of continuous N3 and REM sleep in Figures 1A, B, respectively. We then highlight EDA events in Figure 1C. Finally, we show the EDA signal during an OSA occurrence in Figure 1D.

2.5. Feature extraction and selection

We defined a feature set in the time-domain, frequency-domain, as well as time-frequency domain (these are wavelet-related variables) in a process called feature engineering (Verdonck et al., 2021). In addition to standard statistical features, we used number and energy content of EDA events and storms, as they are known to differ for different sleep stages (Sano et al., 2014) and OSA severity (Arnardottir et al., 2010). Electrodermal activity events are oscillations of the skin voltage of defined amplitudes and frequencies. We are particularly interested in the following three types of oscillations: positive/negative monophasic, biphasic, and triphasic. Electrodermal activity storms are time windows with high concentrations of events. The definition of storms has changed through time (Burch, 1965; Sano et al., 2014), we used an equivalent definition to the one given by Sano and colleagues, that is, a timespan of at least 1 min with a minimum of two EDA events. Particularly, we used the algorithm developed in Piccini et al. (2023) to detect EDA events and storms. Thereafter, we computed the normalized number of samples within either an EDA event or storm, together with their Euclidean norms. Additionally, we added sex as a categorical feature to complete the set of variables and normalized the features across individuals. The full feature set is shown in Table 3.

Finally, after training and testing the model on the complete variable set, we investigated whether we could reduce the feature set dimension by analyzing intra-variable correlation. We identified correlated features by computing the pairwise Pearson correlation coefficient r. We then reduced the dimension of the feature set by retaining only one of the correlated variables. We looked at the correlation matrix to identify the threshold value r_{th}.

2.6. Training procedure

Sleep stages are not equally distributed during the night, this asymmetry caused a significant imbalance in our dataset and affected model performance. To reduce the negative impact of this effect, we performed synthetic minority oversampling (SMOTE) (Chawla et al., 2002), that is, we generated artificial samples for the minority classes to alleviate the bias toward the most dominant class. We then trained models using the extreme gradient boosting (XGBoost) algorithm (Chen and Guestrin, 2016), since a gradient boosting algorithm was recently used in a similar application with promising results (Gashi et al., 2022).

We applied different validation methods. We either used leave-one-subject-out (LOSO) validation (Hastie et al., 2009), where we alternately left out one sample and used the other 59 samples as training data, or we did as previously and in addition, we trained the model using randomly selected 25% of the epochs from the left-out subject's night (Personalized). We always used the same seed for reproducibility. After this random sampling, we applied the SMOTE algorithm to the training data. We evaluated the OSA model only by means of the LOSO scheme. We did so, because of the way that we labeled the data for OSA detection, see Section 2.3.

2.7. Evaluation metrics

We computed different measures to evaluate the models' performances. All indices were obtained using scikit-learn (Pedregosa et al., 2011). F1 and recall scores were used to evaluate the sleep staging performances. While F1-score is a commonly used measure in ML applications, we used the recall score to account for the significant class imbalance (Gashi et al., 2022). Recall score is the ratio between true positives and the sum of true positives and false negatives and, thus, a measure for the number of relevant objects detected by the algorithm. The F1-score is the harmonic mean of precision and recall scores and is used in classification problems with imbalanced datasets, as the precision score on its own may be misleading. As we dealt with a multi-class classification problem, we used the macro version of

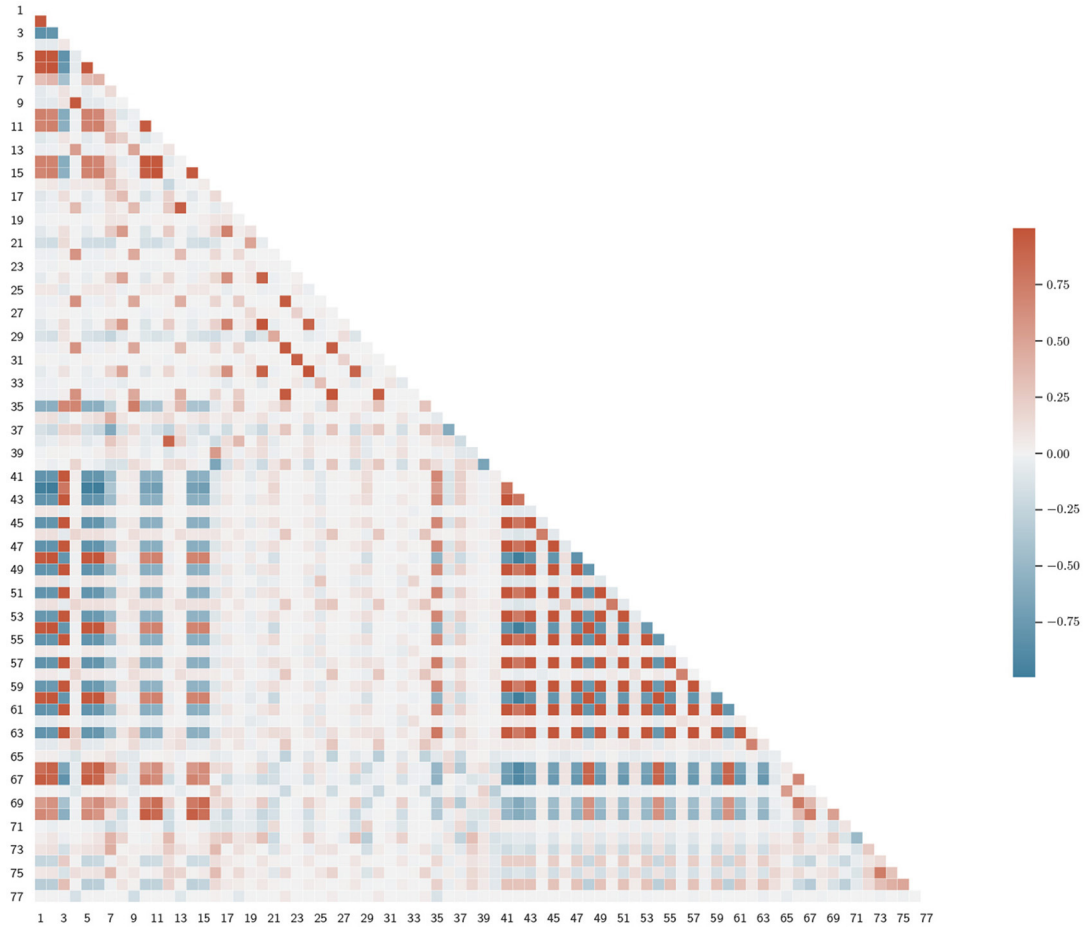

FIGURE 2
Representation of the lower triangular feature correlation matrix. We denoted the variables by index, as in Table 3.

both parameters; the macro F1-score is the average of all F1-scores, and the macro recall is the average of all recalls. For the remainder of the paper, we referred to the macro F1-score and macro recall value simply as F1-score and recall.

For the OSA model, we used the F1-score and accuracy values. Accuracy is the ratio between the number of correctly identified epochs and the total amount of epochs. In addition to these two measures, we evaluated the three-class algorithm's ability to distinguish between non-OSA participants and those with OSA. To do this, we considered all OSA epochs as equivalent, which made the classification problem a binary one; we then computed the accuracy score and referred to it as the adjusted accuracy score. We did not include the recall for OSA models' evaluations, as it deals with all misclassifications in the same way. Particularly, misclassifications between severe and mild OSA conditions and between non-OSA and OSA conditions have different clinical meanings.

2.8. SHapley Additive exPlanations

To evaluate the contribution of each training variable, we used SHapley Additive exPlanations (SHAP) (Lundberg and Lee, 2017). The technique was developed in game theory and only recently adapted to ML interpretability applications (Lundberg et al., 2018). To find the SHAP value of the i-th variable, we computed the predictions for all possible feature combinations with and without the i-th variable. The SHAP value is then the average of the contributions of the i-th variable to each prediction (Molnar, 2022).

3. Results and discussion

3.1. Feature reduction

Before presenting the models' performances, we offer an analysis of the feature set reduction process; for the sake of notation, we refer to variables by index, as in Table 3. We identified three main clusters of correlated variables by looking at the graphical representation of the correlation matrix (Figure 2). The first one involves features 1–15, which are statistical measures, in the time domain, of EDA and detEDA signals. The second one is a large cluster encompassing features 41–64, variables obtained in the time-frequency domain. Finally, non-linear features 65–70 also show meaningful correlation patterns.

After setting $r_{th} = 0.8$, we reduced the number of correlated variables. We decided which feature to eliminate as follows: first,

TABLE 4 Optimized feature set for the sleep staging models, $r_{th} = 0.8$.

Signal	Computed features
EDA	Mode, maximum of absolute value, line length, singular value decomposition (SVD) entropy, non-linear energy, Lyapunov exponent, maximum power spectral density (PSD) estimate, frequency of the maximum PSD estimate, Fisher's g (Posada-Quintero et al., 2016)
detEDA	Mode, maximum of absolute value, line length, singular value decomposition (SVD) entropy, non-linear energy, Lyapunov exponent, requency of the maximum PSD estimate, Fisher's g (Posada-Quintero et al., 2016)
∂_tEDA	Mean, variance, median, number above zero
∂_t^2EDA	Mean, median
∂_tdetEDA	Mean, median
∂_t^2detEDA	Median
EDA detail coefficients decomposition levels (DL) 1–4	Median, normalized numbers above zero
diffEDA	Sum of cross-correlation, maximum convolution value
EDA	Normalized number of event samples, normalized event energy, normalized number of storm samples, normalized storm energy
Individual	Sex

we computed the correlation coefficients between the i-th feature and the remaining ones, then we eliminated the j-th feature, if $r_{i,j} > r_{th}$, where $r_{i,j}$ is the Pearson correlation coefficient between the i-th and the j-th variables and $j > 1$. We started at $i = 1$. In this way, we obtained a reduced set of 40 features, which we present in Table 4. We opted not to decrease further the r_{th}-value, as the resulting feature set did not present any significant clusters, see Figure 3. Also, lower values of r_{th} may result in worse classification performances.

3.2. Interpretation of sleep staging

We summarized the models' performances in Table 5, where the F1-scores and recall values are reported. Our results suggest a need for personalized models (Óskarsdóttir et al., 2022). A possible explanation for the relatively poor performance is that different brain regions can be in different sleep stages at the same time. For instance, sweat glands' activation signals and, thus, EDA, are generated in the hypothalamus (Rothhaas and Chung, 2021), while the EEG, used to manually label sleep stages, measures neocortex activity, and it is known that the two brain areas can be in different sleep stages (Guthrie et al., 2022). However, personalizing the LOSO-based model with a small number of epochs from the left-out sample dramatically improves the algorithm, see also Figures 4, 5, which show confusion matrices normalized such that the sum of each row equals one.

By looking at the confusion matrix in Figure 4B, we concluded that the personalized model cannot characterize the N1 sleep stage using only EDA. Furthermore, N1 detection appeared to be a cumbersome task even when other ML methods and other signals were used, such as EEGs, electrooculograms (EOGs), and electromyograms (EMGs) (Chambon et al., 2018; Korkalainen et al., 2019). A similar disagreement in determining the sleep stage was also found when comparing different manual scorings (Magalang et al., 2013). However, the detection of slow wave sleep (SWS) phases, that is, deep sleep and N3 stage, and REM sleep phases worked well for both models. This was expected, since these are the phases with the most distinct EDA patterns. Notably, by looking at Figure 4B, we can conclude that, based on EDA, the N3 stage is more similar to the N2 stage than any other sleep stage.

Finally, we offer a graphical interpretation of the sleep staging model, trained on the reduced dataset, through the SHAP values of the 20 most influential variables, see Figure 6. It is worth noting that both models considered the number of EDA events to be highly relevant for N3 stage, see Figure 6. The models also predict a significant relationship between EDA storms and REM sleep. Indeed, it is known that EDA activity increases in the third cycle of REM sleep (Boucsein, 2012).

3.3. The need for personalization in sleep staging

Several physiological considerations support the need for personalization in EDA-based sleep staging. Nocturnal sweat, the principal cause of changes in skin electrical properties, is secreted to lower the core body temperature (CBT) (Baker, 2019). However, the thermoregulation process depends on a large number of factors, for example, age, BMI, sex, skin hydration, eccrine sweat gland concentration, and environmental conditions (Speakman, 2018; Grosiak et al., 2020; Yanovich et al., 2020). All the factors mentioned significantly impact sweat and, consequently, the EDA signal. Furthermore, the latter is also affected by subject-dependent brain dynamics.

It is not straightforward to decide which personal subset of epochs to choose, as different EDA patterns arise in different parts of the night; for example, EDA events are more frequent in REM sleep during the last sleep cycle (Boucsein, 2012), while rarer in other REM sleep periods. Furthermore, differences in sleep cycle duration caused by age and OSA condition, among other factors, may hinder the beneficial effect of the algorithm's personalisation. Because of this, we opted for a fixed-seed random-pick approach.

3.4. Interpretation of the OSA model

To evaluate the models' ability to distinguish between non-OSA persons and those with either mild or moderate to severe OSA, we used average values of the accuracy score, the F1-score, and the adjusted accuracy score. We also evaluated a binary classification problem, where participants either had OSA or not, for which we refrained from calculating the adjusted accuracy score. We present the results as we did for the sleep staging models in Table 6. They show that OSA severity determined through the EDA signal rather follows the classification obtained by using the ODI rather than the AHI. A possible explanation for this behavior is how the ODI

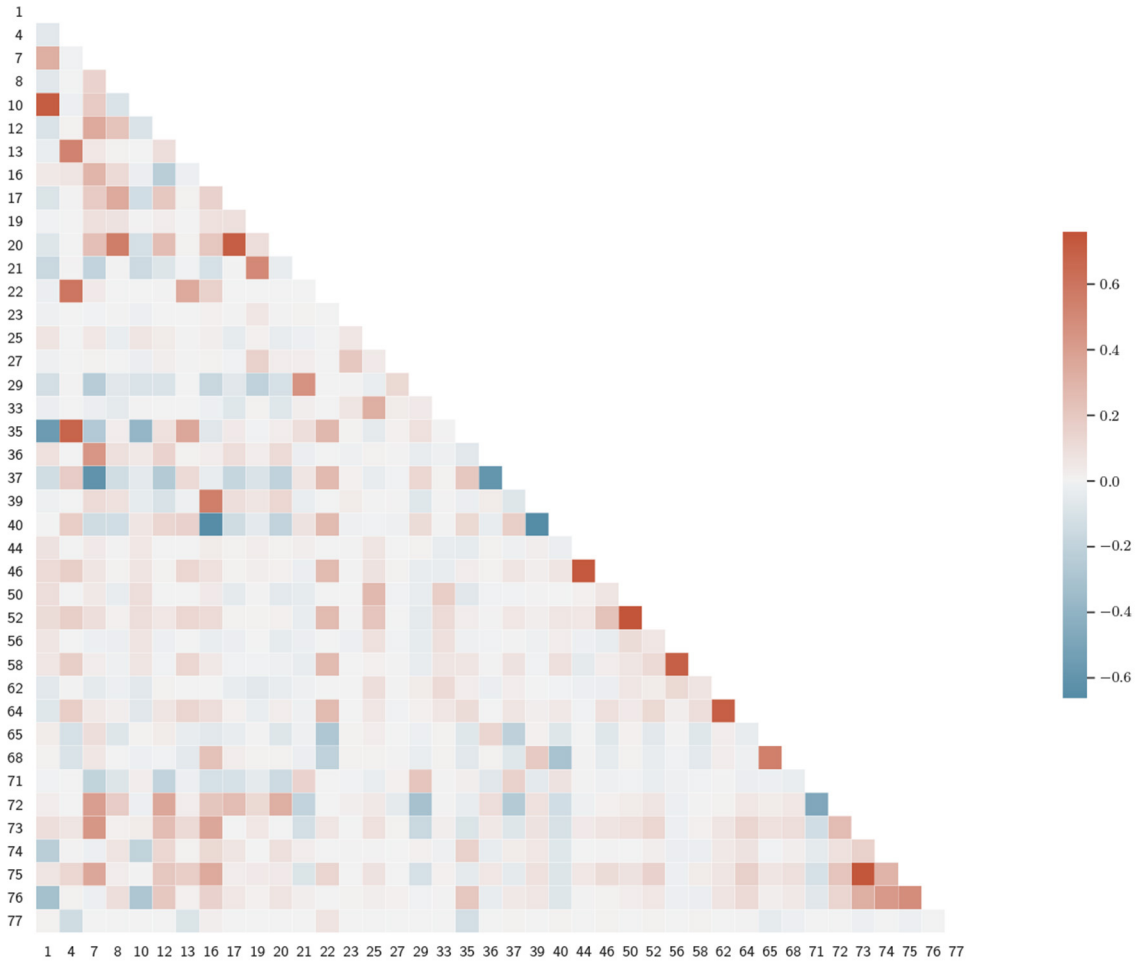

FIGURE 3
Correlation matrix for the reduced feature set. Variables are denoted by index, as in Table 3.

TABLE 5 Summary of sleep staging performance for, both, four stages, and five stages classification.

No. stages	r_{th}	Leave-one-subject-out		Personalized	
		Macro F1-score	Macro recall score	Macro F1-score	Macro recall score
Five stages	0.8	27.3%	32.4%	57.5%	58.0%
Four stages	0.8	32.8%	39.7%	66.6%	66.9%

value divides the participants. Looking at Table 1, we observed that while both the indexes found the mean age to increase with the OSA severity, in ODI classification BMI values also increased with OSA severity. Lower BMI values have been associated with lower mean temperature values, (Waalen and Buxbaum, 2011), which may result in less need for thermoregulation. Consequently, simpler sweating patterns may be observed, which are better learned by the algorithm.

In Figures 7, 8, we used the SHAP values to present the effect of each variables on the different classification problem. Both three-class models choose normalized storm samples as one of the most significant variables, which relates well to the literature (Arnardottir et al., 2010).

3.5. Feature selections comparison

Out of the 77 extracted variables, only eight appear in all models' top 20 most important features. They are EDA mode, ∂_tEDA variance, detEDA mode, EDA maximum power spectral density (PSD) estimate, EDA frequency of the maximum PSD estimate, ∂_tEDA normalized numbers above zero, detEDA frequency of the maximum PSD estimate, and biological sex. The seven numerical variables are computed from two signals, that is, raw and de-trended EDA and the derivative of the raw signal; this subset is composed of variables spanning multiple domains, particularly time, frequency, and EDA-specific. This variety confirms the need to consider different dynamical behaviors

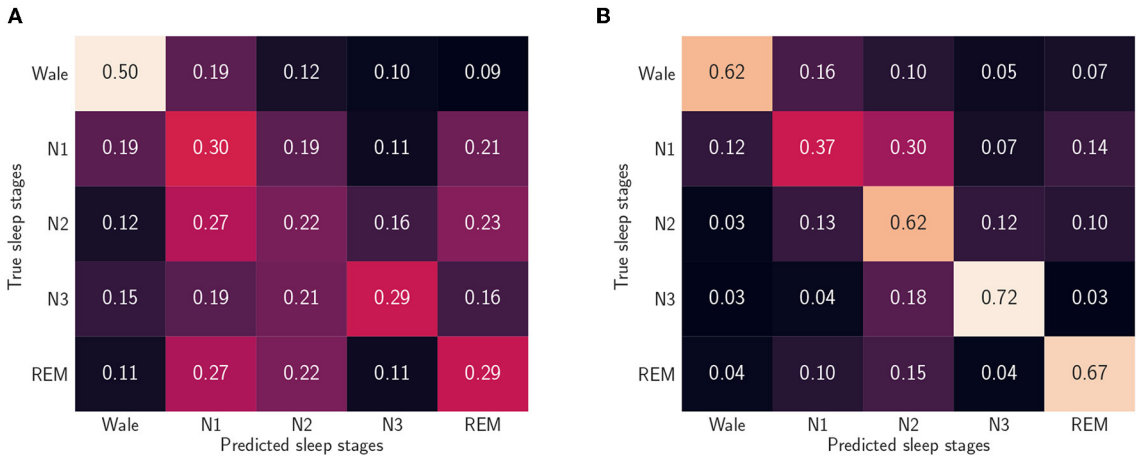

FIGURE 4
Normalized confusion matrices when we consider five sleep stages and use the reduced feature set. **(A)** Leave-one-subject-out (LOSO). We trained the algorithm without including data from the left out participant. **(B)** Personalized model. In addition to the 59 participants training set, we used randomly picked 25% epochs of the test participants.

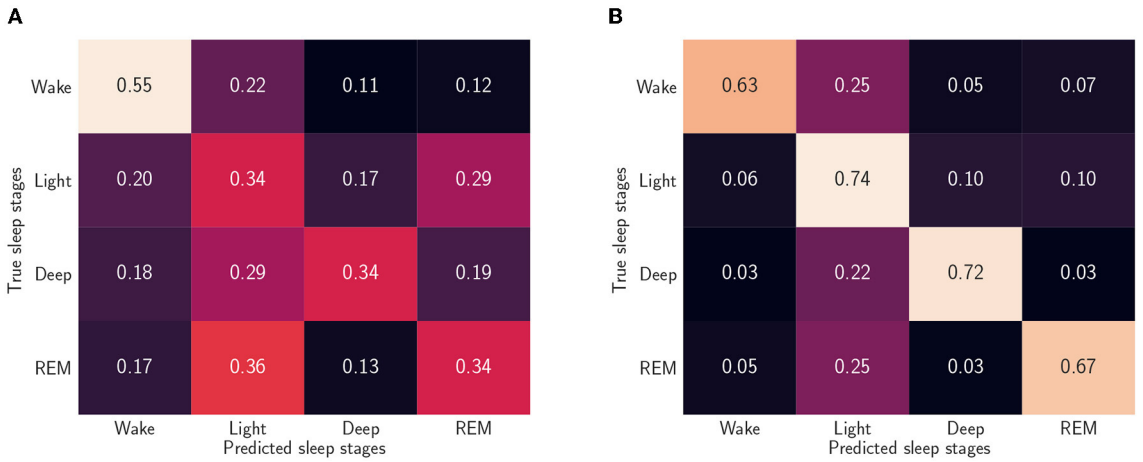

FIGURE 5
Normalized confusion matrices when we consider four sleep stages and use the reduced feature set **(A)** Leave-one-subject-out (LOSO). We trained the algorithm without including data from the left out participant. **(B)** Personalized model. In addition to the 59 participants training set, we used randomly picked 25% epochs of the test participants.

and EDA-related phenomena when using this signal. The most common specific feature is the number of EDA storm samples, which is amongst the top 20 most important features for all models, except for the two-class ODI-based OSA classification problem. However, in the latter problem, normalized storm energy is considered a relevant feature. Works trying to relate EDA and OSA are scarce and based mainly on subjective night sweats reports (Nigro et al., 2022). Although it is well-established that OSA symptomatology includes abnormal sweating episodes (Arnardottir et al., 2010, 2013), there needs to be more understanding of the relationship between OSA and EDA events and storms. Our work concludes that evaluating EDA storms, their lengths or energies, is more decisive in detecting OSA, particularly severe expressions, than evaluating EDA events. This conclusion holds for OSA classifications based on both AHI and ODI severity.

4. Conclusion and future work

The presented work aimed at detecting sleep stages and OSA severity using only the EDA signal. Recently, Anusha and colleagues presented an ML algorithm for identifying the sleep stage of the hypothalamus, the brain region directly responsible for thermoregulation during sleep (Anusha et al., 2022), while, Gashi and colleagues presented a similar algorithm based on EDA that is able to detect wake/sleep stages and high/low sleep quality (Gashi et al., 2022). Latter algorithms are based on self-reported annotations. Despite these significant results, more research on the relationship between EDA and neocortex activity is needed. Our work is the first one, in which neocortex sleep stages are predicted solely based on EDA. In the first part of this research work, we presented a sleep staging algorithm that is

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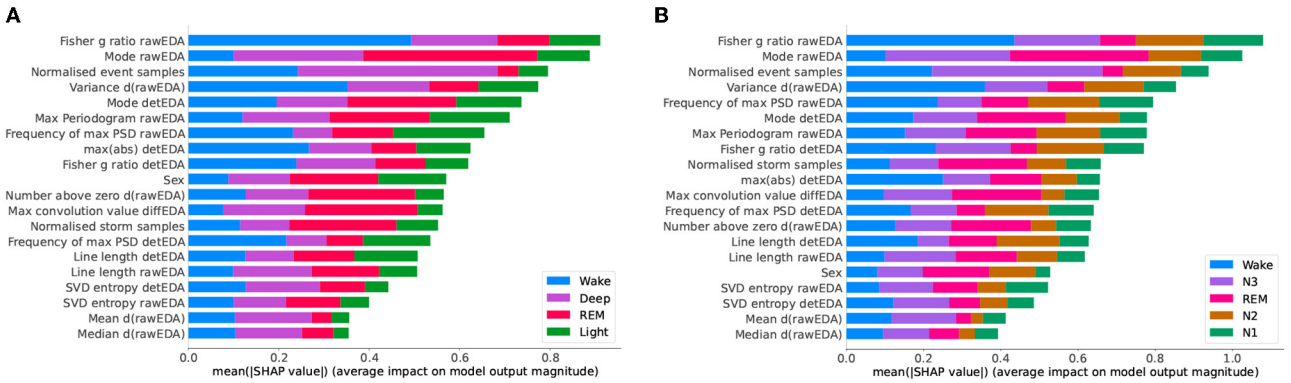

FIGURE 6
SHapley Additive exPlanations (SHAP) values of the sleep staging model trained using the leave-one-subject-out (LOSO) scheme and the reduced feature set. **(A)** Four sleep stages: wake (W), light sleep, deep sleep, rapid eye movement (REM) sleep. **(B)** Five sleep stages: wake (W), sleep stage 1 (N1), sleep stage 2 (N2), sleep stage 3 (N3), rapid eye movement (REM) sleep.

TABLE 6 Results for obstructive sleep apnoea (OSA) detection, based on the apnoea-hypopnoea index (AHI) or on the oxygen desaturation index (ODI).

OSA structure	r_{th}	Mean accuracy score	Macro F1-score	Adj. accuracy score
AHI—non-OSA vs. OSA	0.8	75.7%	65.6%	–
ODI—non-OSA vs. OSA	0.8	82.0%	67.7%	–
AHI—Three groups	0.8	54.8%	32.9%	78.4%
ODI—Three groups	0.8	54.8%	32.9%	83.7%

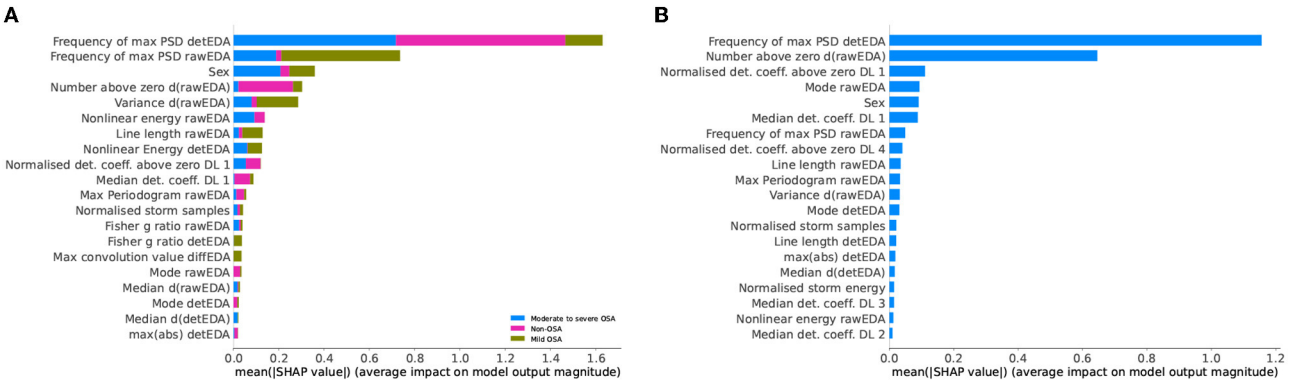

FIGURE 7
SHapley Additive exPlanations (SHAP) values of the obstructive sleep apnoea (OSA) detection model based on apnoea-hypopnea index (AHI) values and the reduced feature set. **(A)** Three-class classification problem: participants with no, mild, or moderate to severe OSA. **(B)** Binary classification problem: non-OSA participants and those with OSA.

particularly accurate in detecting those sleep stages, where specific EDA patterns are known to occur, which are N3 and REM sleep. In the second part, we focused on OSA detection. By using the EDA signal, we distinguished non-OSA participants from those with OSA with reasonable accuracy.

Our work has three main limitations. The first one is that the raw signal was recorded at 200 Hz, an unattainable sampling frequency for current wearables. However, the signal was significantly downsampled, to 35 Hz, before it was handled. Since EDA events occur in the frequency band [0.25–3 Hz] for endosomatic recordings, like the ones used in this study, further downsampling might potentially be performed without a significant loss of information, which we leave for future work. The second limitation is that the sleep staging algorithm requires a certain amount of individual data manually scored by a sleep expert. While this prevents the sleep staging model from being user-independent and, thus, might limit its use in wearables, in clinical studies, requiring only a small part of the signal to be manually scored significantly saves time and cost. Moreover, our work adds to the body of evidence on how crucial it is to include knowledge about sleep processes in ML models. A final limitation is the participants' significant ranges in age and BMI within a relatively small sample size. While the participants' diversity ensured to obtain general models, it also prevented the algorithm

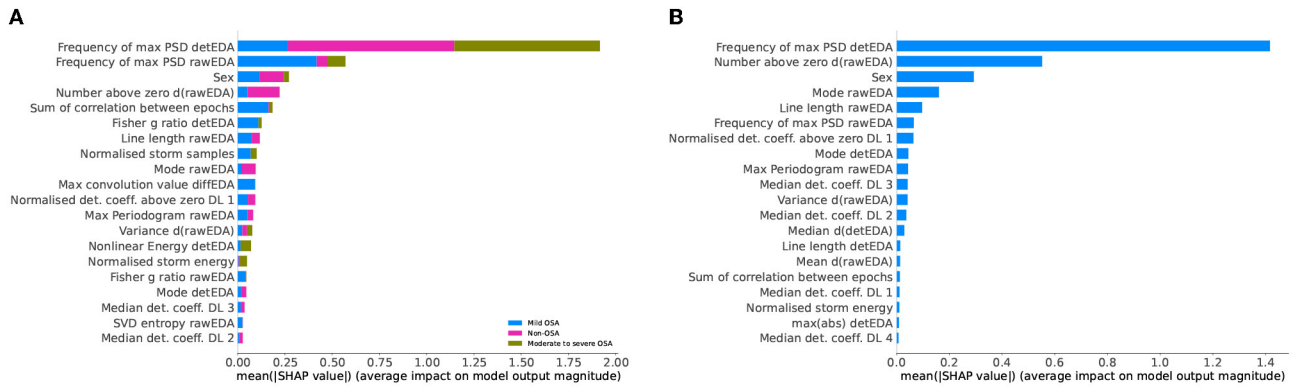

FIGURE 8
SHapley Additive exPlanations (SHAP) values of the obstructive sleep apnoea (OSA) detection model based on oxygen desaturation index (ODI) values and the reduced feature set. **(A)** Three-class classification problem: participants with no, mild, or moderate to severe OSA. **(B)** Binary classification problem: non-OSA participants and those with OSA.

from learning patterns specific to a particular group, for example, individuals of the same biological sex and of similar age. Future studies may overcome this last limitation by using a more selected cohort or by considering the body temperature signal, therefore addressing the differences in mean body temperature due to various aspects such as age, sex, and BMI.

To improve on the reported results, in the future, we will also include additional signals obtainable through wearables, such as acceleration and skin temperature. Doing so might reduce the need for individual tuning of the algorithm and allow it to identify other sleep stages more accurately. More precise sleep staging based on data obtained from wearables will allow the estimation of more advanced sleep parameters used in sleep diagnostics, such as total sleep time and sleep efficiency. Finally, since the algorithm labels each epoch as "non-OSA" or "OSA-prone," it will be possible to track a potential onset or worsening of sleep-disordered breathing. By adequately characterizing the development of OSA symptoms, it will be possible to define a threshold that will lead to suggesting to seek professional advice when exceeded.

Data availability statement

The datasets used for this study is not publicly available due to General Data Protection Regulation (GDPR) reasons. Requests to access the datasets should be directed to jacopop@ru.is.

Ethics statement

The study received the approval of the National Bioethics Committee and the Data Protection Authority of Iceland (Sleep Revolution VSN-21-070). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JP: conceptualization, methodology, software, visualization, and writing. EA and MÓ: conceptualization, methodology, supervision, reviewing, and editing. ESA: supervision, reviewing, editing, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

ESA discloses lecture fees from Nox Medical, Philips, ResMed, Jazz Pharmaceuticals, Linde Healthcare, Alcoa-Fjardaral, and Wink Sleep. ESA is also a member of the Philips Sleep Medicine and Innovation Medical Advisory Board.

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.

Publisher's note

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Development of a combination of noradrenergic and antimuscarinic drugs for the treatment of obstructive sleep apnea: Challenges and progress

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Obstructive sleep apnea (OSA) is a disorder characterized by repetitive collapse of the upper airway during sleep, leading to intermittent hypoxia and sleep fragmentation. The combination of noradrenergic and antimuscarinic drugs has emerged as a potential pharmacological treatment option for OSA, with the most promising combination being atomoxetine plus aroxybutynin. This combination is currently undergoing extensive experimentation and will be soon tested in phase 3 studies. Other noradrenergic drugs including reboxetine, and other antimuscarinics including fesoterodine, hyoscine butylbromide, solifenacin, and biperiden have been tested. The increasing interest in OSA pharmacotherapy is driven by advances in our understanding of the pathophysiology of the disease and accumulating evidence of the surprising effectiveness of this drug combination. However, challenges remain in accurately measuring the severity of OSA, which can impact our ability to fully understand the efficacy of these medications. Further research is ongoing to address these challenges and to optimize the use of noradrenergic and antimuscarinic drugs for the treatment of OSA.

KEYWORDS

combination therapy for OSA, pharmacotherapy for OSA, norepinephrine reuptake inhibitors, antimuscarinics, ato-oxy

Introduction

To date, the search for a pharmacotherapy to treat the underlying cause of obstructive sleep apnea (OSA), i.e., the narrowing and obstruction of the upper airway during sleep, has been largely limited to small observational studies or proof-of-concept, short-term clinical trials mostly performed in academic settings (Taranto-Montemurro et al., 2019b). While these studies show occasionally encouraging results, often they are underpowered to detect an effect on OSA severity and even the positive study results can be difficult to replicate in subsequent clinical trials (Marshall et al., 2008). For these reasons, investigators have been reluctant to test drugs for OSA in large and expensive phase 2 or 3 trials.

The therapeutic space in OSA is largely dominated by continuous positive airway pressure (CPAP) (Sutherland et al., 2018). However, multiple recent trials showed that, due mostly to limited compliance, CPAP is not as effective as thought in treating OSA and in preventing adverse cardiovascular and neurocognitive outcomes (Kushida et al., 2012; Mcevoy et al., 2016). This fact has reinvigorated the research for alternative treatments for OSA. Moreover, recent developments in the understanding of OSA pathophysiology

(Wellman et al., 2013) and the identification in animal models of potential targets for OSA pharmacotherapy (Horner et al., 2017) have generated new interest by pharmaceutical companies in this disorder. This has led to an increased number of large ongoing phase 2 and 3 trials (Clinicaltrials.gov, 2022a,b,c), which will hopefully advance the field of OSA pharmacotherapy in future years.

In this short review we will focus on the ongoing development of combinations of noradrenergic and antimuscarinic drugs for the treatment of OSA. Only published data from peer-reviewed journals will be reported and discussed.

Recent discoveries in animal model

It has been known for many years (Remmers et al., 1978) that falling pharyngeal dilator muscle activity during sleep is one of the principle causes of OSA. However, elucidating the neural mechanisms underpinning this loss of muscle activity has required more modern scientific techniques. Many studies over the years have demonstrated that cells producing excitatory neurotransmitters such as serotonin and norepinephrine decrease their firing frequency during NREM sleep with further reductions during REM sleep (Aston-Jones and Bloom, 1981). In addition, the REM-related broad inhibition of skeletal muscle activity has been shown to result from active inhibition from glycine and GABA (Chase et al., 1989).

Recently, Richard Horner's lab in Toronto developed a rat preparation whereby natural sleep could be monitored using standard techniques, a microdialysis catheter placed in the hypoglossal motor nucleus could both measure and administer neurotransmitters/drugs, and genioglossal EMG (EMGgg) could be continuously recorded. Using this preparation, they first demonstrated that loss of genioglossal muscle activity during NREM sleep was primarily a product of reduced norepinephrine activation of the muscle, a disfacilitation mechanism (Chan et al., 2006). The application of an alpha agonist at the 12th motor nucleus during NREM sleep could largely restore muscle activity in rats. Previous work had suggested that reductions in serotonergic neural input to the genioglossus were most important in mediating sleep-related loss of muscle activity (Fenik et al., 2005). These previous findings led to numerous studies assessing the impact of medications to modify neural serotonin on OSA severity without great efficacy (Taranto-Montemurro et al., 2019b). However, it was later discovered that cutting the vagus nerve may have overemphasized the role of serotonin in regulating the genioglossus (Sood et al., 2005). Nevertheless, some investigators still believe serotonin may have a role in the upper airway muscle activation despite the failure of most such interventions to improve sleep disordered breathing (Kubin, 2016).

Although, as stated above, glycine and GABA are the primary inhibitors of skeletal muscle activity during REM sleep, this REM sleep mechanism is less clear for upper airway dilators muscles. Some data suggest that antagonists to glycine and GABA have little effect on pharyngeal muscle activity during REM sleep (Park et al., 2008). Further work in the Horner lab reported that a potentially important source of falling EMGgg during REM sleep could be active cholinergic (muscarinic) inhibition (Grace et al., 2013). Their application of the antimuscarinic agent scopolamine could largely restore genioglossal muscle activity in rats during REM sleep. Thus muscarinic inhibition may be more important than such inhibition by glycine or GABA in mediating REM sleep loss of pharyngeal dilator muscle activity.

Two unrelated mechanisms may each be contributing to falling pharyngeal dilator muscle activity during sleep, one during NREM and the other during REM sleep. Countering both falling norepinephrine levels during NREM sleep and increased muscarinic inhibition during REM sleep with an oral pharmacological agent may treat sleep apnea. A novel combination of atomoxetine, a selective norepinephrine reuptake inhibitor (SNRI) approved in the US for treating attention deficit/hyperactivity disorder, with oxybutynin, an antimuscarinic approved in the US for treating overactive bladder, has recently been studied for treatment of OSA.

Proof-of-concept clinical trials

Table 1 provides a summary of the proof-of-concept randomized-controlled trials testing the combination of an SNRI and an antimuscarinic. A first trial performed at the Brigham and Women's Hospital in Boston (Taranto-Montemurro et al., 2019a) showed that the combination of atomoxetine and oxybutynin (ato-oxy) at doses of 80 and 5 mg, respectively, led to a clinically meaningful reduction in OSA severity in a group of 20 unselected patients. The reduction in AHI was associated with a ~3-fold increase in genioglossus muscle activity (measured using intramuscular electromyography). Additionally, in a subset of nine patients who returned to perform polysomnography for two subsequent nights, the administration of either agent alone did not lead to an AHI reduction compared to placebo. A follow-up multi-center confirmatory trial (Schweitzer et al., 2022) validated the efficacy of ato-oxy 80/5 mg in a group of 62 patients with low upper airway collapsibility defined as a higher proportion of hypopneas compared to apneas and an average oxygen desaturation of <8% with disordered breathing events. In this crossover trial the authors studied both ato-oxy and atomoxetine alone, showing that atomoxetine had similar effect as the combination in reducing AHI, oxygen desaturation index (ODI) and hypoxic burden (HB). However, contrary to ato-oxy, atomoxetine alone did not reduce the rate of respiratory arousals vs placebo and there was a trend for reduced total sleep time (−26 min) on atomoxetine alone compared to ato-oxy ($p = 0.06$). Oxybutynin's main role may be reducing the sleep disruptive effects of atomoxetine by attenuating its wake-promoting activity. The analysis of the endotypic traits in both ato-oxy trials indicated that, while atomoxetine alone seems to play the largest role in reducing airway obstruction when compared to oxybutynin alone, only the combination improved "active" upper airway collapsibility (collapsibility at maximum ventilatory drive during sleep, Vactive), suggesting that ato-oxy has a stronger effect than atomoxetine alone in recruiting the upper airway dilator muscles and improving ventilation (Figure 1).

Aisha et al. assessed tolerability and safety of three doses of ato-oxy after 30 days of treatment in a placebo-controlled, parallel arms study (Aishah et al., 2022). In this small trial, which enrolled 39 patients across 4 treatment arms, the authors found that ato-oxy

TABLE 1 Summary of proof-of concept clinical trials testing combinations of selective norepinephrine reuptake inhibitors (SNRIs) and antimuscarinics.

First author	Journal (year)	Intervention arms	N, type of study	AHI4			AHI3a			HB		
				Placebo	SNRI Alone	Combination SNRI + Antimuscarinic	Placebo	SNRI Alone	Combination SNRI + Antimuscarinic	Placebo	SNRI Alone	Combination SNRI + Antimuscarinic
Taranto-Montemurro, Luigi	Am J Resp Crit Care Med (2019)	Placebo/Atomoxetine (80 mg) + Oxybutynin (5 mg)	*N* = 20 crossover, 1 night				28.5 (10.9 to 51.6)		7.5*** (2.4 to 18.6)			
Aishah, Atqiya	Journal of Applied Physiology (2021)	Placebo /Atomoxetine 80 mg + Solifenacin 5 mg/Atomoxetine 80 mg + Biperiden 2 mg	*N* = 11 Crossover, 1 night				46 ± 22.5		Ato+Sol 51.0 ± 21.4 Ato+ Bip 48.3 ± 23.6			
Lim, Richard	Journal of Physiology (2021)	Placebo/Reboxetine 4 mg + Hyoscine Butylbromide 20 mg	*N* = 12 Crossover, 1 night				51 ± 30		33 ± 22**			
Perger, Elisa	CHEST (2021)	Placebo/Reboxetine 4 mg + Oxybutynin 5 mg	*N* = 18 crossover, 1 week				38.7 (29.0 to 47.8)		18.0*** (12.5 to 21.4)	75.5 (68.1 to 168.0)		39.7*** (25.4 to 55.3)
Schweitzer, Paula K.	Sleep and Breathing (2022)	Placebo/Atomoxetine 80 mg/Atomoxetine 80 mg + Oxybutynin 5 mg	*N* = 62 Crossover, 1 night	14.2 (5.4 to 22.3)	4.8*** (1.4 to 11.6)	6.2*** (2.8 to 13.6)	23.6 (12.4 to 32.7)	15.4*** (9.0 to 27.9)	14*** (8.1 to 17.1)	30.5 (10.4 to 31.6)	9.7*** (3.3 to 28.8)	13.7*** (4.4 to 30.3)
Rosenberg, Russel	Journal of Clinical Sleep Medicine (2022)	Placebo/AD109 37.5/2.5/AD109 75/2.5	*N* = 31 crossover, 1 night	13.2 (8.0 to 19.1)		AD109 37.5/2.5 7.8* (4.0 to 13.7) AD109 75/2.5 5.5*** (2.2 to 9.6)				13.9 (4.5 to 21.9)		AD109 37.5/2.5 7.3** (2.0 to 12.5) AD109 75/2.5 2.3*** (0.1 to 10.5)
Messineo, Ludovico	Respirology (2022)	Placebo/Atomoxetine 80 mg + Fesoterodine 4 mg	*N* = 12 crossover, 1 night				34.2 ± 19.1		30.1 ± 28.2	52.4 ± 50.5		29.7 ± 78.9
Altree, Thomas J.	Journal of Clinical Sleep Medicine (2022)	Placebo/Reboxetine 4 mg/Reboxetine 4 mg + Oxybutynin 5 mg	*N* = 16 crossover, 1 night	18 ± 17	13 ± 16*	14 ± 17*	36 ± 15	31 ± 14*	32 ± 17	74 ± 60	56 ± 57	56 ± 50*

(Continued)

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TABLE 1 (Continued)

First author	Journal (year)	Intervention arms	N, type of study	AHI4			AHI3a			HB		
				Placebo	SNRI Alone	Combination SNRI + Antimuscarinic	Placebo	SNRI Alone	Combination SNRI + Antimuscarinic	Placebo	SNRI Alone	Combination SNRI + Antimuscarinic
Aisha, Atqiya	Annals of American thoracic society	Placebo /Atomoxetine 80 mg + Oxybutynin 5 mg /Atomoxetine 40 mg + Oxybutynin 5 mg/Atomoxetine 40 mg + Oxybutynin 2.5 mg	$N = 39$ parallel arms, 30 nights	Placebo from 13 ± 12 to 13 ±15		Ato-Oxy 80/5 from 24 ± 18 to 12 ± 11 ($p < 0.05$ at Night 1) Ato-Oxy 40/5 from 22 ± 16 to 20 ± 16 Ato-Oxy 40/2.5 from 23 ± 24 to 19 ± 19*	Placebo from 29 ± 14 to 28 ± 16		Ato-Oxy 80/5 from 39 ± 19 to 29 ± 15 Ato-Oxy 40/5 from 35 ± 23 to 37 ± 18 Ato-Oxy 40/2.5 from 45 ± 24 to 42 ± 22	Placebo from 42 ± 52 to 40 ± 59		Ato-Oxy 80/5 from 84 ± 96 to 34 ± 41 ($p < 0.05$ at Night 1 and 30) Ato-Oxy 40/5 from 76 ± 64 to 70 ± 75 Ato-Oxy 40/2.5 from 77 ± 130 to 47 ± 54

Data are expressed as medians (IQR) or means ± SD. Only double blinded, placebo-controlled trials have been reported here. SNRI, selective norepinephrine reuptake inhibitor; AHI3a, apnea hypopnea index, 3% or arousal definition for hypopneas; AHI4, apnea hypopnea index, 4% definition for hypopneas; AD109, combination of atomoxetine + R-oxybutynin. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. placebo. The trials reported above excluded male patients >65 due to concerns for higher risk of urinary problems with ato-oxy or AD109 in the older male population. Women over 65 years of age were allowed in the trial without any reported safety concerns.

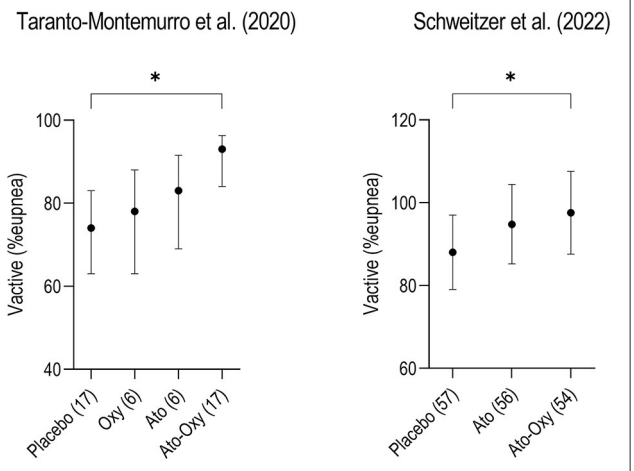

FIGURE 1
Two crossover trials comparing "active" upper airway collapsibility measured as Vactive between placebo, atomoxetine (ato) and atomoxetine plus oxybutynin (ato-oxy) showed that only the combination of drugs significantly increased Vactive compared to placebo, suggesting a synergistic effect of the combination on upper airway muscle activity. Vactive represents the ventilation measured at the arousal threshold, when the upper airway dilator muscles are maximally activated during sleep, just before the arousal. The same pattern is confirmed in another unpublished study with atomoxetine alone vs. AD109 (a combination of atomoxetine and R-oxybutynin, NCT04631107). Although the contribution of oxybutynin (oxy) in recruiting the pharyngeal muscles seems to be inferior compared to atomoxetine, it seems to have an important action in maximizing upper airway patency. Numbers in parenthesis on the x-axis represent the patients studied in each arm. Data for this figure show means (95% CI) and are taken from Taranto-Montemurro et al. (2020) and Schweitzer et al. (2022). *$p < 0.05$.

was well tolerated, with the most common side effects being dry mouth, dyspepsia and nausea. They also observed that only the high dose of ato-oxy, 80/5 mg, reduced the AHI on day 1 ($p < 0.05$) and on day 30 ($p = 0.09$) by ∼50%. HB, a recently introduced OSA severity metric quantitively assessing the oxygen desaturation associated with upper airway obstructive events (Azarbarzin et al., 2018), was also dramatically reduced by >80% vs baseline at both timepoints ($p < 0.01$) with high dose ato-oxy. Interestingly, only when hypopneas were scored using the 4% desaturation criterion according to the American Academy of Sleep Medicine (AASM) alternative definition (AHI4), was there a statistically significant reduction in AHI comparable to previous findings. On the contrary, when hypopneas were scored in association with 3% desaturation or arousal (AHI3a) there was no significant effect of the combination on OSA severity.

In subsequent proof-of-concept studies aimed at identifying the effects of other antimuscarinics in combination with atomoxetine, fesoterodine (Messineo et al., 2022), solifenacin, and biperiden (Aishah et al., 2021) all had lesser efficacy than oxybutynin, possibly due to their more selective action on muscarinic receptors (solifenacin, biperiden). This also could be due to their lower permeability across the blood brain barrier compared to oxybutynin (fesoterodine). A recent study performed in 17 Japanese OSA patients showed no effect of ato-oxy on overall OSA severity, although a subset of patients experienced AHI

reduction (Kinouchi et al., 2022). While this study suffers from methodological limitations such as lack of placebo and blinding, it suggests that ethnicity may play a role in the response to this combination.

Recent research efforts have addressed the development and efficacy of the combination of the R-enantiomer of oxybutynin (aroxybutynin) with atomoxetine (combination named AD109) with the goal of improving risk-benefit in OSA compared to the combination with racemic oxybutynin. Indeed, oxybutynin is commercially available in a racemic form composed of 50% S-oxybutynin and 50% R-oxybutynin (aroxybutynin). The efficacy of oxybutynin in OSA is believed to be related to its antimuscarinic effects. The R-enantiomer of oxybutynin has been shown to confer the antimuscarinic effect of oxybutynin, whereas the spasmolytic effects (and other effects on calcium channel antagonism and local anesthetic effects) are non-stereoselective properties of both the enantiomers (R and S). Most recently, Rosenberg et al. tested two doses of Apnimed's AD109 (37.5/2.5 and 75/2.5 mg of atomoxetine/aroxybutynin) during a crossover trial in patients with mild to moderately severe OSA [AHI4 between 5 and 20 events/h (Rosenberg et al., 2022)]. The combination showed at both doses a statistically significant reduction of AHI4 and HB compared to placebo after acute (1-night) administration. The study demonstrated a dose-response for AD109, with the effect size of high dose AD109 being larger than that of low dose AD109.

Another line of investigation aimed to test the effect of reboxetine, another SNRI, taken alone or in combination with an antimuscarinic, on OSA severity. During a crossover trial, Lim et al. successfully reduced the AHI by ∼35% with reboxetine 4 mg and hyoscine butylbromide 20 mg administered for 1-night and showed an increase in genioglossus activity on drugs vs placebo (Lim et al., 2019). Perger et al. showed, in another crossover trial, that 1 week of reboxetine 4 mg plus oxybutynin 5 mg reduced OSA severity by ∼60% ($p < 0.001$) (Perger et al., 2022).

Finally, Altree et al. recently tested, in a single night, randomized controlled crossover trial, the combination of reboxetine plus oxybutynin vs reboxetine alone vs placebo (Altree et al., 2022). Contrary to the previous experiments, the combination did not significantly reduce the AHI3a, while reboxetine alone showed an average AHI3a reduction of ∼15% vs placebo ($p = 0.03$). As discussed above, the results were different depending on the hypopneas scoring criteria used. When AHI4 was assessed, both reboxetine alone and the combination with oxybutynin reduced OSA severity compared to placebo. Finally, as was observed with atomoxetine, there was a tendency for reboxetine alone to reduce total sleep time by ∼20 mins and sleep efficiency by 6% ($p = 0.11$) compared to the combination with oxybutynin.

Interpretation challenges of the proof-of-concept trials

The proof-of-concept trials mentioned above raised several interpretation challenges. The most important are related to (a) the mechanism of contribution of the antimuscarinics (racemic oxybutynin or aroxybutynin) to the combinations tested and (b) the reconciliation of variable results across multiple trials.

a) The contribution of the antimuscarinics (racemic oxybutynin or aroxybutynin)

The original hypothesis of the investigators was that the main role of oxybutynin was to enhance upper airway dilator muscles activity especially during REM sleep by blocking the muscarinic inhibitory pathway to genioglossus activation. However, it has become clear, after multiple similar findings, that the SNRIs (atomoxetine or reboxetine) have the most important stimulatory action on the pharyngeal dilator muscles, while the antimuscarinic component has a smaller such effect. The available data on the effect of oxybutynin taken alone indicate no specific reduction on REM AHI. A potential explanation for this occurrence might be that rather than a cholinergic mechanism becoming active only during REM sleep to inhibit hypoglossal motor activity, there might exist a constant cholinergic inhibition throughout all states (wake, NREM, and REM), but it is most noticeable in REM sleep due to the absence of inputs that support muscle activation, such as noradrenergic inputs. As a result, the loss of noradrenergic inputs plays a role in reducing muscle activity during non-REM sleep, while both the noradrenergic and cholinergic mechanisms contribute to motor suppression during REM sleep. It is unlikely that a single mechanism is responsible for motor suppression in each state, such as non-REM adrenergic inhibition and REM cholinergic inhibition. The contribution of oxybutynin to upper airway muscle stimulation is revealed by the synergistic effect, during NREM sleep, of the ato-oxy combination on the "active" upper airway collapsibility (Vactive, see Figure 1 for details) (Taranto-Montemurro et al., 2020). It is important to highlight that the analysis of REM data is limited by the acute reduction in REM sleep that is typically seen with SNRIs administration. The longest study (30 days) performed with ato-oxy suggests that a partial recovery of REM sleep is likely to occur after a few weeks of therapy (Aishah et al., 2022) and more data on REM sleep may be available with larger, long-term studies.

A second important contribution of the anticholinergic agent in the ato-oxy combination was discovered to be the mitigation of the wake-promoting effects caused by the SNRIs. Indeed, the monoaminergic and cholinergic systems are largely wake-promoting (Schwartz and Kilduff, 2015) with basal forebrain cholinergic neurons activating cortical pyramidal cells which augment cortical activation and EEG desynchronization (Sofroniew et al., 1982; Dunnett et al., 1991). Conversely, antimuscarinic medications have sedative properties (Thornton, 1977; Weerts et al., 2015) and this effect may be mediated by the reduction in basal forebrain cholinergic activation (Anaclet et al., 2015). Antimuscarinic drugs, such as atropine, have been found to eliminate the fast, low-amplitude brainwaves induced by adrenergic stimulants, such as amphetamine, in animal studies. Instead, these drugs lead to the development of slow, high-amplitude brainwaves that are characteristic of NREM sleep. In the context of OSA treatment, the combined effects of an antimuscarinic which increases pharyngeal muscle activity and improves sleep consolidation may be an ideal solution. Oxybutynin may also have less risk of next morning sedation or muscle relaxation compared to commonly prescribed hypnotics.

b) Reconciliation of variable results across multiple trials

As discussed above, not all the small trials to date involving a combination of SNRI and antimuscarinic have yielded similar

results. Although it is not possible in this short review to provide a detailed discussion of all possible explanations for these different outcomes, there are quite a few possibilities. Among the possible reasons for this lack of reproducibility in proof-of-concept trials results are the different properties of drugs used from the same class, patient heterogeneity, methodological differences, and the spontaneous night-to-night variability in OSA severity. In addition, interscorer variability may cause different interpretation of the sleep studies, and the different definitions of AHI used at different institutions can importantly alter trial results. To address this last issue, according to the AASM criteria, hypopneas may be scored when associated with a 3% desaturation or arousal (AHI3a) or, alternatively, when associated with a 4% oxygen desaturation (AHI4) (Berry et al., 2012). While the second definition of hypopnea is more conservative [AHI4 may be >50% lower than AHI3a (Ruehland et al., 2009)], it also yields the greatest reproducibility across different scorers as it avoids the scoring of arousals in the determination of AHI. It has been clearly observed that arousals are the largest source of interscorer variability and definitions of AHI which include arousal scoring therefore result in less reproducibility across sites and across trials (Loredo et al., 1999). Other scoring criteria for hypopneas may vary from study to study including the required reduction in flow amplitude which may be 30% or 50% from baseline depending on definitions used (Ruehland et al., 2009). A solution to these inconsistent scoring rules could be the adoption of validated automatic scoring services which are increasing in number and quality. In addition, the search for new metrics that may better represent the real ventilatory deficit associated with upper airway obstruction has yielded the HB of OSA (Azarbarzin et al., 2018). This deficit is currently only partially captured by the AHI, which is a simple frequency metric with scarce correlation to clinical symptoms or long-term outcomes of OSA (Malhotra et al., 2021).

Some of these issues related to the diagnostic paradigm of OSA are being discussed by academic experts (Mehra et al., 2023) and have been recently considered while designing larger industry-sponsored trials testing the effects of pharmacotherapies on OSA severity (Clinicaltrials.gov, 2022a,c; Hedner et al., 2022). The Mariposa trial was a large 25-center phase 2b trial recently concluded, which tested the effect of AD109 over a month of therapy in patients with a baseline AHI4 between 10 and 45 events/h. To reduce the effect of night-to-night variability, the AHI was collected and averaged over 2 nights both at baseline and on treatment. This same strategy was used during the investigation of sulthiame, a new carbonic anhydrase inhibitor tested for OSA treatment from Hedner and colleagues. The use of two-night assessments may have played a role in reducing the amount of variability in individual responses compared to other studies on carbonic anhydrase inhibitors (Hedner et al., 2022). In Mariposa, AHI4 was selected as the primary outcome to increase the reproducibility of the results across trials and across scoring centers, and the HB was also quantified as in previous trials with the same therapy (Rosenberg et al., 2022). Longer trials are also exploring several patients reported outcomes. Subjective outcomes in OSA pharmacotherapy have been largely overlooked so far but are clearly important to fully understand the impact of treatment (Hedner and Zou, 2022).

Conclusion

The use of a combination of selective norepinephrine reuptake inhibitors (SNRIs) and antimuscarinic drugs has shown promise in the search for a pharmacotherapy for OSA. While progress has been made in this area, there are still hurdles that need to be overcome in order to bring a treatment based on AD109 to patients. These include the need for larger and longer trials to better define both the subjective and objective outcomes of therapy with this drug combination. In addition, although the AHI is considered the gold standard for evaluating the presence and severity of OSA, there are clear limitations to its accuracy as a metric for measuring the extent of the breathing disorder and the effectiveness of treatments. This problem is still being addressed in ongoing research. Despite these challenges, the prospect of a pharmacotherapy for OSA is becoming increasingly promising, and further research and development in this area may bring us closer to a viable treatment option for this common and debilitating condition.

Author contributions

LT-M contributed to data analysis and interpretation and drafting and review of the manuscript. DW contributed to data interpretation and drafting and review of the manuscript. HP contributed to data analysis and review of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

LT-M is CSO of Apnimed, a company developing pharmacotherapy for obstructive sleep apnea. HP is Clinical Data Scientist of Apnimed. DW is Senior VP of Medical Affairs at Apnimed, is a consultant for Cryosa, Cerebra Health, Xtrodes, Onera, Resonea, Linguaflex, Bairitone, Mosanna, and Philips Respironics, and owns equity in Neumora.

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Innovations in mandibular advancement splint therapy for obstructive sleep apnoea

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Mandibular advancement splint (MAS) therapy emerged as an effective therapy for obstructive sleep apnoea (OSA) in the mid 1990s, and is now the leading treatment alternative for OSA. Since its inception, the field has seen a suite of revisions and advances in relation to design and customisation, fabrication, titration methods, response prediction models and the integration of data collection technology. This paper reviews these current and emerging innovations in MAS therapy and their impact upon sleep apnoea management.

KEYWORDS

oral appliance, mandibular advancement splint, mandibular advancement device, sleep apnoea, obstructive sleep apnoea

1. Background: Mechanism of action and treatment response

MAS is an oral appliance which protrudes the mandible in relation to the maxilla, causing movement of soft tissues (tongue and soft palate) to increase the calibre of the upper airway and reduce its collapsibility. Although continuous positive airway pressure (CPAP) therapy is more effective than MAS at lowering the apnoea hypopnoea index (AHI) (Luz et al., 2022), CPAP acceptance and compliance rates may be low, leading to reduced overall efficacy in eliminating the burden of OSA (Grote et al., 2000; Schwartz et al., 2018). MAS therapy improves blood pressure, daytime somnolence, driving risk and quality of life to the same extent as CPAP, including in patients with severe OSA (Lim et al., 2006; Phillips et al., 2013). Therefore, it is hypothesised that the reduced efficacy of MAS when compared to CPAP may be offset by improved patient tolerance and adherence with MAS therapy (Schwartz et al., 2018), leading to similar benefits in neuro-behavioural and cardiovascular outcomes. However, one of the key barriers to wider uptake has been the variability of patient response, since up to 70% of patients will experience a partial or complete treatment response (Sutherland et al., 2015), leaving around 30% without a beneficial therapeutic outcome. In addition, since a MAS device relies on dental adherence in order to remain *in situ*, patients with inadequate dentition are ineligible and have been excluded from research studies. Prediction tools for a favourable MAS treatment response are an area of ongoing research.

2. Patient selection and prediction of response: Endotypes

Traditionally, demographic and anthropometric characteristics have been explored as markers of MAS treatment response. For example, younger age, less obesity, female gender, milder OSA, and supine-dependent OSA have variously been associated with treatment success, though these have all been weakly predictive (Sutherland et al., 2015). Endotypic profiling has been gaining recognition in Sleep Medicine generally as a means by which to advance precision medicine for OSA patients, and can be applied to MAS treatment response.

An endotype refers to a disease subtype with a distinct functional or patho-biological mechanism (Edwards et al., 2019). OSA endotypes include: arousal threshold (degree of ventilatory drive required to trigger an arousal from sleep), loop gain (instability in ventilatory control in response to a disturbance), pharyngeal collapsibility and compensatory airway muscle responsiveness. Traditionally, these endotypic traits have been determined in a highly controlled research laboratory setting using invasive measurement techniques (Edwards et al., 2016; Bamagoos et al., 2019b). However more recently, methods have been developed to impute endotypic traits from data accessible from routine clinical polysomnography (PSG). For example, Terrill et al. have developed a mathematical method to reliably calculate loop gain from the rise in ventilatory drive that follows an obstructive respiratory event (Terrill et al., 2015). The same group has also developed algorithms for the estimation of pharyngeal collapsibility and compensatory muscle responsiveness from the changes in ventilation and ventilatory drive seen on PSG (Sands et al., 2018). These advances pave the way for more accurate MAS prediction models unencumbered by the need for invasive laboratory studies. In a group of 93 patients with, on average, moderate OSA, greater MAS efficacy was associated with 5 endotypic traits derived using algorithms applied to clinical polysomnographic data: lower loop gain, higher arousal threshold, lower ventilatory response to arousal, moderate pharyngeal collapsibility and weaker muscle compensation (Bamagoos et al., 2019a). The association of lower loop gain and MAS response has also been confirmed in other studies (Edwards et al., 2016; Op de Beeck et al., 2021). These findings may improve prediction models for MAS response, and also raise questions for future research. For example, future studies on combination therapy with MAS plus a carbonic anhydrase inhibitor to facilitate loop gain reduction are warranted (Hedner and Zou, 2022).

Characteristics which act as direct or surrogate markers for the site of airway collapse have also been studied as predictors of response to MAS therapy. For example, the level and specific type of airway collapse observed on drug-induced sleep endoscopy (DISE) has been associated with response to MAS. Tongue-base collapse predicts a favourable response, whereas complete concentric collapse or complete latero-lateral oropharyngeal collapse are seen in those less likely to respond (Op de Beeck et al., 2019). Complete anteroposterior epiglottic collapse predicted an unfavourable response to maxillomandibular advancement surgery (Zhou et al., 2021); however MAS therapy was equally effective in patients with or without epiglottic collapse (Van de Perck et al., 2022). A posteriorly positioned tongue with a less collapsible airway is a positive predictor for MAS therapy (Marques et al., 2019). Further, certain "airflow shapes", once again derived from routine PSG, have been used to predict the site of airway collapse and thereby response to MAS. Increased drop in airflow during respiratory events as well as a "pinched" expiratory flow shape (indicative of palatal prolapse) is associated with the poorest response to MAS therapy (Vena et al., 2020).

3. MAS titration technology

Traditionally, MAS devices are manually titrated under the supervision of a dentist. Various titration methods have been used, for example titrating to a percentage of maximal mandibular advancement, titrating on the basis of symptoms such as the alleviation of snoring or daytime somnolence, or titrating to an improvement in hypoxic burden which may be measured at home on overnight oximetry. Optimal titration is important to maximise the therapeutic benefits of the MAS device. An advancement of at least 50% of maximum mandibular protrusion is required to have a potential therapeutic outcome while minimising adverse side effects (Aarab et al., 2010; de Ruiter et al., 2020). However, manual titration of a MAS remains inefficient in terms of time to achieve optimal therapeutic outcomes (Sharma et al., 2013; Fleury and Lowe, 2014; Kuna, 2014). International guidelines recommend a progress diagnostic sleep study following titration to assess the efficacy of the device (Ramar et al., 2015).

Novel MAS titration techniques such as the use of a remote-controlled mandibular positioner (RCMP) to determine the therapeutic level of mandibular advancement during a single night PSG have been proposed to overcome the inefficiency barriers to MAS therapy (Pételle et al., 2002; Tsai et al., 2004; Dort et al., 2006; Remmers et al., 2013). Single night PSG titration enables reasonable prospective prediction of MAS therapy success as demonstrated by Remmers et al. (2013). However, RMCP is resource intensive, and requires the use of a sleep laboratory and trained and experienced staff.

A feedback-controlled mandibular positioner (FCMP) was recently developed to enable titration of a MAS device outside the laboratory setting (Remmers et al., 2017). The FMCP combines the use of a level 3 home sleep apnoea test (HSAT), the mechanism of the RCMP and machine learning algorithms to analyse the frequency of sleep disordered breathing and automatically titrate the mandibular advancement device accordingly to resolve sleep disordered breathing (Remmers et al., 2017). An early iteration of the FCMP demonstrated a sensitivity and specificity of 85 and 93% respectively for the prediction of therapeutic success, defined as an oxygen desaturation index (ODI) < 10/hr with the device *in situ* (Remmers et al., 2017). A subsequent iteration improved the sensitivity and specificity to 91 and 100% respectively, with 93% prediction accuracy (Mosca et al., 2022). This finding highlights the potential for future use of an auto-titrating mandibular advancement device to efficiently identify the therapeutic mandibular position. One small crossover pilot study ($n = 10$) found no difference in optimal MAS positioning using three titration methods: (1) subjective titration, (2) PSG-guided titration

using a remotely controlled mandibular positioner (RCMP) and (3) DISE-assisted titration using RCMP (Kazemeini et al., 2022). Larger studies will be required to confirm the accuracy of remote titration methods compared with in-laboratory titration.

4. Advances in mandibular advancement splint fabrication

The European Respiratory Society recommends a custom-made titratable MAS device as preferable over non-custom devices (Ramar et al., 2015). Recent implementation of digital technologies to dentistry has transformed dental workflows for custom MAS devices (Tallarico, 2020; Alauddin et al., 2021). The use of intraoral scanners and computer aided design/computer aided manufacturing (CAD/CAM) techniques have streamlined the delivery of dental care (Tallarico, 2020; Alauddin et al., 2021). Benefits in patient preference, time savings and elimination of physical storage make digital workflows superior to conventional dental workflows (Mangano et al., 2017). Accuracy of both intraoral scanners and conventional impression methods are also comparable (Afrashtehfar et al., 2022; Hashemi et al., 2022). Device fabrication *via* CAD/CAM methods allows for the time efficient production of dental devices (van Noort, 2012). The digital technology also provides more accurate measures of tooth and jaw position, improving the quality of device fabrication, as well as facilitating superior observation and monitoring of potential dental side effects from these appliances.

Studies comparing CAD/CAM manufactured MAS devices and conventionally manufactured MAS devices are limited. One study demonstrated a significant increase of 40% in oropharyngeal airway volume in patients who used a CAD/CAM MAS device (Kerbrat et al., 2021). Similar findings were also observed in oral appliance treatment success rates of 63% (Kerbrat et al., 2021) and 80% (Vecchierini et al., 2016) in patients using CAD/CAM devices. In addition, therapy compliance and patient preference favoured the CAD/CAM oral appliances (Vecchierini et al., 2016; Kerbrat et al., 2021). The authors attributed these findings due to the differences in material, shape, and magnitude of vertical opening between devices (Vecchierini et al., 2016).

5. Data collection and remote monitoring

5.1. Adherence data

The collection of efficacy and adherence data is routine for CPAP therapy in clinical practice, and is now available for MAS therapy. The American Academy of Dental Sleep Medicine defines adequate compliance with oral appliance (OA) as a minimum of $\geq$80% of total sleep time per night, starting when the OA is placed in the mouth and ending when the OA is removed from the mouth, $\geq$5 nights per week (Radmand et al., 2021). A number of small studies have looked at objectively recorded MAS compliance over an initial 3 month period, and most have found average compliance rates to be in excess of 6 h per night (Sutherland et al., 2021b). In order to objectively assess compliance data, a temperature sensitive sensor microchip may be embedded within, or attached to, the device. When the temperature lies within a certain range (generally 31.5–39.2°C), it is inferred that the device is *in situ* within the oral cavity, and therefore in use. The device may store from 100 days to many months' worth of compliance information which is available for download *via* a base-station at the time of patient review. There are a number of models available, with sampling intervals ranging from 5 to 15 min. One study compared the accuracy of three commercially available microsensors under *in vitro* and *in vivo*, conditions, and all were found to be highly reliable (Kirshenblatt et al., 2018). Data analysis and display varies according to brand and software. One brand (Dentitrac, Braebon Ltd.) additionally collects and reports positional data (supine vs. non-supine sleep) (Sutherland et al., 2021b). Cluster analysis has identified three main MAS adherence patterns identified over 60 days of objective adherence data recording: "Consistent Users" (48.3%), "Inconsistent Users," (32.8%) and "Non-Users" (19.0%). These usage patterns can be identified within the first 20 days of therapy, providing an early opportunity for intervention for those patients with sub-therapeutic adherence (Sutherland et al., 2021a).

Development of device-imbedded compliance chips within MAS devices opens up the possibility of remote, real-time monitoring of patient compliance. Integration of device recorded compliance data to cloud-based and patient engagement platforms may improve patient compliance to OSA therapies in some patients. For example, the use of cloud-based monitoring for CPAP therapy has demonstrated an extra hour of CPAP use per night (Hwang et al., 2018; Malhotra et al., 2018). Furthermore, the inclusion of a patient engagement tool which provides coaching and the ability for patients to view CPAP use to remote monitoring further improves device usage (Hostler et al., 2017; Hwang et al., 2018; Woehrle et al., 2018). Additionally, the adherence rate was higher compared to usual care without remote monitoring and patient engagement tools (Hostler et al., 2017; Hwang et al., 2018). While platforms for remote monitoring of MAS compliance are currently limited, integration of these platforms and telehealth modes in future oral appliances may increase the uptake of MAS devices and further improve long term adherence rates for some patients. A recent study evaluated the objective compliance with remote monitoring and therapy feedback to patients for MAS devices (Kwon et al., 2022). Similar trends were noted to that of remote monitoring and therapy feedback for CPAP in that, objective compliance to MAS therapy can be increased with remote monitoring and therapy feedback to patients (Kwon et al., 2022).

5.2. Biological signals

Another recent advance for MAS devices is the integration of buccal oximetry sensors. Evidence on their performance is mixed with very early success with these sensors (Rogers and Gan, 1997), but more recent work suggesting these sensors do not provide accurate oxygen saturation (SpO2) measurement and further technological work was needed to determine if it is the site, the sensors or both which is the issue (De Jong et al., 2011). In contrast, a very recent study by Nabavi et al. (2020) successfully developed a smart MAS that monitors cardiorespiratory parameters intraorally

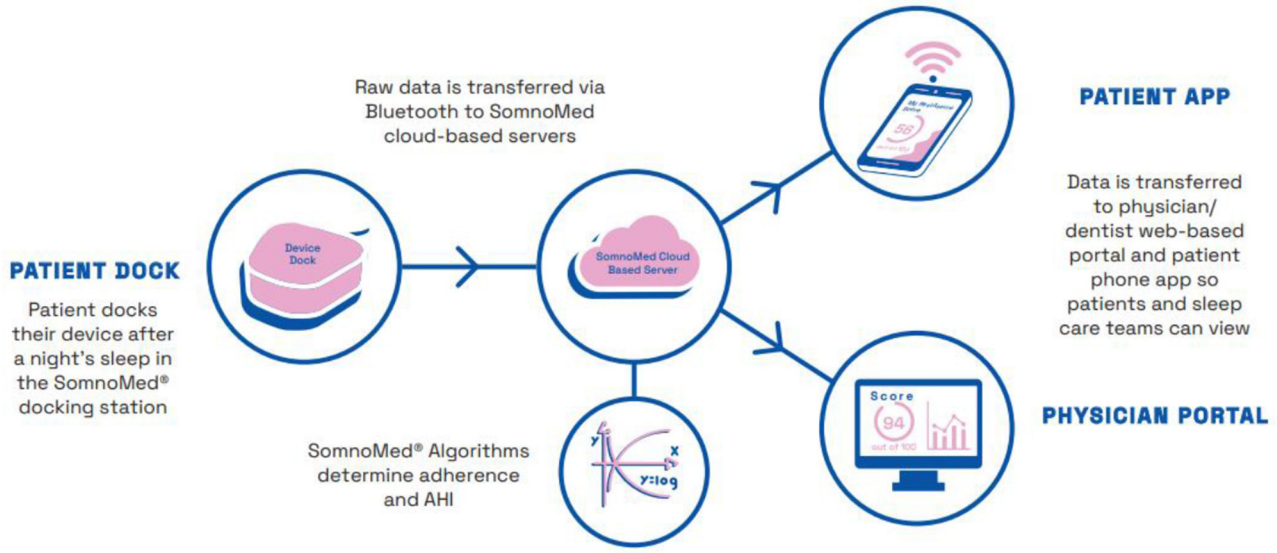

FIGURE 1
Schematic diagram illustrating mandibular movement sensor technology for the collection, storage, analysis and display of sleep data; as used in a commercial application. Image courtesy of Somnomed.

(Nabavi et al., 2020). The device comprised of a flexible hybrid wireless monitoring platform integrated within a MAS, that acquires intraoral photo-plethysmography (PPG) signals. Their results showed that the PPG signals captured intraorally are highly correlated with the conventional PPG signals received and therefore enabled the collection of heart rate (HR), respiratory rate (RR), and SpO2. The estimated values of HR, RR, and SpO2 from the intraoral PPG signals show an accuracy of over 96% with reference to PSG. Further, PPG has been combined in a single device together with positional data and breathing route (mouth vs. nose) (Nabavi and Bhadra, 2021). These developments have exciting potential clinical applications and may translate into a smart MAS device which can facilitate home-based MAS efficacy studies, home-based MAS titration studies as well as capturing data on combination therapy with MAS plus positional devices. Further, the inclusion of physiological sensors highlights the potential for the development of future FCMP devices which can more accurately auto-titrate oral appliance during sleep (Remmers et al., 2017).

Martinot et al. (2019) and Pépin et al. (2020) have shown that mandibular movements measured using midsagittal mounted magnetic sensors on the chin and the forehead, successfully differentiated obstructive and central events (Martinot et al., 2019) and when the signals were combined with machine learning could successfully discriminate controls from apnoea patients (RDI $\geq$ 5) with an area under the receiver operating characteristic curve (AUC-ROC) of 0.95 (Pépin et al., 2020). More recent work by the same group (Le-Dong et al., 2021) demonstrated that machine learning also enabled accurate sleep staging to be performed with an AUC for wake of 0.98, N1/N2 sleep of 0.86, N3 sleep of 0.97, and REM sleep of 0.96. Additionally, mandibular jaw movements (MJM) can be used as a surrogate measure for nocturnal respiratory effort (RE), since the slight protrusions of the mandible during sleep are reflective of respiratory drive (Martinot et al., 2022). Respiratory effort measured *via* MJM was a stronger predictor of prevalent hypertension than AHI (Martinot et al., 2022). Such sensors potentially could be embedded within MAS devices to allow capture of compliance data and cardiovascular risk profiling. European Respiratory Society guidelines have highlighted the need for rigorous validation studies for such diagnostic devices which use intelligent sensors, including the need for appropriate power calculations as well as side effect and failure rate profiling. Importantly, it is noted that since the diagnostic algorithms for such devices are not published, the sleep stages and event scoring cannot be manually reviewed or altered as they can be for level 1–4 diagnostic devices (Riha et al., 2023).

At least one manufacturer has recently recognised the potential benefits of instrumenting MAS, announcing the development of a smart oral appliance prototype hardware and software that provides a smart oral appliance with sensors to monitor efficacy and compliance[1], see Figure 1.

6. Conclusion

Like many areas of medicine, OSA therapy has now entered the age of personalisation. Advances in MAS therapy discussed here will contribute to personalisation of MAS therapy at the level of patient selection, titration, improved adherence and monitoring of treatment. The use of endo-phenotypes for MAS response prediction models is likely to become more refined and

1 https://company-announcements.afr.com/asx/som/e60260ee-9367-11ec-b4cf-6eeaf7b2618c.pdf

thereby more accurate, allowing for targeted patient selection and combination treatment strategies. New MAS prototypes can incorporate a suite of physiological sensors that support clinical decision making with regards to titration, compliance and efficacy of the device. In particular, mandibular movement sensors have emerged which have diagnostic and treatment applications, though these require rigorous validation studies. MAS compliance monitoring and cloud-based platforms will continue to be integrated into clinical practice to improve patient engagement and compliance. These combined advances will increase the quality and safety of MAS therapy, making it available to increasing groups of patients using a targeted therapeutic approach.

Author contributions

AM, BT, and PDC each wrote sections of the first draft of the manuscript. AM drafted the final version. All authors contributed to the scope and structure of the manuscript. All authors contributed to manuscript revisions and approved the submitted version.

Conflict of interest

AM reports in-kind support from Resmed Pty Ltd., Australia and Somnomed Australia for previous researcher-initiated studies; and has received honoraria from Somnomed Australia for presenting at educational meetings. PC has an appointment to an endowed academic Chair at the University of Sydney that was created from ResMed funding. He has received research support from ResMed, SomnoMed, Zephyr Sleep Technologies, and Bayer. He is a consultant/adviser to Zephyr Sleep Technologies, ResMed, SomnoMed, and Signifier Medical Technologies. He has a pecuniary interest in SomnoMed related to a previous role in R&D (2004). PDC holds an endowed academic chair at the University of Sydney, established through funding from ResMed and has received research support from ResMed, SpaceLabs, and Somnomed.

The remaining author declares 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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Evaluation and diagnosis of pediatric obstructive sleep apnea—An update

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Purpose: Formal overnight polysomnography (PSG) is required to diagnose obstructive sleep apnea (OSA) in children with sleep disordered breathing (SDB). Most clinical guidelines do not recommend home-based tests for pediatric OSA. However, PSG is limited by feasibility, cost, availability, patient discomfort, and resource utilization. Additionally, the role of PSG in evaluating disease impact may need to be revised. There is a strong need for alternative testing that can stratify the need for PSG and improve the time to diagnosis of OSA. This narrative review aims to evaluate and discuss innovative approaches to pediatric SDB diagnosis.

Findings: Methods to evaluate pediatric SDB outside of PSG include validated questionnaires, single-channel recordings, incorporation of telehealth, home sleep apnea testing (HSAT), and predictive biomarkers. Despite the promise, no individual metric has been found suitable to replace standard PSG. In addition, their use in combination to diagnose OSA diagnosis still needs to be defined.

Summary: When combined with adjunct assessments, HSAT advancements may accurately evaluate SDB in children and thus minimize the need for overnight in-laboratory PSG. Further studies are required to confirm diagnostic validity vis-à-vis PSG as a reference standard.

KEYWORDS

sleep apnea, pediatric OSA, PSG (polysomnography), update, pediatric OSA diagnosis

Introduction

Sleep-disordered breathing (SDB) in children is characterized by disruption of normal respiration and ventilation cycles during sleep (Gipson et al., 2019), and ranges from mild snoring to obstructive sleep apnea (OSA). Pediatric OSA is associated with lower quality of life (Baldassari et al., 2008), behavior and neurocognitive dysfunction (Landau et al., 2012), impaired growth and development (Nieminen et al., 2000), and greater healthcare utilization (Shehan et al., 2023). Risk factors for OSA in childhood include adenotonsillar hypertrophy (Marcus and Loughlin, 1996), obesity (Mitchell and Kelly, 2007), craniofacial anomalies (Cielo and Marcus, 2015), and neuromuscular disorders (Katz, 2009; Marcus et al., 2012). Prevalence estimates for pediatric OSA range from 1.2 to 5.7% (O'Brien et al., 2003; Bixler et al., 2009; Li et al., 2010), although it approaches 60% in obese children (Verhulst et al., 2008). Pediatric OSA is expected to increase in prevalence with rising childhood obesity (Bryan et al., 2021). Adenotonsillectomy (AT) is the first-line treatment (American Thoracic Society, 1996; Marcus et al., 2012; Mitchell et al., 2019), resulting in resolution or improvement in symptoms in most children. In addition to the obese population, several other cohorts are considered high risk for OSA, with management

nuanced by complexity. These include children with Trisomy 21, craniofacial anomalies, craniosynostoses, achondroplasia, and with neuromuscular disorders (ElMallah et al., 2017). Though AT is still considered the first line of treatment, these children have higher rates of residual OSA (Rosen, 2011; Zandieh et al., 2013; Cielo and Marcus, 2015; Moraleda-Cibrián et al., 2015; Thottam et al., 2015; Simpson et al., 2018; Zambon et al., 2022), often requiring additional therapy. Positive pressure may be added to treat residual disease or primarily used in those unsuitable for AT (Muntz, 2012; Nehme et al., 2019). Weight loss (Verhulst et al., 2009), alone or supported by a multidisciplinary team (Roche et al., 2020), has also been beneficial. Additional surgical procedures can also be considered, such as hypoglossal nerve stimulation, uvulopalatopharyngoplasty, inferior turbinate reductions, or lingual tonsillectomy (Ravutha Gounden and Chawla, 2022). Treatment in these cases must be tailored to the child, considering their comorbidities.

Types of PSG are described in Table 1. Currently, overnight, in-laboratory level I polysomnography (PSG) is the only approved technology for diagnosis of pediatric OSA (Marcus et al., 2012; Kirk et al., 2017). Level I PSG is attended by a sleep technician in an accredited facility and includes a minimum of seven parameters: electrooculography (EOG), electroencephalography (EEG), chin electromyography (EMG), airflow, respiratory effort, oxygen saturations, and electrocardiography (ECG) (El Shayeb et al., 2014). Pediatric OSA is diagnosed when the PSG reports an obstructive apnea-hypopnea index (AHI), defined as the frequency of partial or complete reduction in air flow per hour, ≥1 (Mitchell et al., 2019). The most common stratification for mild, moderate, or severe disease is based on AHI thresholds of <5, 5–9, and ≥10 respectively (Marcus et al., 2013).

The American Academy of Sleep Medicine (AASM) (Aurora et al., 2011) and the American Academy of Pediatrics (AAP) (Marcus et al., 2012) recommend screening children with SDB with PSG. The American Academy of Otolaryngology—Head and Neck Surgery (AAO–HNS) recommends PSG before AT in children <2 years of age or in those with obesity, craniofacial or neuromuscular disorders, Down syndrome, sickle cell disease, or mucopolysaccharidoses (Mitchell et al., 2019). The AAO–HNS also recommends PSG if the need for surgery is uncertain or if the physical exam does not explain the severity of SDB (Mitchell et al., 2019).

Despite these recommendations, only 10% of children scheduled for AT undergo a PSG (Mitchell et al., 2006). Several barriers exist for level I PSG, e.g., access to a certified sleep laboratory and the limited technical expertise required to diagnose infants and younger children with OSA (Bertoni and Isaiah, 2019). Additionally, the test burden poses unique challenges for children and their families to sleep in an unfamiliar environment while wearing monitoring equipment (Bertoni and Isaiah, 2019). Caregivers must be present during the PSG, which can impact caring for other family members overnight and their productivity the following day. Polysomnography is also expensive, ranging from $1,000 to 4,000 dollars (Bertoni and Isaiah, 2020; Mitchell and Werkhaven, 2020). These issues translate into social and economic burdens for this vulnerable population.

Due to these obstacles, there is a strong need for alternative testing that can approximate PSG results. To date, validated questionnaires (Ahmed et al., 2018; Isaiah et al., 2020; Patel et al., 2020; Wu et al., 2020), single-channel recordings (Kirk et al., 2003; Saito et al., 2007; Álvarez et al., 2017; Hornero et al., 2017; Bertoni et al., 2020), incorporation of telehealth (Paruthi, 2020; Schutte-Rodin, 2020; Castner and D'Andrea, 2022; Griffiths et al., 2022), home-based PSG (Brockmann et al., 2013; Marcus et al., 2014; Ioan et al., 2020; Gao et al., 2021), and biomarkers (Patacchioli et al., 2014; De Luca Canto et al., 2015; Kheirandish-Gozal et al., 2015; Bhattacharjee et al., 2016; Elsharkawi et al., 2017; Teplitzky et al., 2019; Martín-Montero et al., 2022) have been assessed. In this review, we aim to examine innovative approaches to diagnosing pediatric OSA, including exploring combinations of existing technology with the potential for the accurate evaluation of pediatric OSA, thus stratifying the need for traditional overnight PSG.

TABLE 1 Types of polysomnography (Collop et al., 2007).

Level of PSG	Channels	Attended?
Level I	≥7 channels	Yes
Level II	≥7 channels	No
Level III	4–7 channels	No
Level IV	1–2 channels	No

Methods

A narrative review of the relevant literature was performed. Sources were identified through PubMed and Google Scholar searches from September 1, 2022, through January 26, 2023. Search terms were broad and included "pediatric OSA," "pediatric obstructive sleep apnea," "pediatric home sleep apnea test," "sleep questionnaires," "pediatric sleep questionnaires," "pediatric OSA diagnosis," "OSA diagnosis," "videotaping OSA," "telehealth pediatric OSA," "HSAT," "home diagnosis OSA." Each article was screened for relevance and quality by the authors and included in the review when deemed appropriate.

Additional approaches

Questionnaires

The OSA-18 quality of life survey includes 18 symptom-specific questions grouped into five categories: sleep disturbance, physical suffering, emotional distress, daytime problems, and caregiver concerns (Franco et al., 2000). Symptom severity is ranked on an ordinal Likert scale from 1 = none to 7 = all the time. In validation studies of the OSA-18, a total symptom score (TSS) between 60 and 80 correlated with a moderate impact on health-related quality of life. In contrast, a score above 80 indicated a significant impact (Constantin et al., 2010). Ishman et al. (2015) compared OSA-18 responses to PSG metrics. In White children, the specificity and positive predictive value (PPV) of diagnosing OSA using the OSA-18 were 100% when a TSS cut-off of ≥60 and obstructive AHI > 1

were used (Ishman et al., 2015). However, in non-White children, the specificity of these cut-offs was only 67%, with a PPV of 94% (Ishman et al., 2015). The authors also noted a low sensitivity and negative predictive value in all children, indicating an inability to rule out OSA (Ishman et al., 2015). The study concluded that while the OSA-18 questionnaire remains a validated tool to assess the impact of OSA on quality of life, it cannot be used for its diagnosis (Ishman et al., 2015). Constantin et al. (2010) reported that OSA-18 did not accurately diagnose OSA compared to PSG, especially in children with moderate to severe disease. A meta-analysis importantly identified that the OSA-18 could be used as a screening tool for pediatric OSA, though it should not replace PSG for diagnosis (Wu et al., 2020).

The Pediatric Sleep Questionnaire (PSQ) is a validated survey that asks caregivers about the frequency and quality of snoring, breathing problems, mouth breathing, daytime sleepiness, inattention/hyperactivity, and other symptoms (Chervin et al., 2000). Answers to the questions are in a "yes/no/don't know" format (Chervin et al., 2000). Canto et al. (2014) performed a systematic review and meta-analysis of questionnaires to assess for pediatric SDB. The authors noted that the PSQ had sufficient accuracy in screening children for OSA, but it was insufficient to replace PSG (Canto et al., 2014). However, Wu et al. (2020) noted that the PSQ is a sensitive tool for detecting pediatric OSA. The authors also reported that it might be used as a screening tool for OSA. They commented that it could be considered in combination with pulse oximetry in children as an early detection tool (Wu et al., 2020).

Rosen et al. (2015) demonstrated that PSQ symptom scores related to behavior impairment, quality of life, and sleepiness could predict improvement after adenotonsillectomy. Though it could not act as a surrogate for PSG, the authors endorsed its utility as an adjunct to help expect treatment response (Rosen et al., 2015). Patel et al. (2020) studied the predictive accuracy of questionnaires. The sleep-related breathing disorder (SRBD) scale of the PSQ had a sensitivity of 71–84% but a low specificity of 13% (Patel et al., 2020). Also, the area under the receiver operating characteristic (ROC) curve was small, demonstrating poor overall diagnostic accuracy (Patel et al., 2020). They also emphasized the critical role of questionnaires in quantifying the negative impact of SDB on a child's physical and psychological health (Patel et al., 2020). Chervin et al. (2007) demonstrated that the SRBD scale of the PSQ may predict OSA-related neurobehavioral morbidity and response to adenotonsillectomy as well as, and sometimes better than, standard PSG testing. The role of the PSQ may therefore be in screening, assessing SDB-related quality of life, and measuring surgical outcomes in children diagnosed with OSA.

The Children's Sleep Habits Questionnaire (CSHQ) (Owens et al., 2000), is a 45-item questionnaire and includes assessments of parent- and child-reported symptoms among school-aged children aged 4–10 years. Categories of symptoms include bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakening, parasomnias, sleep disordered breathing, and daytime sleepiness (Owens et al., 2000). Items are ranked on a 3-point scale: "usually" if the sleep behavior occurs 5–7 times per week, "sometimes" if it happens 2–4 times/week, and "rarely" for 0–1 times/week. Owens et al. (2000) reported the validity of the CSHQ, concluding it can be used to screen and identify children with sleep disturbances who warrant further testing, though it cannot replace a diagnostic PSG. A summary of validated questionnaires is found in Table 2.

TABLE 2 Validated sleep questionnaires.

Questionnaire	Items	Answer format
OSA-18 Quality of Life (OSA-18)	18 symptom specific questions, 5 categories • Sleep disturbance • Physical suffering • Emotional distress • Daytime problems • Caregiver concerns	Likert scale 1 (none) through 7 (all of the time)
Pediatric Sleep Questionnaire (PSQ)	22 questions asked in the following domains: • Snoring—frequency and quality • Breathing problems • Mouth breathing • Daytime sleepiness • Inattention/hyperactivity • Other symptoms	Yes, no, don't know
Children's Sleep Habits Questionnaire (CSHQ)	45-item questionnaire to assess children age 4–10 years. Categories: • Bedtime resistance • Sleep onset delay • Sleep duration • Sleep anxiety • Night wakenings • Parasomnias • Sleep disordered breathing • Daytime sleepiness	3-point scale: • Usually—symptom is present 5–7×/week • Sometimes—symptom is present 2–4×/week • Rarely—symptom occurs 0–1/× week

Isaiah et al. (2020) used feature selection algorithms to identify main SDB-related symptoms to predict OSA severity. The authors noted that the original questionnaires were not successful at predicting OSA (Isaiah et al., 2020). However, the selected features eliminated redundancy, resulting in improved prediction performance for OSA severity with a high pre-test probability (Isaiah et al., 2020). Follow-up validation replicated the findings (Kennedy et al., 2022), an essential advance in evaluation for pediatric OSA. This new finding does require further assessment, with multi-institutional validation. However, it holds promise as a reasonable alternative to PSG in resource-limited situations.

Single channel recordings

The level I polysomnogram measures nine parameters (Bertoni and Isaiah, 2019), of which have been studied in isolation to approximate the overall PSG findings. They are grouped by the system learned; sleep, cardiovascular, oximetry, position, effort, and respiratory (SCOPER) (Collop et al., 2011; Bertoni and Isaiah, 2019, 2020). Of these, cardiovascular, oximetry, position, and respiratory can be measured *via* single-channel recordings.

Cardiovascular

Overnight electrocardiogram (ECG) recordings have been evaluated as a potential single-channel recording for pediatric OSA

diagnosis. Shouldice et al. (2004) investigated the ability to detect OSA in children based on their ECG recordings during overnight PSG. In this study, obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for ≥2 breaths. Hypopneas were defined as 50% or more decrease in nasal airflow with an associated ≥4% desaturation, an arousal, or both but were only scored if the duration was ≥2 breaths. OSA was diagnosed when the obstructive AHI was ≥1. The authors used a different cutoff system for disease severity, with mild having AHI < 10, moderate AHI 10–15, and severe AHI > 15. The authors created a modified quadratic discriminant analysis classification system, which had a sensitivity of 85% and specificity of 81% to diagnose OSA (Shouldice et al., 2004). However, of the four false negatives identified, three were in cases classified as "mild" OSA, indicating slightly reduced accuracy of this system in children with AHI < 10 (Shouldice et al., 2004). Heart rate variability is an ECG-derived measure that may stratify chronic upper airway obstruction due to the detrimental impact of intermittent hypoxia on autonomic control of the heart (Narkiewicz et al., 1998; Baharav et al., 1999; Teplitzky et al., 2019; Bertoni and Isaiah, 2020). Other studies found predictable changes in heart rate variability in confirmed cases of pediatric OSA (Baharav et al., 1999; Nisbet et al., 2013). Avenues for future research include the integration of cardiac rhythm and other screening methods such as questionnaires or other single channel recordings.

Oximetry

Brouillette et al. (2000) evaluated pulse oximetry's utility for diagnosing pediatric OSA. In this study, when a child was suspected of having OSA, a positive nocturnal oximetry trend had at least 97% PPV of OSA (Brouillette et al., 2000). The authors reported that oximetry could be used for definitive diagnosis in children with SDB and adenotonsillar hypertrophy (Brouillette et al., 2000). Garde et al. (2019) evaluated pulse oximetry as an OSA screen for different AHI thresholds. The authors found that with AHI cut-offs of 1, 5, and 10, the models showed good accuracy, sensitivity, and specificity (Garde et al., 2019). They argue that pulse-oximetry based OSA screening at different AHI cut-offs defined referral thresholds for in-laboratory PSG (Garde et al., 2019). Wu et al. (2020) performed a meta-analysis and determined that the combined use of the PSQ with pulse oximetry can detect OSA in children, though only if PSG is not available. The authors noted that pulse oximetry had a high specificity for screening children without mild OSA and the highest overall specificity when compared to PSQ and OSA-18 (Wu et al., 2020).

Nixon et al. (2004) developed an overnight oximetry data scoring called the McGill Oximetry Score (MOS), which ranges from 1 to 4. A score of 1 indicates a normal/inconclusive OSA study, and additional evaluation for OSA is required (Nixon et al., 2004). A score of 2 designates mild OSA, 3 means moderate OSA, and 4 is severe OSA (Nixon et al., 2004). The scoring is based on the number of drops in arterial oxygen percent saturation (SaO2) < 90, <85, <80%, and a number of clusters of desaturation events (Nixon et al., 2004). The authors found that overnight oximetry can estimate OSA severity using this scoring system, allowing prioritization of diagnostic testing and treatment for those with severe OSA (Nixon et al., 2004). The utility of the MOS has been varied in the literature. Chuanprasitkul et al. (2021) evaluated PSG results after children had nocturnal oximetry in the setting of adenotonsillar hypertrophy. The authors found a high rate of OSA in children with inconclusive overnight oximetry, defined as MOS category 1 (Chuanprasitkul et al., 2021). The deficiency of pulse oximetry in isolation was corroborated by Kirk et al. (2003) who found portable oxygen monitoring insufficient to identify OSA in healthy children.

Pavone et al. (2013) studied the role of serial overnight pulse oximetry readings vs. a single night and the ability to diagnose OSA in children. This study identified night-to-night consistent nocturnal pulse oximetry had diagnostic accuracy for OSA (Pavone et al., 2013). The authors argue that two nights of nocturnal pulse oximetry generate an accurate MOS score, which supports a diagnosis of OSA when the category ≥ 2 (Pavone et al., 2013). Similarly, Horwood et al. (2014) evaluated a treatment algorithm based on the MOS. The authors recommended the use of MOS when there is a need to stratify children in resource-limited scenarios (Horwood et al., 2014). Pavone et al. (2017) found that an abnormal pulse oximetry reading predicted the need for AT, supporting its use in contexts where PSG is not readily available (Pavone et al., 2017). Saito et al. (2007) similarly found that pulse oximetry can be used to determine indications for AT. More recently, Hoppenbrouwer et al. (2021) evaluated night-to-night pulse oximetry variability in children by one overnight hospital-based PSG and subsequent home oximetry for two consecutive nights. They found that overall, there was no significant variability between the measurements in the hospital vs. in the home setting (Hoppenbrouwer et al., 2021).

Despite the utility of overnight pulse oximetry as a screening method alone, it remains inferior to PSG. In situations where PSG is feasible, pulse oximetry is not recommended as a substitute. With an improved understanding of optimizing the data from home overnight oximetry and its approximation of PSG data, it holds promise for use in the future as part of a home-based test and potentially as an independent diagnostic tool.

Position

During standard PSG, body position is monitored with apneas, hypopneas, and changes in respiratory patterns (Bertoni and Isaiah, 2019). The most commonly used device is a wrist-worn actigraph (Bertoni and Isaiah, 2019). Less often, body position is detected *via* hip-worn or in-bed pressure sensors (Bertoni and Isaiah, 2019). Actigraphy helps determine several PSG parameters, including total sleep time (TST), wake after sleep onset (WASO), and sleep efficiency (Bertoni and Isaiah, 2019). There are several actigraphs available, including commercially available wristwatches such as the Fitbit Ultra® (Fitbit, San Francisco, CA) and UP® (Jawbone, San Francisco, CA) (Bertoni and Isaiah, 2019). Sleep-focused actigraphs include the Actiwatch-2® (Phillips Respironics, Amsterdam, The Netherlands) and the Motionlogger® Sleep Watch (Ambulatory Monitoring, Ardsley, NY).

Meltzer et al. (2016) compared the Actiwatch-2® to standard PSG for children with suspected OSA. In this study, the authors found that actigraphy underestimated TST and sleep efficiency,

although the sensitivity (0.88) and accuracy (0.84) seemed acceptable (Meltzer et al., 2016). Similar findings were noted when comparing additional brands of actigraphs in children and adolescents (Meltzer et al., 2012), with accurate and sensitive estimations of TST, WASO, and sleep efficiency, though with poor specificity (Toon et al., 2016). The results have been varied, as other studies found commercially available actigraphs poorly approximate sleep compared to PSG (Meltzer et al., 2015). Bertoni et al. (2020) utilized machine learning to generate models which compared overnight PSG parameters to nocturnal actigraphy with the oxygen desaturation index. The goal was to determine if the combination of actigraphy data with oximetry can approximate severe OSA. The authors demonstrated that actigraphy combined with oximetry data could screen for severe OSA (Bertoni et al., 2020), which has implications on postoperative management after AT, as well as a potential diagnostic alternative.

As the data is mixed, further research is needed to help determine the utility of actigraphy in children, particularly in young children who are not yet school age. Given the safety and ease of application, using actigraphy as part of a home sleep evaluation would be beneficial. Their use alone to diagnose OSA is unlikely, though in combination with other single-channel devices shows promise. Further research is needed to assess how to use this technology in the pediatric population effectively.

Respiratory

The AASM suggests that respiratory events be captured using an oronasal thermal airflow sensor or a nasal pressure transducer (Bertoni and Isaiah, 2019). These devices are limited mainly to use in the research setting. There have been studies testing single-channel nasal airflow pressure transducers in diagnosing adult OSA, with some devices having better prediction of OSA than others (Rofail et al., 2010a,b). Small studies have been performed in infants and children regarding the utility and accuracy of using a nasal cannula to detect sleep abnormalities. Trang et al. (2002) evaluated 14 infants to assess the ability of a nasal cannula to detect apneas and hypopneas. The authors found that the nasal cannula was better able to detect hypopneas vs. apneas than a thermistor (Trang et al., 2002). However, an observational study comparing nasal cannula pressure to nasal airflow thermistors in detecting apneas and hypopneas identified that the cannula could detect more events than the thermistor (Serebrisky et al., 2002). This more extensive study in 47 children aged 2–14 years is essential, demonstrating a possible single-channel system for identifying sleep disturbances in children (Serebrisky et al., 2002). However, a recent publication based on 172 children under age 3 demonstrated limited ability for the nasal cannula to detect obstructive events (Jurado et al., 2022). Based on these data, the use of current technology for respiratory monitoring in children is limited. However, its use in combination with other testing metrics or surveys has yet to be evaluated.

Telehealth

The COVID-19 pandemic increased the scope and reach of telehealth services. Sleep medicine is no exception to this movement, demonstrating increased utilization over the pandemic (Paruthi, 2020). Physicians have developed protocols by which to apply telehealth in the evaluation of children with sleep complaints (Witmans et al., 2008). Some pediatric sleep disorders can be adequately evaluated *via* telehealth appointments, particularly when a physical exam does not alter management. For example, circadian rhythm disorders, insomnia, and sleep-related movement disorders can be managed by telemedicine (Paruthi, 2020). Sleep apnea, however, does require a formal oropharyngeal exam and therefore is not always amenable to telehealth at the initial diagnostic encounter. Though possibly used to screen who requires an in-office exam, telehealth's role in diagnosing pediatric OSA has been challenging. However, incorporating telehealth into HSAT has allowed successful diagnosis in 80% of children around age 10 (Griffiths et al., 2022). This demonstrates an essential caveat to newer technologies, in that study of their use in combination is only just beginning. The use of telehealth as an adjunct during diagnostic testing may prove very beneficial, as demonstrated by Griffiths et al. (2022). Further research is required to assess other benefits of telehealth in pediatric OSA.

Videotaping during sleep

The ability of sleep video recordings to approximate PSG findings, or add to home testing, has been studied. Sivan et al. (1996) published the first article describing utility of home video recordings of sleep in screening for OSA. Jacob et al. (1995) similarly noted the value of adding videotape recordings to home testing in children. Lamm et al. (1999) described home videotapes as a useful screening tool in snoring children, though found they cannot distinguish OSA from primary snoring. Given the almost ubiquitous use of smart phones with video technology, Thomas R. J. et al. (2022) recently tested a scoring system for short home sleep videos taken by caregivers during episodes of concerning breathing. The authors found that low scores ruled out moderate-severe OSA, while scores $\geq$ 3 showed a sensitivity of 100%, specificity of 36%, positive predictive value of 53%, and negative predictive value of 100% for moderate to severe OSA (Thomas R. J. et al., 2022). They concluded that this newly validated clinical scoring system is valuable in triaging children with SDB (Thomas R. J. et al., 2022). Despite successful computer-based analysis of video images in adult OSA (Abad et al., 2016; Muñoz-Ferrer et al., 2019), comparable work is lacking in children. Larger studies are needed to elucidate the role of home videos for the screening and diagnosis of pediatric OSA.

Home-based PSG

HSAT aims to replicate the results of an in-hospital PSG with increased comfort and accessibility but lower cost and decreased resource utilization (Kirk et al., 2017; Bertoni and Isaiah, 2020). Typically, HSAT is achieved by combining specific PSG channels *via* portable or wearable sensors (Bertoni and Isaiah, 2020). Once determined to be accessible and feasible (Brockmann et al., 2013; Marcus et al., 2014; Ioan et al., 2020; Lildal et al., 2021), multiple studies have been performed to assess the adequacy of pediatric HSAT.

Gao et al. (2021) performed a systematic review and meta-analysis to determine the diagnostic accuracy of portable, at-home

PSG in children. Home testing showed better specificity than sensitivity, indicating appropriate use as a screening method for OSA (Gao et al., 2021). Brunetti et al. (2001) proposed an algorithm to use home testing as a screening tool to help better utilize overnight in-lab testing.

Scalzitti et al. (2017) performed a prospective comparison of home testing to PSG in children aged 2–17. Despite the variability in results, the AHI and lowest oxygen saturation measurements were similar between tests in children aged ≥ 6 years (Scalzitti et al., 2017). These results were echoed by Withers et al. (2022) who compared level I hospital-based PSG to level II home PSG in children aged 5–16. The authors found that level II PSG had an excellent correlation with level I PSG, with the benefit of higher sleep efficiency (Withers et al., 2022). The conclusion of this report was that level II PSG is can be considered for diagnosis in children aged 5–18 (Withers et al., 2022). A study by Alonso-Álvarez et al. (2015) identified home respiratory polygraphy as a potentially helpful and reliable approach for OSA diagnosis in children compared to in-lab PSG. Bhattacharjee et al. (2021) noted acceptable agreement between AHI and oxygen desaturation index between the home and in-laboratory portable monitors, and in-laboratory PSG in 20 adolescents. When installed correctly by trained technicians, home unattended respiratory polygraphic recordings can be used for OSA screening in otherwise healthy children (Ioan et al., 2023). HSAT results may be improved and comparable to in-lab PSG, with the addition of attendance by an online video technician (Green et al., 2022). These results are essential, as they demonstrate a potential population that may be tested at home, creating more availability for children who need PSG for diagnosis. Additionally, the combination of HSAT with screening questionnaires has been beneficial in identifying (Revana et al., 2022), or excluding (Maggio et al., 2021), moderate to severe OSA, further supporting the use of alternate testing methods for improved accuracy.

At this time, the role of HSAT in children is limited to a screening tool, as the AASM does not support the use of HSAT as a replacement for PSG to diagnose OSA in children (Kirk et al., 2017). Difficulty in feasibility, validity, identifying arousals and hypoventilation, issues with use in young children or children with comorbidities, and differences in body sizes are cited as the key limitations (Kirk et al., 2017). The need for home testing is evident, though to date some of the obstacles related to the mechanics of testing have not been overcome. As more studies are performed showing positive outcomes, the guidelines regarding HSAT may eventually evolve.

Biomarkers

Untreated OSA has lasting implications on overall health and physiology (Archbold et al., 2012; Marcus et al., 2012; Teplitzky et al., 2019). The study of the systemic impact of OSA has led to evaluation of biomarkers as an alternate means, or adjuncts, for the diagnosis of OSA. From a cardiovascular standpoint, untreated OSA is associated with alterations in left ventricular mass and wall thickness, end diastolic dimensions, and interventricular septal thickness (Amin et al., 2002; Bhattacharjee et al., 2009; Teplitzky et al., 2019). Pediatric OSA can result in right heart failure from pulmonary hypertension, resulting from alveolar hypoventilation from the cyclic apneas, and subsequent pulmonary vasoconstriction (Bhattacharjee et al., 2009; Koc et al., 2012; Teplitzky et al., 2019). For these reasons, pre-operative cardiovascular assessment has been considered, though with debated utility (Li et al., 2008a; Teplitzky et al., 2019; Martín-Montero et al., 2022).

An association between OSA and inflammation was first described by Tauman et al. (2004) who showed that elevated levels of plasma C-reactive protein (CRP), a known marker of inflammation, correlated with AHI, oxygen nadir, and arousal index in some children with OSA (Tauman et al., 2004). This elevation in CRP was also associated with development of cardiovascular disease (Dos Santos et al., 2008), particularly in the setting of obesity (Choi et al., 2013). A large body of evidence has developed evaluating the role of CRP in OSA management. Kheirandish-Gozal et al. (2006) demonstrated elevated CRP levels prior to treatment, with reduction in CRP levels after adenotonsillectomy, adding evidence to support OSA leads to systemic inflammation. This finding has been supported by several authors, noting improvement in systemic inflammation and reduced CRP after OSA treatment (Li et al., 2008b; Ingram and Matthews, 2013; Mutlu et al., 2014; Nachalon et al., 2014; Van Eyck et al., 2014). CRP may also be able to identify residual OSA after adenotonsillectomy (Bhattacharjee et al., 2016). However, the role of CRP in pediatric OSA is nuanced, as other research has noted that CRP in isolation is not predictive of OSA (Kheirandish-Gozal et al., 2015), due to confounding factors such as interindividual variability, environmental, and genetic factors (Kheirandish-Gozal and Gozal, 2017).

Additional metabolic markers have been assessed, given the increasing rates of pediatric obesity (Childhood Obesity Facts, 2022), and concomitant obesity in children with OSA (Bachrach et al., 2022). Comorbid diagnoses to obesity, such as insulin resistance and dyslipidemia, have been evaluated in pediatric OSA (Deboer et al., 2012; Zong et al., 2013; Bhushan et al., 2014; Amini et al., 2017; Siriwat et al., 2020). The use of insulin and lipid levels are not suitable for the diagnosis of OSA, but do denote systemic involvement of the disease, and may serve as an adjunct in global evaluation and work up.

Salivary evaluation has identified OSA biomarkers (Patacchioli et al., 2014; Bencharit et al., 2021), some of which have reportedly acceptable diagnostic accuracy (Canto et al., 2015). Urinary biomarkers have also been studied with mixed results (Biyani et al., 2018). However, some values have the possibility to be used in diagnosis and prediction of OSA severity in children (Villa et al., 2014; Thomas S. et al., 2022). To date, studies on these topics are relatively small in number without reproducibility, limiting their use as a surrogate for PSG. However, their implications on the broad effects of OSA with systemic involvement are apparent. Further studies are needed to better evaluate the role of biomarkers in OSA diagnosis.

Special populations

High-risk populations include those with Trisomy 21, craniofacial anomalies, and neuromuscular disorders (ElMallah

et al., 2017). Alterations in craniofacial measurements, commonly observed in children with syndromes such as Trisomy 21, have been associated with OSA (Katyal et al., 2013; Sutherland et al., 2020). Consideration of body mass index (BMI) and BMI percentile should be assessed in all children to identify those with obesity. Obesity may cause, or worsen OSA, and increases the risk of persistent OSA after AT (O'Brien et al., 2006; Andersen et al., 2016). Obesity is a common comorbidity in children with Trisomy 21, making their OSA more challenging to manage. Children with Trisomy 21 typically are also hypotonic, perpetuating their airway collapse and OSA (Ali Khan, 2022). A multidisciplinary approach between otolaryngology, plastic surgery, pediatric dentistry, and pulmonology/sleep medicine for management of OSA high risk children can improve postoperative AT outcomes and treatment of persistent OSA (DeVries et al., 2020).

Other special populations include children with cleft palate, in whom the underdevelopment and unusual orientation of the palatal musculature increase the propensity for airway collapse (Robison and Otteson, 2011; Muntz, 2012). Surgical procedures designed to repair these anatomic problems are also associated with a higher risk of postoperative upper airway obstruction, requiring a high degree of vigilance following surgery (Rose et al., 2002; Bergeron et al., 2019).

Results of screening tools for OSA in children with Trisomy 21 have been mixed. Several authors have found use of questionnaires unreliable (Grantham-Hill et al., 2020; Skotko et al., 2023). However, Hill et al. (2018) successfully screened for moderate to severe OSA *via* home pulse oximetry, helping determine which children need formal PSG to confirm OSA. New technologies are emerging to aid in OSA diagnosis (Bassett and Musso, 2017), particularly in these complicated children. Brockmann et al. (2016) studied the feasibility of home PSG in children with Trisomy 21, and obtained a technically successful and acceptable home PSG in 83% of children, concluding that portable home PSG devices may be considered for diagnosis. Ioan et al. (2022) described the utility of pulse transit time (PTT), a technology shown to detect subcortical autonomic arousals, with ventilator polygraphy (PG) to diagnose OSA in children with Trisomy 21. The authors noted a specificity of 1.0 for oAHI >1 event/hour on PTT-PG. When the autonomic arousal index (PTTAI) on PTT-PG is added, the sensitivity for oAHI > 1 is 1.0. The authors concluded that the use of PTT-PG and PTTAI can be diagnostic, though is dependent on signal quality (Ioan et al., 2022). To assess areas of persistent obstruction, cinematic magnetic resonance imaging ("cine MRI") uses standardized MRI algorithms to localize regions of persistent airway obstruction (Manickam et al., 2016; Isaiah et al., 2018). Another option is drug-induced sleep endoscopy (DISE), with a recent consensus statement on its use in children (Baldassari et al., 2021). In DISE, clinicians can identify potential sites of airway obstruction during sleep using fiberoptic endoscopy to visualize endoluminal upper airway obstruction under anesthesia. The principal uses of cine MRI and DISE are to tailor treatment of upper airway obstruction in children with craniofacial syndromes and potentially in those with recidivism related to OSA. The discussion of OSA in complex children is nuanced and detailed, deserving of its own review. However, it is helpful to address these additional metrics used with PSG, to facilitate personalized approaches for treating pediatric OSA.

Conclusions

Diagnosis of pediatric sleep disordered breathing is limited by access to level I in-lab PSG. Due to the economic burden of this test, patient-family inconvenience, and limited accessibility, additional methods for diagnosis are needed. Though many avenues have been explored, none in isolation has been satisfactory as a replacement to PSG. Further validation efforts are needed to confirm the adequacy of single channel vs. combined channel recordings in the home setting, though data to date are promising. Similarly, adjunct evaluations such as questionnaires and biomarkers, may prove effective when used in conjunction with some of the SCOPER technologies. Newer studies on pediatric HSAT show promise and may eventually be a reasonable option in certain populations. Additional large volume studies are required, but with the great and persistent need for more accessible diagnostic testing, continued research will hopefully identify acceptable and accurate alternatives to level I PSG.

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TT, AZ, and AI: manuscript drafting and revision and final manuscript approval accountable for all aspects of the work.

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Conflict of interest

AI receives patent-related royalties from University of Maryland for inventions related to sleep apnea diagnosis and treatment. These are not discussed in the manuscript.

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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Deep learning-based algorithm accurately classifies sleep stages in preadolescent children with sleep-disordered breathing symptoms and age-matched controls

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Introduction: Visual sleep scoring has several shortcomings, including inter-scorer inconsistency, which may adversely affect diagnostic decision-making. Although automatic sleep staging in adults has been extensively studied, it is uncertain whether such sophisticated algorithms generalize well to different pediatric age groups due to distinctive EEG characteristics. The preadolescent age group (10–13-year-olds) is relatively understudied, and thus, we aimed to develop an automatic deep learning-based sleep stage classifier specifically targeting this cohort.

Methods: A dataset (n=115) containing polysomnographic recordings of Icelandic preadolescent children with sleep-disordered breathing (SDB) symptoms, and age and sex-matched controls was utilized. We developed a combined convolutional and long short-term memory neural network architecture relying on electroencephalography (F4-M1), electrooculography (E1-M2), and chin electromyography signals. Performance relative to human scoring was further evaluated by analyzing intra- and inter-rater agreements in a subset (n=10) of data with repeat scoring from two manual scorers.

Results: The deep learning-based model achieved an overall cross-validated accuracy of 84.1% (Cohen's kappa κ=0.78). There was no meaningful performance difference between SDB-symptomatic (n=53) and control subgroups (n=52) [83.9% (κ=0.78) vs. 84.2% (κ=0.78)]. The inter-rater reliability between manual scorers was 84.6% (κ=0.78), and the automatic method reached similar agreements with scorers, 83.4% (κ=0.76) and 82.7% (κ=0.75).

Conclusion: The developed algorithm achieved high classification accuracy and substantial agreements with two manual scorers; the performance metrics

compared favorably with typical inter-rater reliability between manual scorers and performance reported in previous studies. These suggest that our algorithm may facilitate less labor-intensive and reliable automatic sleep scoring in preadolescent children.

KEYWORDS

Pediatric sleep staging, preadolescent cohort, inter-rater reliability, pediatric sleep-disordered breathing, community controls, deep learning, recurrent neural network, convolutional neural network

Introduction

Sleep is a vital component of health and well-being for children and is particularly important for maintaining normal neurocognitive functions (1–4). Subsequently, sleep disorders are associated with detrimental health consequences such as emotional and behavioral problems (5, 6) and attention deficiency (7). Given that sleep disorders such as obstructive sleep apnea (OSA) are common in children (prevalence of 1%–4%) (8), there is substantial motivation to develop efficient and effective diagnostic systems. Accurate sleep stage classification is an important step in both the diagnosis of pediatric sleep disorders and research investigating normal physiological sleep; and is manually scored according to the American Academy of Sleep Medicine (AASM) (9) guidelines using electroencephalography (EEG), electrooculography (EOG), and submental electromyography (EMG) signals recorded using polysomnography (PSG) (9). However, manual sleep scoring is expensive and time-consuming (10) and is subjective leading to inconsistency between human scorers (11–17). While the typical Cohen's kappa for inter-rater agreement is 0.76–0.78 in adults, it can be as low as 0.57–0.63 between international sleep centers (11, 12); and could be even lower in children due to greater variability in EEG signal characteristics (18–21).

Automated sleep staging systems have been proposed to overcome the limitations of manual sleep stage classification; and such algorithms are already incorporated in some commercial PSG software where they provide a preliminary scoring that is verified and corrected by a human expert. Numerous published studies have also attempted to fully automate the sleep staging process (22–47). Whilst historically, these have used feature engineering approaches or hand-crafted rules (29–32), most recent studies utilize deep learning-based algorithms (22–26, 33–46). Although modern deep learning-based approaches generally perform well (kappa agreement typically ranging between 0.67 and 0.87) (48–51), the majority have focused on adult populations (22, 23, 30–39, 41, 43, 45). Due to the continuous maturation of the brain, EEG signals in children may vary with age (18–20); and therefore, it is uncertain whether the sophisticated sleep staging systems designed for adults generalize well to children.

A smaller number of recent studies have focused on automatic sleep staging in children (24–29, 40, 42, 44, 47). Whilst some of these focus on two- or three-stage sleep classification (24, 26–28) [predominantly those considered infants (26–28)] or using non-EEG-based approaches intended for limited channel screening (29, 47), studies published in parallel with the development of this work using electrophysiological channels have demonstrated high sleep classification performance (40, 42, 44). However, there are some important limitations. Firstly, none of these studies included both children with sleep disorders and asymptomatic controls recruited from the community. Secondly, there are substantial gaps in the ages of the children studied. In particular, the preadolescent children (10–13-year-olds) are not well represented, reflecting them being a relatively understudied group in sleep research more generally. Given the substantial emotional and hormonal changes (52) during this period having an automated tool to better facilitate the investigation of physiological and pathophysiological sleep in this age group is highly desirable.

As such, the overarching aim of this study was to develop a deep learning-based method to automate sleep stage classification, specifically targeting preadolescent children with sleep-disordered breathing (SDB) symptoms and age and sex-matched community controls. We hypothesized that a combined convolutional and long short-term memory network architecture enables accurate pediatric sleep stage classification using raw frontal EEG, EOG, and EMG signals. This algorithm was developed and cross-validated using a dataset of overnight PSG recordings of Icelandic children. Performance relative to human scoring was further evaluated by conducting intra-rater and inter-rater agreement analysis in a subset of data with repeated scorings from two experienced human scorers.

Methods

Dataset

The dataset utilized in this study comprised 10–13 years old Icelandic children from the EuroPrevall-iFAAM birth cohort (53–56). Of the Icelandic EuroPrevall (57) study population, children who were reported to snore at least three times or have witnessed apneas at least once a week ($n = 109$) were invited to engage in a home PSG. Out of the 109 invitees, 55% agreed to participate ($n = 60$). Additionally, 58 children with no snoring or apneas were included in the age and sex-matched control group. Two of the recordings were not completed successfully, and one participant declined the full usage of data. Thus, the total study population included 115 children with almost equal proportions of SDB-symptomatic ($n = 59$) and control participants ($n = 56$).

Informed written consent was obtained from parents or legal guardians for all children who participated in this study; and data collection was approved by the Ethical Committee of Landspitali—the National University Hospital of Iceland and the National Bioethics Committee of Iceland (VSN 18–206). The PSG device used for this

study was Nox A1 (Nox Medical, Reykjavik, Iceland) and was configured by two experienced sleep technologists. All the PSG recordings were conducted at home over a single night. The sleep stages of all 115 PSGs included in the final study population were initially scored once manually into categories: W, N1, N2, N3, and R by one of two human scorers using the full montage of recommended channels in compliance with current AASM guidelines (9). This scoring was treated as the "gold standard" and utilized as the reference to compare with during the neural network training, validation, and testing.

In addition, a subset of this data comprising 10 PSGs was rescored once more by the same manual scorer and twice separately by the other scorer. This yielded a total of four distinct scorings, used solely for the purpose of conducting a separate comparative intra- and inter-rater agreement analysis. This was conducted to demonstrate the reliability of our algorithm by investigating whether our results are comparable to inter- and intra-rater reliability between manual scorers.

Software and hardware configurations for algorithm development and data-analysis

We used Conda (version 4.8.3) environment with Python 3.6.10, Keras API (version 2.3.1), and TensorFlow (version 2.2.0) backend to implement the neural network architecture. The training was conducted using an AMD Ryzen Threadripper 2990WX CPU, x86_64 architecture, 128 GB RAM, and NVIDIA GeForce RTX 2080 GPU. Statistical analyses related to intra-rater and inter-rater reliabilities were conducted in Python 3.6.10 with scikit-learn 0.24.2.

Neural network architecture

We adopted an architecture comprised of a combined convolutional neural network (CNN) and recurrent neural network (RNN) trained in an end-to-end manner that we have previously utilized for automated sleep staging in adult populations (22). The CNN part was chosen to study the unique features of the sleep stages, while the RNN was utilized to learn the temporal distribution. This and similar architectures (i.e., variations of CNN-RNN combined networks) have previously demonstrated competitive results in adult sleep staging (22, 35, 37, 39); and part of our motivation was to examine how generalizable such an architecture is to children in the preadolescent age group.

The CNN part comprised six 1D convolution layers, each of which was followed by batch normalization and a rectified linear unit (ReLU) activation function. Two max-pooling layers and a global average pooling layer were included in the architecture, each situated after every two 1D convolutional layers, respectively (Figure 1). The complete network consisted of a time-distributed layer of the entire CNN part, followed by a gaussian dropout layer, a bidirectional long short-term memory (LSTM) layer, and a time-distributed dense layer with softmax activation (Figure 1). A tanh activation function was used in the LSTM, and a hard-sigmoid activation was used in the recurrent step. The final layer of the complete architecture was a dense layer accompanied by a softmax activation function generating the output sequence of the sleep stage probabilities.

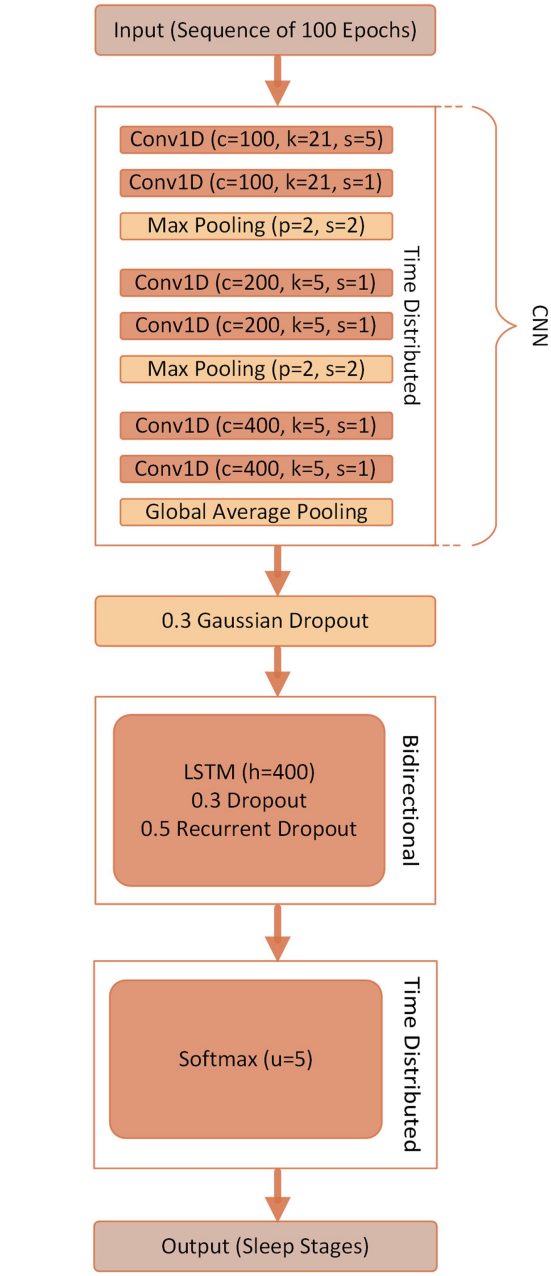

FIGURE 1
Illustration of the combined convolutional neural network (CNN) and long short-term memory (LSTM) network architecture. The parameters of the 1D convolution layers (Conv1D) are provided as (c=number of convolutional filters, k=kernel size, s=stride size). For the max pooling, the parameters are given as (p=pool size, s=stride size). LSTM and the softmax dense layer have the number of units as the parameter (i.e., h=number of hidden/output units in LSTM and u=number of nodes in dense layer). The dropout layers were active only during the training phase. A sequence of softmax values was generated by the model indicating the probabilities of possible sleep stages for every epoch. The sleep stage with the highest softmax value was estimated as the corresponding sleep stage of that epoch.

Automatic sleep staging

Three channels consisting of frontal EEG (derivation F4-M1), EOG (derivation E1-M2), and submental EMG (derivation

Chin1-Chin2) were used as the input for the final neural network architecture. The primary motivations for using these channels were: (1) use of frontal channels to make it more practical for the ambulatory sleep settings and simplify the overall measurement protocol; (2) to maintain consistency with recent literature that is tended towards using minimal channels to perform accurate sleep staging utilizing deep learning techniques; and (3) for consistency with the AASM criteria (9), which explicitly requires EEG, EOG, and EMG signals for sleep stage classification. These signals were initially recorded with a sampling frequency of 200 Hz but downsampled to 100 Hz to reduce the computational load. Signal segments at the beginning and the end of the recordings without manual scorings were excluded from the final analysis.

The complete dataset was initially divided into two individual sets: (1) Analysis set: primary data, which comprised 105 PSGs scored once manually and used for the neural network training, validation, and testing; and (2) Comparison set: which included the remaining 10 PSGs that were manually scored four times, i.e., twice each by two human experts. The comparison set was held out of training and evaluation of the model; and solely used for investigating intra- and inter-rater agreements between the two independent manual scorers and relative to the automated classification.

10-fold cross-validation was performed with the whole analysis set ($n = 105$) to obtain the best estimate of the non-biased model performance. For the cross-validation, the analysis set was first randomly separated into 10 equally sized segments. One of these segments was utilized as an independent test set, while the remaining data were further randomly divided into training (90%) and validation (10%) sets to train and choose the optimal model. The test set was held intact from the model training and validation and used as an unseen data for the model evaluation. This entire process was repeated 10 times with a different subset representing the independent test set in each iteration. The final reported results are for the classification performance in the aggregation of the test set from each of the 10 iterations of the cross-validation ($n = 105$). Figure 2 presents a data flow diagram, which illustrates how the final study data was formed and how it was divided and used for the analysis.

The model was trained in a sequence-to-sequence manner with an input sequence length of one hundred 30-s epochs, i.e., an input sequence of one hundred epochs was mapped to the target reference sleep stage sequence of identical length at once to comprehend inter-epoch dependency. The sequence length was chosen based on initial testing and as a compromise between computational load and capturing a sufficiently long sleep cycle. A categorical cross-entropy loss function, an Adam optimizer with warm restarts (58), and a learning rate range of 0.001 to 0.00001 optimized with a learning rate finder (59) were used during training. In the training set, an overlap of 75% was used to multiply the size of the training data by four when forming the sequences. No overlap was applied to validation or test sets. The maximum number of training epochs was set to 200. However, the training was only conducted until the validation loss function value no longer decreased considerably. For this, an early stopping callback with a patience coefficient of 20 was used, meaning that if validation loss did not improve for 20 consecutive epochs, then the training was stopped. This was done to prevent overfitting and to avoid wasting computational resources on training a model that is unlikely to improve. The final performance of the classifier was obtained by aggregating the test set results across all 10 folds. The accuracies were evaluated in an epoch-by-epoch manner. As an output of the model, the estimated sleep stage was determined to be the one with the highest softmax value. Cohen's kappa coefficient (κ) (60) was utilized to assess the scoring consensus between manual and automatic scorings. Finally, we investigated the model performance separately between the SDB-symptomatic and control groups as well as between PSG-quantified clinical pediatric OSA (AHI ≥ 1) and non-OSA (AHI < 1). Groupwise performance was assessed by aggregating the test set results across all 10 folds and separately calculating the accuracies and kappa coefficients for each group.

For comparison with previous literature, we also separately trained and cross-validated our model to classify sleep into four (W/N1 + N2/N3/R) and three (W/N1 + N2 + N3/R) stages utilizing the analysis set as a secondary analysis. To determine inter-rater agreement-related performance between the automatic classifier and two manual annotators in the comparison set, we retrained the network using the entire analysis set and evaluated it on the unseen comparison set.

Intra- and inter-rater agreement analysis

As a secondary investigation, we performed a separate intra- and inter-rater agreement analysis to examine the reliability of the neural network model by evaluating its predictive performance relative to multiple human scorings. A subset (i.e., the comparison set, $n = 10$, not included in the cross-validated training and evaluation) of the pediatric dataset was utilized for this analysis. Two European Sleep Research Society-certified sleep technologists from Reykjavik University Sleep Institute each scored the 10 PSGs twice (separated by at least 2 weeks); thus, producing four different sets of sleep scoring. Scorers were blinded to patient identities throughout the analysis. The manual scoring was compared with each other and with the neural network-predicted scores to evaluate the intra- and inter-rater reliabilities. In addition, we also examined how the automatic sleep stage classifications compared with the manual scoring when considering only the epochs that achieved a scoring consensus between both human scorers.

Score match percentage (percent accuracy) and kappa coefficient were used to determine the overall intra- and inter-rater agreements between different scorings. Sleep stage-specific intra- and inter-rater agreements were also calculated. Stage-specific agreements between the manual and automatic classifications were calculated with the manual scoring defined as the reference. Stage-specific agreements between manual classifications were defined as the average of the agreements calculated when each of the manual classifications was separately treated as the reference.

Results

Characteristics of the study population

A summary of demographic information and characteristics of the whole study population ($n = 115$), SDB-symptomatic subgroup ($n = 59$), and asymptomatic subgroup ($n = 56$) is presented in Table 1.

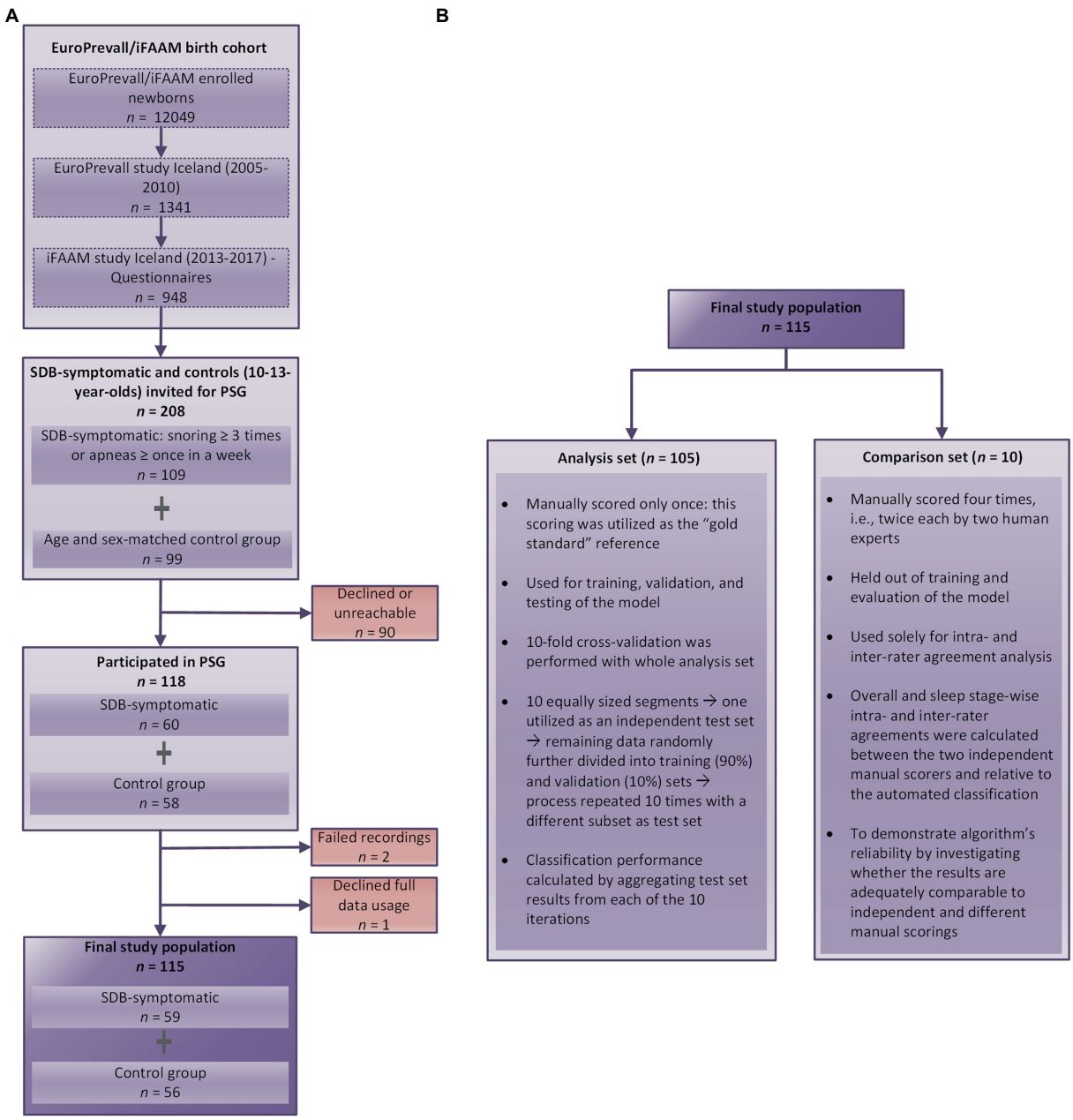

FIGURE 2
Data flow diagram that illustrates **(A)** how the final study data was formed and **(B)** how the data was divided and used for the analyses. PSG, polysomnography; EEG, electroencephalography.

Table 2 depicts the number and the percentage of 30-s epochs of each sleep stage in the whole dataset according to the manual reference scoring.

Classification performances in analysis set

The neural network-based method yielded overall absolute accuracies of 84.6% ($\kappa = 0.78$), 82.3% ($\kappa = 0.76$), and 84.1% ($\kappa = 0.78$) in the training, validation, and test sets, respectively, during the 10-fold cross-validation. There was no meaningful difference in the test set ($n = 105$) performance between individuals recruited with SDB symptoms ($n = 53$) and age and sex-matched controls ($n = 52$) [83.9% ($\kappa = 0.78$) vs. 84.2% ($\kappa = 0.78$)]. In the analysis set, 24 children fulfilled the diagnostic criteria for pediatric OSA (AHI ≥ 1) after PSG. Out of these children, 15 were from the originally recruited SDB-symptomatic subgroup and the remaining 9 were from the asymptomatic control subgroup. There was similarly no meaningful difference in the test set performance between children with PSG quantified AHI ≥ 1 ($n = 24$) and those with AHI < 1 ($n = 81$) [82.9% ($\kappa = 0.77$) vs. 84.3% ($\kappa = 0.78$)].

Considering the class-specific performance of the deep learning-based method, stage N1 had the lowest prediction

accuracy of 17.7%, while the N3 stage attained the highest accuracy of 89.8% in the test set. Figure 3 presents the confusion matrix of the test set classification performance aggregated across all 10 folds of the cross-validation in the analysis set ($n = 105$, total number of epochs = 108,796). Figure 4 shows a summary of the individual-level automatic sleep stage classification performances of all children comprising the aggregated test set across the 10 folds during cross-validation (i.e., analysis set, $n = 105$). In the aggregated test set, our algorithm distinguished sleep epochs from wake epochs (references are based on manual scoring) with a sensitivity of 97.9% and a specificity of 82.1%. Table 3 presents detailed stage-wise classification performance metrics (i.e., sensitivity, specificity, positive predictive value, and negative predictive value) in the aggregated test set ($n = 105$).

The test set accuracies obtained for four- and three-stage classifications were 85.4% ($\kappa = 0.80$) [W: 81.8%, N1 + N2: 85.2%, N3: 85.5%, R: 86.9%] and 92.6% ($\kappa = 0.84$) [W: 79.8%, N1 + N2 + N3: 95.3%, R: 87.3%] respectively.

TABLE 1 The demographics and characteristics of the study population.

	Whole population	SDB-symptomatic group	Control group
n (boys %)	115 (66.1%)	59 (67.8%)	56 (64.3%)
Age (years), mean ± SD	11.8 ± 0.8	11.7 ± 0.8	11.9 ± 0.8
BMI (kg/m^2), median (range)	19.7 (13.5–31.9)	20.6 (15.5–28.7)	18.9 (13.5–31.9)
AHI (events/h), median (range)	0.5 (0.0–6.3)	0.6 (0.0–6.3)	0.3 (0.0–3.2)
TST (min), mean ± SD	479.6 ± 54.1	471.3 ± 59.7	488.3 ± 46.5
Sleep efficiency (%), mean ± SD	93.1 ± 4.2	93.1 ± 4.0	93.1 ± 4.4

SD, Standard deviation; BMI, Body mass index; AHI, Apnea-hypopnea index; TST, Total sleep time; SDB, Sleep-disordered breathing.

Performance relative to intra- and inter-rater agreement in comparison set

The classification model retrained using the whole analysis set and evaluated on the comparison set for the purpose of comparing the automatic scoring with different manual scorings yielded an overall training accuracy of 87.2% ($\kappa = 0.81$) and an overall accuracy of 84.5% ($\kappa = 0.78$) in the unseen test set (i.e., the comparison set).

The overall inter-rater reliability between the two manual scorers was 84.6% ($\kappa = 0.78$) in the comparison set and the neural network-based automatic approach achieved similar agreements with scorers individually: 83.4% ($\kappa = 0.76$) and 82.7% ($\kappa = 0.75$). The intra-rater scoring consensuses were highest for sleep stage R for both scorers. In contrast, inter-rater agreements were highest for N3. As expected, the intra- and inter-rater agreements were lowest for N1 (Table 4). The neural network approach agreed with at least one of the manual scorers in 89.8% of the epochs. Similarly, when considering only the epochs with a scoring consensus between the manual scorers, 90.4% ($\kappa = 0.86$) of those epochs were also scored as the same sleep stage by the automatic classifier. The sleep stage-specific agreement in this instance were W: 88.2%, N1: 28.4%, N2: 93.0%, N3: 91.1%, and R: 89.7%. Figure 5 illustrates an example comparison between hypnograms of an individual annotated by manual scorers and the automatic classifier. The performance of the automated classifier in this individual was close to the population average (i.e., $\kappa = 0.78$ with manual scorer 1 and $\kappa = 0.77$ with scorer 2).

Discussion

The overarching aim of this study was to develop a deep learning-based automatic sleep stage classification system for preadolescent children. As such, we developed a combined CNN-LSTM architecture utilizing a dataset containing overnight PSGs of Icelandic preadolescent children with SDB symptoms and age and sex-matched controls. The cross-validated sleep stage classification performance was evaluated with a 3-channel input (i.e., frontal EEG + EOG + chin EMG). In addition, to further evaluate the performance relative to human scoring and to examine the reliability of the model, we conducted a separate intra- and inter-rater agreement analysis in a subset ($n = 10$) of data with repeated scorings from two expert human scorers. Overall, our algorithm achieved a high classification accuracy and substantial agreement with both manual scorers. The performance metrics compared well with previous automated sleep

TABLE 2 Number and percentage of 30-s epochs of each sleep stage in the pediatric dataset based on initial manual reference scoring.

Sleep stage	Whole dataset (n = 115)		SDB-symptomatic group (n = 59)		Control group (n = 56)	
	Number	Percentage (%)	Number	Percentage (%)	Number	Percentage (%)
W	8,469	7.1	4,455	7.4	4,014	6.8
N1	3,724	3.1	1,657	2.8	2,067	3.5
N2	28,880	24.3	14,170	23.6	14,710	25.0
N3	54,786	46.1	28,055	46.8	26,731	45.5
R	22,917	19.3	11,649	19.4	11,268	19.2
Total	118,776	100	59,986	100	58,790	100

W, Wakefulness; R, Rapid eye movement sleep; N1, N2, N3, Three different levels of non-rapid eye movement sleep; SDB, Sleep-disordered breathing.

staging methods and with inter-rater reliability between manual scorers both in this population and those reported in the literature (14). Moreover, the individual-level automatic classification accuracies and kappa values were consistent across both children with SDB symptoms and non-diseased controls. These findings indicate that our model enables accurate and reliable automatic sleep stage classification for preadolescent children.

In the present study, the classification performance metrics of all sleep stages except for N1 were excellent (Figure 3; Table 3), and the overall performance of this method compares well to the previously published studies involving pediatric populations (24–29, 40, 42, 44). However, direct comparison to previous studies is difficult due to different datasets and age variations. Previously, Huang et al. (25) adopted a timestamp-based segmentation strategy with a deconvolutional neural network for automatic sleep staging in children aged 5–10 years and achieved an accuracy of 84.3%. However, a considerably smaller dataset ($n = 21$) and a complex 11-channel input (i.e., 6 EEG + 2 EOG + 3 EMG) were used in that study (Table 5). In comparison, our study achieved a similar performance with a larger pediatric cohort using only a 3-channel input. In parallel with the development of our work, other studies have also focused on sleep staging including pediatric patients and have demonstrated similar performance metrics (40, 42, 44). Notably, Wang et al. (42) achieved high classification performance (with slightly lower kappa values compared to the present study when using a similar 3-channel input) with a modularized network utilizing a clinical pediatric dataset of 344 SDB patients with age 2–18 years (Table 5). Similarly, Phan et al. (44) demonstrated that different deep learning-based algorithms with good performance in adults also generalized well to 5–10-year-old children with SDB in the Childhood Adenotonsillectomy Trial dataset (62) (Table 5). Likewise, a large-scale study conducted by Perslev et al. (40) utilized multiple adult and pediatric datasets (i.e., PSG recordings from 15,660 participants of 16 clinical studies, including PSGs from 2 public pediatric sets) to train and evaluate a U-net architecture and attained high sleep stage classification accuracies. While our algorithm achieves similar or slightly higher performance to these previous studies, it makes two important unique contributions. Firstly, our study is the first to evaluate and demonstrate equivalent performance in children with both suspected SDB and community controls, thus demonstrating this important aspect of generalizability. Secondly, we specifically focus on preadolescent children, which are either not represented or are under-represented in previous works. This not only confirms the generalizability of such approaches to this age group; but also provides a tool to investigate sleep in this cohort in more detail. This is a period of substantial emotional and hormonal changes (52), and a better understanding of how sleep changes during this period would be highly desirable.

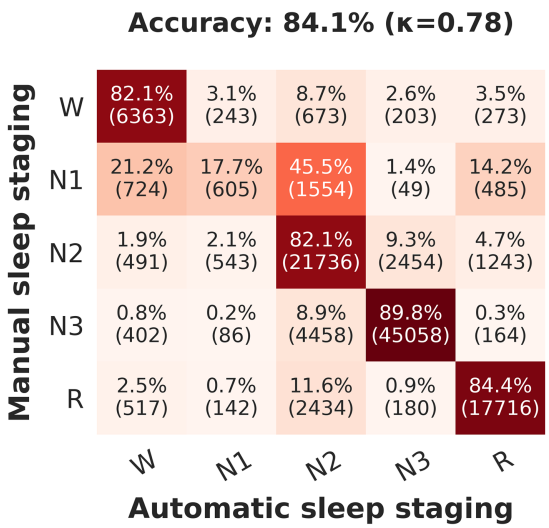

FIGURE 3
Confusion matrix of the test set classification performance aggregated across all 10 folds of the cross-validation in the primary analysis set (n=105, total number of epochs=108,796). Each row of the matrix represents the instances in the manual reference scoring while each column represents the instances in the neural network-predicted sleep scoring. The diagonal of the matrix shows all correct predictions. Values presented inside parentheses denote the number of epochs in each predicted class. W, Wakefulness; R, Rapid eye movement sleep; N1, N2, N3, Three different levels of non-rapid eye movement sleep; κ, Cohen's kappa coefficient.

Our algorithm also performed comparably with the state-of-the-art sleep staging methods developed for adults (22, 23, 30–39, 41, 43, 45), which typically achieve kappa performance in the range of 0.67–0.87 (48–51). We previously demonstrated that a similar CNN-LSTM architecture for sleep staging works well in adult populations and outperformed previously published methods at the

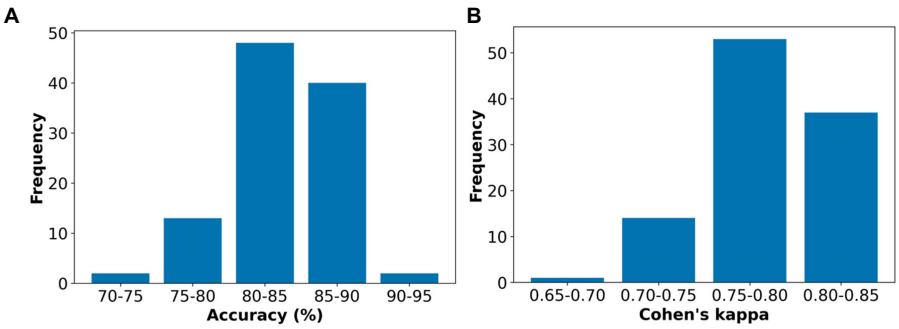

FIGURE 4
A summary of the individual-level automatic sleep stage classification performances: **(A)** Accuracies in percentage (range: 73.3%–90.4%) and **(B)** Cohen's kappa (Range: 0.69 to 0.84) of all children comprising the aggregated test set (n=105) across the 10 folds during cross-validation.

time (22). The accuracy and kappa values achieved in the present study considering a preadolescent cohort are almost identical to the performance metrics obtained in adult cohorts utilized by Korkalainen et al. (22). Therefore, our findings confirm that the considered architecture generalizes well to preadolescent children with SDB and non-diseased controls.

The inter-rater agreements achieved in this dataset are comparable to the consensus between manual scorers, where kappa is typically 0.76–0.78 in adult populations (14, 17). Considering the separate inter-rater reliability analysis conducted in the comparison set, the sleep stage-specific agreements obtained for the automatic method well exceeded the consensus between the two manual scorers in scoring sleep stage N2; were near-identical for W, N3, and R; but were modestly lower for stage N1 [possibly reflecting the relatively small (3.1%) proportion of N1 in this dataset] (Table 4). Nonetheless, our neural network-based approach showed substantial agreements (61) with both manual scorers and matched the concordance between human scorers. Moreover, the automatic approach matched with at least one of the two manual scorers in 89.8% of the epochs, while the match percentage between the manual scorers was only 84.6%, further emphasizing the reliability of the proposed algorithm relative to manual scoring.

Incorporating a reliable and accurate deep learning-based automatic sleep staging system to support the current clinical procedure could significantly benefit pediatric sleep disorder diagnosis. As elucidated in several studies (11–16), the traditional sleep scoring may lack adequate inter-rater reliability and manifest high variability. However, once trained, deep learning-based approaches, including the proposed model, would always classify sleep stages uniformly for the same data. This can be a substantial advantage of our model compared to visual sleep scoring as it eliminates limitations such as human-scorer vigilance-related errors. Finally, manual scoring is laborious, time-consuming, and expensive. The proposed method can perform quickly once trained (i.e., typically well within a minute per overnight study) and would significantly improve the efficiency of the sleep stage classification process.

The main performance limitation of the proposed algorithm is the low classification performance and inter-rater agreements of stage N1 (Figure 3; Tables 3, 4). As expected, the overall accuracy in classifying stage N1 was poor (only 17.7%), and N1 sleep was most frequently confused with N2, and then with wake (Figure 3). One explanation for this is the relatively small amount of N1 epochs in the dataset (only 3.1%) and therefore the algorithm is relatively poorly trained on this stage. However, inter-human-rater agreements for N1 were similarly low in both our study and published literature where N1 agreements range between $\kappa = 0.19–0.31$ (11, 12). This suggests that even for experienced manual sleep scorers, N1 is the hardest sleep stage to identify.

The mean (± SD) total sleep time (TST) of 479.6 ± 54.1 min observed in this dataset is lower than the typical average TST in this age group (63, 64). Similarly, we identified that the proportion of R sleep is slightly lower than what is usually observed in preadolescent children (64). There are two possible explanations for this discrepancy. Firstly, for other scientific purposes, the children wore a double EEG setup with two devices, a scoop cannula over their mouth, and an additional electrodermal activity (EDA) sensor (65); and this may have caused them to wake up earlier than usual and take the equipment off and consequently may have affected the TST and R sleep proportion. Second, this study was performed in Iceland during the summer months with an unusual amount of daylight, which may also have possibly caused early awakenings.

TABLE 3 Detailed stage-wise classification performance metrics in the test set aggregated across the 10-fold cross-validation in the primary analysis set (n=105).

Sleep stage	Sensitivity	Specificity	PPV	NPV
W	82.1%	97.9%	74.9%	98.6%
N1	17.7%	99.0%	37.4%	97.4%
N2	82.1%	88.9%	70.4%	93.9%
N3	89.8%	95.1%	94.0%	91.6%
R	84.4%	97.5%	89.1%	96.3%

W, Wakefulness; R, Rapid eye movement sleep; N1, N2, N3, Three different levels of non-rapid eye movement sleep; PPV, Positive predictive value; NPV, Negative predictive value.

TABLE 4 Intra-rater and inter-rater reliability metrics for individual and overall sleep stage comparisons between manual scorers and the automatic method in a holdout subset of n=10 (i.e., the comparison set).

	Intra-rater agreement: S1	Intra-rater agreement: S2	Inter-rater agreement: S1 versus S2	Inter-rater agreement: S1 versus Auto	Inter-rater agreement: S2 versus Auto
W	88.6%	89.6%	83.6%	80.8%	81.3%
N1	44.3%	63.1%	32.6%	24.9%	14.2%
N2	77.3%	81.4%	72.7%	83.8%	87.3%
N3	91.5%	92.5%	91.5%	87.7%	89.5%
R	92.7%	93.0%	90.7%	86.7%	86.2%
Overall	87.5%	89.3%	84.6%	83.4%	82.7%
κ	0.82	0.85	0.78	0.76	0.75
Remark	Almost Perfect	Almost Perfect	Substantial	Substantial	Substantial

Agreements between manual and automatic classifications were calculated using manual scoring as the reference. Agreements between manual classifications were obtained by averaging agreements calculated with each manual classification as the reference. The remarks on the agreements are based on the guidelines by Landis and Koch (61) for Cohen's kappa values. S1, Human scorer 1; S2, Human scorer 2; Auto, Automatic method; κ, Cohen's kappa coefficient; W, Wakefulness; R, Rapid eye movement sleep; N1, N2, N3, Three different levels of non-rapid eye movement sleep.

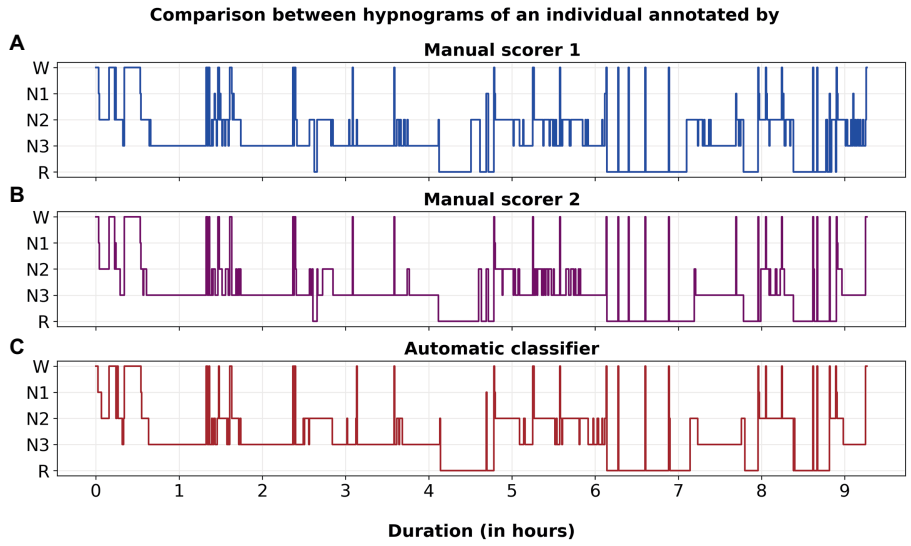

FIGURE 5
An example comparison between hypnograms of an individual annotated by **(A)** Manual scorer 1, **(B)** Manual scorer 2, and **(C)** Automatic classifier. The performance of the automated classifier in this individual was close to the population average (i.e., κ=0.78 with manual scorer 1 and κ=0.77 with scorer 2).

TABLE 5 Performance comparison of the present study with previous deep-learning-based pediatric sleep staging.

	Cohort size (*n*)	Community control group included (Y/N)	Age range	Stages	Accuracy [kappa (κ)]
Present work	115	Y	10 to 13 years	5 (W/N1/N2/N3/R)	84.1% (0.78)
				4 (W/N1 + N2/N3/R)	85.4% (0.80)
				3 (W/N1 + N2 + N3/R)	92.6% (0.84)
Jeon et al. (24)	218	N	-	3 (W/N1/N2)	92.2% (0.88)
Huang et al. (25)	21	N	5 to 10 years	5 (W/N1/N2/N3/R)	84.3% (–)
Wang et al. (42)	344	N	2 to 18 years	5 (W/N1/N2/N3/R)	82.6% (0.76)
				4 (W/N1 + N2/N3/R)	85.8% (0.79)
				3 (W/N1 + N2 + N3/R)	91.4% (0.81)
Phan et al. (44)	1,216	N	5 to 10 years	5 (W/N1/N2/N3/R)	88.8% (0.85)

Only studies utilizing deep learning techniques with EEG-based channels and specifically targeted at pediatric populations excluding infants are included. Y, Yes; N, No.

The study population consisted of Icelandic preadolescent children with symptoms of SDB (n = 59) and age and sex-matched controls (n = 56). However, there were no meaningful differences in the demographic characteristics between these two subgroups. Post PSG, 26 children fulfilled the diagnostic criteria for pediatric OSA (AHI ≥ 1) [17 from the SDB symptomatic subgroup and 9 from the asymptomatic control subgroup]; out of which, only one individual was deemed to have moderate pediatric OSA (AHI ≥ 5). Severe OSA was not found, and the study population did not explicitly include children with other sleep disorders. Different sleep disorders have distinct characteristics and could cause significant sleep architectural changes and deteriorated sleep quality. For example, OSA patients usually have more light sleep stages and less N3 and R sleep (66), whereas narcolepsy patients usually have fragmented sleep and abnormal and frequent sleep stage R occurrences (67). As such, further investigations are required to confirm the generalizability of our algorithm in these other groups, including those with more moderate and severe OSA. We believe these results must be generalized with caution to other heterogeneous clinical populations or centers internationally where participant characteristics may vary substantially; also to children with age range out of that in the present study. Similarly, this was well-curated scientific data. However, in practice, the algorithm would need to cope with artefact typical of clinical sleep studies; and further validation is required to examine the performance of this algorithm in these conditions. Further, it is likely that modern deep learning-based automated sleep classifiers have already achieved near-saturated performance metrics (68). Therefore, to be incorporated into clinical practice, future studies must focus more on improving the generalizability, reliability, uncertainty quantification, and interpretability of deep learning-based sleep staging models (44, 48, 51). Finally, to date, this and other studies focused on the classification of sleep stages without consideration of arousal events. Given the significant physiological overlap between arousal and wake stage, there are likely to be significant advantages to

incorporating arousal event scoring within the same algorithm as sleep stage classification.

Conclusion

Pediatric sleep disorders are prevalent, and manual sleep stage classification has significant challenges. As such, incorporating an accurate and reliable automatic sleep staging method in clinical practice would greatly assist in improving the efficiency of pediatric sleep disorder diagnosis. The proposed deep learning-based classification algorithm enables fast, accurate, and reliable automatic sleep staging based on frontal EEG, EOG, and chin EMG signals in preadolescent children. Our findings favor the utility of deep learning-based approaches for sleep staging over the traditional manual method.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: This dataset is subject to strict ethical restrictions and cannot be shared or distributed without prior approval from the corresponding ethical committee. Access to the data is limited to individuals who have been granted explicit permission for its use. Requests to access these datasets should be directed to PS, p.somaskandhan@uq.edu.au.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of Landspitali—the National University Hospital of Iceland and the National Bioethics Committee of Iceland (VSN 18–206). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JT, TL, PT, and HK devised the project and the main conceptual ideas for the analyses. SÞS and MC designed and carried out the initial study and provided the data for this analysis. SS, EA, KÓ, and MS contributed to data interpretation. PS, HK, PT, TL, and JT carried out the data preparation and the analyses. PS drafted the manuscript and prepared the figures and tables. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Overview of the hypnodensity approach to scoring sleep for polysomnography and home sleep testing

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Human experts scoring sleep according to the American Academy of Sleep Medicine (AASM) rules are forced to select, for every 30-second epoch, one out of five stages, even if the characteristics of the neurological signals are ambiguous, a very common occurrence in clinical studies. Moreover, experts cannot score sleep in studies where these signals have not been recorded, such as in home sleep apnea testing (HSAT). In this topic review we describe how artificial intelligence can provide consistent and reliable scoring of sleep stages based on neurological signals recorded in polysomnography (PSG) and on cardiorespiratory signals recorded in HSAT. We also show how estimates of sleep stage probabilities, usually displayed as hypnodensity graph, can be used to quantify sleep stage ambiguity and stability. As an example of the application of hypnodensity in the characterization of sleep disordered breathing (SDB), we compared 49 patients with sleep apnea to healthy controls and revealed a severity-depending increase in ambiguity and decrease in stability during non-rapid eye movement (NREM) sleep. Moreover, using autoscoring of cardiorespiratory signals, we show how HSAT-derived apnea-hypopnea index and hypoxic burden are well correlated with the PSG indices in 80 patients, showing how using this technology can truly enable HSATs as alternatives to PSG to diagnose SDB.

KEYWORDS

hypnogram, hypnodensity, sleep stage ambiguity, sleep stage continuity, machine learning, cardiorespiratory sleep staging, hypoxic burden

Introduction

Human sleep stage scoring was developed to summarize the information of electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG) correlates of normal sleep for healthy subjects (Rechtschaffen and Kales, 1968). These neurological signals provide the basic information requisite for visually differentiating sleep stages in 30-second epochs. Currently, the recommended rules are summarized in the Manual for the Scoring of Sleep and Associated Events (Version 3) published by the American Academy of Sleep Medicine (Troester et al., 2023). In older subjects and in patients with sleep disturbances, ambiguous epochs are created by intrusions, translocations, or migrations of specific patterns (Keenan et al., 2013). Consequently, visual sleep scoring, even by well-trained and experienced scorers, retains a degree of subjectivity. Limited interrater

reliability is well documented and repeatedly reported (Danker-Hopfe et al., 2004, 2009; Penzel et al., 2013; Rosenberg and Van Hout, 2013; Younes et al., 2016; Cesari et al., 2021; Lee et al., 2022). Recently, we have shown in three different datasets scored by six, nine, and twelve scorers, that sleep stage ambiguity is the rule rather than the exception and that sleep stage probabilities calculated with artificial intelligence (AI) provide an excellent estimate of this ambiguity (Bakker et al., 2023). These sleep stage probabilities, whether based on multiple manual scorings or on autoscoring can be plotted in pseudo colors and have been referred to as hypnodensity graph by Stephansen et al. (2018).

In this topic review we explore how modern AI-based techniques can be used to describe human scoring ambiguity, and how it can be further leveraged to characterize SDB and to unlock the full potential of HSAT. In the first section, we introduce the concept of hypnodensity as a technique to represent the probabilities with which sleep experts assign the 5 sleep stages to each epoch. In the second section, we show how the AI-determined hypnodensity is an excellent estimate of the hypnodensity determined by multiple manual scorings, thus providing an estimate of human ambiguity in sleep scoring. In the third section we provide validation data for hypnodensity-derived sleep staging, and further evaluate the potential benefits of using hypnodensity-derived features to quantify sleep stage ambiguity and stability in patients with sleep apnea. In the fourth section we compare AI-determined sleep stage probabilities estimated from cardiorespiratory signals such as those typically recorded in HSAT, with hypnodensity based on multiple manual scorings. Finally, in the fifth and last section, we show how AI-based scoring of cardiorespiratory signals impacts the agreement between SDB-related sleep parameters derived from reduced montage with those derived from full PSG in patients with sleep disturbances.

Hypnodensity based on multiple manual scorings

As discussed recently by Penzel (2022), error rates of 15% or more are usually accepted for sleep stage scoring. The author stated that an agreement between sleep stage scorers of 85% is acceptable, and it gets worrying if the agreement drops below 70%. However, these values only apply to the comparison between two scorers. As three or more scorers are compared, the percentage of complete agreement between the scorers continues to decrease (Bakker et al., 2023). Figure 1 shows an example of a 30-second epoch with ambiguity, which can be uncovered by independently assessing the study by multiple scorers. The example shown in Figure 1 was taken from a study with independent scorings by 12 human experts. Seven experts scored this epoch as N2, four as N1 and one scorer scored the epoch as W. In the 50 epochs during the sleep onset period, as indicated by the arrow in the top panel of Figure 1, only 2 epochs were unequivocally scored as W and 4 epochs unequivocally as N2. Thus, during this sleep onset period, the 12 scorers agreed completely on only 12% of the epochs (6 out of 50 epochs). The left part of Figure 2 shows the 12 hypnograms for the study used in the example of Figure 1. The hypnograms are sorted from scorer 1 to scorer 12, and epochs where each scorer disagrees with at least one of the upper scorer(s) are grayed out. As it can be seen, that while scorers 1 and 2 agree for 75.6% of the epochs, the percentage of epochs with complete agreement decreases continuously with each additional scorer. The final set of twelve scorers only reach complete agreement for 36.9% of the epochs (390 out of 1,057 epochs). The right part of Figure 2 presents the sleep stage probabilities as hypnodensity graphs based on aggregated scorers: the first graph corresponds to the first scorer (top graph with probabilities of 0 or 1), the second graph, to the first and second scorers (with probabilities 0 or 1 for epochs with agreement or 0.5 for epochs with disagreement) and so on, until the second graph from the bottom, with the probabilities based on all 12 manual scorings. Note that in this example, not a single epoch of N1 and N3 was scored unequivocally by all 12 experts. Furthermore, only isolated epochs N2 have been scored with complete agreement. Longer periods of complete agreement are mostly found in epochs scored as wake or rapid-eye movement (REM) sleep.

If multiple manual expert scorings are available for a study, it is possible to determine a consensus scoring. In this case, consensus is based on a majority vote. In the 30-second epoch example of Figure 1, the consensus score would be N2 since 7 out of 12 scorers assigned this epoch as N2. To avoid ties, one could weigh the assessments of scorers with a higher agreement with the other scorers (as measured by Cohen's kappa) more than the assessments of scorers with lower agreement (Stephansen et al., 2018). This approach was used in the examples of Figures 2, 4, resulting in the consensus scorings shown in the bottom left as hypnograms and in the bottom right superimposed on the hypnodensity graphs.

Since the amount of agreement progressively displayed in Figure 2 depends on the order of the scorers, we performed all possible order permutations across the twelve scorers and averaged the percentages of epochs with complete agreement. Figure 3 shows the averaged percentages of complete agreement across scorers for all 10 studies with 12 scorings, vs. the number of scorers compared. The number of permutations which depends on the number of scorers compared is shown in the table on the top. Interestingly, the decline in agreement can be modeled almost perfectly by a power function $y = ax^b$ where y is the percentage of epochs with complete agreement, x is the number of scorers, a is the coefficient (in %), and b is the exponent. This model explained almost 100% of the variance not only for PSG 1 (blue line, corresponds to the study illustrated in Figure 2) but for each of the 10 PSGs (all $R^2 > 0.99$) with a constant close to 100% and an exponent between −0.31 and −0.74, depending on the study. The worst complete agreement between the 12 scorers (16.7%) was found for PSG 5, where like for PSG 3, the agreement already falls below 50% when comparing three scorers. Figure 4 illustrates the study PSG 5 in the same way as PSG 1 was illustrated in Figure 2. Note that there are only a few isolated epochs of N2 and some epochs of W that have been scored unequivocally by the 12 experts. In Bakker et al. (2023), we described that the power functions were very similar also for two other datasets with 70 PSGs scored by 6 scorers and 15 PSGs scored by nine scorers, indicating a robust effect independent of the dataset and the scorers. On average, the exponent of the power function is close to −0.5 indicating that the scoring agreement is approximately inversely proportional to the square root of the

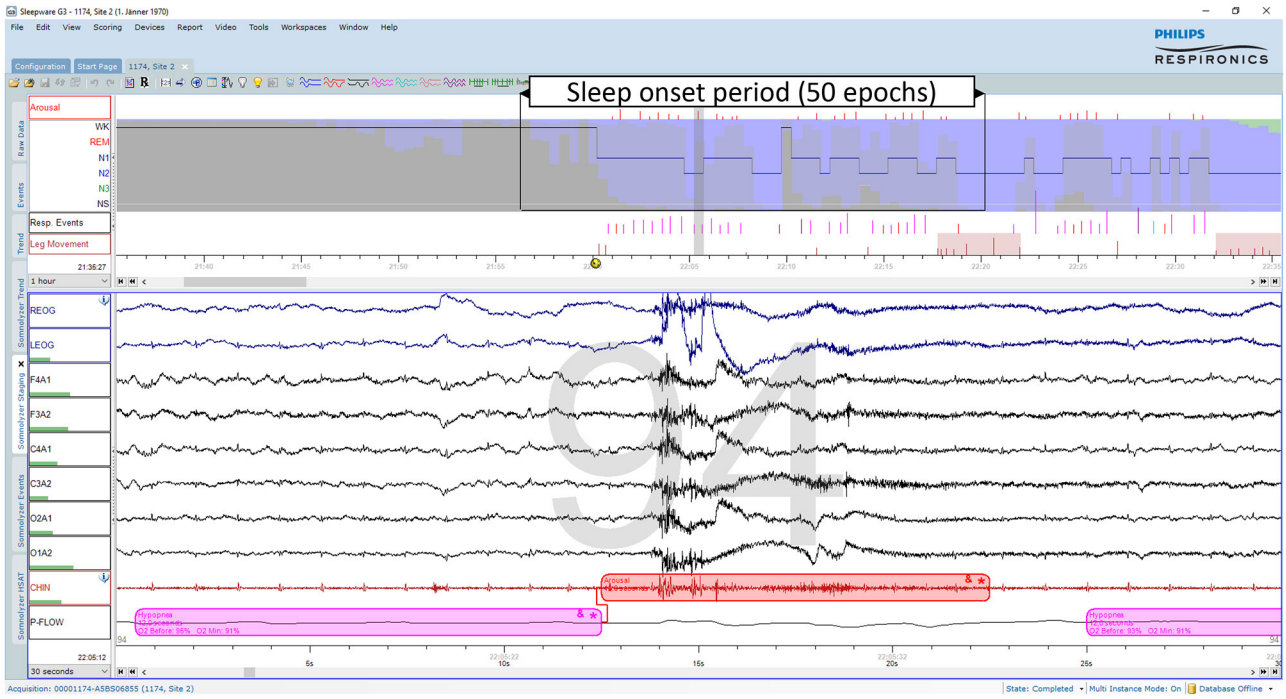

FIGURE 1
Example of an ambiguous sleep epoch during sleep onset (PSG1: OSAS patient, male, 76 years). Upper part (first hour): The trends from top to bottom are: "Arousals", arousal events; the hypnogram superimposed on the hypnodensity graph with the color codes W, gray; R, red; N1, cyan; N2, blue; N3, green; "Resp. Events", respiratory events; "Leg Movements", leg movement events. Lower part (30-s window): The signals from top to bottom are: "REOG" and "LEOG", right and left EOG; "F4A1", "F3A2", "C4A1", "C3A2", "O2A1", and "O1A2", the six EEG channels; "CHIN": chin EMG; "P-Flow": nasal pressure airflow. This epoch containing an arousal due to a hypopnea was scored as N2 by 7, as N1 by 4 and as W by one out of 12 scorers. Thus, based on 12 manual scorings the sleep stage probabilities for this epoch are for W: 0.08, for N1: 0.33, for N2: 0.58, for N3: 0.0, and for R: 0.0.

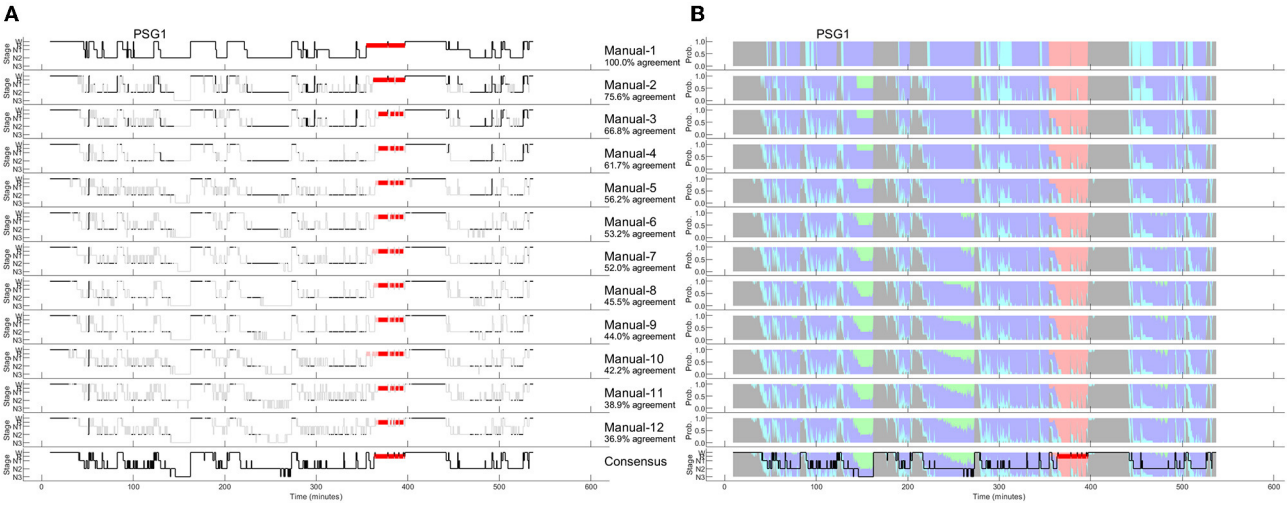

FIGURE 2
A representative example of 12 manually scored hypnograms and the derived hypnodensities (PSG1: OSAS patient, male, 76 years). **(A)** The individual hypnograms sorted from scorer 1 to scorer 12 (Manual-1 to Manual-12) where epochs with disagreement to the upper scorer(s) are grayed out. The bottom hypnogram depicts the consensus scoring based on majority vote. **(B)** The corresponding hypnodensity graphs based on the sorted scorings (Manual-1 to Manual-12). Thus, the first hypnodensity graph is based on Manual-1 scoring only, the second on Manual-1 and Manual-2 scorings, etc. The (two) last hypnodensity graphs are based on all 12 manual scorings where the consensus hypnogram is superimposed on the last hypnodensity. The color codes are W, gray; R, red; N1, cyan; N2, blue; N3, green. Note that while the agreement between the first two scorers is 75.6%, the agreement decreases continuously with each new scorer included in the comparison so that if 12 scorers are compared the percentage of epochs with complete agreement is reduced to 36.9%.

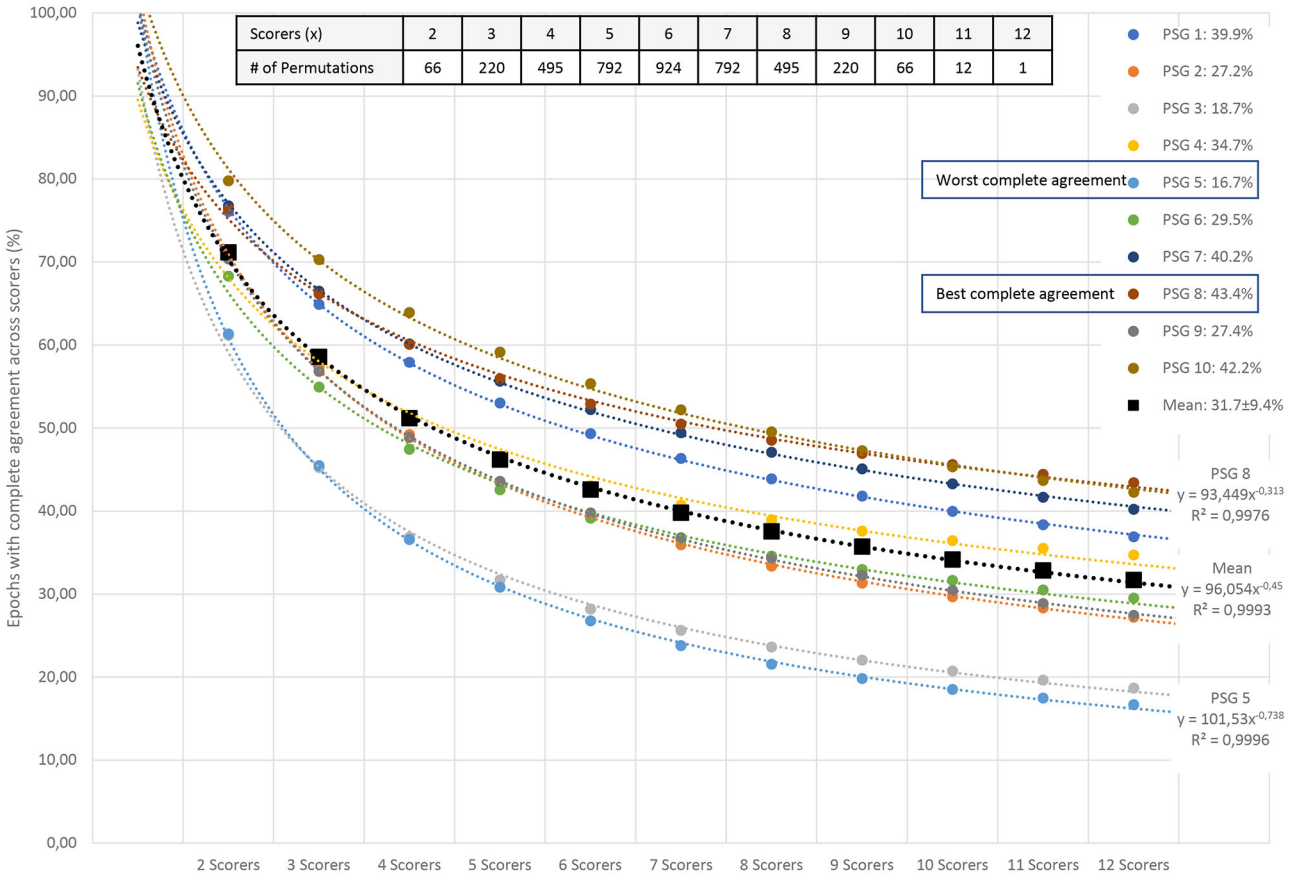

FIGURE 3
Percentage of all epochs with complete sleep staging agreement across 12 scorers in 10 PSGs. The number of scorers compared is shown on the x-axis; the percentage of complete agreement across the compared scorers is shown on the y-axis. The mean of all possible permutations for choosing x scorers out of the available scorers are shown for each PSG (colored filled circles) and for the mean of the 10 PSGs (black filled squares). The table in the upper right corner describes the number of permutations for each combination of scorers. The reduction in complete agreement alongside the increasing number of scorers follows an almost-perfect power function (dashed lines for each dataset). In addition to the coefficients and exponents, the explained variances (R^2) are shown. Modeled together, the power function $y = ax^b$ has a coefficient a_{MEAN} of 96 and an exponent b_{MEAN} of −0.45. This function explains more than 99% of the variance.

number of scorers included in the analysis. This means that on average, the complete agreement drops to 50% when four or more scorers are compared [100%/sqrt(4) = 50%].

To derive the AASM-recommended sleep parameters, one can use the consensus hypnogram. Alternatively, all the parameters could be determined from each of the 12 hypnograms and subsequently averaged to achieve a more robust estimate of the patients' sleep characteristics. Table 1 compares the results for both approaches for the example study shown in Figure 2 and demonstrates once more the impact of between-scorer variability on the derived sleep parameters. As shown in Table 1, the total sleep time varies between 348 and 408 min, the time spent in N1 varies between 23.5 and 134 min, the time in N2 varies between 180 and 311.5 min, the time in N3 varies between 0 and 67 min and the time in R varies between 22 and 42 min, depending on which expert scored this study. Averaged over the 10 studies with 12 scorers, total sleep time varied between 319 and 390 min, the time in N1 varies between 29 and 127 min, the time in N2 varies between 125 and 250, the time in N3 varies between 7 and 56 min, and the time in R varies between 42 and 63 min. Since each expert typically interprets the rules consistently, paired samples t-tests comparing the parameters based on the two extreme values are all significant at $p < 0.01$. Moreover, significant differences in the total sleep time, and the time spent in each of N1, N2, N3, and R were also found for many of the 66 possible pairwise comparisons between two scorers. For example, 15 scorer pairs differed significantly at $p < 0.01$ in the scoring of total sleep time. The number of significant t-tests were 25, 28, 27, and 9 for the time spent in N1, N2, N3, and R, respectively. Only 5 out of the 66 scorer pairs showed no significant difference in any of the 5 parameters (i.e., scorer 1 vs. scorer 2, scorer 1 vs. scorer 6, scorer 2 vs. scorer 3, and scorer 6 vs. scorer 7).

Similar high inter-scorer ranges have been reported by Magalang et al. (2013) averaged over 15 PSGs scored by 9 experts (N1: 32 to 111 min; N3: 25 to 73 min) as well as by Younes et al. (2018) averaged over 70 PSGs scored by 10 experts (N1: 16 to 155 min; N3: 4 to 111 min). The consequences of these different interpretations are certainly significant. Younes et al. (2018) stated that in nearly all the 70 PSGs, regardless of the average value obtained from the 10 scorers, stage N1 sleep time could be reported as well below normal or well above normal just depending on who

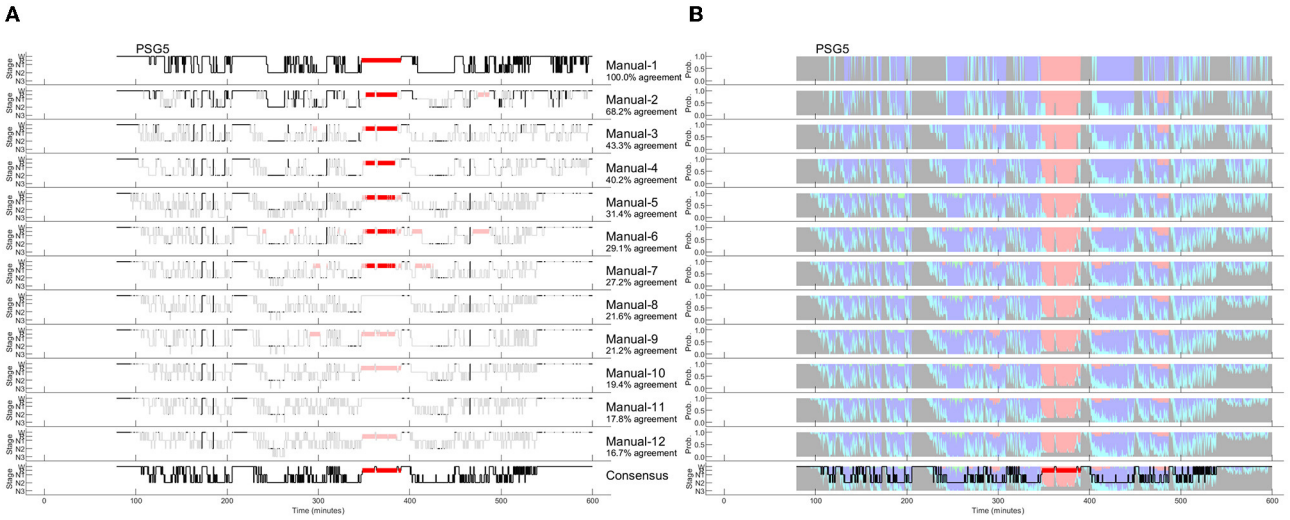

FIGURE 4
Manually scored hypnograms and the derived hypnodensities for the study with the worst agreement between the 12 scorers (PSG5: Hypersomnia with sleep apnea, male, 78 years). **(A)** The individual hypnograms sorted from scorer 1 to scorer 12 (Manual-1 to Manual-12) where epochs with disagreement to the upper scorer(s) are grayed out. The bottom hypnogram depicts the consensus scoring based on majority vote. **(B)** The corresponding hypnodensity graphs based on the sorted scorings (Manual-1 to Manual-12). Thus, the first hypnodensity graph is based on Manual-1 scoring only, the second on Manual-1 and Manual-2 scorings, etc. The (two) last hypnodensity graphs are based on all 12 manual scorings where the consensus hypnogram is superimposed on the last hypnodensity. The color codes are W, gray; R, red; N1, cyan; N2, blue; N3, green. Note that while the agreement between the first two scorers is 68.2%, the agreement decreases continuously with each new scorer included in the comparison so that if 12 scorers are compared the percentage of epochs with complete agreement is reduced to 16.7%.

TABLE 1 Sleep parameters derived from multiple manual scorings (OSAS patient, male, 76 years).

Scorer	TST (min)	N1 (min)	N2 (min)	N3 (min)	R (min)
Manual-1	356.5	83	231.5	0	42
Manual-2	381.5	74.5	253	21	33
Manual-3	357.5	88	247	0	22.5
Manual-4	387	48	311.5	0	27.5
Manual-5	408	94.5	264	18.5	31
Manual-6	360	53.5	245.5	33.5	27.5
Manual-7	382	83.5	248	19.5	31
Manual-8	370.5	45	228.5	67	30
Manual-9	370.5	23.5	255.5	62.5	29
Manual-10	399	115.5	200	45	38.5
Manual-11	348	96	217	13	22
Manual-12	375.5	134	180	39	22.5
Manual-Mean = Manual-Hypnodensity	374.7	78.3	240.1	26.6	29.7
Manual-Consensus Hypnogram	372.5	62	259	20.5	31

Manual-1 to Manual-12: parameters derived from the twelve individual manual scorings. Manual-Mean: mean value of the 12 parameters, which is equal to parameters derived from the hypnodensity based on the manual scorings. Manuel-Consensus Hypnogram: parameters derived from the manual consensus hypnogram. Light and dark ocher cells indicate per parameter the lowest and highest value, respectively; gray cells indicate parameters based on multiple manual scorers.

scored the PSG. Similarly, reported stage N3 sleep time ranged from zero to high values regardless of average stage N3 sleep time of the PSG.

To avoid individual scorer bias in the estimation of sleep parameters, one may make use of multiple expert scorings. The averaged parameters are given in the penultimate row of Table 1 (Manual-Mean). Alternatively, these averaged parameters can be computed directly from the hypnodensity graph by calculating the area under the sleep stage probability curves of the respective stages (Manual-Hypnodensity). Note that these mean parameters are not necessarily equal to the parameters computed from a majority vote hypnogram. Based on the

TABLE 2 Overview of sleep staging validation studies with algorithms outputting the hypnodensity graph.

Author, year, algorithm name	Training dataset	Feature extraction / epoch encoder	Classifier/Sequence encoder	Test dataset	Cohen's κ	Hypnodensity
Stephansen et al. (2018) *Stanford-STAGES*	Cohort: $N = 2{,}784$; 10 cohorts	EEG, EOG, EMG: Cross-correlation encoding+CNN	Unidirectional LSTM	Cohort: $N = 70$; IS-RC, 6 scorers	0.75	
Cesari et al. (2021) *Stanford-STAGES*	Stanford-STAGES algorithm			Cohort: $N = 1{,}066$; SHIP, 2 scorers	0.68	
Vallat and Walker (2021) *YASA*	Cohort: $N = 3{,}163$; 7 cohorts	EEG, EOG, EMG (time-domain features and spectrogram)	LightGBM	HC: $N = 25$; DOD-H, 5 scorers PAT(OSA): $N = 55$; DOD-O, 5 scorers	0.80 0.77	
Anderer et al. (2022b) *Somnolyzer*	Cohort: $N = 588$; SIESTA (7 sleep centers) 2–6 scorers	EEG, EOG, EMG (Sleep/wake related features) + MLP/CNN	bidirectional LSTM (→RandK) + CNN + unidirectional LSTM (→AASM)	Cohort: $N = 426$; ABC, homePAP, MESA, 1 scorer	0.74	
Bakker et al. (2023) *Somnolyzer*	Somnolyzer algorithm			Cohort: $N = 70$; IS-RC, 6 scorers PAT: $N = 15$; SAGIC, 9 scorers PAT: $N = 10$;Somnoval,12 scorers	0.78 0.75 0.76	ICC: 0.91 ICC: 0.91 ICC: 0.91
Cesari et al. (2022) *Stanford-STAGES*	Stanford-STAGES algorithm			PAT (Narcolepsy type1 and 2, idiopathic hypersomnia, subjective EDS): $N = 143$, 1 scorer	0.75	
Cesari et al. (2022) *YASA*	YASA algorithm				0.76	
Brandmayr et al. (2022) *ENGELBERT*	HC: $N = 20$;Sleep-EDF-20 HC: $N = 78$;Sleep-EDF-SC Cohort: $N = 62$;MASS-SS3	Single-channel EEG (raw signal) + CNN	Local MHSA on overlapping windows	HC: $N = 20$; Sleep-EDF-20 (CV) HC: $N = 78$; Sleep-EDF-SC (CV) Cohort: $N = 62$; MASS-SS3 (CV)	0.82 0.79 0.80	
Fiorillo et al. (2023b) *DeepSleepNet-Light*	Cohort: $N = 70$; IS-RC, 6 scorers HC: $N = 25$; DOD-H, 5 scorers PAT (OSA): $N = 55$; DOD-O, 5 scorers	Single-channel EEG (raw signal) + CNN	Deep CNN (Soft consensus label smoothing)	Cohort: IS-RC, 6 scorers (CV) HC: DOD-H, 5 scorers (CV) PAT (OSA): DOD-O,5 scorers (CV)	0.67 0.76 0.71	ACS: 0.85 ACS: 0.91 ACS: 0.89
Fiorillo et al. (2023b) *Simple Sleep Net*		EEG, EOG, EMG (spectrogram) + bidirectional GRU + Attention Layer	Bidirectional GRU (Soft consensus label smoothing)	Cohort: IS-RC, 6 scorers (CV) HC: DOD-H, 5 scorers (CV) PAT (OSA): DOD-O,5 scorers (CV)	0.73 0.84 0.80	ACS: 0.82 ACS: 0.91 ACS: 0.91

Cohort, cohort study; HC, healthy controls; PAT, patients with sleep disturbance; OSA, patients with obstructive sleep apnea; PD, Parkinson's Disease; IS-RC, Research study on sleep disordered breathing in women in midlife, University of Pennsylvania, Philadelphia; SIESTA, SIESTA sleep database; Somnoval, Somnolyzer validation study dataset; Sleep-EDF, Sleep-EDF Database Expanded; DOD-H, Dreem Open Dataset – Healthy Volunteers; DOD-O, Dreem Open Dataset – Obstructive Sleep Apnea Patients; homePAP, Home Positive Airway Pressure study; ABC, Apnea, Bariatric surgery, and CPAP study; SHIP, Study of Health in Pomerania; MESA, Multi-Ethnic Study of Atherosclerosis; SAGIC, Sleep Apnea Genetics International Consortium, The Ohio State University Medical Center, Columbus; CNN, Convolutional neural network; LSTM, long short-term memory; MLP, multilayer perceptron; LightGBM, decision tree-based gradient-boosting machine; decision tree; MHSA, Multi-head self-attention.

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consensus hypnogram (last line in Table 1) the time in N1 is 62 min, while the time in N1 is 78.3 min (+16.3 min) if averaged across the times derived from each of the 12 hypnograms or if the N1 probabilities of the hypnodensity curve are integrated. Specifically, the time in N1 is typically underestimated if the parameters are derived from a consensus scoring, since the epoch-by-epoch agreement for stage N1 is generally low between manual scorers. Given the wide variability in the interpretation of the recorded neurological signals by manual experts, it is highly questionable to rely on a single expert's assessment. Furthermore, none of the 12 hypnograms or the consensus hypnogram provide insights into this inter-scorer variability. In contrast, the hypnodensity reflects sleep stage ambiguity while retaining all the information contained in a consensus hypnogram.

Hypnodensity based on autoscoring using neurological signals

Autoscoring with artificial intelligence enables the direct quantification of sleep stage ambiguity by determining sleep stage probabilities for each epoch. Based on these probabilities, it is possible to create a hypnodensity chart from autoscoring which can be directly compared to the hypnodensity chart based on multiple expert scorings. In Table 2 we summarize publications using AI-algorithms for sleep staging and reporting autoscored hypnodensity graphs (Stephansen et al., 2018; Cesari et al., 2021, 2022; Vallat and Walker, 2021; Anderer et al., 2022b; Brandmayr et al., 2022; Bakker et al., 2023; Fiorillo et al., 2023b). In addition to information regarding the training datasets, the epoch encoder including feature extraction, the sequence encoder and classifier, and the test datasets, the Cohen's kappa values obtained in each study are given. Two publications describe quantitative comparisons between the hypnodensity graph derived from autoscoring vs. the hypnodensity graph derived from multiple manual scorings. Bakker et al. (2023) computed the intra-class correlation coefficient (ICC) for absolute agreement between the probability curves from auto and manual scoring per sleep stage as well as overall sleep stages for the entire night, while Fiorillo et al. (2023b) computed the cosine similarity between the probability values from auto and manual scoring per 30-s epoch and averaged these values over the entire night resulting in average cosine similarity (ACS) measures. As can be seen in Table 2, both approaches indicate a high agreement between the autoscored and the manually derived hypnodensity graphs with an ICC of 0.91 and an ACS of up to 0.91.

The Stanford-STAGES, YASA, Somnolyzer and Simple Sleep Net algorithms use EEG, EOG and chin EMG channels as inputs, while the ENGELBERT and DeepSleepNet-Light algorithms are based on a single EEG channel only, offering sleep staging for reduced montage recordings. The Somnolyzer autoscoring system uses all recorded frontal, central and occipital EEG channels, left and right EOG channels, as well as the chin EMG channel for feature extraction. Somnolyzer feature extraction includes identification of artifacts, detection of slow waves, k-complexes, sleep spindles, and episodes with alpha waves, determination of the EEG background activities (delta, theta, alpha, slow and fast beta activities) based on the EEG channels. EOG channels were used for detecting slow and rapid eye movements as well as eye-blinks. The chin EMG channel was used to detect tonic and transient EMG activities (Anderer et al., 2005, 2010). The original Somnolyzer algorithm (Version 1.7; 2005) was developed according to the criteria defined by Rechtschaffen and Kales (1968) (R&K) and subsequently modified (Version 1.8; 2009) to comply with the AASM 2007 criteria (Iber et al., 2007). For version 4.0 of Somnolyzer released commercially in 2021, a supervised deep learning algorithm was used to train a neural network where 472 PSGs from the SIESTA database (Klosch et al., 2001) were used for parameter optimization, and the remaining 116 PSGs were used for early-stopping to prevent the model from overfitting. Each PSG was scored by two independent technologists and one consensus scorer chosen from a pool of 30 scorers to obtain R&K sleep stage probabilities as training targets. This corresponds to the soft consensus labels smoothing approach using an alpha coefficient of 1 as presented by Fiorillo et al. (2023b). The categorical cross-entropy between the sleep stage probabilities and the network output with softmax activation was used as loss function during the training. In a further step, arousals, sleep spindles, and k-complexes were added to the feature set and a convolutional neural network (CNN) followed by a bidirectional long short-term memory (LSTM) layer was trained using data from 72 PSGs scored according to AASM criteria to sub-classify NREM sleep stages.

The final Somnolyzer network output assigned AASM-related sleep stage probabilities of W, N1, N2, N3, R to each 30-sec epoch. Figures 5, 6 compare the hypnodensity derived from the 12 manual scorings with the hypnodensity determined by the Somnolyzer autoscoring system for the two studies shown in Figures 2, 4, respectively. As can be seen in the examples from this independent test set, the sleep stage probabilities of Somnolyzer match almost perfectly with the sleep stage probabilities based on the 12 human scorings. The ICCs for absolute agreement between the two probability curves are 0.97 for PSG 1 (Figure 5) and 0.89 for PSG 5 (Figure 6). Also note the high similarity in the probability curves for each sleep stage. In Figure 5, we highlighted 6 periods. Box 1 comprises sleep onset with a change from W to a small amount of N1 probability at the start, back to definite W, and then with increasing N1 probability via sleep onset, which is the first epoch with sleep probability higher than wake probability (solid line), to definite sleep with N1+N2 probability above 0.95 with approximately equal amount of N1 and N2 probability at the end of the box 1. Note that just before the end of box 1, there are epochs which were assigned still as W by some scorers, while others assigned these epochs already as N2 sleep. Boxes 2, 3, 4, and 6 indicate periods where at least two experts scored N3. Note that the N3 probabilities derived from autoscoring follow the N3 probabilities derived from the 12 manual scorings not only in respect to the timing, but also in respect to the amount, with the highest N3 probability reaching 0.75 (8 out of 12 scorers) in box 3 and the lowest at 0.17 (2 out of 12 scorers) in box 2. Finally, also for the R probabilities (box 5) the manually- and autoscoring-based curves match in terms of time and magnitude. Interestingly, even for the study with the worst agreement between scorers, the manually- and autoscoring-based probability curves match closely (Figure 6).

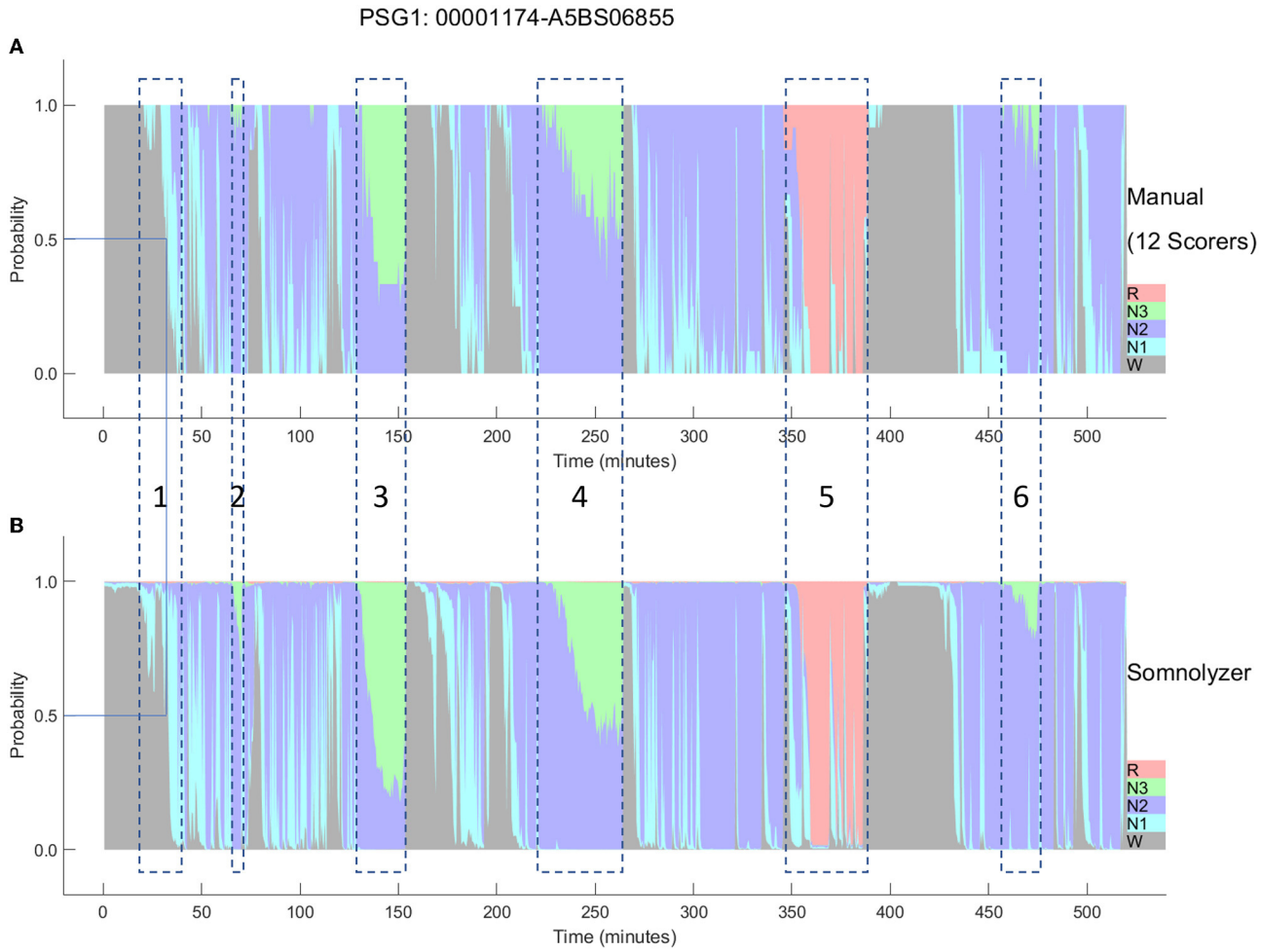

FIGURE 5
A representative example comparing the hypnodensities derived from 12 manual scorings **(A)** and from autoscoring **(B)** for the same PSG shown in Figure 2 (PSG1: OSAS patient, male, 76 years). The color codes are W, gray; R, red; N1, cyan; N2, blue; N3, green. The time period depicted in box 1 highlights the sleep onset period with the actual sleep onset at W_{prob} <0.5 indicated as solid line; Boxes 2, 3, 4, and 6 indicate time periods where at least 2 scorers have scored N3; Box 5 indicate the time period where at least one scorer has scored R. Note the similarity of the manually-derived and the autoscoring-derived sleep stage probabilities.

As presented in Bakker et al. (2023) the ICCs for absolute agreement between sleep stage probabilities derived from manual- and Somnolyzer autoscoring were, on average 0.91 for all stages for all three datasets with multiple scorers (Table 2). For the individual sleep stages the ICCs were as follows: 0.93-0.94 for stage W; 0.72–0.74 for stage N1; 0.88–0.89 for stage N2; 0.85–0.94 for stage N3; and 0.96–0.97 for stage R. Thus, according to the thresholds defined by Koo and Guideline (2016) the probability curves for all stages, as well as for individual stages W and R show excellent agreement; good agreement for stages N2 and N3; and, moderate agreement even for stage N1.

The hypnodensity graph based on the manual scorers shown in Figure 5 clearly indicates that although all experts follow the well-established AASM rules for scoring PSGs, the interpretation of the rules may, and often does vary substantially between scorers, specifically for epochs or events with equivocal features (Rosenberg and Van Hout, 2013; Younes et al., 2016, 2018). Experts, when scoring these epochs, may be biased toward sensitivity or specificity, probably depending on their internal representation of the features (i.e., their personal feature template or prototype). As soon as the features in the epoch are close enough to their subjective template, the scorer will score this epoch accordingly. Consequently, if the following epoch shows features that are similar or even closer to their template, the scorers will continue to score the same sleep stage. This also explains the gradual increase in epochs scored as sleep (box 1) or in epochs scored as N3 (boxes 3 and 4). If the features never match close enough their personal template of slow wave sleep, scorers may never even start scoring N3 in the entire recording, which is the case for scorers 1, 3, and 4 in the recording shown in Figure 5 (see also Table 1). In contrast, scorers 8 and 9 have obviously a very sensitive template of slow wave sleep resulting in 4 periods of slow wave sleep with a total time in N3 of more than 1 h (Table 1). Younes et al. (2018) showed that some technologists scored stage N3 sleep when delta wave duration was well below 6 s whereas for others much greater durations were required.

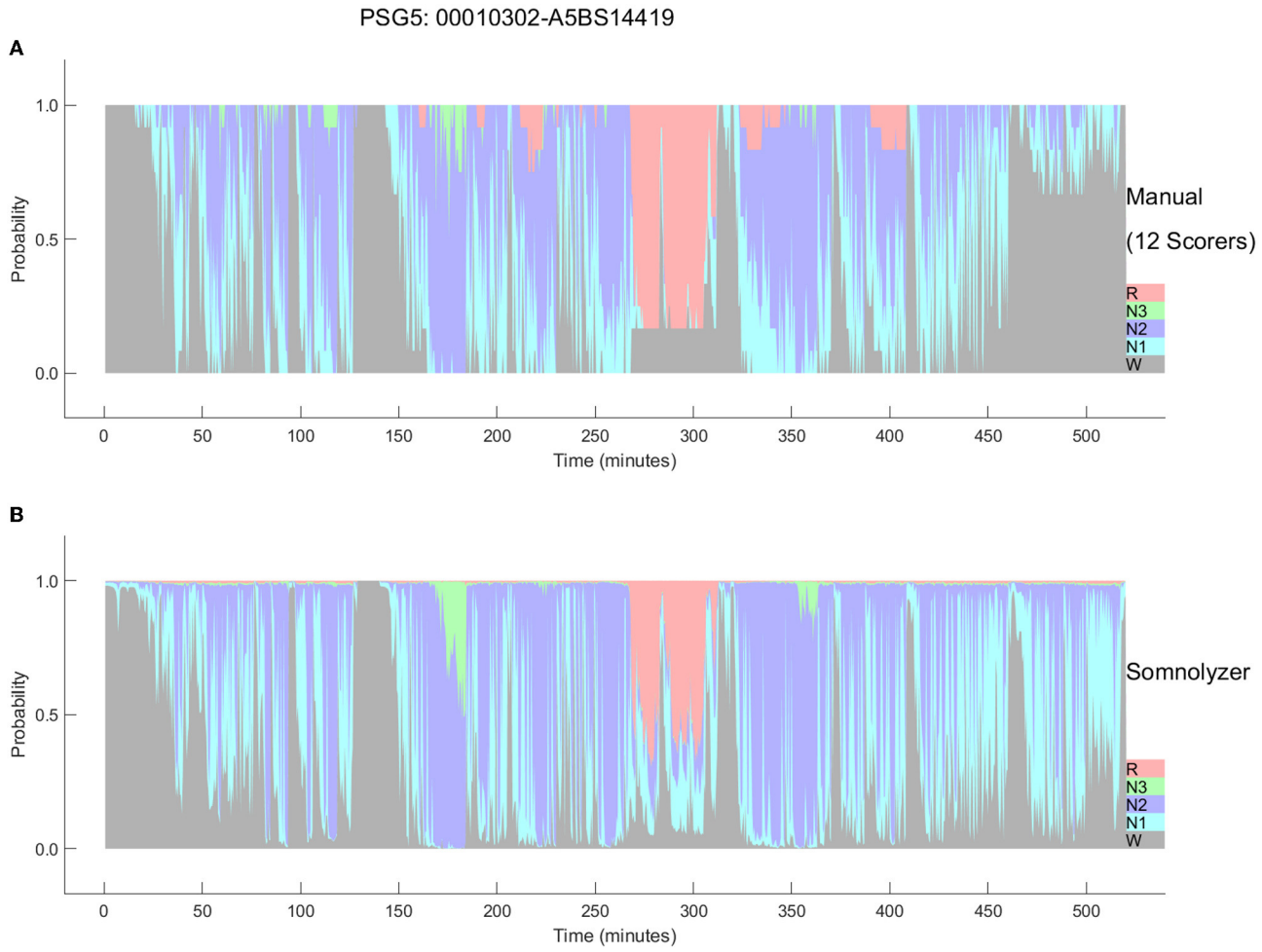

FIGURE 6
Comparison between the hypnodensities derived from 12 manual scorings **(A)** and from autoscoring **(B)** for the PSG with the worst agreement between manual scorers (PSG5: Hypersomnia with sleep apnea, male, 78 years). The color codes are W, gray; R, red; N1, cyan; N2, blue; N3, green. Note the similarity of the manually-derived and the autoscoring-derived sleep stage probabilities.

Interestingly, by varying sensitivity settings, an autoscoring can mimic these different interpretations. The Somnolyzer autoscoring system has the option to select different sensitivities for arousal, spindle/k-complex, slow wave, apnea and hypopnea event detection. In Anderer et al. (2022b) we reported the effects of changing these sensitivity settings in a study based on 10 PSGs from 10 apnea patients (5 diagnostic-, 2 titration- and 3 split-nights) each scored independently by 8 experts. Sleep parameters derived from the manual scorings varied considerably between the 8 scorers (time in N1: 29–127 min, time in N2: 125–209 min, time in N3: 19–56 min, time in R: 42–63 min). With the default (= balanced) setting, Somnolyzer autoscoring was close to the mean of the 8 manual scorings (time in N1: 82 and 85 min, time in N2: 184 and 176 min, time in N3: 41 and 42 min, time in R: 59 and 56 min, for the Somnolyzer scoring and the mean of the 8 manual scorings, respectively). Moreover, by varying the sensitivity settings in 5 steps (from maximal precision to maximal sensitivity), the autoscoring perfectly mimicked the variability observed in the 8 manual scorers. Thus, by merely varying the sensitivity settings, the inter-scorer variability observed in manual scorings can be explained. Furthermore, the high agreement between the hypnodensity based on the manual scorings and the autoscoring indicates that the 30 scorers who participated in the scoring of our training set covered the full spectrum from maximal sensitivity to maximal precision. In a recent paper on interpretation and further development of the hypnodensity, Huijben et al. (2023) concluded based on theoretical analyses and empirical evidence that the hypnodensity graph, predicted by a classifier that had been trained in a supervised manner, resembles the inter-rater disagreement across the scorers that annotated the PSGs of the training set. Consequently, training sets used to develop classifiers for sleep staging have to be scored by experts covering the full spectrum from highly sensitive to highly precise within the AASM scoring rules in a sufficiently large sample of subjects of both sexes, including healthy controls and a wide range of patients with different sleep disturbances, to ensure that the hypnodensity output of the trained neural network reflects this full spectrum.

Hypnodensity-derived sleep stages and parameters

Based on the hypnodensity, a sleep stage can be assigned as the stage with the highest probability (argmax). The Somnolyzer algorithm, however, uses a hierarchical approach to assure that for instance epochs with a higher probability for sleep than for wake are scored as sleep, even if the probability for wake is higher than for any individual sleep stage. In the hierarchical approach a sleep stage is assigned to each epoch as follows: if the wake-probability was > 0.5, assign W; else if the REM-probability was higher than the NREM probability (sum of the probabilities of N1, N2, and N3), assign R; else if the N3-probability was higher than the sum of the N1- and N2-probabilities, assign N3; else if the N2-probability was higher than the N1-probability, assign N2; otherwise assign N1. In an additional post-processing step, Somnolyzer enforces the AASM smoothing rules for scoring R as well as N2, based on the occurrence (start and duration) of arousals, sleep spindles and K complexes (Troester et al., 2023).

A validation study of the Somnolyzer algorithm by Anderer et al. (2022b) with 426 PSGs (224 PSGs from the MESA study (Chen et al., 2015), 178 PSGs from the HomePAP study (Rosen et al., 2012) and 24 PSGs from the ABC study (Bakker et al., 2018) scored by one scorer resulted in a Cohen's kappa between Somnolyzer autoscoring and manual scoring of 0.739 (with a 95% confidence interval of 0.737 to 0.741), reflecting substantial agreement according to the thresholds defined by Landis and Koch (1977). In agreement with human inter-rater reliability studies, the highest kappa values were observed for wake and REM detection (0.85 and 0.87) followed by N2 and N3 detection (0.72 and 0.73), while the detection of N1 resulted in the lowest kappa value of 0.46.

Another Somnolyzer validation study based on the three external datasets scored by six, nine, and twelve scorers, demonstrated for each dataset that the agreement between autoscoring and consensus manual-scoring was significantly higher than agreement between manual-scoring and consensus manual-scoring (Bakker et al., 2023). In the dataset with 70 PSGs and 6 scorers, autoscoring achieved a Cohen's kappa of 0.78, vs. 0.69 for manual scorings; for the dataset with 15 PSGs and 9 scorers, autoscoring achieved 0.74 vs. 0.67 for manual scorings; and for the dataset with 10 PSGs and 12 scorers, 0.75 vs. 0.67 (all $p < 0.01$). As shown by the authors in supplementary tables, the percentage of agreement between autoscoring and consensus scoring was 85, 83 and 83% for the three studies. Thus, in 15–17% of the epochs, Somnolyzer disagreed with the consensus. However, in almost all of these epochs at least one scorer disagreed with the consensus and more importantly, autoscoring agreed in these cases with at least one of the deviating scorers. By considering as a correct detection, all epochs where autoscoring and at least one manual scorer agreed, the percentage of agreement increases to 97.9, 98.3, and 99.1% for the three datasets with 6, 9, and 12 scorers. In addition, the authors showed that sleep staging derived from autoscoring was for each individual PSG non-inferior to manual-scoring.

Many AI-based sleep scoring algorithms have been developed and validated in the last few years. In Tables 3, 4 we summarize publications using AI-algorithms for sleep staging based on neurological signals that reported Cohen's kappa for the 5-stage comparison. Note the large difference in the size of the training data (between 10 and more than 15,000 PSGs) as well as in the size of the test data (between 8 and close to 3000). Table 3 summarizes validation results of AI-algorithms that applied a hold-out or cross-validation; i.e., an internal validation based on data from the same dataset that has been used for training (Supratak et al., 2017; Sors et al., 2018; Phan et al., 2019; Zhang et al., 2019; Abou Jaoude et al., 2020; Guillot et al., 2020; Korkalainen et al., 2020; Sun et al., 2020a; Alvarez-Estevez and Rijsman, 2021; Fiorillo et al., 2021, 2023b; Jia et al., 2021; Nasiri and Clifford, 2021; Olesen et al., 2021; Pathak et al., 2021; Vallat and Walker, 2021; Brandmayr et al., 2022; Cho et al., 2022; Ji et al., 2022; Li C. et al., 2022; Li T. et al., 2022; Sharma et al., 2022; Yubo et al., 2022). Table 4 summarizes the validation results of AI-algorithms which have been validated in datasets completely unseen by the model (Anderer et al., 2018, 2022b; Biswal et al., 2018; Patanaik et al., 2018; Stephansen et al., 2018; Zhang et al., 2019; Abou Jaoude et al., 2020; Alvarez-Estevez and Rijsman, 2021; Cesari et al., 2021, 2022; Vallat and Walker, 2021; Bakker et al., 2023). The reported Cohen's kappa values ranged between 0.60 [external validation in 70 patients with Parkinson's disease (Patanaik et al., 2018)] to 0.91 [internal 20-fold epoch-wise cross validation in 8 healthy subjects (Li C. et al., 2022)]. Cohen's kappa values reported for the 45 internal validation studies using hold-out or cross-validation were significantly higher than for the 19 studies using external test sets for validation (0.79 ± 0.04 vs. 0.72 ± 0.06; $p < 0.001$ independent samples t-test). In all studies that reported Cohen's kappa for both, an internal and an external test set the kappa for the internal testing was always higher than for the external testing (Zhang et al., 2019; Abou Jaoude et al., 2020; Alvarez-Estevez and Rijsman, 2021; Vallat and Walker, 2021). Moreover, in studies reporting Cohen's kappa for patients and for healthy controls, the kappa for controls was always higher than for patients (Supratak et al., 2017; Guillot et al., 2020; Korkalainen et al., 2020; Vallat and Walker, 2021; Ji et al., 2022; Yubo et al., 2022). Accordingly, Korkalainen et al. (2020) reported a decrease in Cohen's kappa depending on OSA severity in a clinical dataset of 891 patients, with a kappa of 0.79 for individuals without OSA diagnostic ($n = 152$) to a kappa of 0.68 for patients with severe OSA ($n = 254$). Consequently, performance measures of sleep stage validation studies need to be interpreted depending on the validation method used and the characteristics of the subjects included in the test dataset.

Table 2 summarizes the kappa values for the 20 validation studies of the 6 AI-based autoscoring algorithms outputting the hypnodensity graph (Stephansen et al., 2018; Cesari et al., 2021, 2022; Vallat and Walker, 2021; Anderer et al., 2022b; Brandmayr et al., 2022; Bakker et al., 2023; Fiorillo et al., 2023b). As can be seen in Table 2, Cohen's kappa for the 5-stage comparison was comparable between the six algorithms. Stephansen et al. (2018), Bakker et al. (2023) and Fiorillo et al. (2023b) validated their algorithms in the same IS-RC cohort and reported, as compared to the consensus of 6 scorers, kappa values between 0.67 and 0.78. Cesari et al. (2022) compared the Stanford-STAGES and YASA algorithm in a dataset of patients with central disorders of hypersomnolence and reported almost identical kappa values for the two algorithms (0.747 and 0.755 for Stanford-STAGES and YASA, respectively). These findings suggest that modern

TABLE 3 Overview of sleep staging validation studies with AI-algorithms providing Cohen's kappa based on internal validation.

Author, Year *Name*	Training dataset	Input signals	Test dataset	Cohen's κ
Supratak et al. (2017) *DeepSleepNet*	Cohort: $N = 62$; MASS HC: $N = 20$; Sleep-EDF	Single-channel EEG	Cohort: MASS (CV) HC: Sleep-EDF (CV)	0.80 0.76
Sors et al. (2018)	Cohort: $N = 5{,}793$; SHHS	Single-channel EEG	Cohort: $N = 1738$; SHHS (HO)	0.81
Phan et al. (2019) *SeqSleepNet*	Cohort: $N = 200$; MASS	EEG, EOG, EMG	Cohort: MASS (CV)	0.82
Zhang et al. (2019)	Cohort: $N = 5{,}213$; SHHS	EEG, EOG, EMG	Cohort: $N = 580$; SHHS (HO)	0.82
Sun et al. (2020a)	Cohort: $N = 147$; MASS	EEG, EOG, EMG	Cohort: MASS (CV)	0.80
Guillot et al. (2020) *SimpleSleepNet*	HC: $N = 25$; DOD-H, 5 scorers PAT (OSA): $N = 55$; DOD-O, 5 scorers	EEG, EOG, EMG	HC: DOD-H, 5 scorers (CV) PAT (OSA): DOD-O, 5 scorers (CV)	0.85 0.82
Korkalainen et al. (2020)	HC: $N = 153$; Sleep-EDF PAT (OSA): $N = 891$; Clinical Dataset	Single-channel EEG (and single-channel EOG)	HC: Sleep-EDF (CV) PAT (OSA): Clinical datsaset (CV)	0.78 0.78
Abou Jaoude et al. (2020)	PAT: $N = 6{,}341$; MGH	4 EEG channels	PAT: $N = 791$; MGH (HO)	0.74
Alvarez-Estevez and Rijsman (2021)	Cohort: $N = 443$; 6 datasets	EEG, EOG, EMG (raw signal) + CNN	Cohort: $N = 88$ (HO)	0.80
Olesen et al. (2021)	Cohort: $N = 15{,}684$; 5 cohorts	EEG, EOG, EMG	Cohort: $N = 1{,}584$ (HO)	0.80
Vallat and Walker (2021) *YASA*	Cohort: $N = 3{,}163$; 7 cohorts	EEG, EOG, EMG	Cohort: $N = 585$ (HO)	0.82
Nasiri and Clifford (2021)	PAT: $N = 994$; PhysioNet	6 EEG channels	PAT: PhysioNet (CV)	0.75
Fiorillo et al. (2021) *DeepSleepNet-Lite*	HC: $N = 39$; Sleep-EDF 2013 HC: $N = 153$;Sleep-EDF 2018	Single-channel EEG	HC: Sleep-EDF 2013 (CV) HC: Sleep-EDF 2018 (CV)	0.78 0.73
Pathak et al. (2021)	Cohort: $N = 5{,}793$; SHHS PAT: $N = 1418$; Clinical	EEG, EOG, EMG	Cohort: $N = 579$; SHHS (HO) PAT: $N = 142$; Clinical (HO)	0.79 0.68
Jia et al. (2021)	HC: $N = 10$; ISRUC-S3 HC: $N = 62$; MASS-SS3	EEG (6 channels ISRUC, 20 channels MASS)	HC: ISRUC (CV) HC: MASS (CV)	0.77 0.84
Li T. et al. (2022)	HC: $N = 61$; Sleep-EDF 2013 HC: $N = 197$;Sleep-EDF 2018	Single-channel EEG	HC: Sleep-EDF 2013 (CV) HC: Sleep-EDF 2018 (CV)	0.78 0.74
Ji et al. (2022)	HC: $N = 10$; ISRUC-S3 PAT: $N = 100$; ISRUC-S1	EEG, EOG, EMG, ECG	HC: ISRUC-S3 (CV) PAT: ISRUC-S1 (CV)	0.78 0.77
Li C. et al. (2022) *EEGSNet*	HC: $N = 8$; Sleep-EDF-8 HC: $N = 39$; Sleep-EDF-20 HC: $N = 153$; Sleep-EDF-78 Cohort: $N = 329$; SHHS	Single-channel EEG	HC: Sleep-EDF-8 (CV) HC: Sleep-EDF-20 (CV) HC: Sleep-EDF-78 (CV) Cohort: SHHS (CV)	0.91 0.82 0.77 0.79
Sharma et al. (2022)	Cohort: $N = 8{,}455$; SHHS	EEG, EOG, EEG	Cohort: $N = 580$; SHHS1 (HO) Cohort: $N = 2651$; SHHS2 (HO)	0.77 0.80
Cho et al. (2022) *StageNet*	PAT: $N = 530$; Clinical dataset	EEG, EOG, EMG	PAT: $N = 72$, Clinical dataset (HO)	0.84
Yubo et al. (2022) *MMASleepNet*	HC: $N = 39$; Sleep-EDF-20 HC: $N = 153$; Sleep-EDF-78 HC: $N = 10$; ISRUC-Sleep3 PAT: $N = 100$; ISRUC-Sleep1	EEG, EOG, EMG	HC: Sleep-EDF-20 (CV) HC: Sleep-EDF-78 (CV) HC: ISRUC-Sleep3 (CV) PAT: ISRUC-Sleep1 (CV)	0.83 0.76 0.77 0.73
Brandmayr et al. (2022) *ENGELBERT*	HC: $N = 20$; Sleep-EDF-20 HC: $N = 78$; Sleep-EDF-SC Cohort: $N = 62$; MASS-SS3	Single-channel EEG	HC: $N = 20$; Sleep-EDF-20 (CV) HC: $N = 78$; Sleep-EDF-SC (CV) Cohort: $N = 62$; MASS-SS3 (CV)	0.82 0.79 0.80

(Continued)

TABLE 3 (Continued)

Author, year *Name*	Training dataset	Input signals	Test dataset	Cohen's κ
Fiorillo et al. (2023b) *DeepSleepNet-Light*	Cohort: $N = 70$; IS-RC, 6 scorers HC: $N = 25$; DOD-H, 5 scorers PAT (OSA): $N = 55$; DOD-O, 5 scorers	Single-channel EEG	Cohort: IS-RC, 6 scorers (CV) HC: DOD-H, 5 scorers (CV) PAT (OSA): DOD-O, 5 scorers (CV)	0.67 0.76 0.71
Fiorillo et al. (2023b) *Simple Sleep Net*	Cohort: $N = 70$; IS-RC, 6 scorers HC: $N = 25$; DOD-H, 5 scorers PAT (OSA): $N = 55$; DOD-O, 5 scorers	EEG, EOG, EMG	Cohort: IS-RC, 6 scorers (CV) HC: DOD-H, 5 scorers (CV) PAT (OSA): DOD-O, 5 scorers (CV)	0.73 0.84 0.80
			N-studies	45
			Cohen's κ Mean ± SD	0.79 ± 0.04
			Min	0.67
			Max	0.91

Internal validation, CV, cross-validation; HO, hold-out validation; Cohort, cohort study; HC, healthy controls; PAT, patients with sleep disturbance; OSA, patients with obstructive sleep apnea; MASS, Montreal Archive of Sleep Studies; Sleep-EDF, Sleep-EDF Database Expanded; SHHS, Sleep Heart Health Study; MGH, Massachusetts General Hospital; IS-RC, Research study on sleep disordered breathing in women in midlife, University of Pennsylvania, Philadelphia; DOD-H, Dreem Open Dataset – Healthy Volunteers; DOD-O, Dreem Open Dataset – Obstructive Sleep Apnea Patients; PhysioNet, PhysioNet database resources; ISRUC, ISRUC-SLEEP Dataset.

AI-based autoscoring systems offer valid alternatives to manual expert scoring and that the role of manual adjustment and expert review of automatic scorings might no longer be required.

While the most obvious application of the hypnodensity is the determination of the traditional sleep stages, additional information may be derived from the sleep stage probabilities. Stephansen et al. (2018) extracted features from the hypnodensity in patients with narcolepsy by quantifying sleep stage mixing/dissociation. Examples for these features are the time taken before 5% of the sum of the product between W, N2, and REM, calculated for every epoch, has accumulated, weighted by the total amount of this sum or the time taken before 50% of the wakefulness in a rerecording has accumulated, weighted by the total amount of wakefulness. In addition to these hypnodensity-derived features describing unusual sleep stage overlaps, the authors added features expected to predict narcolepsy based on prior knowledge, such as REM sleep latency and sleep stage sequencing parameters. By means of a Gaussian predictor classifier they achieved a specificity of 96% and a sensitivity of 91% for classifying narcolepsy type-1 as validated in independent datasets. In a more recent study, Cesari et al. (2022) investigated whether biomarkers describing sleep instability and architecture derived from both manual hypnogram and automatic hypnogram and hypnodensity graphs might differentiate between distinct disorders of hypersomnolence, such as narcolepsy type-1, narcolepsy type-2, idiopathic hypersomnia and subjective excessive daytime sleepiness. They extracted features from manual and automatic hypnograms, such as standard features, transition features, bouts features, features describing stability and fragmentation of sleep stages as well as the distribution of sleep stages across the night, and REM sleep-specific features such as the number of nightly sleep onset REM periods. In addition, they extracted features from the hypnodensity, including the features proposed by Stephansen et al. (2018) and features reflecting certainty and amount of sleep stages per epoch and across the night. Their results confirmed narcolepsy type-1 specific sleep structure which made it possible to discriminate narcolepsy type-1 from the other groups with high performance (88% accuracy) and narcolepsy type-2 from idiopathic hypersomnia with moderate performance (65% accuracy). Future studies in larger cohorts are needed to improve the differentiation of disorders of hypersomnolence, but these preliminary findings already highlight the promise of hypnodensity in exploiting sleep stage ambiguity and overlap as clinical hallmarks of certain sleep disorders.

In a recent study using the Somnolyzer algorithm (Anderer et al., 2022a), we compared the standard sleep parameters such as total sleep time (TST), sleep latency (SL), REM latency (REML), sleep efficiency (SEFF), wake after sleep onset (WASO), and the time in N1, N2, N3, and R derived from the autoscored hypnogram, to the standard sleep parameters derived from the autoscored hypnodensity in young (20 – < 40 years), middle-aged (40 – < 60 years) and older (60–95 years) healthy controls from the Siesta database ($n = 195$, 93 males and 102 females aged 20 to 95 years). Overall, the hypnogram-derived and the hypnodensity-derived standard parameters showed very similar age-related changes. However, the age-related changes based on the hypnodensity-derived parameters were consistently slightly higher than the coefficients derived traditionally from the hypnogram.

Moreover, we determined a quantitative measure of sleep stage ambiguity in percent [$100^*(1\text{-}p(i)_{MAX}$) where $p(i)_{MAX}$ is the highest sleep stage probability for epoch i] and a measure of sleep stage continuity in percent [$100^*(1\text{-abs}(p(i)_{MAX} - p(i+1)_{MAX})$] if epochs i and i+1 are from the same class. In the case of no ambiguity, $p(i)_{MAX}$ is 1 and thus the ambiguity for that epoch is 0%. As can be clearly seen in Figures 5, 6 for both manually-determined and Somnolyzer-determined sleep stage probabilities, the vast majority of epochs have a $p(i)_{MAX} < 1.0$, indicating some amount of ambiguity. In the case of only small changes in the hypnodensity between two adjacent epochs the continuity measure is close to 100%. If the change in the hypnodensity between two adjacent epochs increases, the continuity measure will decrease accordingly. Interestingly, sleep stage ambiguity and continuity showed opposite changes with age for epochs scored as sleep as compared to epochs scored as wake: in wake, ambiguity decreases and continuity increases with age, while during sleep, ambiguity

TABLE 4 Overview of sleep staging validation studies with AI-algorithms providing Cohen's kappa based on external validation.

Author, Year *Name*	Training Dataset	Input Signals	Test Dataset	Cohen's κ
Biswal et al. (2018)	PAT: $N = 9{,}000$; MGH	2-6 EEG channels	Cohort: $N = 580$; SHHS	0.73
Patanaik et al. (2018)	HC: $N = 1{,}330$; Duke-NUS	2 EEG and 2 EOG channels	PAT: $N = 210$; SDU PAT(PD): $N = 77$; UCSD	0.74 0.60
Stephansen et al. (2018) *Stanford-STAGES*	Cohort: $N = 2{,}784$; 10 cohorts	EEG, EOG, EMG	Cohort: $N = 70$; IS-RC, 6 scorers	0.75
Anderer et al. (2018) *Somnolyzer*	Cohort: $N = 588$; SIESTA (7 sleep centers) 2–6 scorers	EEG, EOG, EMG	PAT (OSA): $N = 97$; Somnoval, 4 scorers	0.79
Zhang et al. (2019)	Cohort: $N = 5{,}213$; SHHS	EEG, EOG, EMG	Cohort: $N = 461$; SOF Cohort: $N = 2{,}907$; MrOS	0.68 0.70
Abou Jaoude et al. (2020)	PAT: $N = 6{,}341$; MGH	4 EEG channels	PAT: $N = 243$; homePAP PAT: $N = 129$; ABC	0.69 0.66
Alvarez-Estevez and Rijsman (2021)	Cohort: $N = 443$; 6 datasets	EEG, EOG, EMG	Cohort: $N = 20$-154; inter-cohort performance	0.63
Cesari et al. (2021) *Stanford-STAGES*	Cohort: $N = 2784$; 10 cohorts	EEG, EOG, EMG	Cohort: $N = 1{,}066$; SHIP, 2 scorers	0.68
Vallat and Walker (2021) *YASA*	Cohort: $N = 3{,}163$; 7 cohorts	EEG, EOG, EMG	HC: $N = 25$; DOD-H, 5 scorers	0.80 0.77
Anderer et al. (2022b) *Somnolyzer*	Cohort: $N = 588$; SIESTA (7 sleep centers) 2–6 scorers	EEG, EOG, EMG	Cohort: $N = 426$; ABC, homePAP, MESA	0.74
Bakker et al. (2023) *Somnolyzer*	Cohort: $N = 588$; SIESTA (7 sleep centers); 2–6 scorers	EEG, EOG, EMG	Cohort: $N = 70$; IS-RC, 6 scorers PAT: $N = 15$; SAGIC, 9 scorers PAT: $N = 10$; Somnoval, 12 scorers	0.78 0.75 0.76
Cesari et al. (2022) *Stanford-STAGES*	Cohort: $N = 2{,}784$; 10 cohorts	EEG, EOG, EMG	PAT (hypersomnia): $N = 143$	0.75
Cesari et al. (2022) *YASA*	Cohort: $N = 3{,}163$; 7 cohorts	EEG, EOG, EMG	PAT (hypersomnia): $N = 143$	0.76
			N-studies	**19**
			Cohen's κ Mean ± SD	**0.72 ± 0.06**
			Min	**0.60**
			Max	**0.80**

External validation, performance in datasets completely unseen by the model; Cohort, cohort study; HC, healthy controls; PAT, patients with sleep disturbance; OSA, patients with obstructive sleep apnea; PD, Parkinson's Disease; SHHS, Sleep Heart Health Study; MGH, Massachusetts General Hospital; Duke-NUS, Medical School, Singapore; SDU, Sleep Disorders Unit, Singapore General Hospital; UCSD, University of California, San Diego School of Medicine; IS-RC, Research study on sleep disordered breathing in women in midlife, University of Pennsylvania, Philadelphia; SIESTA, SIESTA sleep database; Somnoval, Somnolyzer validation study dataset; SOF, Study of Osteoporotic Fractures; MrOS, Osteoporotic Fractures in Men study; DOD-H, Dreem Open Dataset – Healthy Volunteers; DOD-O, Dreem Open Dataset – Obstructive Sleep Apnea Patients; homePAP, Home Positive Airway Pressure study; ABC, Apnea, Bariatric surgery, and CPAP study; SHIP, Study of Health in Pomerania; MESA, Multi-Ethnic Study of Atherosclerosis; SAGIC, Sleep Apnea Genetics International Consortium, The Ohio State University Medical Center, Columbus.

increases, and continuity decreases with age. Together with the significant increase in WASO with age, this means that with increasing age subjects are awake longer, and these wake periods are more definite and stable. On the other hand, during sleep, ambiguity increased, and continuity decreased over age, indicating more uncertainty and less sleep stability with increasing age. The highest correlation with age was the increase in ambiguity of epochs scored as sleep (with a Pearson correlation coefficient of $r = 0.62$; $p < 0.01$) and the highest partial correlation with the arousal index (controlling for the effect of age) was the decrease in sleep continuity with increasing arousal index ($r = -0.79$; $p < 0.01$) (Anderer et al., 2022a).

Besides sleep duration, depth, and continuity, sleep restorative properties depend on the capacity of the brain to create periods of sustained stable sleep (Parrino et al., 2012). As discussed by Parrino et al. (2022), NREM sleep is bimodal with stable and instable periods, or alternatively conceptualized by the authors as effective and ineffective. Thus, the stability domain has only 2 forms of NREM sleep—stable and unstable where N3 is usually stable, N1 is always unstable, but N2 may be stable or unstable. To characterize

the differences between apnea patients and healthy controls, we derived further features from the hypnodensity graph to cover these aspects of sleep physiology: the percentage of ambiguous NREM and REM epochs, where an epoch is defined as ambiguous if $p(i)_{MAX}$ is ≤ 0.95; the percentage of stable NREM epochs, where two adjacent NREM epochs are considered as stable if $(p(i)_{N2} + p(i)_{N3}) > 0.95$ and $(p(i+1)_{N2} + p(i+1)_{N3}) > 0.95$; the percentage of stable REM epochs, where two adjacent REM epochs are considered as stable if $p(i)_R > 0.95$ and $p(i+1)_R > 0.95$; the percentage of NREM sleep depth defined as a weighted average of NREM probabilities: $100^*((p(i)_{N1} + 2^*p(i)_{N2} + 4^*p(i)_{N3}))/4)$. Table 5 provides the demographic data and the standard sleep parameters derived from the hypnogram for the controls and the apnea patients, as well as for the subgroup of mild to moderate apnea patients (apnea-hypopnea index, AHI < 30) and severe apnea patients (AHI ≥ 30). The four groups did not differ in age and sex distribution. When compared to healthy controls the apnea patients did not differ in total sleep time, sleep efficiency, wake after sleep onset, sleep latency, REM latency and time in stage R, but showed increased time in N1 and decreased time in N2 sleep, while the time in N3 sleep was reduced only in patients with severe apnea.

Figure 7 summarizes the differences in the additional features between the 3 groups of apnea patients and age- and sex-matched healthy controls for the 5 NREM-features and the 4 REM-features derived from the hypnodensity graph. Concerning the differences between mild-to-moderate apnea and controls, we observed significant increases in the percentage of ambiguous NREM epochs (67 vs. 53%) and in the amount of the mean ambiguity (19 vs. 15%) as well as significant decreases in the percentage of stable NREM epochs (58 vs. 68%). These findings reflect the reduction of stable NREM sleep in patients with mild-to-moderate apnea (see also the significant shift from N2 to N1 sleep in Table 4). In contrast, REM sleep features are not significantly different between mild-to-moderate apnea and controls. While standard REM parameters such as REM latency and time and percentage in stage R are, even in patients with severe apnea, not significantly different to controls (Table 4), the hypnodensity-derived REM sleep features show significant increases in ambiguity and decreases in REM sleep stability in severe apnea (Figure 7). Parameters not determinable from the classical hypnogram, such as sleep stage ambiguity, reflecting the uncertainty of manual expert scorers, as well as sleep stage continuity, reflecting epoch-to-epoch changes of these uncertainties, may give valuable additional insights in the effects of different disorders in sleep architecture. A possible source of this ambiguity captured by the hypnodensity may be sleep stage shifts occurring within one 30-s epoch. Korkalainen et al. (2021a) used a deep learning approach based on the traditional 30-s epoch duration as well as based on shorter epoch durations (15-, 5-, 1-, and 0.5-s) to evaluate differences in sleep architecture between obstructive sleep apnea (OSA) severity groups. The authors reported decreases in sleep continuity with increases in OSA severity using Cox proportional hazards ratio or Kaplan–Meier survival curves, and these group differences became larger

TABLE 5 Demographic and standard sleep parameters for apnea patients and controls.

	Controls	Apnea-All	Apnea-AHI < 30	Apnea-AHI ≥ 30
N	49	49	18	31
Age (years)	47.4 ± 15.4	50.8 ± 9.6	52.6 ± 8.4	49.8 ± 10.1
Sex (f/m)	7/42	7/42	4/14	3/28
AHI (#/hr TST)	1.4 ± 1.3	46.9 ± 28.7*	18.5 ± 7.4*	63.4 ± 22.8*
HB (%min/hr TST)	2.4 ± 3.9	187.6 ± 196.5*	49.4 ± 32.7*	267.9 ± 207.5*
ArI (#/hr TST)	15.1 ± 5.8	39.4 ± 23.1*	21.3 ± 9.1*	50.0 ± 22.2*
TST (min)	367.7 ± 54.9	382.0 ± 65.7	359.8 ± 84.3	394.8 ± 49.1
Sleep latency (min)	27.7 ± 23.5	25.6 ± 29.7	34.3 ± 44.5	20.5 ± 14.6
REM latency (min)	103.4 ± 44.2	199.9 ± 70.9	104.1 ± 47.3	127.2 ± 80.6
WASO (min)	80.8 ± 55.6	86.2 ± 55.4	102.4 ± 69.3	76.7 ± 44.0
Sleep efficiency (%)	77.4 ± 11.3	77.3 ± 12.8	72.2 ± 15.7	80.3 ± 10.0
N1 (min)	44.8 ± 22.3	121.7 ± 71.8*	70.6 ± 30.8*	151.3 ± 72.4*
N2 (min)	205.4 ± 42.7	158.8 ± 63.3*	169.4 ± 62.4*	152.7 ± 65.5*
N3 (min)	43.2 ± 30.4	29.4 ± 24.9	44.3 ± 22.5	20.7 ± 22.3*
R (min)	74.3 ± 24.6	72.1 ± 26.7	75.4 ± 29.5	70.1 ± 25.2
N1 (% TST)	12.5 ± 6.5	32.1 ± 18.0*	20.3 ± 9.3*	38.9 ± 18.4*
N2 (% TST)	55.8 ± 8.0	41.1 ± 13.5*	46.0 ± 9.7*	38.2 ± 14.7*
N3 (% TST)	11.7 ± 8.3	8.3 ± 7.5	13.4 ± 7.9	5.3 ± 5.6*
R (% TST)	20.0 ± 5.5	18.6 ± 6.4	20.3 ± 7.6	17.5 ± 5.4

*$p < 0.01$ as compared to controls. AHI, apnea-hypopnea index; HB, hypoxic burden; ArI, arousal index; TST, total sleep time; WASO, wake after sleep onset.

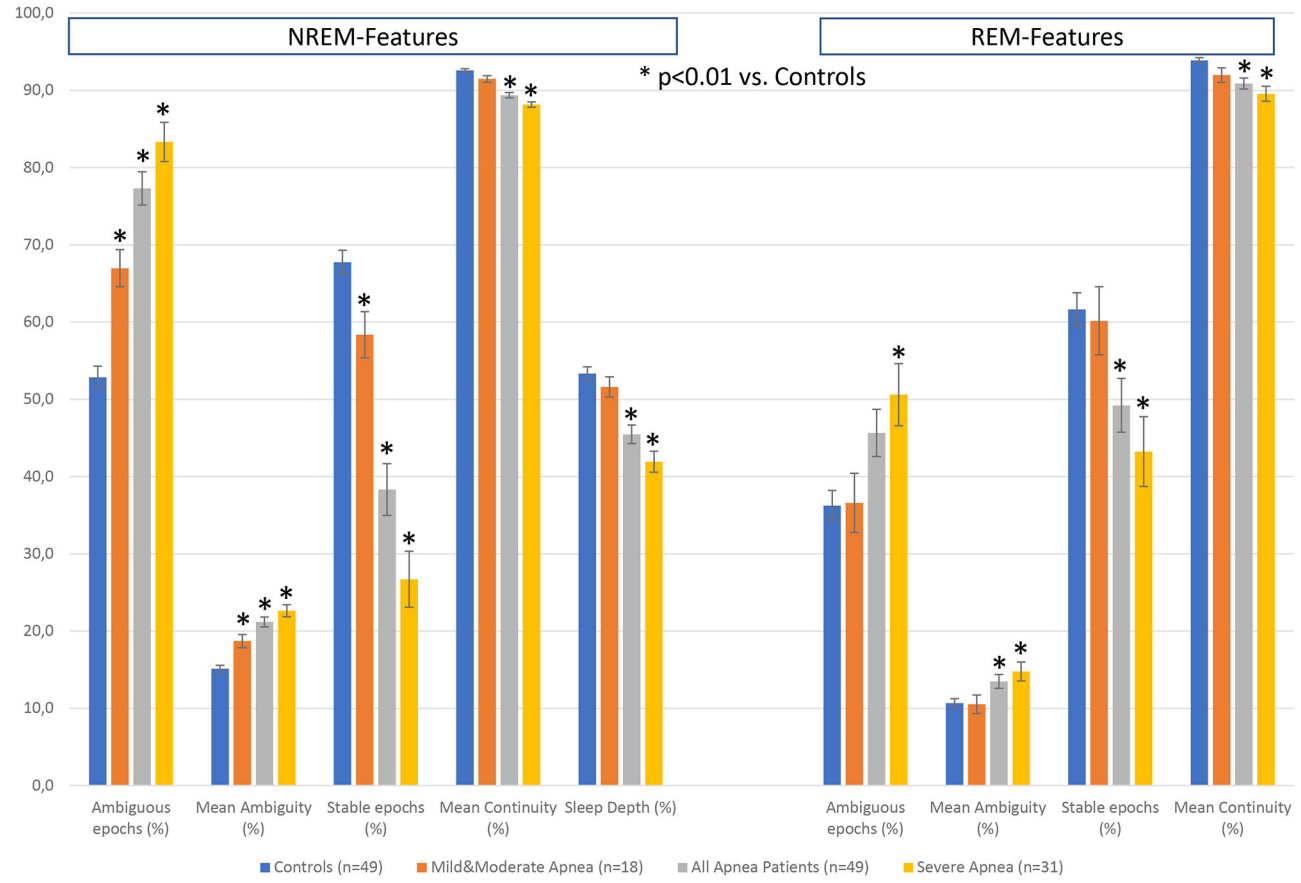

FIGURE 7
Differences in hypnodensity-derived features between patients with sleep apnea and age- and sex-matched healthy controls ($n = 2 \times 49$). The left part depicts hypnodensity-derived NREM-features and the right part REM-features for the controls and the three patient groups mild & moderate apnea with AHI<30 ($n = 18$), all 49 apnea patients, and severe apnea with AHI≥30 ($n = 31$). *Indicates significant differences based on independent samples t-tests between patients and controls at $p < 0.01$.

the shorter the epoch duration used was. The U-sleep model as presented by Perslev et al. (2021) can evaluate sleep architecture with even higher temporal resolution of up to 128 Hz which could provide additional diagnostic information and possible new ways of analyzing sleep. Interestingly, as shown recently by Fiorillo et al. (2023a) the U-sleep architecture successfully encoded sleep patterns even from non-recommended electrode derivations based on a large and heterogeneous dataset of 28,528 PSG recordings from various sleep centers (Fiorillo et al., 2023a). The authors wonder, given the criticisms of the AASM rules, the limited interrater reliability of manual scoring according to these rules, and the complexity of sleep, whether an unsupervised deep learning sleep scoring algorithm (i.e., without using manual sleep scorings as training targets) might be a better approach to describing human sleep.

Future studies in larger samples of patients with sleep related respiratory disturbance including measures of clinical outcome will be necessary to assess the relevance of hypnodensity-derived features for the development of physiological biomarkers. Of course, such endeavor should not be limited to apnea patients. Penzel et al. (2017) suggested that physiological biomarkers might be appropriate to characterize functional characteristics, as seen in the variety of sleep disorders. As stated above, the first promising examples for the construction of narcolepsy biomarkers including variables derived from hypnodensity have been already published (Stephansen et al., 2018; Cesari et al., 2022).

Hypnodensity based on autoscoring using cardiorespiratory signals

HSAT studies are increasingly used as an alternative to PSG studies to diagnose SDB (Rosen et al., 2018). While less rich than the traditional PSG, HSATs are considerably less expensive due to a reduced cost of equipment and lower setup effort, enable increased access in remote or underserved areas, higher patient turnover, are much more comfortable and thus, less disruptive of sleep, and importantly, enable the opportunity to monitor patients in conditions that are more representative of their habitual sleep (Kim et al., 2015; Kundel and Shah, 2017; Rosen et al., 2018). HSAT studies record as a minimum set of signals, airflow, pulse oximetry, and respiratory effort for identification and classification of apneas and hypopneas. Relying on this reduced

signal montage has obvious drawbacks compared to PSG studies. The absence of neurological signals required for manual sleep staging means that the AHI cannot be determined based on manual scoring. Instead, total sleep time is substituted by either monitoring time or recording time for calculation of the respiratory event index (REI) (Zhao et al., 2017). Reliance on the REI in place of the AHI results in reduced SDB diagnostic sensitivity that is not easily quantifiable, without knowing the amount of wakefulness in the individual recording (Bianchi and Goparaju, 2017). Further, there is no ability to screen for REM-related OSA or identify abnormalities in sleep architecture which may impact the subsequent treatment plan or signify the need for further testing (Kapur et al., 2017).

This limitation of HSATs motivated attempts to leverage the known expression of autonomic nervous system activity in sleep by analyzing cardiorespiratory signals, which are in fact routinely recorded with these polygraphic systems: the non-REM progression from N1 to N3 is typically accompanied by an increase in cardiovagal drive and parasympathetic activity, which translates to a lower heart rate, more regular breathing, and an increased respiratory mediation of heart rate variability (Eckert and Butler, 2016; Lanfranchi et al., 2016). REM sleep is characterized by a state of autonomic instability where sympathetic and parasympathetic nervous system activity fluctuate, producing abrupt changes in heart rate, and irregular breathing. In the absence of neurological signals, these algorithms are typically limited to the estimation of the stages wake, light sleep (LS; comprising the combination of N1 and N2), deep sleep (DS; corresponding to N3), and REM sleep. The differentiation between N1 and N2 based on neurological signals requires not only the timing of arousals but also sleep spindles and k-complexes, neither of which are available with cardiorespiratory inputs. These algorithms, of course, cannot mimic human scoring, since there are no rules, nor is it feasible, to visually relate changes in heart rate and respiration to sleep stages. However, advanced AI methods can often leverage, and go beyond what humans can possibly encode, to find relations in the data based on patterns that span entire recordings, while simultaneously analyzing numerous characteristics of the various signals.

The AI-based Somnolyzer-CReSS algorithm uses as input cardiorespiratory signals, and outputs sleep stage probabilities per 30-s epoch for stages Wake, LS, DS and REM sleep (Bakker et al., 2021). The CReSS-derived probability curves can be directly compared to the probabilities derived from multiple manual scorings using neurological signals as input. Figures 8, 9 compare the manually-derived sleep stage probabilities to the sleep stage probability of the CReSS autoscoring for the two studies shown in Figures 5, 6. Note that the probabilities for N1 and N2 are summed up to a single LS probability. The ICCs for absolute agreement between the two probability curves are 0.91 for PSG 1 (Figure 8) and 0.84 for PSG 5 (Figure 9). While these correlation coefficients are slightly lower than the coefficients between autoscoring based on neurological signals and multiple manual scorings (0.97 for PSG1 and 0.89 for PSG 5), they still indicate good agreement between cardiorespiratory- and manually- determined sleep stage probabilities. In Figure 8, we highlighted the same 6 periods as in Figure 5. Box 1 comprises again sleep onset with increasing LS probability via sleep onset, which is the first epoch with sleep probability higher than wake probability (solid line), to definite sleep with LS probability $>$ 0.95 at the end of the box 1. Boxes 2, 3, 4, and 6 indicate periods were at least two experts scored N3. Note that the DS probabilities derived from CReSS autoscoring closely resemble the N3 probabilities derived from the 12 manual scorings. Finally, also for the R probabilities (box 5) the manually- and autoscoring-based curves match in terms of timing and magnitude. Interestingly, even for the study with the worst agreement between scorers, the manually- and autoscoring-based probability curves match closely (Figure 9). The ICCs between manually-derived probabilities and CReSS-derived probabilities range from 0.81 to 0.95 (mean: 0.88 $\pm$ 0.05) for the 10 studies, indicating good agreement between the probability curves.

Consequently, the CReSS-derived hypnodensity also reflects a good estimate of the epoch-by-epoch ambiguity of manual scorings. The fact that very similar probabilities are derived from cardio-respiratory signals and neurological signals suggests that many of these uncertainties between sleep stages manifest in both, the central and the autonomic nervous system activity. This supports the view that states in-between two sleep stages are normal physiological states and that much of the uncertainty observed in sleep scorings is of an aleatoric nature, limiting the potential for further increases in inter-scorer agreement by efforts in improving scoring rules, training, or models. In a recently introduced framework to analyze uncertainty in sleep staging, van Gorp et al. (2022) differentiate aleatoric uncertainty, that arises from biological factors (such as age, drugs, pathologies, or local sleep) or measurement factors (such as placing of electrodes or interferences and artifacts), from epistemic uncertainty that arises from a lack of knowledge about the data or the optimal model.

Agreement between sleep parameters derived from cardiorespiratory signals with sleep parameters derived from full PSG signals

Most of the early algorithms for cardiorespiratory sleep staging relied on manually engineered features carefully crafted to capture changes in autonomic nervous system activity during sleep, leveraging domain knowledge of sleep and cardiorespiratory physiology. In 2015, Fonseca et al. (2015) presented an algorithm to estimate sleep based on cardiorespiratory signals using manually-engineered features and a linear discriminant classifier, and reported a Cohen's kappa of 0.49 for the 4-stage comparison validated in 48 healthy subjects. By incorporating time information and replacing the classifier by conditional random fields, Cohen's kappa increased to 0.53 in 100 healthy subjects (Fonseca et al., 2018). In 2017, Tataraidze et al. (2017) reported a kappa of 0.56 based on respiratory inductance plethysmography (RIP) signals using an extreme gradient boosting classifier in 658 healthy subjects and Beattie et al. (2017) reported a kappa of 0.52 based on photoplethysmography (PPG) and actigraphy signals using a linear

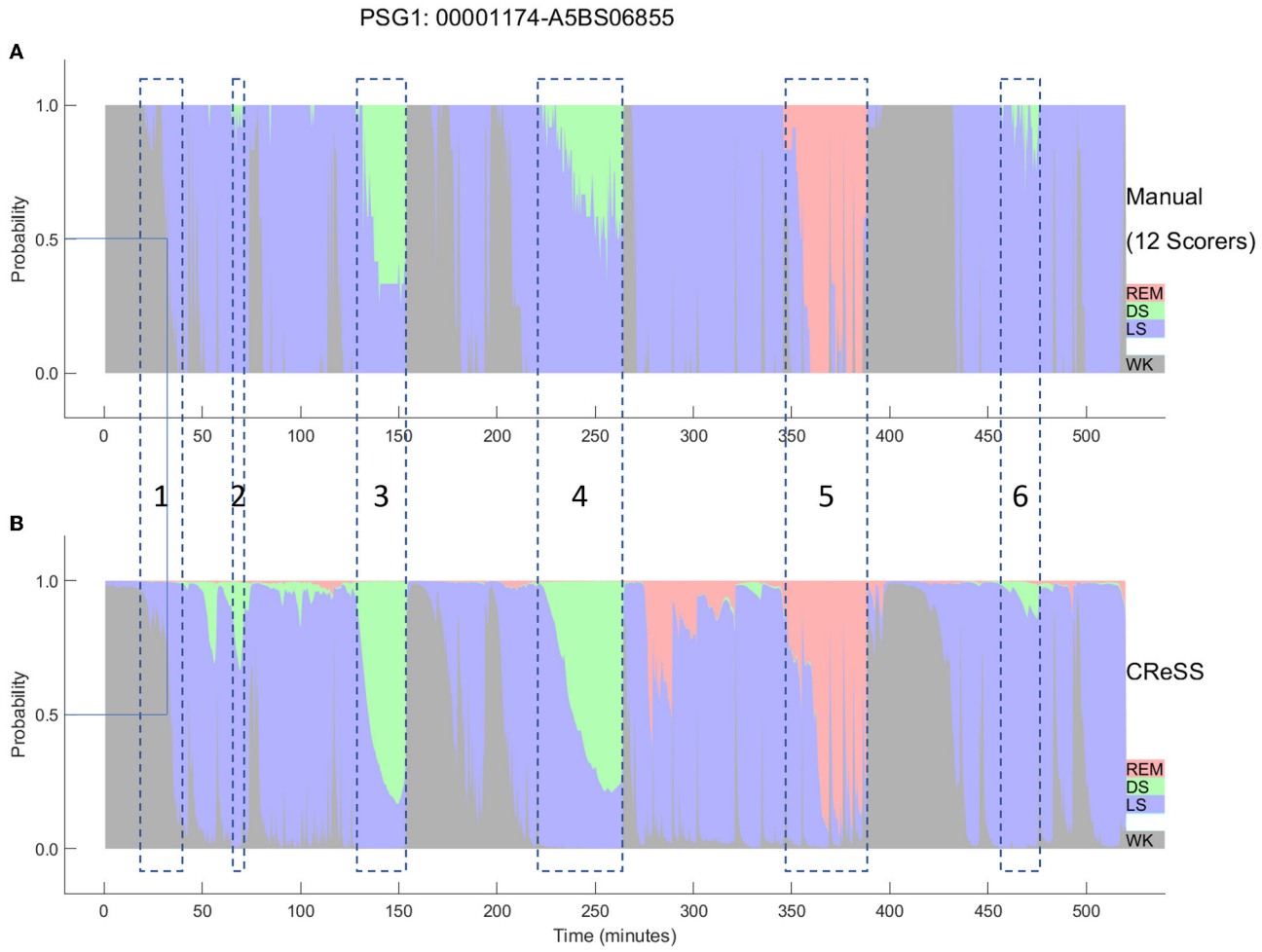

FIGURE 8
A representative example comparing the hypnodensities derived from 12 manual scorings **(A)** and from cardiorespiratory autoscoring **(B)** for the same study shown in Figure 2 (PSG1: OSAS patient, male, 76 years). The color codes are WK, gray; REM, red; LS, blue; DS, green. The time period depicted in box 1 highlights the sleep onset period with the actual sleep onset at W_{prob} <0.5 indicated as solid line; Boxes 2, 3, 4, and 6 indicate time periods where at least 2 scorers have scored N3; Box 5 indicate the time period where at least one scorer has scored R. Note the similarity of the manually-derived and the cardiorespiratory autoscoring-derived sleep stage probabilities.

discriminant classifier in 60 healthy controls. In recent years, various machine learning approaches for scoring sleep based on cardiorespiratory signals have been developed and validated in internal and external datasets. Cohen's kappa for the 4-stage comparison (wake, light sleep, deep sleep, REM) were in the average 0.56 ± 0.12 for 11 datasets with internal testing (cross-validation or hold-out validation) (Li et al., 2018; Radha et al., 2019; Wei et al., 2019; Sridhar et al., 2020; Huttunen et al., 2021; Zhao and Sun, 2021; Garcia-Molina and Jiang, 2022) and 0.47 ± 0.15 for 10 datasets with external testing (Fonseca et al., 2020; Sridhar et al., 2020; Sun et al., 2020b; Bakker et al., 2021; Garcia-Molina and Jiang, 2022).

The Somnolyzer-CReSS algorithm was validated in a test set of 296 PSGs from the Multi-Ethnic Study of Atherosclerosis [MESA (Chen et al., 2015)] and achieved a kappa value of 0.68 and in a second test set of 296 PSGs from the Sleep Heart Health Study [SHHS (Quan et al., 1997; Redline et al., 1998)], a kappa value of 0.64, which are the two highest kappa values for external testing of cardiorespiratory sleep staging algorithms reported to date (Bakker et al., 2021). Sensitivity and precision for detecting wakefulness based on cardiorespiratory signals was 76.0 and 88.1%, respectively. This indicates good performance of the cardiorespiratory sleep staging for discriminating wake and sleep, which is important for determining total sleep time, and consequently, indices relating the number of respiratory events or the hypoxic burden (HB) to the hours of sleep. When compared to indices computed based on the duration of recording or monitoring time, the indices related to CReSS-determined total sleep time show a higher sensitivity, specifically in recordings with a significant amount of wake periods. To demonstrate the clinical relevance of CReSS, we determined the number of correctly diagnosed patients by HSAT as compared to the gold standard AHI in the 296 studies from the MESA dataset for a threshold of 15 events per hour. Using the CReSS-derived TST instead of the recording time as denominator for the calculation of the indices reduced the false negative diagnosis from 33 patients (11.1%) to only 5 patients (1.7%). Moreover, sensitivity and precision for

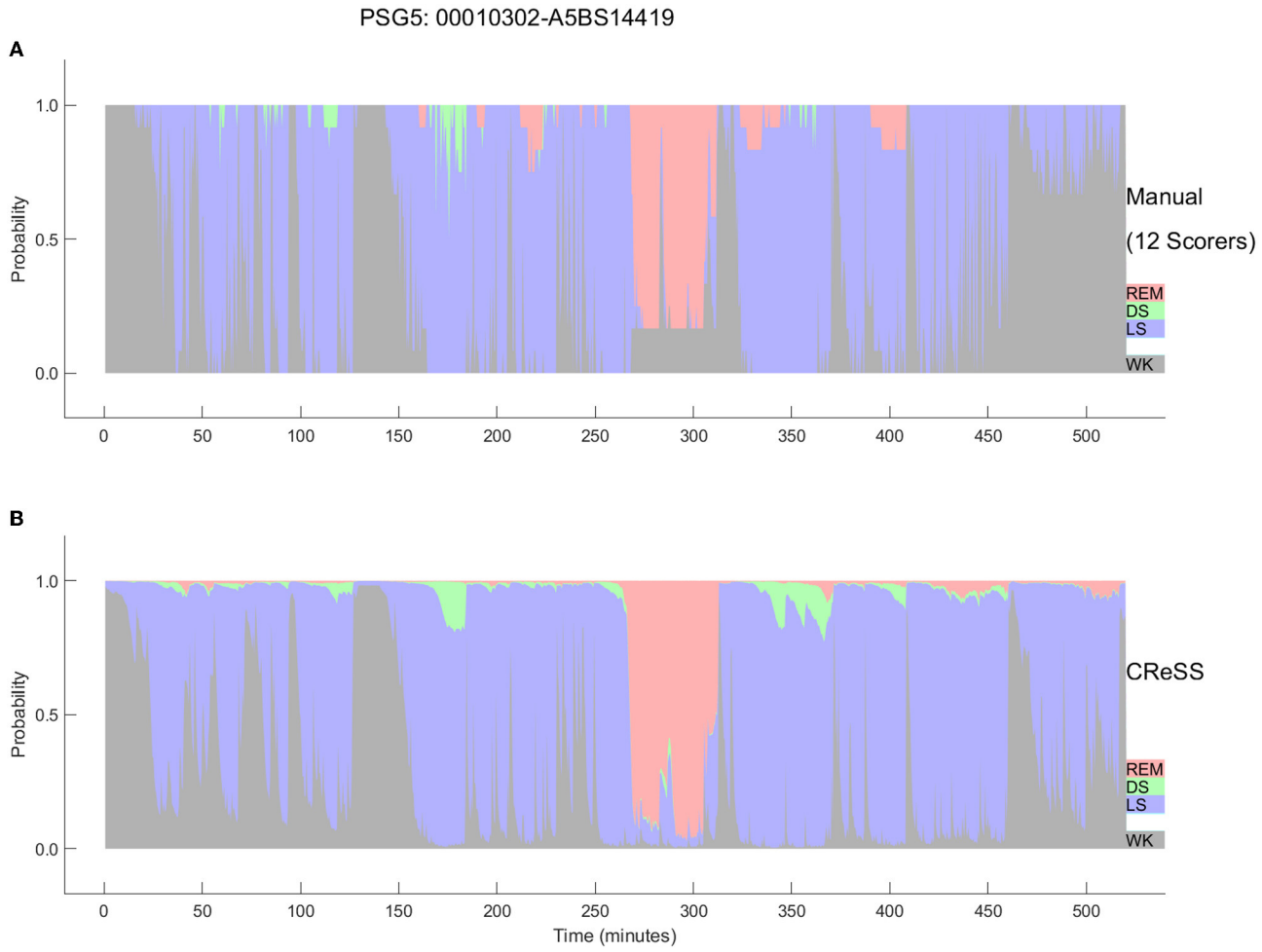

FIGURE 9
Comparison between the hypnodensities derived from 12 manual scorings **(A)** and from cardiorespiratory autoscoring **(B)** for the study with the worst agreement between manual scorers (i.e., the same study as in Figure 4, PSG5: Hypersomnia with sleep apnea, male, 78 years). The color codes are WK, gray; REM, red; LS, blue; N3, green. Note the similarity of the manually-derived and the cardiorespiratory autoscoring-derived sleep stage probabilities.

detecting REM sleep based on cardiorespiratory signals was 85.3 and 79.6%, respectively (Anderer et al., 2022b). This indicates the good performance of CReSS for discriminating REM sleep from Wake and NREM sleep. Using the definition for REM-related OSA by Mokhlesi and Punjabi (2012) (i.e., an AHI_{NREM} of fewer than 5 events/h and an AHI_{REM} of at least 5 events/h with at least 30 min of REM sleep), we achieved a sensitivity of 91% and a specificity of 98% for detecting REM-related OSA by means of CReSS as compared to gold standard PSG scoring. This suggests that REM-related OSA can be detected based on CReSS-determined REM sleep with a clinically acceptable accuracy (Anderer et al., 2022b).

In addition to the AHI, which indicates the number of respiratory events per hour of sleep, we determined the hypoxic burden as proposed by Azarbarzin et al. (2019). The hypoxic burden is determined by measuring the respiratory event-associated area under the desaturation curve from pre-event baseline. The authors showed, in a large sample from the Sleep Disorder in Older Men study [MrOS (Orwoll et al., 2005)] and the SHHS (Quan et al., 1997; Redline et al., 1998), that the hypoxic burden strongly predicted cardiovascular disease-related mortality, indicating that not only the frequency (as measured by the AHI), but the depth and duration of the desaturations caused by sleep-related upper airway obstructions (as measured by the hypoxic burden), are important disease-characterizing features. Figure 10 shows based on Somnolyzer autoscoring, in the upper part, scatter plots relating the AHI to the HB for TST as well as for NREM and REM sleep. As can be seen, the HB for events occurring during REM sleep is, in our dataset, ~50% larger than for events in NREM sleep. Note that patients with a relatively low overall AHI may be experiencing severe OSA during REM, which is particularly important given that events taking place during REM are longer, and are associated with more pronounced hypoxemia, higher sympathetic activation, and greater surges in blood pressure and heart rate (Findley et al., 1985; Peppard et al., 2009; Lechat et al., 2022a,b). This characteristic of the disease may very well help

explain the link between REM-related OSA and its association with adverse cardiovascular, metabolic, and neurocognitive outcomes (Varga and Mokhlesi, 2019).

In their comprehensive review on the hypoxic burden in obstructive sleep apnea , Martinez-Garcia et al. (2023) suggested a threshold HB > 60% min/h (i.e., 15 min of 4% desaturation every hour) to identify patients who are at increased risk of cardiovascular morbidity and mortality. In the lower part of Figure 10, we enlarged a portion of the scatterplot of AHI vs. HB and marked the values for two studies with approximately the same AHI close to 15, but with very different HB values (20.4% min/h and 78.2% min/h). In addition, we show for both studies the averaged oxygen saturation curves, time-aligned by the termination of the respiratory events, which are used to determine the subject-specific search window. While the number of respiratory events (100 and 106) and the duration of the search window (54s and 55s) are almost identical, the averaged desaturation is much deeper in subject M0037, reflecting the large difference between the two studies.

Figure 11 compares standard sleep parameters based on Somnolyzer autoscoring derived from full PSG signals vs. the same parameters derived from HSAT signals in patients with sleep disturbance from the SIESTA database. Hypopneas were scored in the PSG studies using the 3% oxygen desaturation and/or arousal rule, and in the HSAT studies using 3% desaturation and/or autonomic response (heart rate increase ≥ 5bpm) to enable a direct comparison between the PSG- and the HSAT-derived indices. In addition to the 49 apnea patients, we also included the 26 patients with insomnia related to generalized anxiety disorder or depression, and the 5 patients with periodic limb movement disorder in the analysis to cover the full spectrum from no to severe SDB. In addition to the scatter plots for TST, AHI and HB per hour total sleep time, the scatter plots for NREM and REM are shown. The CReSS algorithm estimated TST as well as time in NREM and REM sleep with high accuracy. The ICC for absolute agreement are for TST 0.92 (95%–CI 0.83 to 0.95) for time in NREM 0.88 (95%–CI 0.75 to 0.93), and for time in REM 0.88 (95%–CI 0.82 to 0.92). Consequently, the indices per hour sleep also show almost perfect agreement between the analysis based on PSG signals and the analysis based on the reduced HSAT montage (all ICCs ≥ 0.98 with a 95%–CI from 0.97 to 0.99). Thus, analyses based on signals recorded typically in HSAT by means of CReSS are a valid alternative to full PSG studies in patients with suspected OSA for determining the severity based on the AHI and HB per hour sleep and for diagnosing REM-related OSA.

Conclusions and future directions

There is convincing evidence that manual sleep staging, even when performed by experienced, well trained, and motivated scorers without the usual time constraints of clinical routine, results in significant interrater differences. We have shown in three independent datasets scored by six to twelve experienced scorers that sleep stage ambiguity is the rule rather than the exception (Bakker et al., 2023). Recent papers investigating reasons for this ambiguity discuss scorers' uncertainty in applying the rules as well as contradictory patterns within one epoch as possible explanations (van Gorp et al., 2022; Huijben et al., 2023). van Gorp et al. (2022) introduced a theoretical framework to analyze uncertainty in sleep staging, differentiating aleatoric uncertainty that arises from biological factors (such as age, drugs, pathologies, or local sleep) or measurement factors (such as placing of electrodes or interferences and artifacts) and epistemic uncertainty that arises from a lack of knowledge about the data or the optimal model. In standard sleep staging, scorers are forced to decide based on the information obtained in the EEG, EOG, and chin EMG signals. This process involves matching the pattern observed in an epoch with a template or prototype and putting them into the context with patterns from previous epochs. Depending on the scorers' personal template, this may result in significantly different sleep parameters derived from the manually-scored hypnogram as shown in Table 1 for one PSG. In autoscoring systems these different interpretations can be modeled by varying the sensitivity settings for the detection of sleep/wake related features such as sleep spindles, k-complexes, slow waves or arousals without changing the scoring rules. This provides evidence that large parts of the inter-scorer differences in the derived sleep parameters are not due to violations of the scoring rules by one or the other scorer, but rather due to the room for interpretation left open by the visual identification of these sleep/wake related patterns. These interpretations range from high sensitivity to high precision sometimes resulting in extreme differences where one expert scores 67 min of N3 (high sensitivity for slow wave detection) while another expert scores no N3 sleep at all (high precision in slow wave detection) in the same study, despite following the same rule (≥20% of the epoch consisting of slow wave activity). This means that a decision for an epoch does not only affect this one epoch but can have consequences for a whole series of subsequent epochs resulting in the observed large differences in sleep parameters.

When we compared sleep parameters averaged over 10 PSGs between all 66 possible pairs of 12 scorers, we found in 61 of these pairs a significant t-value at $p < 0.01$ in at least one of 5 tested parameters (TST, time in N1, N2, N3, and R), most frequently in the time spent in N3 sleep. This implies that when comparing two conditions (patients vs. controls, baseline vs. therapy, etc.) that were scored by different (groups of) scorers, it cannot be distinguished whether significant results describe a difference between the conditions or a bias of the scorers. Possible solutions to this problem include having all PSGs from a study (at least all PSGs from one subject, in case of repeated measurements) scored by the same expert, having all PSGs scored by multiple manual scorers, or by using a clinically validated autoscoring algorithm.

In future research, it is therefore strongly recommended that the performance of sleep scoring algorithms should be independently validated in datasets which were completely unseen by the models both during training and internal validation, that are representative of the population to be tested, and ideally, that are collected in different centers and scored by different (pools of) human experts. In fact, the AASM has announced such an AI/Autoscoring Pilot Certification program at their website. The program intends to test the various scoring solutions to one and the same external dataset with representative recordings vs. multiple manual expert scorers. This will allow a direct

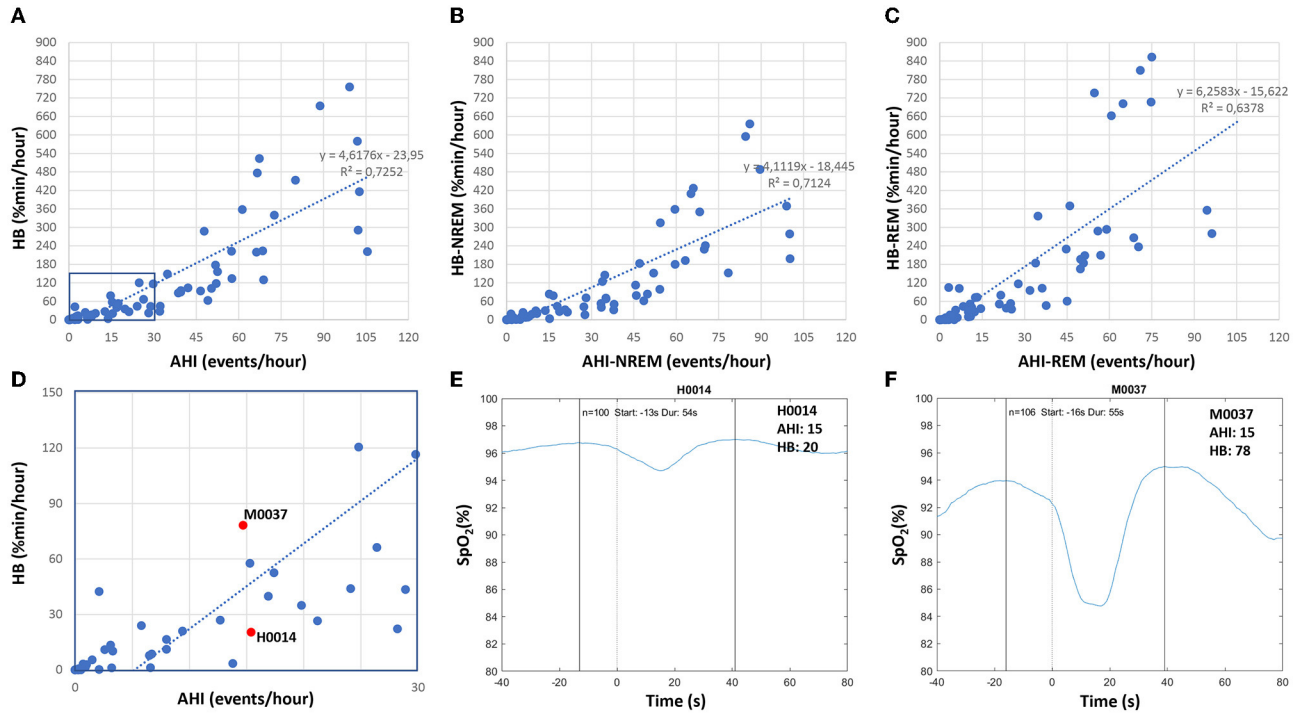

FIGURE 10
Correlation between apnea-hypopnea index (AHI) and hypoxic burden (HB) in patients with sleep disturbance ($n = 80$; 49 apnea patients, 26 insomnia patients, 5 PLMD patients). Upper part: scatter plots relating the AHI to the HB for TST **(A)** as well as for NREM sleep **(B)** and REM sleep **(C)**. Lower part: enlarged scatterplot of AHI vs. HB with red marks for two studies with approximately the same AHI of 15, but with significantly different HB values **(D–F)** show the averaged oxygen saturation curves, time-aligned by the termination of the respiratory events (time = 0), which are used to determine the subject-specific search window for the two studies marked in red in **(D)**.

comparison of the performance of the published algorithms and will give the sleep centers an objective measure for deciding which algorithm to use. Since multiple human expert scorings will be available in this project, the hypnodensity graphs provided by the different algorithms could be compared to the hypnodensity graph based on human scorings so that the hypnodensity from certified algorithms may be established as standard representation of sleep into the clinic. In this context, it will be an interesting topic of future research to determine and establish well-accepted metrics for assessing the quality of hypnodensity graphs. While the overall agreement on the traditional five-stage hypnogram is often measured using the Cohen's kappa coefficient, the F1 score or class-wise metrics like the Mathews correlation coefficient, no metric for comparing sleep stage probabilities has been widely adopted by the field of sleep medicine, yet. Possible metrics include the ICC to compare probabilities for individual stages, their average (macro average), their average weighted by the sum of the probabilities per stage (weighted macro average) or the ICC based on the concatenated probability curves over all five stages (micro average), as well as the ACS to compare sleep stage probability distributions (Bakker et al., 2023; Fiorillo et al., 2023b). In fact, both metrics yield very similar results and others such as cross-entropy or Kullback–Leibler divergence might become relevant for measuring the difference between the sleep stage probability distributions based on multiple manual scorings and autoscoring.

We presented examples of potential valuable hypnodensity-derived features such as sleep stage ambiguity, continuity, depth, and stability for describing differences between patients with sleep apnea and healthy controls. Stephansen et al. (2018) and Cesari et al. (2022) derived up to 1000 features of sleep structure, transitions, and instability from the hypnodensity to train a classifier for diagnosing narcoleptic patients. Further examples for hypnodensity-derived features including pre-softmax features as well as features obtained from unsupervised learning are also being researched (Huijben et al., 2023). Future research should evaluate and test these features for their usefulness in biomarker research.

Concerning HSATs, AI-based cardiorespiratory sleep staging offers reliable estimates of total sleep time, as well as time spent in light, deep, and REM sleep (Li et al., 2018; Radha et al., 2019; Wei et al., 2019; Sridhar et al., 2020; Sun et al., 2020b; Bakker et al., 2021; Huttunen et al., 2021; Zhao and Sun, 2021; Garcia-Molina and Jiang, 2022; Pini et al., 2022). This allows for determining indices of SDB severity per hour of sleep as well as per hour of NREM and REM. In contrast with the classical recommendations for HSATs which do not measure sleep but instead rely on the total monitoring/recording time, the accurate estimates of sleep time can be used to increase the sensitivity of these tests, making the indices immune to the duration of wakefulness in these unsupervised studies. In addition, they allow the identification of patients with REM-related obstructive sleep apnea, the computation of hypoxic burden as a function of the total sleep time as well as the times in NREM and REM.

With the recent advances in autoscoring in general, and the development of hypnodensity in particular, it is increasingly clear

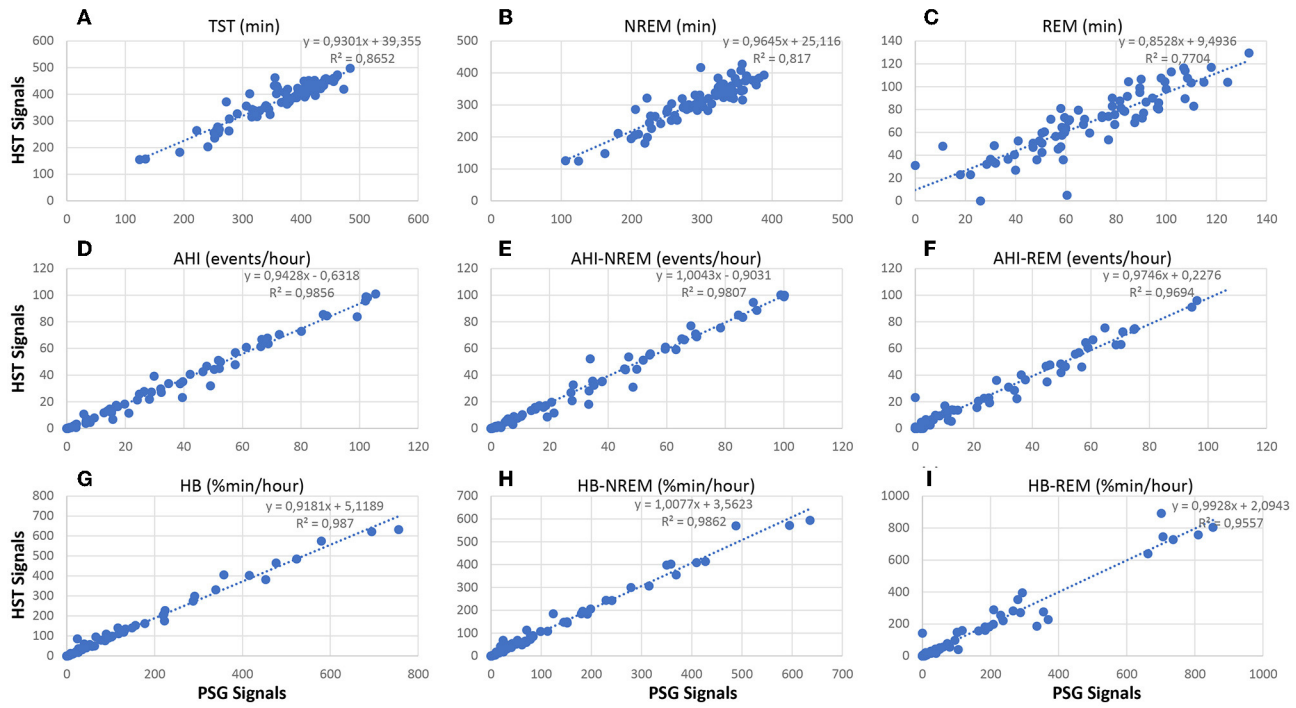

FIGURE 11
Correlation between neurological signal-based and cardiorespiratory signal-based sleep parameters in patients with sleep disturbance (n = 80; 49 apnea patients, 26 insomnia patients, 5 PLMD patients). Upper part: scatter plots relating TST **(A)**, time in NREM **(B)** and time in REM **(C)** based on the analysis using PSG signals with the values obtained from the analysis using HSAT signals only. Middle part: scatter plots relating AHI **(D)**, AHI in NREM sleep **(E)** and AHI in REM sleep **(F)** based on the analysis using PSG signals with the values obtained from the analysis using HSAT signals only. Lower part: scatter plots relating HB **(G)**, HB in NREM sleep **(H)** and HB in REM sleep **(I)** based on the analysis using PSG signals with the values obtained from the analysis using HSAT signals only.

that AI may have a defining role in future sleep research, and eventual clinical applications. The development of new biomarkers may help us understand pathophysiological mechanisms that were until now simply not accessible from hypnograms scored by individual human experts. On the other hand, this technology shows promise in the routine home testing and diagnosis of SDB. By enabling an estimate of TST with HSATs, AHI and HB across total sleep time and during REM can be estimated, until now an exclusive of the more inconvenient and expensive PSG studies. To further improve the estimation of these indices, several attempts to determine autonomic arousals as surrogate of cortical arousals for the confirmation of hypopneas have been published (Pillar et al., 2002; Olsen et al., 2018; Li et al., 2020). Taranto-Montemurro et al. (2023) recently reviewed challenges and progress in the development of a combination of noradrenergic and antimuscarinic drugs for the treatment of OSA. The authors concluded that there are still hurdles in quantifying presence and severity of OSA to fully understand the impact of treatment. The authors concluded that the usage of alternative measures to the standard AHI, such as the HB might better represent treatment effects on the ventilatory deficit associated with upper airway obstruction. In a recent review, Korkalainen et al. (2021b) discussed self-applied home sleep recordings including wearable sensing solutions and AI-based scoring for screening and long-term monitoring of sleep disorders. Besides the obvious advantages in clinical practice, the larger scale and higher throughput of AI-enabled HSATs may also facilitate larger population-wide research studies that help us understand the link between SDB and other health conditions and outcomes.

Author contributions

PA, MR, and AC contributed to conception and design of the presented topic review and drafted the manuscript. RV, ES, and PF contributed to the final version of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

PA, MR, AC, RV, ES, and PF are employees of Philips. PA is, in addition, a freelancer and shareholder of The Siesta Group.

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Mandibular jaw movements as a non-invasive measure of respiratory effort during sleep: application in clinical practice

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Assessment of respiratory effort (RE) is key for characterization of respiratory events. The discrimination between central and obstructive events is important because these events are caused by different physio-pathological mechanisms and require different treatment approaches. Many of the currently available options for home sleep apnea testing either do not measure RE, or RE signal recording is not always reliable. This is due to a variety of factors, including for instance wrong placement of the respiratory inductance plethysmography (RIP) sensors leading to artifacts or signal loss. Monitoring of mandibular jaw movements (MJM) provides the ability to accurately measure RE through a single point of contact sensor placed on the patient's chin. The inertial unit included in the capturing technology and overnight positional stability of the sensor provide a robust MJM bio-signal to detect sleep-disordered breathing (SDB). Many of the pharyngeal muscles are attached to the mandible directly, or indirectly via the hyoid bone. The motor trigeminal nerve impulses to contract or relax these muscles generate discrete MJM that reflect changes in RE during sleep. Indeed, the central drive utilizes the lower jaw as a fine-tuning lever to stiffen the upper airway musculature and safeguard the patency of the pharynx. Associations between the MJM bio-signal properties and both physiological and pathological breathing patterns during sleep have been extensively studied. These show a close relationship between changes in the MJM bio-signal as a function of RE that is similar to levels of RE measured simultaneously by the reference bio-signals such as esophageal pressure or crural diaphragmatic electromyography. Specific waveforms, frequencies, and amplitudes of these discrete MJM are seen across a variety of breathing disturbances that are recommended to be scored by the American Academy of Sleep Medicine. Moreover, MJM monitoring provides information about sleep/wake states and arousals, which enables total sleep time measurement for accurate calculation of conventional hourly indices. The MJM bio-signal can be interpreted and its automatic analysis using a dedicated machine learning algorithm delivers a comprehensive and clinically informative study report that provides physicians with the necessary information to aid in the diagnosis of SDB.

KEYWORDS

mandibular jaw movements, obstructive sleep apnea, respiratory effort, home sleep apnea test (HSAT), respiratory drive, automated analysis

Introduction

The American Academy of Sleep Medicine (AASM) scoring rules for sleep-related respiratory events are based on changes in airflow captured by dedicated sensors and associated with an arousal and/or oxygen desaturation. Another key physiologic parameter required to assess sleep-disordered breathing (SDB) is respiratory effort (RE) to allow differentiation between central and obstructive apneas; while increased RE reflects obstructive SDB events, which are the most frequent breathing disturbances, decreased RE is mandatory for a reliable scoring of central events including hypopneas (Berry et al., 2012, 2017).

The gold standard marker of RE during sleep is the amplitude of the esophageal pressure (PES) curve, a surrogate for diaphragmatic muscular contraction in the presence of increased flow resistance in the upper airway. However, esophageal manometry is an invasive method that is rarely used in clinical practice because of associated patient discomfort and related sleep alterations (Vandenbussche et al., 2015). Failure to correctly detect increased RE when present may result in incorrect classification of breathing disturbances and contribute to incorrect therapeutic decision making (Randerath et al., 2013; Martinot et al., 2019; Randerath, 2021). In addition, the high and rising prevalence of obstructive sleep apnea (OSA) highlights the need for reliable home sleep apnea testing (HSAT) options (Raphelson et al., 2022). However, measurement error compared with conventional polysomnography (PSG) can be problematic with HSAT. This is due to several factors, including inappropriate placement of sensors, use of recording time rather than sleep time as a denominator for calculation of SDB indices, technical issues leading to failed studies, and many others as previously summarized (Malhotra et al., 2015). Also, some specific clinical conditions, including associated cardiovascular comorbidities that favor central events, can preclude performance of HSAT.

This article details the use of a new-generation bio-signal, mandibular jaw movements (MJM), easily captured using a connected device set up on the chin by the patient at home, and recently validated against the gold standard measurement of RE, i.e., PES monitoring (Pépin et al., 2022).

PSG evaluation of normal respiratory activity of the mandibular jaw

During normal sleep the mandibular jaw moves slightly around a fixed position and the mouth is almost closed. However, MJM behind closed lips can be recorded. A physiological displacement of the jaw of only a few 10ths of a millimeter is seen during normal or mildly limited breathing superimposed on the respiratory cycle based on airflow or the respiratory impedance plethysmogaphy (RIP) thoracic and abdominal bands (Figure 1).

Rationale for evaluating sleep respiratory activity at the mandibular jaw level

Essentially the mandibular jaw plays the role of a lever to stabilize the pharynx. During sleep it is important to ensure upper airway patency in the presence of negative and suctioning pressure inside the upper airway. The latter is countered by the leverage effect of the mandibular jaw that moves a few 10ths of a millisecond before the diaphragm contracts.

By stiffening the pharyngeal walls, the position and movements of the mandible during sleep are important to preserve or restore upper airway patency. These MJM reflect both the central drive and variations in upper airway resistance that typically occur during abnormal respiratory events. As sleep deepens into non-rapid eye movement (NREM) stage 3 (N3) sleep, the upper airway resistance is known to increase, and this is reflected by an increase in the amplitude of MJM (Le-Dong et al., 2021). It can be hypothesized that this increase in MJM amplitude reflects the central drive to the mandibular muscles (depressors and elevators) that act as a lever to stiffen the oral floor (mylohyoid, geniohyoid, and the anterior belly of the digastric muscle) during elevation.

Beyond the longitudinal traction determined by changes in lung volume accompanied by a decrease in the transmural pressure gradient applied to the pharyngeal walls and by an increase in longitudinal airway wall tension, horizontal traction can contribute to upper airway patency via the hyoid bone when this mobile bone is immobilized by tightening of the posterior and inferior muscles (the stylo and mastoido-hyoid and the sterno and crico thyroid-hyoid muscular groups) during a complex coordinated interplay. As suggested by Hollowell et al., the respiratory activity of the mandibular jaw can be described as a co-activation of the depressors/elevators of the mandibular jaw that occurs to finely tune the position of the mandible and ensure upper airway patency during normal sleep (Hollowell and Suratt, 1991). Small increases in upper airway inspiratory resistance are accompanied by small increases in the MJM amplitude, as shown by the arrow D in the zoomed in part of Figure 1.

Technology for monitoring and recording mandibular jaw movements in the home setting

The first studies validating the clinical use of MJM relied on magnetometry measurements (Nomics, Liège, Belgium; Martinot et al., 2017). More recently, MJM could also be captured using a single point of contact sensor (Sunrise, Namur, Belgium) attached to the patient's chin (in the mentolabial sulcus). This new home sleep apnea test is composed of a coin-sized, tri-axial sensor including a gyroscope and an accelerometer. Jaw displacement is calculated from the rotational speed measured by the gyroscope. This rotational movement is produced by rotation of the mandibular condyle in the temporo-mandibular joint. The

position of the mandible resulting from elevation and depression in relation to gravity is provided by the accelerometer.

Recorded MJM data by the sensor are transferred to a smartphone application via Bluetooth for external control. Then, at the end of the night, MJM data are transferred via wireless connection to a cloud-based infrastructure, and data are analyzed with a dedicated machine-learning algorithm that simulates the process of PSG manual scoring. To do so, the algorithm has been trained to recognize stereotypical MJM patterns matching specific PSG signals related to physiological or pathological events (such as sleep stages, arousals, apneas or hypopneas) in order to predict them and compute associated clinical scores delivered in a comprehensive report generated within minutes.

Compared with magnetometry, the tri-axial sensor has some advantages, its ease of use with a single point of contact at the chin level, the higher signal resolution and its ability to record MJM in three dimensions (rather than only vertical movements). Even though there are similarities between the two devices in terms of signal frequency during normal breathing or increased RE, and common specific MJM patterns related to arousals, apnea or hypopnea events, data processing of both devices is different. The machine learning task for the magnetometry bio-signal utilizes only one channel and remains to be further developed and validated, whereas the Sunrise algorithm has been extensively trained and validated over recent years, and utilizes six channels of raw data (x, y, z components of the gyroscope and accelerometer) providing different information at a given time (Pépin et al., 2020; Le-Dong et al., 2021; Martinot et al., 2021, 2022).

Other measurements of related bio-movements also exist, they use surface EMG of the jaw-closing masseter muscles during polysomnography (Kato et al., 2013; Shiraishi et al., 2021). The dissemination of this technique is not possible currently for repeated home sleep apnea testing.

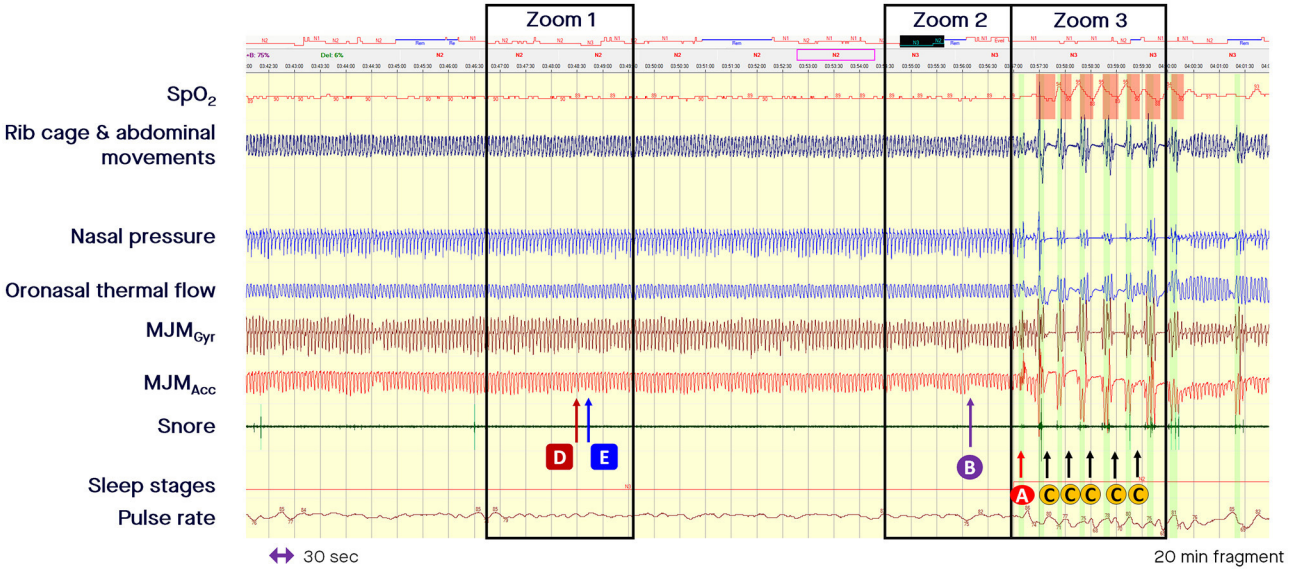

Figure 1 zoom 1:

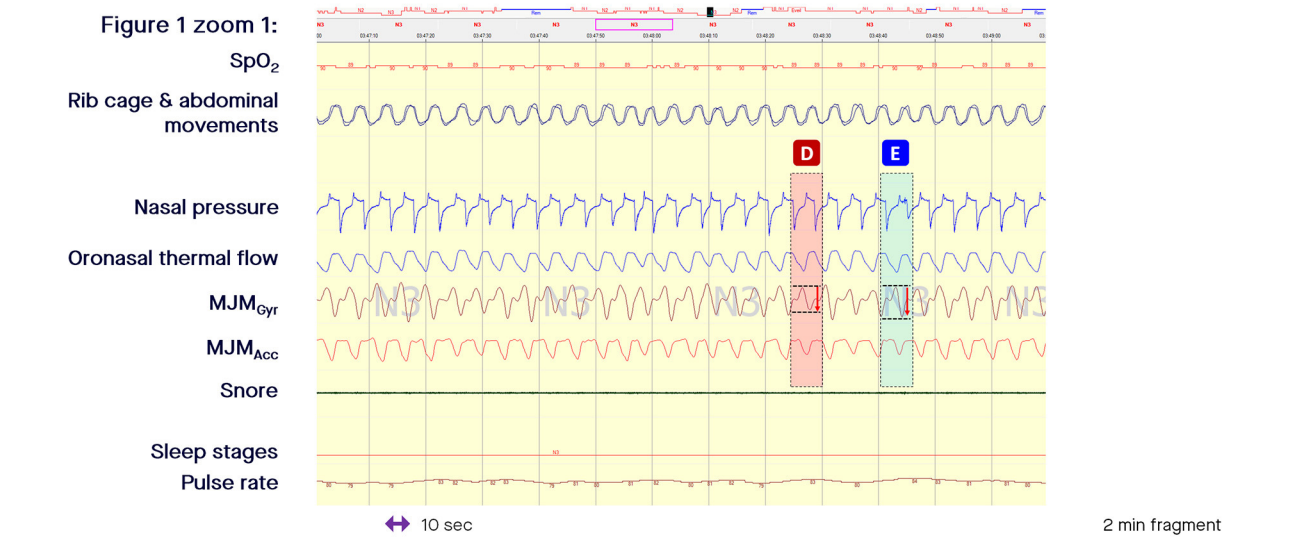

FIGURE 1 (Continued)

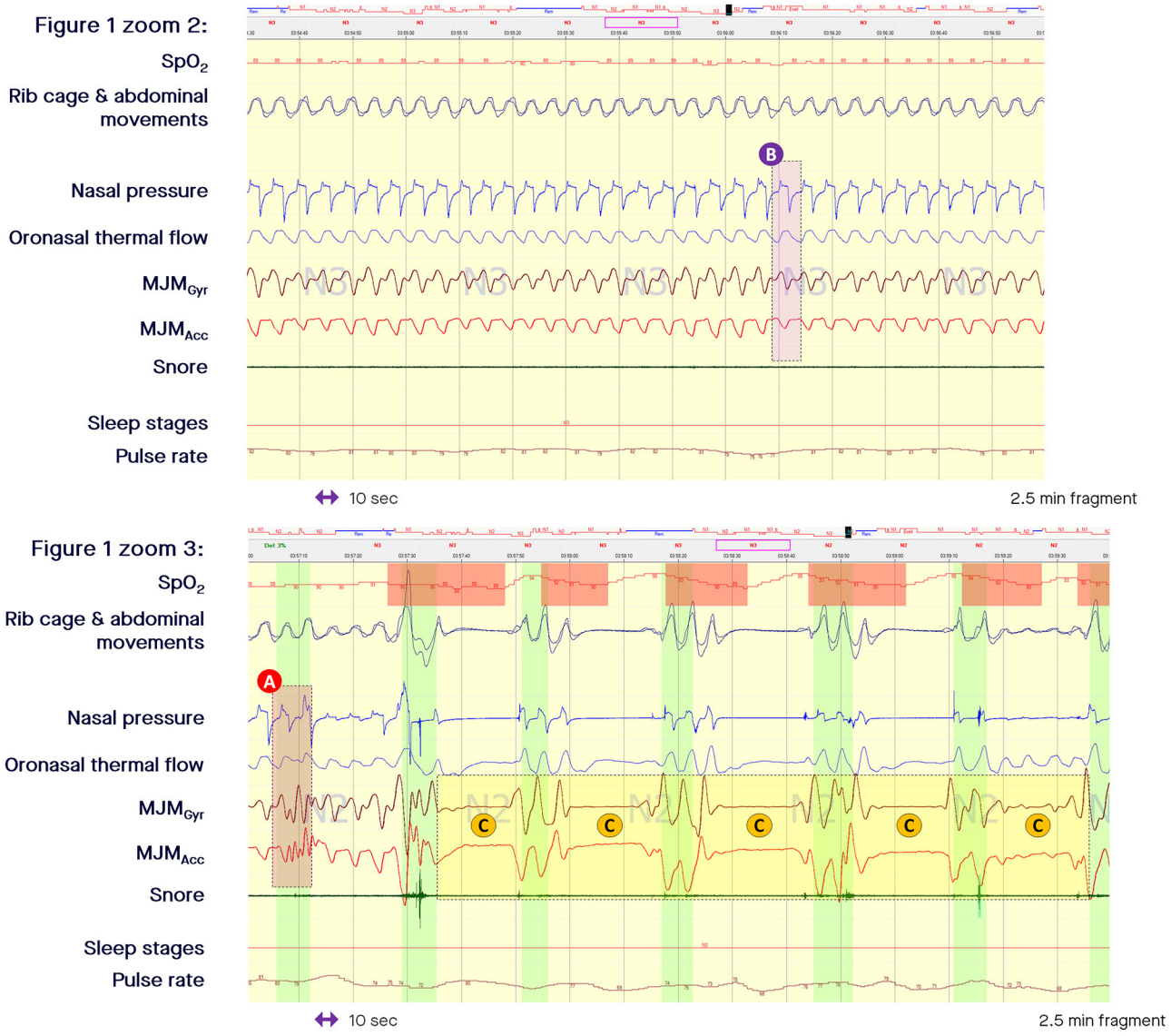

FIGURE 1 (Continued)
Fragment of polysomnography including the mandibular jaw movements bio-signal showing a long period of respiratory effort-related arousal and then successive episodes of apneas. From the top to the bottom: Oxygen saturation from pulse oximetry; Rib cage and abdominal movements captured by respiratory inductive plethysmography; Nasal pressure canulae; Oronasal thermistor; Mandibular jaw movements (MJM) recorded by the gyroscope (Gyr) and the accelerometer (Acc) of the Sunrise device; Snore monitored by a microphone; Sleep stages; Pulse rate derived from oximetry. The highlighted vertical bars depict the cortical arousals scored with EEG/EMG based rules. **(A)** MJM on arousal, which is significant and of large amplitude due to the related cortical activation intensity. **(B)** Arousals associated with subcortical activation are accompanied by a smaller magnitude of displacement. **(C)** Show the decrease in MJM during central sleep-disordered breathing events. **(D)** Shows that small increases in upper airway inspiratory resistance are accompanied by a small increase in the MJM amplitude. **(E)** Shows how much respiratory effort increases as intraluminal pressure decreases, suctioning the pharyngeal walls during an intra-event negative effort dependence pattern.

Clinical applicability of mandibular jaw movement recording to estimate conventional PSG-derived indices

Measurement of MJM enables accurate sleep time measurement. The shapes, frequencies, and amplitudes of these discrete MJM vary between different sleep stages and breathing disturbances as described by Le-Dong et al. (2021) and Pépin et al. (2020; see the related supplemental documents). When asleep and driven in synchronicity with the respiratory oscillators, mandibular displacements are quite stable compared with awake MJM that are highly variable, often fast, and unpredictable in amplitude and frequency (see arrows A in Figure 2). On arousal, jaw movements are significant and of large amplitude due to the related cortical activation intensity (see arrow A in Figure 1). Arousals associated with subcortical activation are accompanied by a smaller magnitude of displacement (see arrow B in Figure 1). The intensity of these arousals correlates well with the amplitude of the concomitant mandibular jaw displacement, likely due to

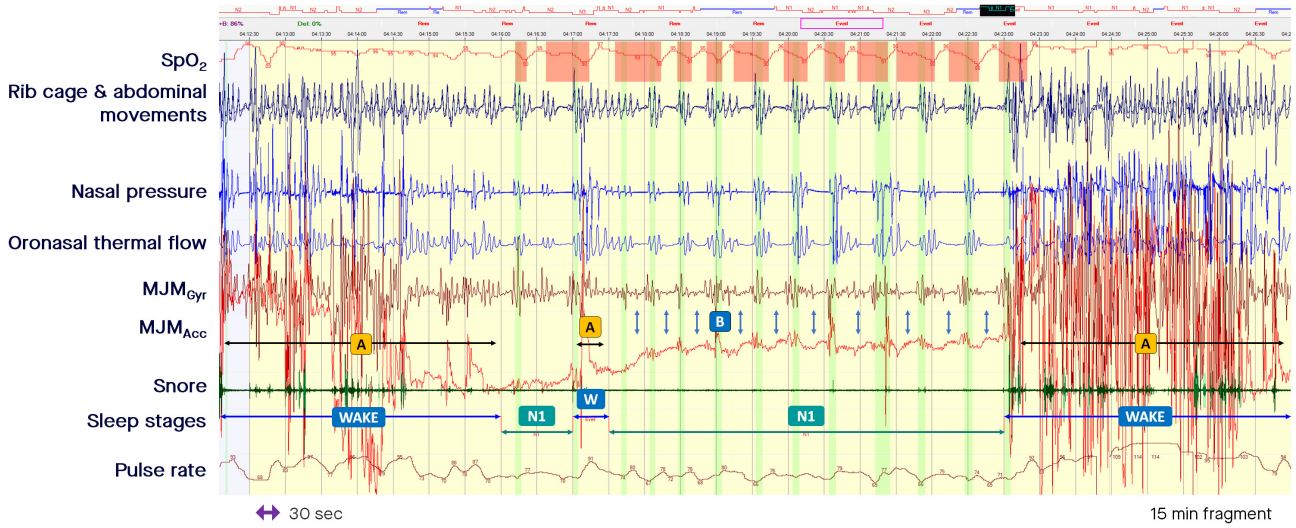

FIGURE 2
Fragment of polysomnography including the mandibular jaw movements bio-signal showing alternate periods of awakening with non-rapid eye movement light sleep stage. From the top to the bottom: Oxygen saturation from pulse oximetry; Rib cage and abdominal movements captured by respiratory inductive plethysmography; Nasal pressure canulae; Oronasal thermistor; Mandibular jaw movements (MJM) recorded by the gyroscope (Gyr) and the accelerometer (Acc) of the Sunrise device; Snore monitored by a microphone; Sleep stages; Pulse rate derived from oximetry. The highlighted vertical bars depict the cortical arousals scored with EEG/EMG based rules. **(A)** Indicate MJM that are highly variable, often fast, and unpredictable in amplitude while awake. **(B)** Show a decrease of the amplitude in the MJM bio-signal, sometimes reduced to a background noise while asleep. The decrease in central drive can be accompanied by a slight mouth opening.

a related cortico-bulbar reflex. Therefore, the analysis of MJM provides an accurate estimate of sleep/wake states and of the arousal hourly index. Sleep quality metrics showed clinically relevant agreement with manual polysomnographic staging: median [95%CI] differences of −10.25 min [−52.87 to +19.00], 0 min [−23.37 to +6.50], −2.22% [−11.06 to +3.80] for Total Sleep Time, Sleep Onset Latency, and Sleep Efficiency, respectively (Le-Dong et al., 2021).

The use of MJM-derived sleep time instead of recording time as a denominator for calculation of SDB-related indices improves the agreement between the calculated values based on MJM and those visually scored during conventional PSG. The Sunrise derived respiratory disturbances index showed diagnostic capability with ROC AUC of 0.95 (95% CI: 0.92–0.96) and 0.93 (95% CI: 0.90–0.93) for corresponding PSG index of 5 and 15 n/h, respectively (Pépin et al., 2020). Applying the near boundary double labeling method would improve the agreement between Sunrise automated scoring and PSG, by reducing the bias due to inter-human PSG scoring of AHI with an overall agreement (Kappa coefficient) that was 0.80 and 0.86 without and with near boundary double labeling, respectively (Martinot et al., 2022).

During the periods of pharyngeal obstruction that are characteristic of obstructive SDB events, the mouth opens (sometimes with a crescendo pattern, mimicking the typical pattern of crescendo changes in PES during an obstructive apnea or hypopnea) before an arousal occurs, closing the mouth (Figure 3). This is likely due to different carbon dioxide sensitivities between the mandibular jaw depressors and elevators. There is first a more intense phasic recruitment of the depressors leading to mouth opening until an arousal occurs with a peak in airflow coinciding with mouth closure due to a greater recruitment of the elevators. In Figure 3, a decrease in airflow is accompanied by a persistently elevated or increasing rotational speed of the mandible, indicating a persistent high central drive or increasing drive against the upper airway obstruction. During the period of such obstructive episodes different means of MJM amplitudes can be observed possibly as a function of their dominant endotypes (with more or less upper airway muscle gain).

During central SDB events, the amplitude of MJM decreases and the bio-signal can be reduced to a background noise (see arrows C in Figure 1). Due to a decrease in central drive, a slight mouth opening can occur when the elevators cannot sustain the mandible at an upper position. The arrows B in Figure 2 mark a decrease in the MJM bio-signal amplitude, showing a decrease in the trigeminal output. Therefore, changes in MJM amplitude can be used to classify SDB events as central or obstructive based on the ongoing or underlying level of RE. Distribution of MJM amplitude differs significantly between event types: median (95% confidence interval) values of 0.60 (0.16–2.43) for central apnea, 0.83 (0.23–4.71) for central hypopnea, 3.23 (0.72–18.09) for obstructive hypopnea, and 6.42 (0.88–26.81) for obstructive apnea (Martinot et al., 2019; Pépin et al., 2022).

In addition, prolonged periods of sustained inspiratory and/or expiratory effort are well-represented by a progressive increase in MJM amplitude until a relief occurs by way of an arousal (Figure 1). These prolonged periods of RE also called respiratory effort-related arousals (RERAs) can last for more than 1 min, are sometimes accompanied by snoring, and are characterized by a progressive increase in the rotational speed of the mandible. The increased central drive observed through the MJM gyroscopic bio-signal

FIGURE 3
Fragment of polysomnography including the mandibular jaw movements bio-signal to show episodes of "classic" and "drive-dependent" obstructive sleep apnea (OSA). From the top to the bottom: Oxygen saturation from pulse oximetry; Rib cage and abdominal movements captured by respiratory inductive plethysmography; Nasal pressure canulae; Oronasal thermistor; Mandibular jaw movements recorded by the gyroscope (Gyr) and the accelerometer (Acc) of the Sunrise device; Snore monitored by a microphone; Pulse rate derived from oximetry. The highlighted vertical bars depict the cortical arousals scored with EEG/EMG based rules. **(A, B)** Represent episodes of "classic" and "drive-dependent" OSA, respectively. The accelerometer channel shows the changes in the mandible position during the period of crescendo pattern: the more the signal is negative, the more the mouth opens until an arousal occurs, characterized by an abrupt and positive displacement of the mandible reflecting the closure of the mouth and peaking the airflow.

can be stable or unstable, and is marked by several subcortical activations identified by concomitant changes in heart rate, pulse tonometry or pulse transit time when these metrics are evaluated using in-laboratory PSG. Most of the time, these changes are ended by a cortical arousal corresponding to a salient movement of the mandibular jaw to close the mouth.

Hypopnea is the most frequent respiratory event reported during sleep. AASM rules recommend that hypopneas are classified as either obstructive or central depending on the associated RE, reflecting an increase or decrease in the central respiratory command for obstructive and central events, respectively. Correct characterization of the hypopnea sub-type provides information about its origin and contributes to a personalized therapeutic decision-making process (Martinot et al., 2019). As a metric, the overall apnea-hypopnea index (AHI) does not provide accurate clinical risk stratification because it includes both central and obstructive events.

On polygraphy, the presence of elevated RE is assessed by the examination of the dual RIP belt signals (e.g., amplitude and phase shift) and changes in the shape of inspiratory nasal pressure (e.g., flow limitation or plateau aspect) and/or the appearance of a crescendo or stable snoring. Information provided by the RIP belt signals can be misleading in obese patients for instance, since obesity can cause misclassification of obstructive events as central, especially in the unsupervised home setting, and RIP belt signals are prone to fail or disappear (Loube et al., 1999; Masa et al., 2003). A shift phase of the RIP thoracic and abdominal bands belt signals could indicate increased RE and classify the hypopnea as obstructive, although the signal remains difficult to interpret during rapid eye movement (REM) sleep where the tone in the accessory respiratory muscles is lost. In addition, the shape of the nasal pressure signal is altered by mouth breathing and primarily reflects increased upper airway resistance rather than the underlying central drive. A typical flattening waveform strongly suggests an increase in upper airway resistance that could also occur at low levels of RE (Hosselet et al., 1998; Ayappa et al., 2000; Pamidi et al., 2017; Mann et al., 2021). Therefore, a reliable backup signal for RE is required to increase robustness and reliability.

When the nasal pressure signal is superposed on the MJM bio-signal at the time of an intra-event negative effort dependence pattern, the increased stimulation of trigeminal motor neurons is clearly associated with a curvilinear decrease in flow signal during the second part of the inspiration with a termination peak. This pattern is well-depicted by an increased peak-to-peak amplitude of the MJM bio-signal (arrow E in the zoomed in part of Figure 1, and zoomed in part of Figure 4). This shows how much RE increases while the intraluminal pressure decreases, suctioning the pharyngeal walls.

The RE measured through MJM monitoring determines the airflow amplitude (central drive) as a function of the residual pharyngeal permeability during the period of obstruction. In the "classic" model of OSA, apneas and hypopneas are characterized by a loss of airway patency precipitating increased central drive, as shown by an increase in the rotational speed of the mandible while the mouth opens more and more until an arousal occurs, closing the mouth and reopening the upper airway, with an associated

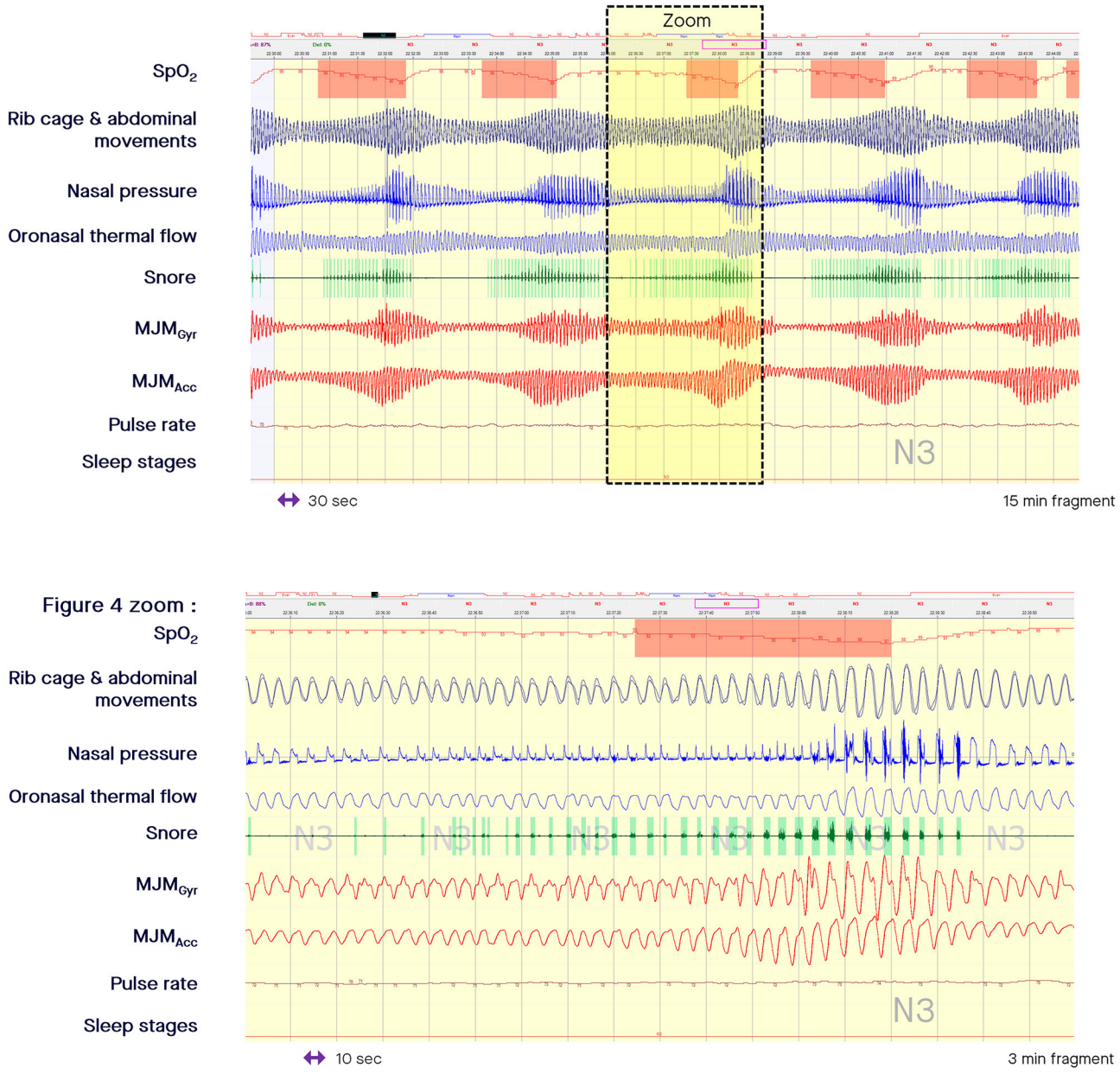

FIGURE 4
Fragment of polysomnography including the mandibular jaw movements bio-signal showing a period of cyclical breathing. From the top to the bottom: Oxygen saturation from pulse oximetry; Rib cage and abdominal movements captured by respiratory inductive plethysmography; Nasal pressure canulae; Oronasal thermistor; Snore monitored by a microphone; Mandibular jaw movements recorded by the gyroscope (Gyr) and the accelerometer (Acc) of the Sunrise device; Pulse rate derived from oximetry; Sleep stages. In the zoomed in part, the presence of inspiratory flow limitation at the ventilatory peak is clearly evident suggesting that the pharynx is not fully open. Intra-event negative effort dependence patterns are well depicted in the zoomed in part of the figure showing how much respiratory effort increases as intraluminal pressure decreases, suctioning the pharyngeal walls.

peak in airflow (arrow A in Figure 3). Until the upper airway reopens, the airflow is abolished or is minimal despite an increase in the central drive. By contrast, the "drive-dependent" model of OSA is characterized by a loss of central drive, promoting dilator muscle hypotonia and, consequently, precipitating respiratory events for many patients. "Drive-dependent" events are depicted by concomitant changes in airflow and MJM amplitude in relation to the degree of pharyngeal obstruction (arrow B in Figure 3; Gell et al., 2022).

During periodic breathing (central SDB), the airflow oscillates between apnea or hypopnea and hyperpnea (where the breathing frequency can accelerate). In Cheyne Stokes respiration (common in patients with heart failure), the airflow follows a characteristic waxing-waning pattern. The Biot's (or ataxic) respiration is characterized by variable changes in flow, random apneas or hypopneas, and no regularity. The specific MJM patterns associated with each change in breathing are detectable based on the level of central drive, as shown in Figure 4. In the zoomed in part

of Figure 4, the presence of inspiratory flow limitation at the ventilatory peak, and the presence of snoring strongly suggest that the pharynx is not fully open.

Conclusion

MJM provide a robust and comprehensive bio-signal to detect SDB. During normal periods of breathing during sleep, the mandible (or lower jaw) moves slightly around a fixed position. The shapes, frequencies, and amplitudes of these discrete MJM vary between different sleep stages and breathing disturbances. Chemoreceptors and upper airway pressure sensors inform the brain about breathing disturbances. In response, an increase in the central motor drive will recruit and stiffen the pharyngeal muscles so that normal breathing resumes. Many of these muscles are attached to the mandible. Therefore, contracting or relaxing these muscles generates discrete and informative MJM. The ability of MJM to accurately measure RE during sleep has been confirmed during simultaneous, synchronized in-laboratory PSG (Pépin et al., 2022).

Overall, the measurement of MJM provides the clinician with deep insights into the work of breathing, including intra-event negative effort dependence patterns and differentiation between central and obstructive SDB events, including central hypopneas. Essentially, monitoring MJM is like having a probe in the brainstem to observe the regulating activity of the brain during sleep. This provides a new, comprehensive, reliable, validated and objective way of detecting and characterizing SDB.

Author contributions

Both authors contributed to manuscript preparation, revision, read, and approved the submitted version.

Conflict of interest

J-BM reports being a scientific advisor to Sunrise and being an investigator in pharmacy trials for Jazz Pharmaceuticals, Theranexus, and Desitin. J-LP reports being a scientific advisor to Sunrise; receiving grants and/or personal fees from ResMed, Philips, Fisher & Paykel, Sefam, AstraZeneca, AGIR à dom, Elevie, VitalAire, Boehringer Ingelheim, Jazz Pharmaceuticals, and Itamar Medical Ltd; and receiving research support for clinical studies from Mutualia and Air Liquide Foundation.

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Sleep monitoring based on triboelectric nanogenerator: wearable and washable approach

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KEYWORDS

triboelectric nanogenerator, sleep monitoring, portable equipment, smart mattress, smart pillow

Introduction

In order to further promote miniaturization, convenience and intelligence of sleep monitoring devices, a novel method using triboelectric nanogenerator (TENG) for sleep monitoring and analysis has attracted attention gradually (1–9). TENG is an energy collection technology (10–12), which based on coupling of triboelectric electrification and electrostatic induction during the conversion of mechanical energy to electrical energy (13). with advantages of low cost, diverse structure, stable output, high energy conversion efficiency, strong shape adaptability, eco-friendly (14, 15), TENG can harvest mechanical energy from water waves, vibration, raindrops, wind and other environments (16). Its unique working modes also enables TENG to obtain biomechanical energy under sports and physiological conditions (17), including body movement, respiration, and heartbeat, which enables sleep monitoring free from the lack of batteries with a smaller volume and better use experience.

At present, sleep monitoring based on TENG mainly focuses on respiratory rate, head movement, eye changes and limb movements, which are important parameters related to sleep quality. For example, Yue et al. (1) prepared a self-powered all-nanofiber electronic skin based on TENG, which integrates a series of complex flexible sensors to analyze sleep quality by detecting respiratory rate and carotid signal frequency. However, the preparation process is relatively complex. Zhang et al. (5) fabricate a self-powered waist wearable respiratory monitoring device by taking advantage of the characteristics that the abdomen will deform during breathing. The respiratory information is retrieved by detecting the changes in abdominal circumference during human respiration to monitor sleep status. In addition, the energy generated by clearing abdominal deformation during breathing can also provide energy for the sensor. Kou et al. (9) prepared an intelligent pillow based on a flexible and breathable triboelectric nanogenerator (FB-TENG) sensor array, and evaluated the sleep quality by detecting the real-time head movement trajectory during sleep by the self-powered pressure sensor array, as shown in Figure 1a. On the other hand, Cao et al. (18) proposed a free deformable tribo-sensor (FDTS) based on nanofiber reinforced ultra-thin elastomer. After integrating the FDTS with the eye mask, the sleep state is evaluated by sensing the blinking action of the human body during sleep. In the research of limb motion, there are many sensitive and TENG-based limb motion sensors (7, 8). By monitoring the voltage output signal generated by the relative motion of the triboelectric layer in the device caused by human body movement in sleep, the time and number of human body movements in sleep can be collected and recorded in real time. The monitoring of sleep quality is mainly realized by pressure sensors, but the existing monitoring system still needs to improve the

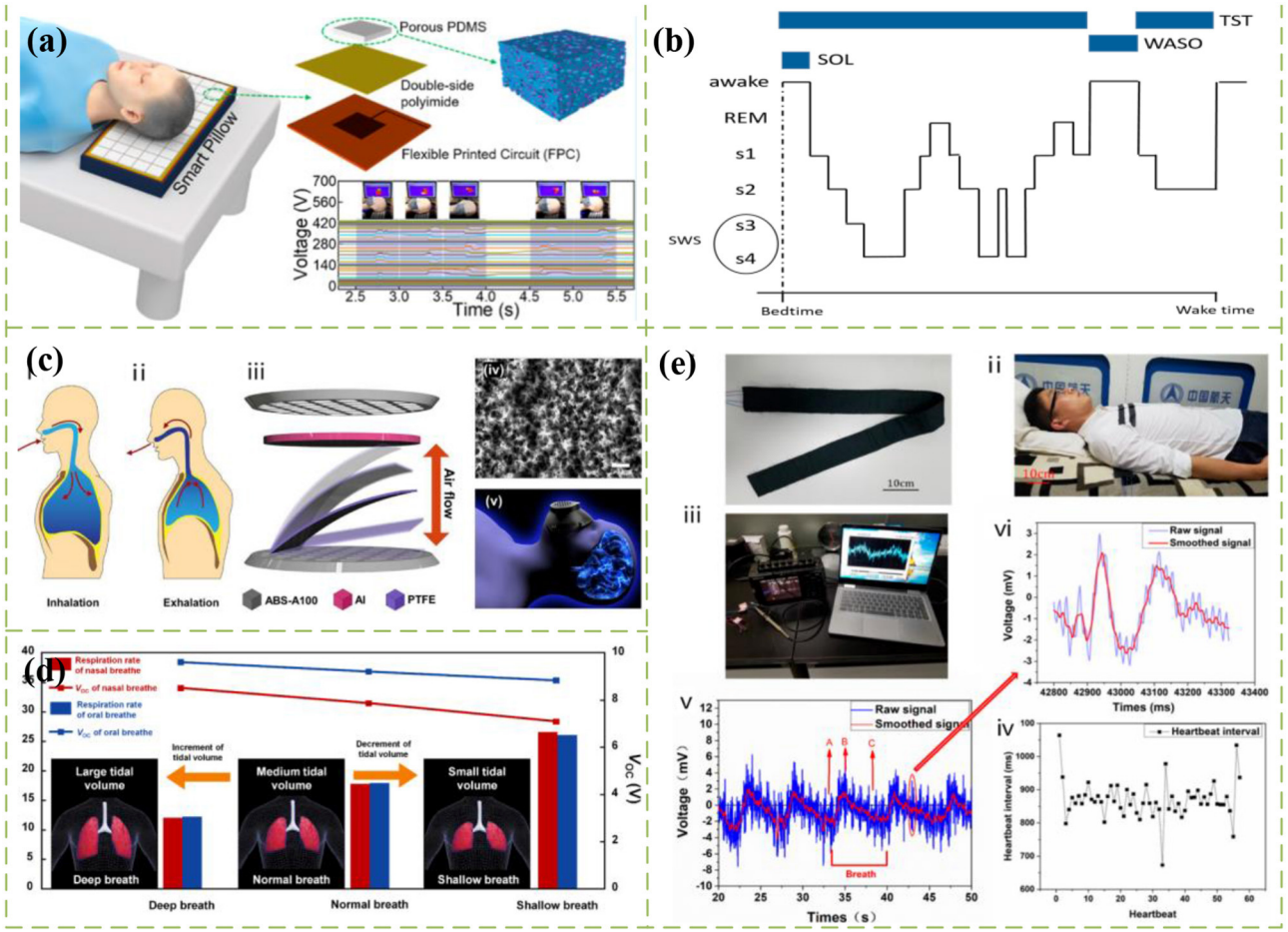

FIGURE 1
(a) Self-powered intelligent pillow based on TENG monitors head movement track (9). **(b)** An example of hypnogram (21). **(c)** Self-powered mask shape wearable device based on TENG (28). **(d)** Schematic diagram of breathing mode (28). **(e)** Test process of sleep monitoring belt made by porous TENG self-powered tactile sensor with CNT doping (3).

sensitivity and stability of detection and faces challenges such as complex structure, high manufacturing cost, and difficulty in washing, which limits the application in real-time sleep posture detection and physiological analysis.

This paper analyzes the work of current researchers in respiratory rate, head movement, eye changes and limb movements, which are important parameters related to sleep quality. At the same time, it also analyzes the development direction of emerging electronic devices for sleep monitoring and analysis in the future, which has certain reference significance.

TENG and sleep disorders

Due to the accelerated pace of modern life, more and more people are experiencing sleep disorders such as insomnia, obstructive sleep apnea-hypopnea syndrome (OSAHS), and circadian rhythm disorders, often caused by increased work pressure and irregular lifestyles (19, 20). Effective sleep monitoring and analysis are crucial in identifying sleep quality problems promptly, adjusting health habits, and seeking medical advice in a timely manner (21, 22). Figure 1b displays a typical sleep architecture, which represents the cyclic pattern of sleep (21). Numerous energy harvesters were developed in the past decades (23). Wherein TENGs can convert mechanical energy in the environment into electrical energy for self-power supply, and obtain information regarding environmental changes by analyzing the generated electrical signals (24, 25), even improve the overall performance of the system (26). In addition, these sleep monitoring devices generally use a sensitive motion sensor based on TENG. The relative movement of the triboelectric layer in the device which is caused by the tiny movements of the human body during sleep can generate a voltage output signal of up to tens of volts, thus reflecting the sleep situation in real time. For instance, we can analyze the signal frequency to determine wakefulness, shallow sleep, and deep sleep stages, as well as use the recorded time to determine the sleep duration and time taken to fall asleep.

High sensitive triboelectric nanogenerator wearable devices

To facilitate and quickly implement sleep monitoring, TENGs are usually fabricated as various wearable devices, such as electronic

skin patches (7), belts (5), goggles (18), which can analyze sleep behavior by monitoring limb movements, breathing or eye movements. In recent years, there has been a lot of research on the performance improvement and function optimization of wearable devices for TENG. For example, Chen et al. (27) vertically integrated the single-electrode TENG and the fiber-based piezoelectric nanogenerators (PENG) to further improve the self-power efficiency of wearable devices. At the same time, the piezoelectric nanofibers are used to monitor human physiological signals quantitatively and realize sleep monitoring. Salauddin et al. (6) combined MXene/Ecoflex nanocomposites with fabric to build a waterproof triboelectric nanogenerator device (FW-TENG) with advantages of self-powering and mechanical comfortable. Besides, it is also very reliable and stable underwater, which is an important feature for next generation of wearable/portable technology. On the optimization of data processing based on TENG wearable devices, Yun et al. (28) proposed a mask-shaped triboelectric nanogenerator (M-TENG) using mechanical energy generated by respiratory airflow, as shown in Figure 1c. This wearable device can detect the electrical signals generated by the breathing patterns in different sleep stages (as shown in Figure 1d). These electrical signals can be classified with the assistance of machine learning. Considering the optimization of sensor preparation methods for wearable devices, Ding et al. (3) designed a self-powered tactile sensor with CNT-doped porous TENG. This self-powered sensor has low cost, high durability and good sensitivity. In the test, the sleep monitoring belt prepared by this sensor can obtain accurate data about real-time heartbeat and respiration, as shown in Figure 1e.

Although wearable devices based on TENGs have achieved great progress in recent years, it is inevitable that wearable devices will affect the natural sleep state of the human body to some extent during use. In this regard, many researchers start with intelligent textiles based on TENG, and prepare them into more comfortable bedding to maximize the restoration of the natural sleep state of the human body.

Washable intelligent mattress for sleep monitoring

A non-invasive sleep monitoring scheme that does not need to attach any sensor or transducer to the human body has been proposed. The method is to use large pressure-sensitive and washable smart textiles based on TENG array to make them into smart mattresses, which can detect sleep behavior in real time. This smart mattress is mainly composed of three layers: the top layer and the bottom layer are composed of cross and vertical conductive layers, and the middle of the two conductive layers is a wavy polyethylene terephthalate (PET) film interlayer. When external pressure is applied to the smart mattress, the structural change of the middle PET layer will lead to the change of its contact area with the two conductive layers, thus producing potential difference. In current work, the intelligent mattress which proposed by Lin et al. (4) has excellent pressure sensitivity (0.77 V/Pa), fast response time (80 ms), and can still generate stable external pressure signal after washing in tap water. However, the wave-shaped structure embedded in its mattress lacks comfortable materials, which can bring a certain sense of discomfort. Moreover, the size magnitude of the array element is 10×10 cm^2, resulting in low resolution. Further, Zhou et al. (2) proposed a single layer soft intelligent textile that can be used for mattresses has solved the issue of comfort in terms of material selection, but its resolution remains the same. Intelligent mattress devices generally offer the advantages of low cost, fast response time, and deep stability. However, their sleep monitoring detection methods are relatively simple, which makes it difficult to accurately reflect specific sleep statuses.

Head movement monitoring during sleep

Considering the relationship between head posture changes and sleep state during sleep, an intelligent pillow which based on a flexible and breathable triboelectric nanogenerator (FB-TENG) sensor array was developed (9). This method uses intelligent pillow to realize sleep state monitoring with characteristics of high resolution, pressure sensitivity, non-intrusive, comfort and breathability. Each FB-TENG sensor unit that touched by the human head will output a voltage signal during sleep, and the output voltage signal which is generated by each FB-TENG sensor unit is different due to the different touching force. It can monitor and record the movement track of the human head by sorting each voltage output signal in chronological order. These changes are mainly caused by body turnover, and then these can be used to analyze the change of sleeping posture and reflect the sleep situation directly. In addition, the intelligent pillow does not need to wear any wearable electronic equipment during use, which can greatly reduce the impact of monitoring equipment on the human body's natural sleep state.

Discussion

Through the coupling effect of triboelectric electrification and electrostatic induction, TENG is not only a low-cost and reliable energy collection technology, but also a combination of self-driving pressure sensing technology to achieve the monitoring of sleep quality. The only restriction on its application is the anti-cleaning performance of materials. Some of the sleep monitors need to be worn by users, which can't maintain the most natural state of sleep. And the use of patches or electronic skin with poor permeability may also cause skin itching, inflammation and other uncomfortable symptoms. In this regard, a large pressure-sensitive and washable smart textile which based on the TENG array can be used to make intelligent instruments, it can detect sleep behavior in real time, such as smart mattresses, smart pillows, etc. Among them, the TENG unit is made of conductive material and elastomer material of waveguide structure, with excellent characteristics such as high sensitivity, fast response time, durability and water resistance, and is connected to form a self-driving pressure sensor array. At the same time, it is equipped with an additional integrated data acquisition, processing and wireless transmission system, which can realize real-time sleep behavior monitoring and sleep quality evaluation. Therefore, the application of nano-triboelectric generator in the field of

bedding is more feasible and available than the solution of using wearable devices.

On the other hand, to further improve the accuracy and specificity of sleep monitoring, an interesting idea is to use TENG based smart textiles with smart pillows in conjunction, and comprehensive analysis of sleep data with machine learning which is obtained from multiple intelligent bedding products, so as to provide targeted recommendations for different sleep behaviors of different patients. Further, because of the real-time collection of patients sleeping posture through intelligent bedding, it is possible to achieve poor sleeping posture reminders. For infants and incapacitated patients, smart textiles and smart pillows can add certain control programs to prevent falling out of bed issues. For example, an alarm function can be added to the TENG arrays in the row closest to the edge of the bed for smart pillows or smart textiles, and trigger the alarm function when they are contacted simultaneously.

Moreover, TENG can harvest mechanical energy from body organs (heart beating, muscle contraction and gastrointestinal peristalsis) to form electric field and generate electricity to realize electrical stimulation, which can help regulate the heartbeat, relieve muscle atrophy and promote wound healing. At the same time, the electricity which generated by TENG can be used to stimulate cells, tissues and organs directly (29). This shows the potential application in rehabilitation and treatment. Secondly, different external stimulation may lead to different output signals of TENG, which can work as self-powered sensors to monitor real-time physiological signals. In addition, in order to improve stability and provide more choices of triboelectric materials, TENG is integrated with other sensors to form an impedance matching system or hybrid system. TENG has great potential in the field of medical care, but it still has a certain distance between experiment and practical application.

Ethics statement

Written informed consent was obtained for the publication of any potentially identifiable images or data included in this article.

Author contributions

Writing—review and project administration: ZZ. Writing—original draft preparation and editing: MP. Investigation and supervision: ZX. All authors have read and agreed to the published version of the manuscript.

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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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Sleep apnea endotypes: from the physiological laboratory to scalable polysomnographic measures

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Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent upper airway obstruction during sleep. Despite the availability of continuous positive airway pressure (CPAP) as the gold standard treatment, it is not well tolerated by all patients. Accordingly, research has increasingly focused on developing methods for OSA endotyping, which aims to identify underlying pathophysiological mechanisms of the disorder to help guide treatment for CPAP-intolerant individuals. Four key endotypic traits have been identified, namely: collapsibility, upper airway muscle compensation, arousal threshold and loop gain. However, most methods for extracting these traits require specialized training and equipment not available in a standard sleep clinic, which has hampered the ability to assess the full impact of these traits on OSA outcomes. This paper aims to provide an overview of current methods for OSA endotyping, focusing on the Endo-Phenotyping Using Polysomnography (PUP) method and its cloud-based extension, PUPpy, which offer scalable and accessible ways to estimate endotypic traits from standard polysomnography. We discuss the potential for these methods to facilitate precision medicine for OSA patients and the challenges that need to be addressed for their translation into clinical practice.

KEYWORDS

sleep disordered breathing, pathophysiology, precision medicine, endotyping, phenotyping

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder that has major consequences for neurocognitive, cardiovascular, and metabolic health. Unfortunately, the leading therapeutic intervention, continuous positive airway pressure (CPAP), is limited by patient tolerance despite its otherwise excellent efficacy (Lozano et al., 2010; Weaver et al., 2012; Rotenberg et al., 2016; Bakker et al., 2019; Shapiro et al., 2021; NCA-CPAP, 2022; Šiarnik et al., 2022). Of the array of available and experimental non-CPAP

interventions—including weight loss (Schwartz et al., 1991), oral appliances (Ng et al., 2003; Chan et al., 2010; Edwards et al., 2016a; Dissanayake et al., 2021; Pattipati et al., 2022), positional therapy (Randerath W. et al., 2021), hypoglossal nerve stimulation (Certal et al., 2015; Costantino et al., 2020; Op de Beeck et al., 2021b), pharyngeal surgery [particularly in pediatrics (Schwartz et al., 1992; Joosten et al., 2017; Gozal et al., 2020)], supplemental oxygen (Wellman et al., 2008), pharmacological interventions to: activate dilator muscles (e.g., atomoxetine-plus-oxybutynin) (Taranto-Montemurro et al., 2019, 2020; Hedner and Zou, 2022a; Schweitzer et al., 2022), decrease arousability from sleep (e.g., eszopiclone) (Eckert et al., 2011), and stabilize ventilatory control (carbonic anhydrase inhibitors) (Hedner and Zou, 2022a; Hedner et al., 2022)—each appears to be efficacious in some patients more than others. For the most part, non-CPAP therapies are administered in an empirical (i.e., trial-and-error) manner, with limited mechanistic information available to the clinician to predict the likelihood of a successful intervention in individual patients.

Over the last decade, the field of sleep medicine has come to the consensus that (1) there are different underlying pathophysiological causes of OSA (i.e., endotypic traits) (Younes, 2003; Younes et al., 2007; McGinley et al., 2008; Edwards et al., 2012, 2019; Sands et al., 2014), (2) that these traits differ considerably between patients (Wellman et al., 2011; Eckert et al., 2013; Xie et al., 2013; Sands et al., 2023), and (3) that individual differences in traits provide a mechanistic explanation for why some patients respond preferentially to one therapy over another (Wellman et al., 2008; Stanchina et al., 2015; Edwards et al., 2016a; Joosten et al., 2017; Landry et al., 2017; Sands et al., 2018a; Light et al., 2019). These concepts provide a potential avenue for *precision medicine*, whereby a subgroup of patients sharing a common underlying pathophysiology could be judiciously administered a therapy with preferential benefit. Accordingly, investigators have recently accelerated efforts to subclassify OSA based on mechanistic endotypic traits (i.e., endotypes) or other clinically-observable characteristics more generally (i.e., phenotypes), with the goal of better matching interventions to patients in a way that maximizes efficacy and tolerability (Edwards et al., 2019; Light et al., 2019; Malhotra et al., 2020).

Key endotypic traits

There are at least four key endotypic traits that contribute to OSA (Younes et al., 2007; Ratnavadivel et al., 2010; Wellman et al., 2011; Eckert et al., 2013; Sands et al., 2018a; Light et al., 2019; Malhotra et al., 2020). Increased pharyngeal *collapsibility* is the primary determinant of OSA (Kirkness et al., 2008; Eckert et al., 2013; Sands et al., 2018b, 2023; Alex et al., 2022), and is characterized by an increased tendency of the pharyngeal tissues to obstruct the upper airway during sleep. Specifically, greater collapsibility manifests as a reduction in the ventilatory flow rate. Second, reduced pharyngeal dilator muscle activity is characterized by a failure of the dilator muscles (including the genioglossus muscle) to provide a normal baseline level of activation and/or the reflex increase in activation as ventilatory drive rises with obstruction (Wellman et al., 2011; Sands et al., 2018b). Low reflex *compensation* may be consequent to reduced neural responsiveness to stimuli and/or reduced neuromechanical efficiency. Third, a low *arousal threshold* is also a key trait contributing to OSA pathophysiology and is defined by a lower ventilatory drive threshold that triggers arousal (Heinzer et al., 2008; Wellman et al., 2011). Mechanistically, a lower arousal threshold places a limit on the ventilatory drive stimulus that the dilator muscles normally rely on to provide compensation support to the upper airway. Finally, a greater ventilatory instability or *loop gain* is defined as an excessive ventilatory drive response opposing a change in ventilation from baseline eupneic breathing (Wellman et al., 2011; Terrill et al., 2015). Despite being the hallmark of central sleep apnea, increased loop gain is also a key factor in the pathophysiology of OSA and is largely dominated by the dynamic ventilatory response to carbon dioxide (Younes et al., 2007). Conceptually, a higher loop gain contributes to OSA by exacerbating the transient loss of ventilatory drive stimuli needed to maintain muscle compensation in the presence of a vulnerable airway.

An important advance in the understanding of OSA pathophysiology is the notion that each of the four key traits are defined by ventilation and ventilatory drive (Younes, 2003; Wellman et al., 2011, 2013; Owens et al., 2015; Sands et al., 2018b) (see Figure 1). Collapsibility determines the ventilation during sleep at eupneic (normal resting baseline) ventilatory drive. Compensation is the increase in ventilation between eupneic drive and the maximum drive achievable during sleep, occurring at the arousal threshold, e.g. just before the termination of a respiratory event. Arousal threshold is the ventilatory drive that causes arousals. Loop gain is the ventilatory drive response to changes in ventilation from eupnea. Using this conceptual framework, it is possible to combine the endotypes mechanistically to explain the absence or presence of OSA and to understand the degree to which the traits causing OSA can be leveraged to ameliorate it (Wellman et al., 2013; Owens et al., 2015). For example, lowering loop gain is unlikely to be beneficial in patients with severe collapsibility and a poor muscle response, since such patients will incur pharyngeal collapse and loss of ventilation regardless of the level of ventilatory drive stimuli. For patients with ineffective upper airway muscles, raising the arousal threshold is unlikely to be helpful. These patients are expected to exhibit pharyngeal collapse regardless of their ability to tolerate increased ventilatory drive.

Accumulating evidence supports the concept that differences in these traits can explain responses to available and emerging CPAP and non-CPAP therapies. Key examples include the following: Patients with a high arousal threshold tend to adhere more to CPAP treatment, and increasing the arousal threshold pharmacologically with eszopiclone has been found to further improve CPAP adherence (Schmickl et al., 2020). Supplemental oxygen therapy to lower loop gain appears to be most efficacious in patients with less severe collapsibility, greater compensation, and higher loop gain (Wellman et al., 2008; Edwards et al., 2016b; Sands et al., 2018a). We caution that the use of hypnotics and supplemental oxygen as OSA therapies is still experimental and has not been approved

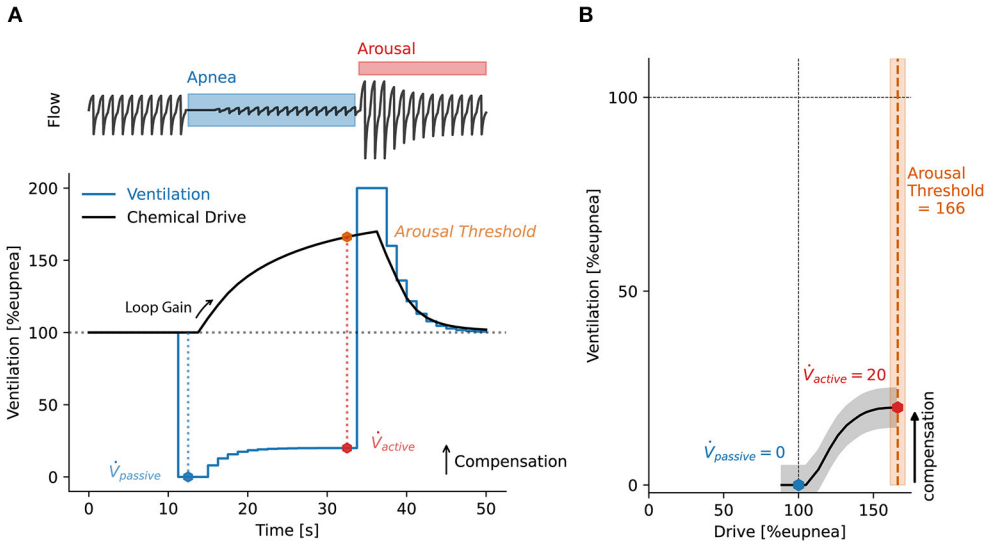

FIGURE 1
(A) Simulated respiratory event to illustrate the key concepts behind deriving sleep apnea endotypes from a ventilation signal. A simulated flow signal is shown above to help visualize the respiratory event. Ventilation is derived from the flow signal. A mathematical model of the chemoreflex control of breathing is fit to the unobstructed ventilation data, shown as a stepped blue line. The model is used to derive a continuous estimate of chemical drive, shown as a black continuous line. The chemical drive can be interpreted as the intended ventilation, which was not achieved due to the airway obstruction. Loop gain is then derived from the fitted model as the ratio of the output signal (chemical drive) to the input signal (ventilation). Collapsibility is measured as the ventilation at 100%$_{eupnea}$ drive ($\dot{V}_{passive}$). Arousal threshold is defined as the chemical drive preceding arousal. Upper airway muscle compensation ($\dot{V}_{comp}$) is the difference in ventilation at eupneic drive (100%$_{eupnea}$) and ventilation at the arousal threshold. **(B)** From the minute ventilation and drive data on **(A)** we create a ventilation-vs.-drive plot or "endogram." Here, drive is binned into centiles and the median ventilation value within each drive bin is plotted against the median value of the binned drive data. The ventilatory endotypes: *compensation*, $\dot{V}_{passive}$ and $\dot{V}_{active}$ can be read directly from the plot. The endogram is used to aggregate and visualize the characteristic ventilation-drive relationships for a whole sleep study.

for clinical use. Oral appliance therapy appears most beneficial in patients with less severe collapsibility and lower loop gain (Edwards et al., 2016a; Vena et al., 2020; Op de Beeck et al., 2021a), and may also be more efficacious in those with lower compensation and higher arousal threshold (Bamagoos et al., 2019). Hypoglossal nerve stimulation was most successful in patients with a higher arousal threshold, lower loop gain and good compensation; it may also be more efficacious in those with greater collapsibility (Op de Beeck et al., 2021b). On the other hand, according to a recent analysis (Wong et al., 2022), endotyping does not seem to be predictive of pharyngeal surgical outcomes. A key point emerging from the available response to therapy studies is that there is often no single trait that predicts the response to any non-CPAP therapy–even when the trait is explicitly targeted. Rather, knowledge of the traits in combination appears to be required. While further prospective validation studies are needed to confirm the use of endotypes in this context, knowledge of endotypic traits provides a promising means to identify subgroups of patients who are most likely to benefit from different therapies. Ultimately, clinically-applicable measurements of these traits will be needed before clinicians can utilize them to make treatment decisions for different subgroups of patients, i.e., precision medicine (Eastwood et al., 2011; Eckert et al., 2011; Edwards et al., 2012; Joosten et al., 2017; Randerath et al., 2018; Sands et al., 2018a; Bamagoos et al., 2019; Light et al., 2019; Taranto-Montemurro et al., 2019, 2020; Vena et al., 2020, 2022; Carter and Eckert, 2021; Op de Beeck et al., 2021a,b; Duong-Quy et al., 2022; Hedner and Zou, 2022b).

Methods for quantifying endotypic traits

Here, we review current sleep apnea endotyping methodologies and how they can be translated from laboratory research into standard clinical practice. There are three streams of research methods for investigating endotypic traits. First, the simplest method for trait estimation is to relate direct output parameters from standard polysomnography (PSG) to the underlying sleep apnea pathophysiology [e.g., high apnea index (AI) as an indicator for high upper airway collapsibility]. These methods often require minimal additional calculations but do not take advantage of the wealth of mechanistic information available in PSG studies. Second, in the physiological laboratory, gold standard signals are *directly measured* to assess ventilation and ventilatory drive, with or without careful experimental procedures to manipulate ventilatory drive. Such studies typically seek to demonstrate physiological differences between patients or effects of therapies. These methods require invasive measurements using specialized equipment and training that are not available in standard sleep clinics. Finally, in the clinical setting, methods of *estimating* ventilation and ventilatory drive have been developed, with the goal of translating physiological knowledge from the physiology laboratory to the clinical arena where gold standard recordings are not feasible. Such studies use data collected during a routine sleep study and seek to provide a physiologically-sound means to predict the likelihood of

responding to different interventions. These three approaches are summarized below.

Pathophysiological insights from the polysomnography report

Useful but somewhat rough estimates of most OSA endotypes can be garnered without complex calculations or non-standard measurement equipment. One common approach is to estimate upper airway collapsibility from routine PSG indices as well as anthropometric measures. Several indicators have been explored in the literature, including the fraction of hypopnea vs. apnea (i.e., $F_{hypopnea}$; lower values reflect greater collapsibility), apnea index (Vena et al., 2022), waist circumference, mean obstructive apnea duration, rapid eye movement apnea hypopnea index (REM-AHI), and non-REM obstructive apnea index (NREM-OAI) over NREM-AHI (Genta et al., 2020).

In addition, nadir oxygen saturation, high AHI and $F_{hypopnea}$ have been found to be independent predictors of arousal threshold (Edwards et al., 2014a), and short respiratory event duration has been used as an indicator for increased arousability from sleep (Sands et al., 2018c; Butler et al., 2019). Quantifying loop gain from PSG using simple approaches has remained elusive. Algorithms have been developed for predicting high loop gain from the cyclical self-similarity of respiratory events during sleep (Oppersma et al., 2021). A simpler approach was proposed recently where higher AHI and lower hypopnea-percentage (i.e., $F_{hypopnea}$) were used to predict higher loop gain values with moderate accuracy (Schmickl et al., 2022). Furthermore, high AHI during NREM vs. REM may indicate high loop gain, as loop gain has been shown to be lower in REM sleep (Landry et al., 2018; Joosten et al., 2021).

While, to our knowledge, no simple approaches have been published for deriving upper airway muscle compensation, there have been recent developments in training machine learning models to predict OSA endotypes and responses to treatment. These models utilize PSG variables and anthropometric measures as inputs and use machine learning or decision trees to classify patients for precision medicine in sleep apnea (Dutta et al., 2021, 2022).

Overall, these methods underline the fact that there is a wealth of physiologically relevant information in routine PSG reports that are not yet fully utilized for precision diagnoses.

Specialized CPAP manipulation in the physiology laboratory

CPAP manipulations have been used for decades in OSA research to investigate OSA pathophysiology (Younes, 2003, 2004; McGinley et al., 2008; Wellman et al., 2011, 2013; Edwards et al., 2012, 2014b; Eckert et al., 2013; Sands et al., 2014; Messineo et al., 2018). Many permutations of these methods involved the following concepts: (1) Patients are placed on an optimal CPAP that resolves flow limitation and provides stable breathing. Conceptually, at quiet, stable breathing; ventilation and ventilatory drive are at eupneic levels and are considered to be equal to each other. (2) Abruptly "dropping" CPAP to a subtherapeutic level reveals a flow-limited airway with reduced capacity for ventilation due to the maximally "passive" pharyngeal dilator muscles. (3) Over time (e.g., with more gradual CPAP dial-downs), ventilatory drive rises and activates the pharyngeal muscles, which typically yields an improvement in ventilation that is considered to reflect dilator muscle compensation. (4) The arousal threshold is typically measured as the ventilatory drive (e.g., diaphragm EMG via catheter) or esophageal pressure on breaths preceding arousals during the experimental reductions in CPAP levels. (5) Measurement of gold standard loop gain typically involves quantifying the size of the increase in ventilatory drive that occurs in response to a controlled reduction in ventilation.

The most widely used approach for OSA endotyping avoids the need for invasive measurements of ventilatory drive through the use of judicious CPAP dial-ups to optimal pressure. The underlying basis for this method was that ventilatory drive equals ventilation during these periods (Wellman et al., 2011, 2013). This method allows for the derivation of the endotypes without the use of specialized equipment that is not present in a standard PSG lab, such as diaphragm EMG and esophageal/epiglottic manometry for measuring respiratory effort (Eckert et al., 2011, 2013; Sands et al., 2014; Edwards et al., 2016b). Using non-standard methodologies or equipment requires higher levels of training and longer setup time, and often results in a more invasive experience for the patient. These factors all hinder large scale adoption of the methods, despite their potential for guiding treatment selection (Terrill et al., 2015; Sands et al., 2018b; Finnsson et al., 2021).

Nonetheless, specialized CPAP manipulation studies require advanced training and are limited to only several laboratories worldwide. Specialized CPAP equipment that allows pressure drops to lower than 4 cmH_2O are also not commercially available. Further, the average success rate of the CPAP drop method for estimating the four endotypic traits for each individual patient has been reported to be from 69% (Eckert et al., 2013) to 76% (Wellman et al., 2013), with difficulty initiating or maintaining sleep throughout the study procedures being a commonly reported issue (Edwards et al., 2012, 2014b; Eckert et al., 2013). The ratio of analyzable CPAP-drops per patient varied from a low of 16% (Edwards et al., 2014b) to a high of 70% (Eckert et al., 2013). These methods are therefore most suitable for assessing patients who are solid sleepers (higher arousal threshold) during periods of the night with the deepest sleep (Ratnavadivel et al., 2009, 2010). As a result, this approach is limited in its translational potential.

Gold standard signals during spontaneous breathing without CPAP

An important step in the transition from the physiology laboratory to non-invasive clinical measurements involves the assessment of traits from spontaneous breathing, measuring ventilation and ventilatory drive, without the use of CPAP manipulation.

For many years, investigators have measured the arousal threshold without CPAP manipulation, using direct, invasive, measurement of the ventilatory drive (typically via catheters placed

to assess negative esophageal or epiglottic pressures) prior to a scored arousal (Berry et al., 1996; Haba-Rubio et al., 2005; Eckert et al., 2011; Edwards et al., 2014a; Carter et al., 2016; Sands et al., 2018c). Extending this approach, a method was developed to assess collapsibility and muscle compensation directly from invasive measurement of ventilation (oronasal mask and pneumotach) and ventilatory drive (intraesophageal diaphragm EMG) (Sands et al., 2018b). The approach provides a ventilation-vs.-drive curve (see example in Figure 1B) describing pharyngeal mechanics that is conceptually similar to that measured via CPAP drops, but has the advantage of using direct measurement of these two variables, and captures the pathophysiology without disrupting the cyclic events that define the disorder.

Polysomnographic method

The Endo-Phenotyping Using Polysomnography (PUP) method was developed by Sands and colleagues to translate the above methods to estimates that could be used clinically (Terrill et al., 2015; Sands et al., 2018b). The approach was designed to estimate the pathophysiological endotypes of OSA from a standard clinical PSG without the need for invasive measurements. Currently, this method extracts an estimate of ventilatory flow from the nasal pressure signal. Tidal volume is calculated by integrating the flow signal, where ventilation is derived by dividing the tidal volume by each breath's duration. Ventilation is presented as a percentage of a local 7-min average, with 100% considered to represent eupneic ventilation. Thus, ventilation at 0% represents a complete apnea, 100% is eupneic breathing, and >100% is hyperpnea. Rather than invasively measuring ventilatory drive, an estimate is calculated from the ventilation signal, leveraging the assumption that ventilation reveals the ventilatory drive when the airway is open but not when it is obstructed. A drive estimate is derived using a chemoreflex model which takes the ventilation signal as input and outputs chemical drive according to the dynamics dictated by the model parameters (gain, time constant, delay). This chemical drive signal is best fit to the ventilation signal using least squares; specifically, the chemoreflex model parameters are adjusted. In addition, the presence of arousal is also used in the model. Namely, an additional wakefulness/arousal drive is considered during any breath that lies within the margins of a scored arousal; a single additional parameter (ventilatory response to arousal) (Edwards et al., 2013) is added to the chemical drive to yield the overall ventilatory drive; when arousals are scored, it is this ventilatory drive signal that is best fit to the ventilation signal. Goodness of fit, for least squares minimization, is only evaluated between scored events, i.e., when the airway is expected to be unobstructed. These estimates of ventilation and ventilatory drive are used in place of the gold standard signals (Terrill et al., 2015; Sands et al., 2018c; Finnsson et al., 2021; Gell et al., 2022). An illustration of estimated ventilation and ventilatory drive is shown in Figure 1A. With the normalized ventilation values and corresponding drive values, the PUP method can be used to derive loop gain (Terrill et al., 2015), arousal threshold (Sands et al., 2018c), upper airway collapsibility, and upper airway compensation (Sands et al., 2018b). Typically, these traits are derived and presented for NREM sleep. See an application of the method to patient data in Figure 2.

Scalability

PSG endotyping has since been used in multiple research applications (Wellman et al., 2011, 2013; Terrill et al., 2015; Sands et al., 2018b,c; Taranto-Montemurro et al., 2019, 2020; Finnsson et al., 2021; Alex et al., 2022), primarily in studies seeking to identify a patient subgroup that responds preferentially to existing and experimental interventions. However, authors of the work have required specialized software (MATLAB) and some training to independently generate trait data. To demonstrate that the approach is truly *scalable*, our team recently introduced "PUPpy" (Finnsson et al., 2021), a new independent implementation in the Python programming language of the PUP method, that was originally implemented in MATLAB. PUPpy is a cloud-enabled solution based on the original PUP method principles (Finnsson et al., 2021), and directly provides the user with endotypic trait values from uploaded clinically-collected PSG data. The trait values are congruent with the PUP method and demonstrated that there are no major hurdles anymore to making the analysis widely accessible to researchers and clinicians. To maintain the alignment of the PUPpy method with the original validation of the PUP method, it would be helpful to validate it against gold standard methods (e.g., CPAP drop method/gold standard ventilation and drive signals) to provide an opportunity for ongoing enhancement and development.

Normative values and demographic differences

As endotyping is an emerging field in sleep research, thresholds for abnormal endotypic trait values have not yet been established. Several studies have reported the range of values of different endotypic traits calculated using the PUP method. Table 1 describes two previously published datasets where PUP has been used for analysis: Osteoporotic Fractures in Men Study (MrOS) and Multi-Ethnic Study of Atherosclerosis (MESA) (Blackwell et al., 2011; Chen et al., 2015; Zhang et al., 2018; Alex et al., 2022). Here we also include a new dataset collected in Taiwan at the China Medical University Hospital (CMUH) that is unique for its clinical population, which we analyzed using PUPpy (Finnsson et al., 2021). The low, moderate, and high values for each trait are described for each of the three datasets based on their tertiles (Table 2). Notably, compared to the community studies, the clinical population appears to exhibit greater collapsibility and lower compensation, consistent with greater pharyngeal deficits, as expected. The clinical population also exhibited a higher average arousal threshold, perhaps a reflection of an increased physiological "sleepiness" (Edwards et al., 2014a) that may be expected of symptomatic individuals attending a sleep clinic. It is also possible that differences in race/ethnicity of the populations contribute to these differences, noting that Asian populations often exhibit greater anatomical compromise and collapsibility in obesity-adjusted analyses (O'Driscoll et al., 2019). Further

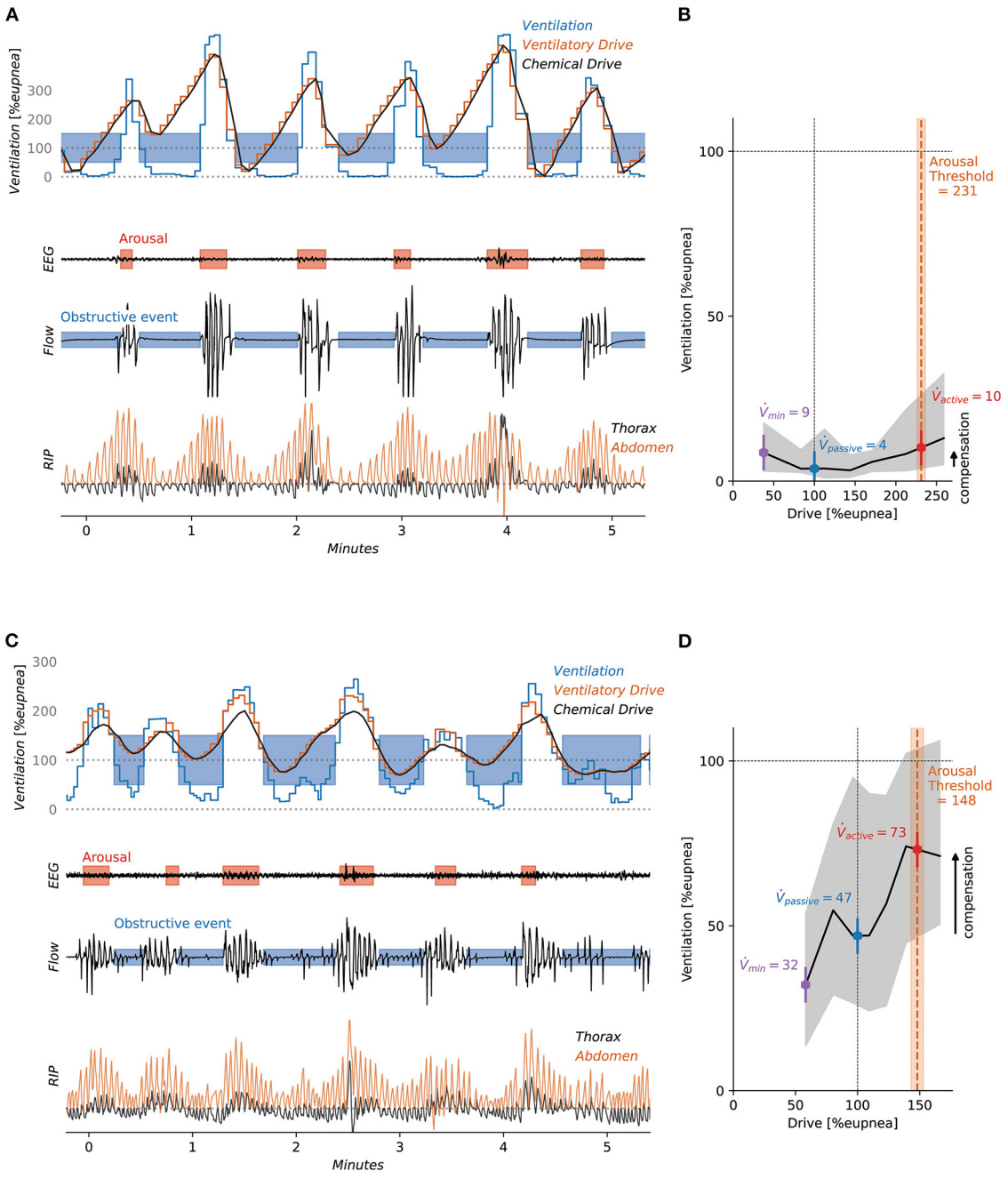

FIGURE 2
The figure shows two patients with different OSA expressions. Patient 1 **(A, B)** displays classic sleep apnea with high collapsibility and low upper airway compensation. Patient 2 **(C, D)**, has drive-dependent sleep apnea (Gell et al., 2022) where respiratory events correspond to reductions in chemical drive. As the drive increases the upper airway dilators are activated and some ventilation is restored, hence the upper airway compensation is larger.

understanding of the OSA etiology of different demographics via sleep apnea endotyping has the potential to provide insight into optimal treatment pathways.

Future methodological developments

The non-invasive PSG method described has several limitations with respect to accurately capturing ventilation and ventilatory drive. A recent debate on the topic highlighted some of the limitations of the method as well as giving suggestions for improvements (Sands and Edwards, 2023; Younes and Schwab, 2023). Here, we discuss areas of current development.

Limitations of manual scoring of respiratory obstruction

A fundamental assumption of the model-based endotype approach is that the airway is unobstructed and not flow-limited

TABLE 1 Descriptive statistics and endotype values in NREM sleep for different cohorts.

	PUP with cannula flow and modeled drive in NREM sleep	PUP with cannula flow and modeled drive in NREM sleep	PUPpy with cannula flow and modeled drive in NREM sleep.
	N = 2,316 [MrOS]	*N* = 1,792 [MESA]	*N* = 765 [CMUH]
Setting	Unattended in-home PSG, manually scored	Unattended in-home PSG, manually scored	In-lab PSG, manually scored PSG
Population	Community cohort	Community cohort	Clinical cohort
Age	76 [72–80]	68 [61–76]	41 [34–51]
Sex (M:F)	2316:0	866:926	641:124
Race/Ethnicity	3% Black, 91% White, 2% Hispanic, 3% Asian, 1% Other	27% Black, 24% Hispanic, 12% Chinese, 37% White	100% Southeast Asian***
BMI	27.0 [25.0–30.0]	28.2 [25.0–32.1]	28.9 [25.8–32.4]
AHI	20.0 [12.0–33.0]	20.8 [12.2–34.9]	25.9 [13.3–52.1]
Collapsibility ($\dot{V}$passive, %)†	71.5 ± 15.6	77.5 ± 14.4	62.0 ± 22.8
Collapsibility ($\dot{V}$min, %)	50.9 ± 22.5	63.7 ± 20.4	50.5 ± 17.2
Compensation ($\dot{V}$active-$\dot{V}$passive, %)	5.7 ± 24.1	6.1 ± 18.2	−3.6 ± 20.3
Loop gain (LG_1^*)	0.62 ± 0.17	0.58 ± 0.18	0.55 ± 0.18
Loop gain (LGn**)	0.50 ± 0.12	0.44 ± 0.11	0.38 ± 0.10
Arousal Threshold (%)†	148.2 ± 26.5	139.5 ± 23.9	159.10 ± 28.26

Values either presented as Median [IQR] or Mean ± SD *LG_1, the loop gain at 1 cycle/min, is typically used for endotyping from PSG instead of the steady-state loop gain (LG_0). This is because natural respiratory events rarely reach steady state, so LG_0 does not have good observability. LG_1 is more accurately observed since 1 cycle/min is closer to the frequency of respiratory events. **LGn represents the loop gain at the system's natural frequency. ***Based on knowledge of the Taiwanese population. †The values for Collapsibility ($\dot{V}$passive) and Arousal Threshold have been square root transformed for normality (Sands et al., 2018a; Alex et al., 2022 - Identifying obstructive sleep apnoea patients responsive).

TABLE 2 33rd percentile and 66th percentile (i.e., trentiles) of the endotypic traits in NREM sleep for different cohorts.

	33.3 percentile			66.6 percentile		
	MrOs	MESA	CMUH	MrOs	MESA	CMUH
Collapsibility ($\dot{V}$passive, %)†	70.3	76.8	58.7	78.7	83.7	75.5
Collapsibility ($\dot{V}$min, %)	46.1	63.2	45.7	64.9	74.8	59.4
Compensation ($\dot{V}$active-$\dot{V}$passive; %)	4.1	4.3	−7.4	11.1	8.2	6.2
Loop gain (LG1)	0.54	0.49	0.46	0.68	0.62	0.60
Loop gain (LGn)	0.45	0.38	0.34	0.55	0.47	0.42
Arousal threshold (%)†	134.9	127.7	142.4	156.0	144.4	165.3

†The values for Collapsibility ($\dot{V}$passive) and Arousal Threshold have been square root transformed for normality (Sands et al., 2018a; Alex et al., 2022 - Identifying obstructive sleep apnoea patients responsive).

during recovery hyperpnea as well as during periods where no respiratory events are scored (Terrill et al., 2015; Sands et al., 2018b; Finnsson et al., 2021). Recently our colleagues showed that some patients consistently exhibit flow-limited recovery breaths (Mann et al., 2021). In those patients, the ventilatory drive will be underestimated. To mitigate this, continuous measures of the severity of upper airway obstruction could be used to improve the model-estimated drive signal. Flow-shape-derived (Mann et al., 2019, 2021; Parekh et al., 2021) and RIP-derived (Finnsson, 2017; Parekh et al., 2021) breath-level obstruction measures have been explored with promising results. Continuous quantification of obstruction could further enhance the precision of drive and ventilation estimates in the presence of sustained flow limitation and a concomitant rise in baseline drive above eupneic levels.

Passive upper airway collapsibility

Passive upper airway collapsibility is most commonly represented by P_{crit} (Kirkness et al., 2008; Eckert et al., 2013) and represents the x-intercept of a plot of airflow or ventilation vs. CPAP pressure level. P_{crit} can be interpreted as the theoretical CPAP pressure level where the airway closes. Although P_{crit} has been considered a gold standard method for upper airway collapsibility, it requires manipulation of airway pressures (Kazemeini et al., 2022) and is inherently not observable during spontaneous breathing. By contrast, the y-intercept of the same ventilation-vs.-CPAP relationship, called "$\dot{V}_{passive}$," similarly provides a gold standard collapsibility measure in units of ventilation (Younes, 2003). $\dot{V}_{passive}$ represents the maximum level of ventilation that can be achieved at normal

ventilatory drive through a passive airway at atmospheric pressure. Importantly, patients spend their time spontaneous breathing at atmospheric pressure (by definition), so this variable is potentially both observable and physiologically relevant to their OSA pathophysiology.

Estimating passive upper airway collapsibility (ventilation at eupneic drive, "$\dot{V}_{passive}$") from non-invasive signals during spontaneous breathing requires an accurate assessment of the ventilatory drive. As discussed above, any underestimation of the ventilatory drive is expected to provide an overestimation of $\dot{V}_{passive}$. To address this concern, Vena et al. recently examined an alternative measure of passive collapsibility: ventilation at nadir drive ($\dot{V}_{min}$), a measure which is independent of systematic bias in drive levels (Vena et al., 2022). P_{crit} was found to be more strongly correlated with $\dot{V}_{min}$ ($r = -0.54$) than it is with $\dot{V}_{passive}$ ($r = -0.38$). We emphasize, however, that a perfect correlation is not necessarily expected since P_{crit} and $\dot{V}_{min}/\dot{V}_{passive}$ are inherently different measures. Nonetheless the modest correlation indicates that there remains room for further development. We also emphasize that $\dot{V}_{passive}$ measured from spontaneous breathing is systematically greater than that measured following an acute reduction in CPAP, likely because the baseline dilator muscle activity is greater off CPAP than immediately after an abrupt CPAP drop, even at similar drives. While the spontaneous breathing methods capture less of a truly passive tissue mechanical behavior, it may be advantageous to quantify the degree of collapsibility as it contributes to the pattern of cyclic events that define each patient's disorder.

Oral breathing

A key limitation of nasal pressure is that it captures nasal rather than combined oronasal airflow. Unfortunately, oral breathing is both prevalent and significant in OSA (Gleeson et al., 1986; Nascimento et al., 2019) and can be invoked by obstructive respiratory events (Suzuki et al., 2015; Lebret et al., 2018). Errors in trait estimates are expected for those with the most pervasive mouth opening during sleep (Redline et al., 2007).

Several auxiliary flow sensors have been proposed to mitigate the effects of oral breathing. An oronasal thermistor is frequently invoked (Redline et al., 2007), yet this sensor technology does not provide a linear flow measurement for quantitative use (Farré et al., 1998; Redline et al., 2007). When properly calibrated and processed, respiratory inductance plethysmography (RIP) can be used to assess ventilation (Montazeri et al., 2021). With careful calibration, RIP could provide a flow signal to generate traits similar to those derived from oronasal flow and may provide a more reliable alternative to nasal pressure in circumstances with considerable mouth breathing.

Repeatability and physiological variability

It is established that some traits vary within a night. Given both physiological variability and measurement noise, there may be concerns about repeatability of estimated trait values generated from PSG methods. Most notably, collapsibility is greater in supine position than in lateral position (Ong et al., 2011) but often appears unaffected by sleep stage (Ong et al., 2011; Joosten et al., 2021; Messineo et al., 2022). Loop gain, however, is lower during REM sleep than during NREM (Joosten et al., 2021). Interestingly, upper airway muscle compensation is largely unaffected by state (Messineo et al., 2022). As with prior physiology studies, trait values reported by the PUP method for these traits are the medians during NREM for the night of study, and physiological variations are incorporated into the 95 percentile confidence intervals of the estimated values.

The traits derived from PUP have been shown to have a moderate-to-good within-night repeatability, with correlations (Pearson correlation) ranging from 0.69 to 0.83 (Alex et al., 2022) for two independent measures taken from the same night. Night-to-night repeatability is similar, with correlations (intra-class correlation) ranging from 0.72 to 0.83 (Strassberger et al., 2023) in one study, and 0.67–0.91 in another (Tolbert et al., 2023). In general, intraclass correlations for collapsibility, loop gain, and arousal threshold have been >0.8 but lower for compensation. Of note, compensation is calculated as the difference in two collapsibility measures (V̇active minus V̇passive) such that measurement error is augmented. Overall, however, night-to-night repeatability is similar to that observed for apnea-hypopnea index (Alex et al., 2022). Long term repeatability (6–7 years between studies), at least in an elderly male population, has been shown to be more modest with r = 0.36–0.61.

With the goal of increasing repeatability, incorporating the effects of sleep state, position, arousal intensity (Azarbarzin et al., 2014; Amatoury et al., 2016), or other covariates may be beneficial, but the optimal means to do so remains an area for future research.

Future clinical utility

Over the last decade, the field of sleep medicine has actively investigated novel clinically-applicable measurements that capture differences in underlying disease pathophysiology to aid clinicians in selecting the most appropriate treatments for their patients (Wellman et al., 2011; Carberry et al., 2018; Schmickl et al., 2018; Sutherland et al., 2018; Edwards et al., 2019; Light et al., 2019; Martinez-Garcia et al., 2019; Lyons et al., 2020; Siriwardhana et al., 2020). Until now, clinical interventions for the treatment of OSA have primarily followed a one-dimensional treatment pathway: A single diagnostic parameter, the AHI, or one of its analogs (Epstein et al., 2009; LCD, 2022; NCA- CPAP, 2022) was used to determine the need for a single intervention, CPAP. This pathway from diagnosis to treatment involves minimal mechanistic information which may lead to simplistic decision-making, which in turn may deter new physicians from entering the field (Watson et al., 2017). On the other hand, OSA is a highly complex disorder that manifests as the downstream product of interacting deficits in multiple pathophysiological traits, and involves aspects of upper airway anatomy, pulmonary mechanics, ventilatory control, pharyngeal muscle control, and sleep neurobiology. Unfortunately, many of these academically challenging aspects are not currently considered in daily clinical sleep medicine to benefit patients. Novel clinically available tools to capture these underlying mechanisms

could potentially change the nature of clinical sleep medicine. Once available–and supported by data on their clinical utility–we consider that clinicians will have the means available to better understand the etiology of an individual's disorder and use this information to select the optimal treatment for their patient.

The pathway to widespread use of endotypic traits is expected to involve several research and clinical challenges. Greater accuracy of the estimates of traits through improved processing and estimation of ventilation and ventilatory drive will be needed. Such studies will need to be guided by gold standard signals obtained from physiology laboratory settings with simultaneous clinical signals. The field will further benefit from a shift toward improved respiratory signal fidelity (perhaps in the opposite direction to the current approach of determining how few signals can be used to obtain a diagnostic AHI value). Currently, some in-laboratory clinical sleep recording systems over-filter airflow signals well beyond AASM criteria: High pass filters (baseline drift filter) should be set to "off" (per AASM recommended filter settings); while the AASM recommended filter setting criteria allows up to 0.03 Hz, even this level compromises advanced flow waveform analysis. Low pass filters, often used by technicians to remove snoring vibrations to assess score flow reductions for hypopneas, should be no lower than 12.5 Hz to evaluate flow limitation (Mann et al., 2019, 2021), but AASM recommends no lower than 100 Hz (equivalent to "off" for sampling rates 25–200 Hz). The field is also lacking a standardized system for signals storage (e.g., signal labels vary widely) and annotations tabulations (e.g., event and epoch names vary widely, often durations are not available) to facilitate automated analyses. Manual sleep and event scoring will presumably be replaced with automatic scoring, that for many years may require manual quality control review. The software for analyzing traits needs to be at the fingertips of clinical sleep laboratories through data uploading or built as an add-on to commercially available sleep systems so that summary data can make their way into the "future PSG report." The feasibility of this has been demonstrated through the PUPpy cloud-based implementation of the method (Finnsson et al., 2021). Clinicians will need guidance on how to interpret trait data with respect to the reliability and the likely responses to different therapies. For this to be evidence-based, substantially larger datasets containing raw PSG data before and after different therapies are needed to better define the expected treatment responses for different endotypic subgroups, ultimately allowing a clinician to see the expected treatment effects (and 95% confidence) for a host of therapies based on their values of collapsibility, loop gain, etc. Such data is also needed to better define "high" and "low" values for a given trait. In the meantime, the current use of endotypic traits in recent clinical trials is encouraging. Subsequently, larger studies will be needed to show that knowing the endotypic traits provides better patient outcomes and is more cost-effective than not knowing them (and using trial-and-error to select therapeutic interventions). Potentially, these studies could extend to whether endotypes should serve as an aid in deciding if a patient's OSA is severe enough to warrant treatment or not, although novel phenotypic traits such as hypoxic burden (Azarbarzin et al., 2019), heart rate response to events (Azarbarzin et al., 2021), or baseline levels of sleepiness/hypertension (Randerath W. J. et al., 2021) could be better suited for that purpose. There is a substantial amount of challenging work to do for investigators, clinicians, and engineers to make precision sleep medicine a reality.

In summary, it is now attainable to estimate individual differences in the key traits contributing to sleep apnea–collapsibility, compensation, arousal threshold, and loop gain–through analysis of ventilation and ventilatory drive in a routine clinical sleep study, i.e., without invasive measurements or specialized operators. Multiple challenges are being overcome for the translation of these endotypic traits into clinical practice. We consider that such mechanistic information will facilitate precision medicine for OSA, and in doing so, make clinical sleep medicine a more enriched and rewarding field.

Ethics statement

This study involved secondary analysis of anonymized data. MESA and MrOS were multi-site cohort studies; data is publicly available at the National Sleep Research Resource Repository, at www.sleepdata.org/datasets and https://mrosonline.ucsf.edu/ respectively. The studies were reviewed by Institutional Review Boards at each site. The analysis of data from the CMUH cohort was reviewed and approved by the Institutional Review Board of China Medical University Hospital (CMUH109-REC3-018). All participants for all studies provided written informed consent.

Author contributions

EF, EA, SH, JÁ, and SS contributed to the conception of the review. EF, EA, SH, and JÁ wrote sections of the manuscript with revisions from SS. SS, W-JC, RA, and L-WH contributed the data. ÞS and RA organized the data and performed statistical analysis. EF performed statistical analysis and created all figures. JÁ and SS supervised the work. All authors read, revised, and approved the submitted manuscript.

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Conflict of interest

AW served as a consultant for Apnimed, Nox Medical, Inspire, Takeda, Mosanna, and Somnifix. He has received grants from Regeneron and Somnifix. He also has a financial interest in Apnimed Corp., a company developing pharmacologic therapies and wearable oximetry devices for sleep apnea. AW's interests were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. SS served as a consultant for Nox Medical, Merck, Apnimed, Inspire, Eli Lilly, Respicardia, Forepont, and LinguaFlex, and has project grant support from Apnimed, Prosomnus, and Dynaflex; his financial interests are managed by his institution. EA, EF, SH, ÞS, and JÁ were all employees of Nox Medical.

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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Risk assessment model for sleep disturbance based on gastrointestinal myoelectrical activity in middle-aged and elderly people

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Background: Sleep disturbance has become a considerable factor affecting the quality of life for middle-aged and elderly people; however, there are still many obstacles to screening sleep disturbance for those people. Given the growing awareness of the association between gastrointestinal function and sleep disturbance, our study aims to predict the risk of sleep disturbance using gastrointestinal electrophysiological signals.

Methods: The Pittsburgh Sleep Quality Index and gastrointestinal electrophysiological signals of 914 participants in western China were used to establish the model. Demographic characteristics and routine blood test were collected as covariates. Participants were randomly assigned into two sets with a 7:3 ratio for training and validation. In the training set, the least absolute shrinkage and selection operator (LASSO) regression and stepwise logistic regression were used, respectively for variables selection and optimization. To assess the model performance, receiver operator characteristic (ROC) curve, calibration curve and decision curve analysis (DCA) were utilized. Then, validation was performed.

Results: Thirteen predictors were chosen from 46 variables by LASSO regression. Then, age, gender, percentage of normal slow wave and electrical spreading rate on the pre-meal gastric channel, dominant power ratio on the post-meal gastric channel, coupling percent and dominant frequency on the post-meal intestinal channel were the seven predictors reserved by logistic regression. The area under ROC curve was 0.65 in the training set and 0.63 in the validation set, both exhibited moderate predictive ability. Furthermore, by overlapping the DCA results of two data-sets, there might be clinical net benefit if 0.35 was used as reference threshold for high risk of sleep disturbance.

Conclusion: The model performs a worthy predictive potency for sleep disturbance, which not only provides clinical evidence for the association of gastrointestinal function with sleep disturbance, but also can be considered as an auxiliary assessment for screening sleep disturbance.

KEYWORDS

sleep disturbance, Electrogastroenterography, LASSO regression, decision curve analysis, ROC curve

Introduction

Sleep disturbance is one of the most prevalent mental disorders, especially among the middle-aged and elderly people (1), which generally manifest insomnia, narcolepsy, poor sleep quality, and obstructive sleep apnea (OSA) syndrome (2). According to epidemiological surveys, the prevalence of sleep disturbance increases significantly with aging and affects more than half of those over the age of 60 (3); and moreover, the COVID-19 pandemic has exacerbated the effects of sleep disturbance (4). Sleep disturbance could drastically reduces a person's quality of life (5), and raises the chance of developing a mental disorder, such as depression or anxiety, or both, especially in the middle-aged and elderly individuals (6–9). Furthermore, it has been shown that elderly individuals who have sleep disturbance exhibit a higher risk of developing neurological diseases including Parkinson's and Alzheimer's diseases as well as stroke, migraine, and cognitive impairment (10–14). On the other hand, elderly people with sleep disturbance are more reliant on sleeping pills (15, 16), which adds to their illness burden, impacts the ability to communicate with others, and injures the energy in social activities during the day (17).

A general community screening is required for such individuals due to the significance of sleep disturbance in the senior population, although there are some challenges. Currently, patient-rated questionnaires, such the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI), are trustworthy tools for estimating the severity of sleep disturbance (18). However, since the use of PSQI and ISI necessitates that participants have the necessary cognitive capacities and educational levels, it is challenging to become effective and widely accessible community screening tools for all middle-aged and elderly people or those with cognitive decline. In addition, polysomnography could provide precise estimations of sleep duration and quality, but due to its costly and time-consuming drawbacks, it is also difficult to become a routine clinical procedure (19). Therefore, a practical, effective, and objective instrument is urgently needed to aid to the screening of sleep disturbances in the middle-aged and elderly people.

In recent years, the bidirectional regulatory mechanism of gut-brain axis has attracted a lot of scientific attention, which highlights the close connection between the gastrointestinal homeostasis and the health of the central nervous system (CNS), and reveals the significant effect of gastrointestinal function changes on the CNS (20). The conception of the gut-brain axis also corresponds to an old Chinese proverb saying that a disturbed stomach makes it impossible to go asleep, which was an early exploration in the association between gastrointestinal function and sleep disturbance.

Numerous studies have shown this close association between gastrointestinal dysfunction and sleep disturbance. For instance, some clinical studies have found that gastrointestinal diseases like inflammatory bowel disease, gastro-oesophageal reflux disease, digestive disease, and functional gastrointestinal disorders are more likely develop symptoms of sleep disturbance, and these diseases that most frequently impair sleep are acid-related (21–23). Additionally, Zhe Wang et al. (24) pioneered the microbiota-gut-brain axis that the gut microbiota is bidirectional correlated with sleep behavior, which may contribute to the regulation of sleep quality. These findings raise the prospect of predicting the risk of sleep disturbance by using diagnostic tools for gastrointestinal function.

Electrogastroenterogram (EGEG) is a non-invasive method that uses cutaneous electrodes applied to the abdominal skin across the stomach and intestine to capture myoelectrical activity (25). The myoelectric activity of the gastrointestinal tract is primarily composed of slow wave and spinal potential. Since its popularization in the 1990s, EGEG has been used as an auxiliary method of diagnosing a variety of gastrointestinal functional disorders (26). Furthermore, W C Orr et al. (27) revealed that patients with irritable bowel syndrome had significantly different manifestations of EGEG during sleep compared to normal people. Anjiao Peng et al. (28) also demonstrated that patients with rapid eye movement sleep behavior disorder also had irregular changes of EGEG. Based on these lines of evidences, our study aims to compare the differences in gastrointestinal myoelectrical activity by EGEG between patients with sleep disturbance and healthy controls, and establishes a risk assessment model with the expectation of considering as an auxiliary assessment for sleep disturbance in the middle-aged and elderly people.

Methods and materials

Subjects

In this cross-sectional research, participants over the age of 40 were recruited from 60 communities in western China between January 2020 and December 2021. All subjects voluntarily participated in our study and signed informed consent, and they were required to possess the necessary knowledge and communication ability to complete the relevant questionnaire and clinical diagnostic. The exclusion criteria for subjects included: 1) Subjects diagnosed with gastrointestinal diseases such as gastritis and gastric ulcer, within the last 6 months, 2) Subjects with gastrointestinal discomfort such as diarrhea and constipation, 3) Subjects with a history of drug use within the past week, 4) Subjects with severe cardio, liver and kidney dysfunction or metabolic diseases such as diabetes, 5) Subjects with major mental illness. Following that, all subjects were told to abstain from alcohol and follow a light diet for 3 days in order to complete the EGEG test, along with a sleep disturbance questionnaire and a routine blood test on the same day. All clinical examinations and questionnaire assessments were conducted jointly by neurology physicians from the West China hospital and community health service staff. For each subject, general information on age, gender, body mass index (BMI), and the history of smoking and alcohol drinking was collected, clinical information including the results of PSQI questionnaire, routine blood tests, and EGEG examination was also collected. This study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 2018–491, 2022–1,138).

Routine blood test

We required each participant in our study undergo a routine blood test, and collected their most common blood glucose and lipid information such as glucose, triglyceride (TG), total cholesterol (Tch), high density lipoprotein (HDL) and low density lipoprotein (LDL).

EGEG records

We used an eight-channel gastrointestinal electromyograph (XDJ-S8, Hefei Kaili Company, Hefei, China) to measure the gastrointestinal myoelectrical activity. Prior to the EGEG examination, all participants were instructed to fast for at least 6 hours and to refrain from consuming alcohol and spicy, greasy, or irritating foods for at least 3 days. In a supine position, the measurement of EGEG was performed. Eight gastrointestinal electrodes, including four gastric electrodes (corpus gastricum, gastric antrum, gastric lesser curvature, and gastric greater curvature), and four intestinal electrodes (ascending colon, transverse colon, descending colon, and rectum), were positioned on the abdominal skin (Hanjie Company. Ltd., Shanghai, China), as shown in Figure 1.

The reference electrode was positioned on the medial wrist of the right hand, and the grounding electrode was positioned on the medial ankle of the right leg. Participants were instructed to remain still for the whole 6 minutes of the pre-meal EGEG recording. Following that, they were received a mealtime functional load test, which providing about 200 kcal of food, and accepted a 6 minutes post-meal EGEG recording after waiting 5 minutes.

EGEG data processing

The background noise was filtered out from the EGEG recordings by setting a high cutoff frequency of 0.1 Hz and a low cutoff frequency of 0.008 Hz. The EGEG recordings were produced at sampling rate of 1 Hz.

After visual inspection for artifacts, the raw EGEG data was automatically calculated by the computer alongside the EGEG, and the following indicators of each electrode were collected separately: 1) mean amplitude of waveform (MAW), 2) mean frequency of waveform (MFW), 3) electrical rhythm disturbance (ERD), 4) reaction area of waveform (RAW), 5) electrical spreading rate (ESR), 6) dominant frequency (DF), 7) dominant power ratio (DPR), 8) percentage of normal slow wave (PNSW), 9) coupling percent (CP).

Given the high degree of internal consistency among the electrode recording data on the gastric and intestinal channels, we merged the electrode indicators by averaging four gastric and four intestinal electrodes separately. Meanwhile, due to the EGEG tests were conducted pre-meal and post-meal, a total of 36 EGEG parameters were eventually derived for each participant.

Sleep disturbance assessment

The PSQI questionnaire was used to assess sleep quality of the participants in the past month, and to diagnose whether they had a sleep disturbance. The PSQI questionnaire consists of 19 self-reported questions and five questions that should be answered by roommates, which are used only for clinical information and not tabulated in the scoring. The 19 self-reported questions were used to calculate the PSQI score, which could divided into seven components, with each component scored from 0 to 3. The seven components separately are: 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbances, 6) use of sleeping medication, and 7) daytime dysfunction. The sum of these components produces a global score, which ranges from 0 to 21, where a higher score indicates worse sleep quality. A total score over than eight points is considered as having a sleep disturbance, and whether the subjects had a sleep disturbance is the outcome variable in our study (29).

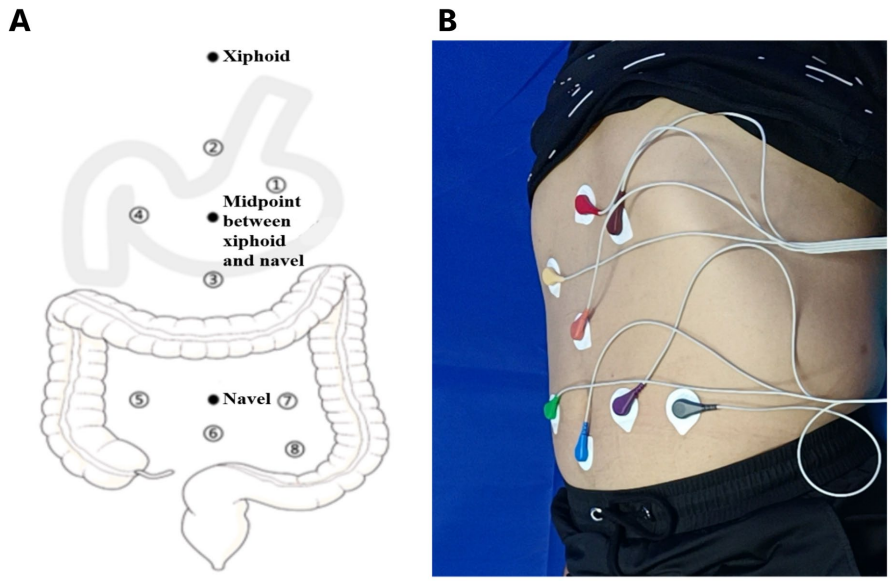

FIGURE 1
(A) A pattern diagram of electrodes positioning for EGEG recording. Eight electrodes from gastric and intestinal channels reflect the myoelectrical activity, including four gastric electrodes (corpus gastricum, gastric lesser curvature, gastric greater curvature, gastric antrum), and four intestinal electrodes (ascending colon, transverse colon, descending colon, rectum). **(B)** A sample diagram of the positioning process in EGEG examination. EGEG, electrogastroenterogram.

Statistic analysis

Variables selection

In linear regression models, the least absolute shrinkage and selection operator (LASSO) regression is a shrinkage and variable selection approach that might aid to the identification of significant predictors. LASSO regression could shrink a portion of the regression coefficients towards zero, and any predictors with a coefficient of zero are eliminated from the model. For forecasting the response variable, the remaining predictors with nonzero coefficients are regarded as being the most crucial (30). Using the type measure of-2log-likelihood and the binomial family to centralize and normalize the included variables, and the optimum lambda value was chosen by LASSO regression with 10 fold cross-validation. The best performing model was created using the "Lambda.min" setting.

According to the theoretical requirements for external validation, the total number of participants in our study were randomly split into a training set and a validation set in a 7:3 ratio. We included a total of 46 variables for variables screening, including the demographic characteristics, the results of routine blood test, and 36 EGEG parameters.

Considering the large number of variables included in this study, in order to ensure sufficient statistical efficiency of the assessment model in the training set, we required that the sample size of the training set should be at least 10 times more than the number of variables, and therefore the estimated total sample size for this study should be at least 658 people.

Setting risk assessment model

The statistic analysis in our study consisted of two parts: variables selection and assessment of predictive power. The data in the training set was analyzed using the LASSO regression in order to select the optimal predictors from all the variables. The predictors chosen from LASSO regression was further optimized by using stepwise multivariable logistic regression. Then, final version of risk assessment model was established and plotted the nomogram of the model. The odds ratio (OR) and 95% confidence interval (CI) were used in our study to define the contributions and to produce the nomogram.

Furthermore, several validation methods were used to evaluate the predicting efficiency of the risk assessment model, both into the training set and the validation set. The area under the receiver operating characteristic (ROC) curve was used to evaluate the performance of the risk assessment model in identifying true positive patients with sleep disturbance from participants. The calibration curve, accompanied by the Hosmer-Lemeshow test, was used to assess the calibration of this model (31). The decision curve analysis (DCA) was used to determine the clinical practicability of model according to searching the best net benefit under the different threshold probabilities (32). All analyzes were performed using R version 4.1.3 with packages glmnet and rms, and the significance level was set as a two tailed alpha <0.1.

Results

A total of 914 subjects, comprising 275 males and 639 females, were included in the study and completed relative clinical examinations. Of these, 301 participants (32.93%) were diagnosed with sleep disturbance. 639 and 275 participants were assigned to the training and validation sets, respectively, as a result of the random assignment in a 7:3 ratio. We compared each variable between patients with sleep disturbance and healthy controls in both groups, as detailed in Table 1.

According to the results, age, ESR and DF on the pre-meal gastric channel, as well as DF on the post-meal intestinal channel were shown to be significantly different between patients with sleep disturbance and healthy control in both sets ($p < 0.1$). In addition, variables that had significant differences between sleep disturbance and healthy control in the training set alone included gender, ERD, DPR, PNSW and CP on the post-meal gastric channel, DPR, PNSW, and CP on the intestinal gastric channel; in the validation set alone included MAW and RAW on the pre-meal gastric channel, MFW, ERD and DF on the pre-meal intestinal channel, MFW and RAW on the post-meal intestinal channel.

Among the 46 associated variables, 13 potential predictors were chosen in the training set by binomial LASSO regression. These predictor variables were age, gender, LDL, ESR, DF, and PNSW on the pre-meal gastric channel, DPR on the pre-meal intestinal channel, RAW, DPR, and CP on the post-meal gastric channel, DF, DPR and CP on the post-meal intestinal channel. The variables screening processed by LASSO regression and ten-fold cross validation is shown in Figure 2, and the coefficients of retained variables are shown in Supplementary Sup S1.

The retained 13 predictors variables used stepwise binomial logistic regression for further optimization, and established the final risk assessment model. The final risk assessment model for sleep disturbance consists of seven predictors, including age, gender, PNSW and ESR on the pre-meal gastric channel, DPR on the post-meal gastric channel, DF and CP on the post-meal gastric channel. Among these predictors, increasing age associated with a higher risk of sleep disturbance, and male had a lower risk of sleep disturbance than female. With the exception of the DPR on the post-meal gastric channel, the EGEG variables were both negative associated with the risk of sleep disturbance, and details are presented in Table 2. All predictors except gender were significant at the 0.05 level. To facilitate risk assessment of sleep disturbance using these predictor variables, the nomogram and dynamic nomogram were both created and are shown in Figure 3, which is helpful to carry out personalized clinical evaluation.

In terms of model validation and efficiency evaluation, we utilized the model to generate the predicted probability for 275 subjects in the validation set, and plotted the corresponding ROC curve to evaluate its sensitivity and specificity. The area under ROC curves were both above 0.6 in the two groups, indicating that the model exhibited a satisfying robustness. The results of sensitivity were 0.74 and 0.81 in the training and validation set respectively, meaning that the risk assessment model performed well in identifying true positive patients of sleep disturbance, but the results of specificity were 0.51 and 0.43, respectively, indicating that the model has insufficient ability to identify false negative patients, as shown in Figure 4.

Furthermore, we plotted the calibration curve and decision curve of the model both in two datasets, as shown in Figures 5, 6. The results of calibration curves in both datasets showed consistency between ideal curve and bias-correct curve; however, due to insufficient number of patients in the validation set, the curve deviated slightly from the apparent line. In the DCA, the threshold range of prediction probability were 0.34–0.63 and 0.29–0.35 in two sets, respectively, and

TABLE 1 The demographic characteristics, hematological parameters, and EGEG variables of the middle-aged and elderly subjects in training and validation set.

Variables	Training set (*N* =639)			Validation set (*N* =275)		
	Sleep disturbance (*N* =219)	Health control (*N* =420)	*p* value	Sleep disturbance (*N* =82)	Health control (*N* =193)	*p* value
Demographic characteristics						
Gender			0.092*			0.289
Male	160 (73.06)	278 (66.19)		64 (78.05)	137 (70.98)	
Female	59 (26.94)	142 (33.81)		18 (21.95)	56 (29.02)	
Smoking	30 (13.70)	51 (12.14)	0.663	9 (10.98)	23 (11.92)	0.986
Alcohol	50 (22.83)	100 (23.81)	0.858	12 (14.63)	43 (22.28)	0.199
Age	57.39 ± 6.29	55.63 ± 5.92	0.001***	56.73 ± 6.14	55.11 ± 6.35	0.050**
BMI	24.11 ± 3.27	24.22 ± 2.89	0.654	24.07 ± 3.38	24.64 ± 3.26	0.195
Hematological parameters						
Glucose	5.59 ± 1.57	5.45 ± 1.19	0.275	5.33 ± 1.15	5.39 ± 1.05	0.695
TG	1.65 ± 1.25	1.60 ± 1.07	0.620	1.51 ± 0.80	1.74 ± 1.72	0.128
Tch	5.47 ± 0.93	5.36 ± 0.97	0.143	5.30 ± 1.04	5.44 ± 0.99	0.291
HDL	1.80 ± 0.48	1.76 ± 0.49	0.339	1.78 ± 0.49	1.76 ± 0.50	0.756
LDL	3.07 ± 0.75	2.98 ± 0.70	0.167	2.96 ± 0.79	3.03 ± 0.71	0.457
Gastric channel pre-meal						
MAW	174.88 ± 93.31	174.28 ± 87.87	0.938	195.28 ± 97.57	168.92 ± 87.10	0.036**
MFW	3.50 ± 0.31	3.47 ± 0.32	0.279	3.42 ± 0.29	3.45 ± 0.32	0.485
ERD, %	20.93 ± 3.54	20.96 ± 3.75	0.906	21.49 ± 4.78	20.97 ± 3.60	0.374
RAW	62.54 ± 33.04	62.95 ± 31.61	0.880	69.45 ± 35.68	60.38 ± 30.69	0.047**
ESR	0.87 ± 1.51	1.17 ± 1.94	0.031**	0.62 ± 1.13	1.17 ± 1.81	0.002***
DF	3.02 ± 0.24	2.98 ± 0.25	0.054*	2.95 ± 0.24	3.00 ± 0.26	0.097*
DPR, %	60.98 ± 6.38	61.08 ± 6.19	0.861	62.40 ± 6.63	61.24 ± 5.95	0.175
PNSW, %	58.38 ± 8.00	59.36 ± 8.47	0.148	60.19 ± 8.81	59.49 ± 7.73	0.532
CP, %	90.81 ± 7.07	90.04 ± 7.98	0.216	89.70 ± 8.06	90.93 ± 6.89	0.228
Intestinal channel pre-meal						
MAW	186.70 ± 115.78	191.62 ± 117.46	0.612	167.35 ± 98.65	183.66 ± 111.59	0.230
MFW	12.81 ± 2.30	12.98 ± 2.40	0.376	12.12 ± 2.02	12.83 ± 2.26	0.011**
ERD, %	23.98 ± 5.88	23.34 ± 5.78	0.196	25.11 ± 4.97	23.01 ± 5.59	0.002***
RAW	70.06 ± 41.83	72.18 ± 43.04	0.547	62.71 ± 36.76	68.60 ± 40.19	0.240
ESR	0.38 ± 0.77	0.45 ± 0.92	0.333	0.49 ± 1.07	0.41 ± 0.79	0.545
DF	11.57 ± 2.66	11.80 ± 2.86	0.312	10.91 ± 2.44	11.61 ± 2.73	0.035**
DPR, %	30.16 ± 6.00	30.98 ± 6.25	0.108	30.71 ± 6.60	31.22 ± 6.23	0.557
PNSW, %	51.84 ± 11.28	52.43 ± 13.17	0.553	54.84 ± 10.80	52.79 ± 13.17	0.179
CP, %	82.32 ± 17.60	82.97 ± 18.24	0.665	82.78 ± 18.99	83.47 ± 16.57	0.776
Gastric channel post-meal						
MAW	206.86 ± 93.50	211.29 ± 94.21	0.571	221.58 ± 98.08	204.96 ± 106.15	0.212
MFW	3.42 ± 0.33	3.42 ± 0.31	0.871	3.37 ± 0.27	3.42 ± 0.29	0.108
ERD, %	20.47 ± 4.04	21.10 ± 4.00	0.062*	20.19 ± 3.47	20.68 ± 3.90	0.299
RAW	73.44 ± 33.55	75.93 ± 33.44	0.373	79.07 ± 34.85	72.71 ± 36.26	0.173
ESR	1.31 ± 2.33	1.10 ± 2.13	0.252	1.17 ± 2.73	1.15 ± 2.05	0.937
DF	2.98 ± 0.27	2.97 ± 0.29	0.720	2.96 ± 0.26	2.96 ± 0.27	0.858
DPR, %	62.86 ± 6.07	61.5 ± 6.08	0.007***	63.44 ± 6.39	62.60 ± 6.18	0.313
PNSW, %	60.95 ± 8.35	59.67 ± 8.26	0.065*	61.63 ± 8.23	61.11 ± 8.50	0.637
CP, %	93.90 ± 5.85	92.58 ± 7.27	0.013**	92.40 ± 7.82	93.11 ± 5.95	0.465
Intestinal channel post-meal						
MAW	177.24 ± 96.21	187.78 ± 97.48	0.192	160.37 ± 76.60	176.75 ± 92.01	0.129
MFW	12.01 ± 1.89	12.13 ± 2.16	0.490	11.28 ± 1.77	12.16 ± 2.22	0.001***
ERD, %	25.73 ± 4.95	25.04 ± 5.23	0.102	25.94 ± 4.54	25.03 ± 4.77	0.134
RAW	66.12 ± 34.92	69.95 ± 35.32	0.191	58.96 ± 27.24	65.90 ± 33.23	0.073*
ESR	0.54 ± 1.02	0.57 ± 1.33	0.770	0.71 ± 1.18	0.56 ± 1.03	0.322
DF	10.46 ± 2.10	10.81 ± 2.51	0.059*	10.05 ± 1.96	10.85 ± 2.44	0.004***
DPR, %	28.96 ± 4.79	29.79 ± 5.03	0.042**	29.34 ± 4.94	29.77 ± 4.54	0.505
PNSW, %	53.60 ± 9.30	53.96 ± 10.44	0.649	54.30 ± 8.32	53.73 ± 10.66	0.635
CP, %	89.85 ± 10.33	91.71 ± 10.25	0.031**	91.26 ± 9.83	90.92 ± 10.42	0.799

TG, triglyceride; Tch, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; MAW, mean amplitude of waveform; MFW, mean frequency of waveform; ERD, electrical rhythm disturbance; RAW, reaction area of waveform; ESR, electrical spreading rate; DF, dominant frequency; DPR, dominant power ratio; PNSW, percentage of normal slow wave; CP, coupling percent. Classification variables are described in the form of frequency (%); Statistical significance, *$p < 0.10$; **$p < 0.05$; ***$p < 0.01$.

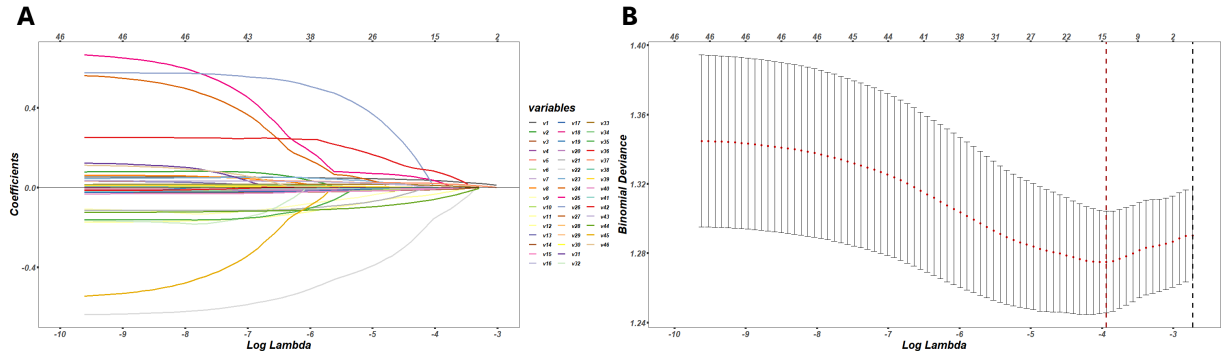

FIGURE 2
(A) The process of variables selection by binomial LASSO regression, a coefficient profile plot was produced against the log (lambda) sequence, different colors represent the different variables. **(B)** The results of ten-fold cross validation, by verifying the optimal lambda in the LASSO model, the partial likelihood deviance (binomial deviance) curve was plotted, and dotted vertical lines were drawn based on minimum lambda and standard error criteria.

TABLE 2 Risk assessment model of sleep disturbance in middle-aged and elderly people.

Variables	Beta	Std.error	Z value	OR	95%CI		*p* value
					Lower	Upper	
Age	0.050	0.015	3.446	1.052	1.022	1.082	0.001***
Gender, ref. = female	−0.340	0.193	−1.763	0.711	0.485	1.035	0.078*
Pre-meal							
PNSW of gastric channel	−0.024	0.011	−2.211	0.976	0.956	0.997	0.027**
ESR of gastric channel	−0.127	0.053	−2.381	0.881	0.790	0.974	0.017**
Post-meal							
DPR of gastric channel	0.041	0.015	2.774	1.042	1.012	1.073	0.006***
CP of intestinal channel	−0.017	0.008	−2.015	0.984	0.968	1.000	0.044**
DF of intestinal channel	−0.089	0.039	−2.283	0.914	0.845	0.986	0.022**

OR, odds ratio; ESR, electrical spreading rate; DF, dominant frequency; DPR, dominant power ratio; PNSW, percentage of normal slow wave; CP, coupling percent.
Classification variables are described in the form of frequency (%); Statistical significance, *$p < 0.10$; **$p < 0.05$; ***$p < 0.01$.

the threshold probability selection range was significantly narrowed in the validation set. The overlap of threshold probabilities in the two sets is between 0.34 and 0.35. Therefore, in the EGEG-based risk assessment model, patients with a predicted probability higher than 0.35 were considered to be high risk of sleep disturbance, and this reference threshold might provide a clinical net benefit.

Discussion

Sleep disturbance is a crucial factor affecting many nervous system diseases and mental disorders (33, 34). The development of sleep disturbance is also more likely to occur in middle-aged and elderly people. Improving the diagnosis rate of sleep disturbance in this population is conducive to earlier detection and treatment, which will significantly enhance their quality of life and reducing the burden of disease. However, extensive community screening is still difficult due to the limitations of self-reported questionnaires and polysomnography, leaving many people with sleep disturbance are never detected (35, 36). This deficiency is anticipated to be remedied by the risk assessment model of sleep disturbance based on EGEG that our research has developed. By using multiple evaluation indicators including ROC curve, calibration curve and DCA curve, the performance of the risk assessment model was compared and verified in the training set and verification set. It was discovered that the predictive ability of the model was stable and that it was effective at identifying positive patients with sleep disturbance. In the future, it is possible to use this model extensively in the community for sleep disturbance screening due to its satisfactory model performance.

For clinicians, the precise diagnostic of gastrointestinal inflammation, irritable bowel syndrome, functional gastrointestinal disorders, and digestive dysfunction is greatly benefited by the use of EGEG (37, 38). However, because the gastrointestinal channel has weaker myoelectrical activity than the heart and brain, there have not been many studies to explore EGEG's potential for broader applications and connections to other disorders (39). Combining the risk prediction model developed based on EGEG for mild cognitive impairment (MCI) (40), EGEG demonstrated worthy predictive potential for both sleep

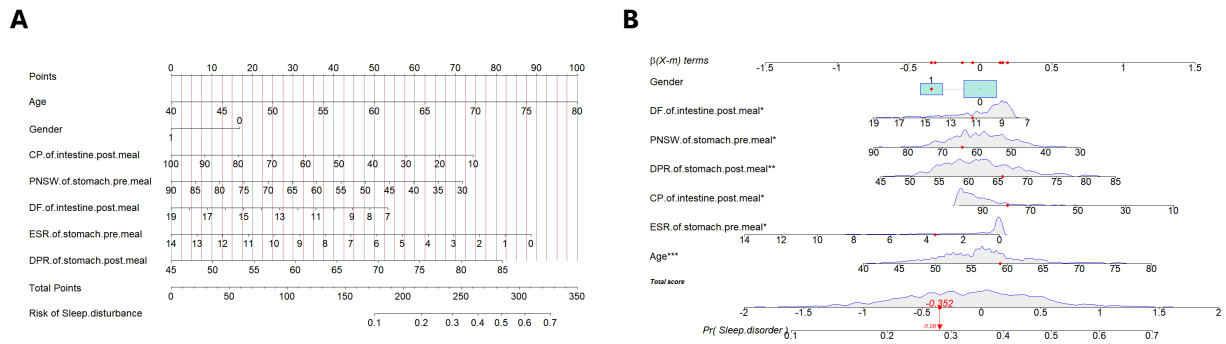

FIGURE 3
(A) The nomogram of the risk assessment model for sleep disturbance in training set. **(B)** The dynamic nomogram of the risk assessment model for sleep disturbance in training set. The nomogram of the sleep disturbance was developed with the predictors: age, gender, PNSW of gastric channel pre-meal, ESR of gastric channel pre-meal, DPR of gastric channel post-meal, CP of intestinal channel post-meal, DF of intestinal channel post-meal. PNSW, percentage of normal slow wave; ESR, electrical spreading rate; DPR, dominant power ratio; CP, coupling percent. *$p < .05$; **$p < .01$; ***$p < .001$.

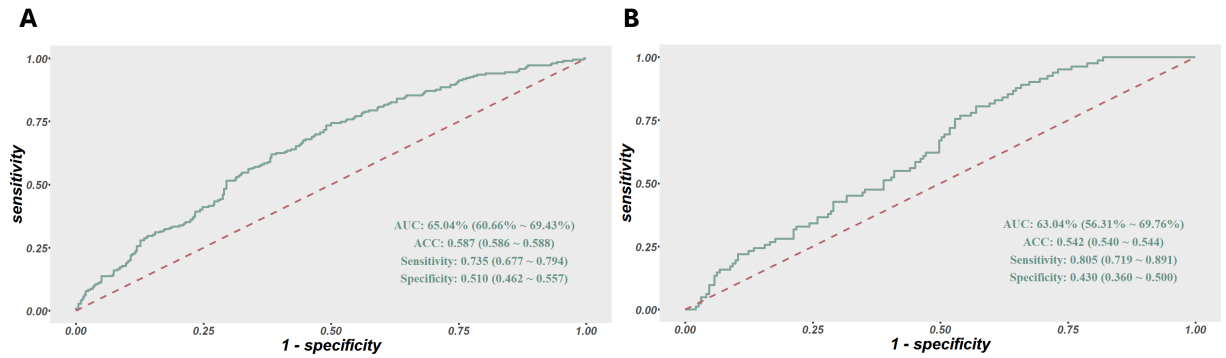

FIGURE 4
(A) ROC curves of the risk assessment model for sleep disturbance in the training set. **(B)** And in the validation set. The y-axis indicates the true-positive rate of the risk prediction. The x-axis indicates the false-positive rate of the risk prediction.

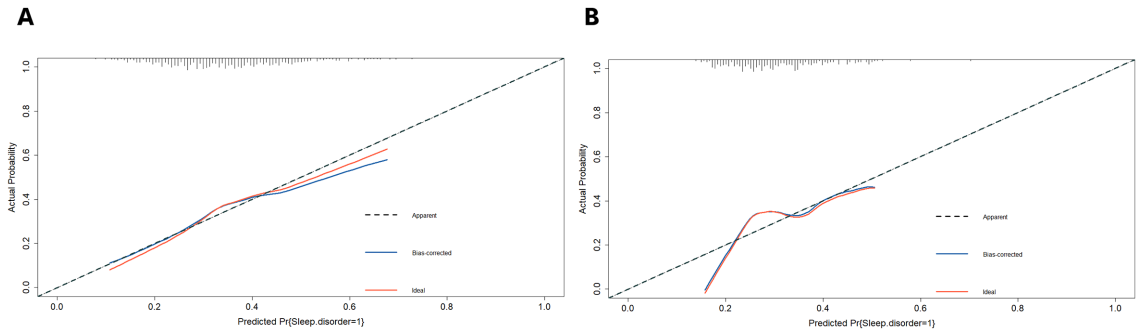

FIGURE 5
(A) The calibration curves of the risk assessment model for sleep disturbance in the training set. **(B)** And in the validation set. The y-axis indicates the actual probability of sleep disturbance. The x-axis indicates the predicted risk of sleep disturbance. The diagonal dotted line indicates perfect prediction by an ideal model. The solid line represents the model performance, a closer fit to the diagonal dotted line represents a better prediction.

disturbance and MCI. In the future, for middle-aged and elderly people with cognitive decline, communication disorders, and other difficulties to ensure the accuracy of questionnaire screening, EGEG may have excellent potential for detection of sleep disturbance and MCI.

In our risk assessment model, there are five parameters of EGEG contributed major value for predicting sleep disturbance, namely, PNSW and ESR on the pre-meal gastric channel, DPR on the post-meal gastric channel, DF and CP on the post-meal gastric channel.

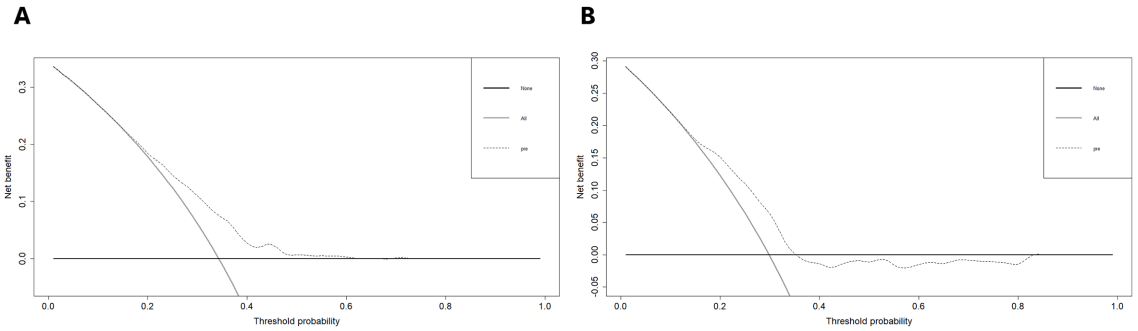

FIGURE 6
(A) Decision curve analysis of the risk assessment model for sleep disturbance in the training set. **(B)** And in the validation set. The y-axis measures the net benefit. The thick solid line represents the assumption that no patients have sleep disturbance. The thin solid line represents the assumption that all patients have sleep disturbance. The dotted line represents the risk nomogram.

Comparing to the previous studies, PNSW, DF and CP also provide significant values in the diagnosis of gastrointestinal dysfunction (41, 42). For instance, a meta-analysis of EGG in patients with functional dyspepsia concluded that pre-meal PNSW and post-meal CP were important indicators (43). Another meta-analysis of EGG in patients with nausea and vomiting syndrome also found that post-meal DF was lower than that of healthy individuals (44). Our findings suggest that, in contrast to healthy individuals, the changes in gastrointestinal myoelectrical activity do exist not only in the sleep disturbance patients with gastrointestinal diseases, but also in the patients without the symptoms of gastrointestinal dysfunction.

Overall, our study demonstrates that sleep disturbance can be manifested by the changes of myoelectrical activity on the gastrointestinal channel. The risk assessment model established based on EGEG has important clinical significance and is promising to be used in the community screening for sleep disturbance in middle-aged and elderly people. However, our study still has some limitations. Since our subjects were recruited from the voluntary participation of middle-aged and elderly people in the community, and a perfect sampling procedure was not used, the representativeness of the samples is lacking, which cannot exclude potential selection bias. In addition, our study only included participants from the western region, which may have distinct population characteristics compared to other regions, and can be resolved by including other areas. In addition, the overall prediction accuracy of the model is less than 0.70, which may be due to the limited sample size, and may be clarified with a larger sample size.

Conclusion

The risk assessment model based on EGEG indicators exhibits an acceptable efficiency and satisfying robustness of predicting the risk of sleep disturbance. Our findings also provide evidence for a close association between the gastrointestinal myoelectrical activity and sleep disturbance in middle-aged and elderly people. With the widely applied risk assessment model based on EGEG as an auxiliary method to diagnose sleep disturbance, it would be likely to achieve a full coverage of sleep disturbance screening for the middle-aged and elderly population in the community.

Data availability statement

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

Ethics statement

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

Author contributions

LC: conceptualization, methodology, investigation, resources, data acquisition, writing – review & editing, and supervision. SJ: methodology, formal analysis, writing-original draft, visualization, and writing – review & editing. BL: writing-original draft, methodology, and validation. CZ: data collection, formal analysis, data regulation, and supervision. YT: conceptualization and investigation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1183108/full#supplementary-material

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Investigating associations between social determinants, self-efficacy measurement of sleep apnea and CPAP adherence: the SEMSA study

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Study objectives: The prospective Self-Efficacy Measure for Sleep Apnea study (SEMSAS) is investigating thresholds for health literacy, self-efficacy and precariousness at obstructive sleep apnea (OSA) diagnosis to predict CPAP adherence. This paper describes the study protocol and presents baseline data from the ongoing study.

Methods: Eligible individuals had confirmed OSA and were referred to a homecare provider for continuous positive airway pressure (CPAP) therapy initiation. Data on patient characteristics and comorbidities were collected, along with baseline evaluations of self-efficacy [15-item Self-Efficacy Measure for Sleep Apnea tool (SEMSA-15)], precariousness [Deprivation in Primary Care Questionnaire (DipCareQ)], and health literacy (Health Literacy Questionnaire). CPAP adherence over 12months of follow-up will be determined using remote monitoring of CPAP device data. The primary objective is to define an optimal SEMSA-15 score threshold to predict CPAP adherence at 3- and 12-month follow-up.

Results: Enrollment of 302 participants (71% male, median age 55years, median body mass index 31.6kg/m^2) is complete. Low self-efficacy (SEMSA-15 score≤2.78) was found in 93/302 participants (31%), and 38 (12.6%) reported precariousness (DipCareQ score>1); precariousness did not differ significantly between individuals with a SEMSA-15 score≤2.78 versus >2.78. Health literacy was generally good, but was significantly lower in individuals with versus without precariousness, and with low versus high self-efficacy.

Conclusion: SEMSAS is the first study using multidimensional baseline assessment of self-efficacy, health literacy and precariousness, plus other characteristics, to determine future adherence to CPAP, including CPAP adherence trajectories. Collection of follow-up data is underway.

KEYWORDS

obstructive sleep apnea, continuous positive airway pressure, adherence, health behavior, health literacy

1. Introduction

Obstructive sleep apnea (OSA) is an important chronic condition that is characterized by repetitive complete (apnea) or partial (hypopnea) cessation of airflow due to collapse of the upper airway during sleep that induce symptoms or harms. The factors underlying these events are multifactorial and not fully understood, but are likely to include obesity, craniofacial features/changes, altered upper airway function, fluid shift towards the neck when in a supine position, and pharyngeal neuropathy (1).

OSA of at least mild severity has been estimated to affect nearly 1 billion adults aged 3–69 years worldwide (2). This is clinically relevant due to well-documented associations between OSA and several important neurocognitive, cardiovascular and metabolic comorbidities, including hypertension, cardiovascular disease, atrial fibrillation, diabetes, and even cancer (3–12). In addition, undiagnosed and untreated OSA have been associated with major depressive disorder, reduced quality of life, and increased healthcare utilization (13–19).

The standard treatment for moderate-to-severe OSA is continuous positive airway pressure (CPAP), which splints the upper airway open during sleep (20). When used correctly and for an adequate duration each night, CPAP is highly effective in suppressing sleep-related respiratory events, and improving symptoms and cognitive function (20, 21). However, in real-life clinical practice settings, the effectiveness of CPAP for suppressing apneas and hypopneas, and ameliorating the negative clinical consequences of OSA, is limited by poor adherence rates and high rates of therapy termination (22–24).

Numerous studies have investigated the clinical and physiological determinants of adherence to CPAP therapy. A high residual apnea-hypopnea index during treatment (>5–10 per hour) has been associated with poor adherence and high rates of therapy termination (25). In addition, device factors, such as the type of interface and its supply, have also been shown to influence longer-term adherence to PAP therapy (26). With respect to patient factors, higher income, educational level and number of household members have been associated with increased CPAP adherence in some studies, but currently available data are not consistent (27–29). Low socioeconomic status (SES) is another predictor of poor adherence to CPAP, and individuals with higher SES are more likely to start therapy (27, 30–32). Other factors that individually have been shown to increase the risk of non-adherence to CPAP therapy include low health literacy, forgoing healthcare, and precariousness (33–35). OSA health literacy has been found to be lower in individuals with lower educational attainment and socioeconomic status (36). Socioeconomic disparities were acknowledged as contributing to sleep health disparities and CPAP adherence in a recent American Thoracic Society consensus document (37).

A good understanding of individual characteristics at the time of the diagnosis could help to predict CPAP adherence after treatment initiation and allow clinicians and homecare providers to better manage patient adherence trajectories by selecting and implementing the most appropriate strategies to increase adherence. However, the majority of currently published studies have only investigated a single, or small number of, determinants of CPAP adherence and no one factor has been consistently identified has having high predictive value. In addition, no study has yet investigated the contribution of health literacy, precariousness and self-efficacy measures, as well as clinical characteristics, to CPAP therapy adherence.

The Self-Efficacy Measure for Sleep Apnea (SEMSA) tool is a psychometrically acceptable self-report questionnaire for the measurement of health beliefs and behaviors in individuals with OSA being treated with CPAP (38). It was developed based on Bandura's social cognitive theory (39) and originally included 26 items (38, 39). A shorter 15-item version (SEMSA-15) was developed to improve usability in clinical practice (40) while retaining similar psychometric properties to the original version. The SEMSA study (SEMSAS) has been designed to identify specific thresholds for health literacy, self-efficacy and precariousness assessed at the time of OSA diagnosis to predict CPAP adherence over the short (3 months) and long (12 months) term. The objective of this paper is to describe the study protocol and present baseline data relating to self-efficacy based on the SEMSA-15, precariousness and health literacy from the ongoing SEMSAS, which will soon complete follow-up.

2. Materials and methods

2.1. Study design

SEMSAS is a multicenter ($n = 3$), prospective observational cohort trial (NCT04894175) that started in May 2021 and finished recruiting in December 2022. All participants are from the North of France (Bétune, Denain and Lille), a region that includes areas that have differing levels of precariousness. The study protocol was approved by the French Comité de protection des personnes Nord Ouest III (ref 2020-68). As an observational study without changes in patient care or management, potential participants were provided with information about the study. Those who did not object to the use of their data for the study were included, in accordance with French law and European General Data Protection Regulation (GDPR).

2.2. Study participants

Eligible individuals were adults with a physician diagnosis of OSA who were referred for initiation of CPAP therapy managed by a homecare provider. Individuals without OSA or those with OSA that was not being treated with CPAP were not eligible.

2.3. Data acquisition and assessments

Clinicians collected demographic and clinical data at baseline (after enrollment/provision of informed consent), including age, height, weight, sex, comorbidities (hypertension, cardiovascular disease, diabetes, COPD, and asthma), OSA-related symptoms (presence or absence of any of the following: severe snoring, daytime sleepiness, daytime tiredness, morning headache, and nycturia), and method used for OSA diagnosis (single night polysomnography or polygraphy). The following data were collected at CPAP initiation: device, interface, pressure, and use of a humidifier (Figure 1). Data on CPAP adherence, residual AHI and leak were collected during follow-up, and data on quality of life and the ESS score were collected at the end of follow-up (Figure 1).

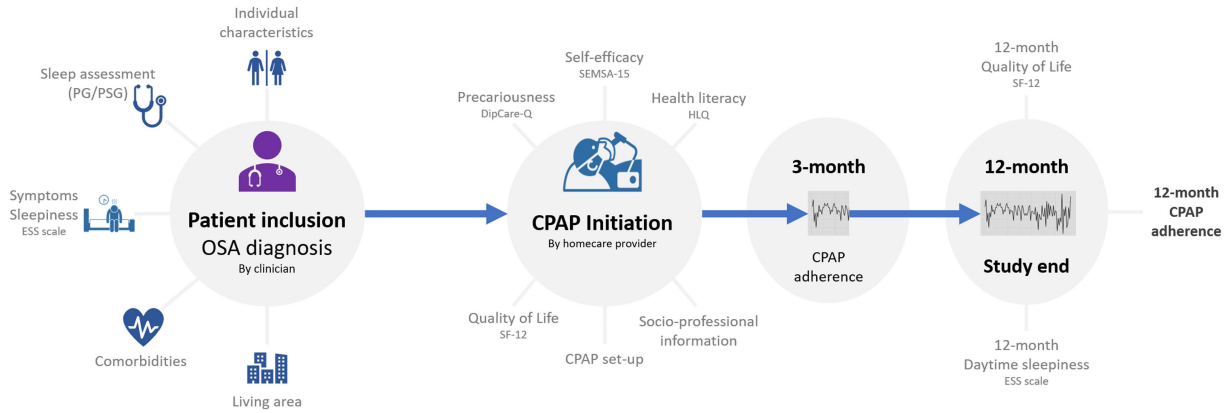

FIGURE 1
Study design and assessments. CPAP, continuous positive airway pressure; DipCare-Q, deprivation in primary care questionnaire; ESS, epworth sleepiness scale; HLQ, health literacy questionnaire; OSA; obstructive sleep apnea; PG, polygraphy; PSG, polysomnography; SEMSA-15, 15-item self-efficacy measure for sleep apnea; SF-12, Short Form-12.

Participants completed several baseline questionnaires that were provided by the homecare provider involved in setting up and initiating CPAP. These questionnaires gathered data relating to following parameters: personal characteristics (marital status, socioeconomic information, and health insurance); precariousness [the Deprivation in Primary Care Questionnaire (DipCareQ)] (41); health literacy [the Health Literacy Questionnaire (HLQ)] (42); chronotype (the degree to which individuals are active and alert at certain times of the day, primarily in the morning or evening); the shortened version of SEMSA (SEMSA-15 scale) (40); the 12-item Short Form health survey for quality of life (SF-12) (43); and the Epworth Sleepiness Scale (ESS) (44). The ESS and SF-12 will also be completed at the 12-month follow-up to allow assessment of the evolution of daytime sleepiness and quality of life during CPAP therapy.

2.3.1. DipCareQ

The DipCareQ questionnaire includes 16 questions about subjective social status, education, source of income, welfare status and subjective poverty that define deprivation in three distinct dimensions: material deprivation (eight items), social deprivation (five items), and health deprivation (three items) (41). Patients provide a yes or no answer to each question, with a score of 1 for yes and 0 for no. A score for each type of deprivation is determined, then a formula is used to calculate an overall score from 0 to 5, with higher scores indicating greater deprivation. For this study, DipCareQ score groups of 0–1 and 2–5 were used.

2.3.2. HLQ

The HLQ includes 44 items and covers nine distinct scales representing health literacy: (1) feeling understood and supported by healthcare providers; (2) having sufficient information to manage my health; (3) actively managing my health; (4) social support for health; (5) appraisal of health information; (6) ability to actively engage with healthcare providers; (7) navigating the healthcare system; (8) ability to find good health information; and (9) understand health information enough to know what to do (42). Responses for items in scales 1–5 are: strongly agree, disagree, agree and strongly agree. Responses for items in scales 6–9 are: cannot do, very difficult, quite difficult, easy, and very easy. Scale scores are determined by summing the item scores and then dividing by the number of items in the scale.

For scales 1–5 (four possible responses from strongly disagree to strongly agree), scores below 2.5 indicate that, on average, respondents tend to disagree with the statements within a scale. For scales 6–9 (five possible responses from cannot do/always difficult to always easy), scores below 3.5 indicate that, on average, respondents find the task within a scale difficult to do.

2.3.3. SEMSA-15

The SEMSA-15 includes five items each relating to perceived risks, outcome expectancies and self-efficacy, and has been shown to have the same good psychometric properties as the 26-item version (40). Items are groups into three subscales: perception of the consequences and risks of OSA (perceived risk); perception of the expected benefits of CPAP (outcome expectations); and feeling of self-efficacy in regular use of CPAP (self-efficacy). Each item is rated on a Likert scale from 1 to 4, with higher scores indicating greater risk perception, higher benefit expectancy with treatment, and greater perceived self-efficacy (38, 39). The final score is obtained by averaging scores for each item. With the SEMSA-15, the best classification performance for prediction of CPAP adherence was for the self-efficacy sub-score, with a cut-off value of 2.78 (sensitivity 57%, specificity 79%, positive predictive value 31%, and negative predictive value of 92%) (40).

2.4. Validity and reliability of measures

Exploratory and confirmatory factor analyses were conducted for each measurement scale. A Structural Equation Model (AMOS 26.0) tested the measurement models among all four using full information maximum likelihood estimation (FIML) with missing values estimation. The following criteria were used to assess configural invariance: χ^2 and degrees of freedom ($\chi^2/df < 5$), Tucker–Lewis index (TLI >0.90), comparative fit index (CFI >0.90), incremental fit index (IFI >0.90), and root mean square error of approximation (RMSEA <0.10). The reliability coefficients for all constructs were acceptable

(all Cronbach alpha's > 0.70). Convergent validity (AVE >0.50) was based on Fornell and Larcker (45).

2.5. CPAP adherence and follow-up

CPAP adherence will be determined from remote monitoring of device data, and will be reported at 3 and 12 months after CPAP initiation. CPAP adherence will be reported as both a continuous variable and as a binary variable (threshold of 4 h/night).

Over the 12-month follow-up period reasons for loss of follow-up will be identified to differentiate between participants who stop using CPAP and are therefore non-adherent and those who stop participating in the study but remain adherent to CPAP or those who are deceased. In addition, the number and nature of physical interventions performed by the homecare provider technician during the follow-up period will be recorded.

2.6. Study objectives

The primary objective of SEMSAS is to define an optimal SEMSA-15 score threshold to predict adherence to CPAP at 3- and 12-month follow-up. The study also had a number of secondary objectives (Table 1). The objective of the current report is to present full details of the study protocol and describe baseline data relating to self-efficacy based on the SEMSA-15, precariousness and health literacy for enrolled participants.

2.7. Sample size

The sample size calculation was based on achieving 90% power to identify an optimal threshold for the primary objective (i.e., the SEMSA-15 score threshold to predict 3- and 12-month CPAP adherence) with a minimum area under the receiver operator characteristic curve (ROC AUC) of 0.63. Assuming a CPAP non-adherence or therapy termination rate of 25% and a 20% loss to follow-up rate of 20%, it was calculated that 300 individuals would need to be included in the study.

TABLE 1 Secondary study endpoints.

Secondary endpoint	Time of assessment
Define patient phenotypes based on all available baseline clinical and socio-demographic data	Baseline
Compute an overall SEMSA-15 score to predict CPAP adherence	3-month and 12-month follow-up
Determine the impact of health literacy on CPAP adherence (based on the HLQ)	3-month and 12-month follow-up
Determine the impact of precariousness on CPAP adherence (based on the DipCareQ)	3-month and 12-month follow-up
Determine the impact of patient quality of life on CPAP adherence (based on the SF-12)	3-month and 12-month follow-up
Construct an overall predictive model of CPAP adherence	3-month and 12-month follow-up
Assess interactions between CPAP adherence trajectories and patient characteristics	3-month and 12-month follow-up
Assess improvements in quality of life based on health literacy and precariousness	12-month follow-up

CPAP, continuous positive airway pressure; DipCareQ, deprivation in primary care questionnaire; HLQ, health literacy questionnaire; SEMSA-15, 15-item self-efficacy measure for sleep apnea; SF-12, short form-12.

2.8. Statistical analysis

2.8.1. Baseline data

In the current paper, qualitative variables are described using number and percentage, and qualitative variables as median and interquartile range (IQR). A Chi-squared test was used to compare qualitative variables and the Mann–Whitney test was used to compare quantitative variables. Effect sizes were computed using Cohen' d coefficient for quantitative variable and phi coefficient for binary variables. Statistical analyses of baseline data were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, United States). A value of p threshold of 0.05 was used to define statistical significance.

2.8.2. Methodology for follow-up analysis

The imputation strategy for missing values will be considered based on patterns of missingness and rate of missing values. For the primary objective, predictors of CPAP adherence (as a binary variable: <4 vs. ≥4 h/night) will be determined using a multivariable mixed logistic regression model, with a random effect on center determine possible variability between centers. Various parameters, including demographic and clinical covariables, will be considered as possible confounding factors based on clinical expertise and the results of univariable analysis. ROC AUC values for different models will be compared using the Delong method to identify which has the best performance and the Youden index will be used to define the optimal threshold for the SEMSA-15 questionnaire score. The dataset will be divided into two for training and validation (75% and 25% of the total sample, respectively). The model will be developed using the training dataset and then tested on the validation dataset. Performance of the final model, including sensitivity, specificity, and positive and negative predictive values, will be computed on the validation dataset.

Trajectories of CPAP adherence will be clustered by using specific approaches for time series, such as dynamic time warping, as previously described (46). Associations between patient characteristics and CPAP adherence trajectory clusters will be investigated by using comparison tests.

Multivariable linear generalized mixed effect models will be used to study the evolution of quality of life (SF-12 score) and daytime sleepiness (ESS score) over time. Confounding factors will be selected using univariable analyses and introduced into the model. Finally, unsupervised clustering will be performed to identify specific phenotypes at the time of the diagnosis and to investigate the impact of individual determinants such as health literacy, precariousness and SEMSA-15 score on patient clinical phenotype at baseline.

Finally, a structural equation model will be considered to identify direct and indirect relationships between measured variables and 12-month CPAP adherence. This approach will allow assessment of

causal relationships between different measured factors and the outcome. For this approach, exploratory and confirmatory factorial analyses will be performed for each score to assess convergent and discriminant validity. Moderating effects, including precarity and individual determinants, will be considered by performing subgroup models.

Statistical analyses will be performed using a variety of different software, including SAS, R, and AMOS.

3. Results

3.1. Study population

A total of 302 individuals were included in the study. Participant characteristics were typical of an OSA population, being predominantly male, older age and high body mass index (Table 2). There were some differences between study centers with respect to OSA diagnosis, OSA severity, rate of hypertension, and SEMSA-15 score at baseline (Supplementary Table S1); these will be corrected for in the statistical analysis of follow-up data. Hypertension was the most common comorbidity, occurring in nearly half of the study population. Based on the apnea-hypopnea index (AHI), baseline OSA was severe, and the prevalence of symptoms was high. A majority of participants reported daytime sleepiness or tiredness, almost all had severe snoring, and more than half had morning headache. Most individuals (82.5%) were married or in a permanent relationship [median duration 26 years (range 12–42)]. Nearly half of all participants (44.5%) had children living at home. More than half (58.6%) reported a professional activity (of whom 40.2% were a worker or employee), 35.8% reported being a senior manager or business owner, while 24% reported an "intermediate" profession. Validity and reliability data for all measures being used in the study are shown in Supplementary Tables S2, S3.

3.2. Self-efficacy at baseline

The median (IQR) SEMSA-15 score at baseline was 3 (2.7–3). Overall, 31% of the study population ($n = 93/302$) had low self-efficacy based on a SEMSA-15 score of was ≤2.78 in 93 patients. Overall demographic and clinical characteristics were generally comparable between individuals with a low SEMSA-15 score

TABLE 2 Participant demographic and clinical characteristics at baseline, overall and in patient subgroups based on baseline 15-item self-efficacy measure for sleep apnea (SEMSA-15) score.

Characteristic	Total (n =302)	SEMSA-15 score		
		Low (≤2.78) (n =93; 31%)	High (>2.78) (n =209; 69%)	Value of $p^{\#}$ (ES)*
Age, years	55 (47–64)	59 (48–68)	55 (47–63)	0.07
Male sex, n (%)	213 (70.5)	70 (75.3)	143 (68.4)	0.23
Body mass index, kg/m^2	32 (28–36)	31 (28–34)	32 (28–36)	0.09
Comorbidities, n (%)				
Hypertension	145 (48.0)	42 (45.2)	103 (49.3)	0.51
Diabetes	42 (13.9)	18 (19.4)	24 (11.5)	0.07
Heart failure	14 (4.6)	8 (8.6)	6 (2.9)	0.03 (0.12)
Dyslipidemia	64 (21.2)	25 (26.9)	39 (18.7)	0.11
Mode of sleep apnea diagnosis, n (%)				
Single night polygraphy	234 (77.5)	66 (71)	168 (80.4)	0.07
Single night polysomnography	68 (22.5)	27 (29)	41 (19.6)	
Apnea-hypopnea index, /h	43 (35–57)	43 (34–55)	43 (35–58)	0.23
Oxygen desaturation index, /h	34 (23–50)	36 (27–52)	33 (23–48)	0.09
ESS score	12 (8–15)	10 (7–14)	12 (8–17)	<0.01 (0.37)
ESS score > 10, n (%)	170 (56)	44 (47.3)	126 (60.3)	0.04 (0.12)
OSA symptoms, n (%)				
Severe snoring	287 (95.0)	87 (93.5)	200 (95.7)	0.43
Daytime sleepiness	260 (86.1)	75 (80.6)	197 (94.3)	<0.01 (0.02)
Daytime tiredness	272 (90.1)	75 (80.6)	197 (94.3)	<0.01 (0.21)
Morning headache	170 (56.3)	51 (54.8)	119 (56.9)	0.73
Nycturia	206 (68.2)	62 (66.7)	144 (68.9)	0.70

Values are median (interquartile range) or number of patients (%).
$^{\#}$ Value of p calculated using the Mann–Whitney test for quantitative variables and Chi-square test for qualitative variables.
* Effect size (ES) computed using Cohen D coefficient for continuous variables and Phi coefficient for binary variables.
ESS, epworth sleepiness scale; OSA, obstructive sleep apnea; SEMSA-15, 15-item self-efficacy measure for sleep apnea.

TABLE 3 Self-efficacy based on the SEMSA-15 score, overall and by subscale.

SEMSA-15	Total (n=302)	SEMSA-15 score		
		Low (≤2.78) (n=93; 31%)	High (>2.78) (n=209; 69%)	Value of p (ES)*
Total score	3.0 (2.7–3.3)	2.5 (2.3–2.7)	3.1 (3.0–3.3)	<0.01 (2.7)
Perceived risk	2.6 (2.2–3.0)	2.0 (1.6–2.4)	2.8 (2.4–3.0)	<0.01 (1.5)
Outcome expectations	3.4 (2.8–3.6)	2.8 (2.4–3.0)	3.4 (3.2–3.8)	<0.01 (1.5)
Self-efficacy	3.2 (2.8–3.6)	2.6 (2.2–3.0)	3.4 (3.0–3.8)	<0.01 (1.7)

Values are median (interquartile range).
*Effect size (ES) computed using Cohen D coefficient. SEMSA-15, 15-item self-efficacy measure for sleep apnea.

compared with those who had a high SEMSA-15 score. However, those with a SEMSA-15 score of ≤2.8 were significantly more likely to have heart failure and an ESS score of >10, but significantly less likely to report daytime sleepiness or daytime tiredness, compared with individuals who had a higher SEMSA-15 score (Table 2). Although statistically significant, the effect sizes for these differences were small. Most of the fit indices for each of these measurement models were within the acceptable range suggested by Collier (47). With respect to socio-economic characteristics, individuals with a high SEMSA-15 score usually had a graduate education and were in the high socio-professional category. Of the different SEMSA-15 subscales, scores were lowest for perceived risk and highest for outcome expectations (Table 3). The total score, and scores for all three subscales were significantly higher in the high versus low SEMSA-15 score group with a large effect size (Table 3).

3.3. Precariousness at baseline

A total of 38 participants (12.6%) reported precariousness (based on a DipCareQ score > 1). Precariousness did not differ significantly between those with a SEMSA-15 score ≤ 2.78 versus >2.78, indicating that there was no association between self-efficacy and precariousness.

3.4. Health literacy and impact of precariousness and self-efficacy

Based on a threshold score of 2.5 for each item on the HLQ, the individuals with OSA enrolled in this study had a good level of health literacy (Table 4). Health literacy across most domains did differ significantly based on precariousness and self-efficacy, with median scores being significantly lower in patients with versus without precariousness (DipCareQ score > 1 vs. ≤1) and low versus high self-efficacy (SEMSA-15 score ≤ 2.78 vs. >2.78) (Table 4). Distributions around median values also varied between participant subgroups (Supplementary Figure S1).

4. Discussion

The SEMSA study (SEMSAS) is the first to propose a multidimensional evaluation of determinants of CPAP adherence based on a combination of data including self-efficacy, precariousness, health literacy and individual characteristics/demographics. Data on these parameters will be used to predict CPAP adherence at 3 months and 1 year, and also to relate individual characteristics to CPAP adherence trajectories using remote monitoring data. It will be interesting to see associations between self-efficacy based on the SEMSA-15 score and other sociological evaluations. The inclusion and assessment of a broad range of potential factors that could influence adherence to CPAP should facilitate the identification of new predictors of CPAP adherence in conjunction with SEMSA-15, as well as confirm those already known to influence use of CPAP after therapy initiation.

Participants enrolled in SEMSAS have clinical characteristics that are indicative of a cohort with severe OSA and a clear indication for CPAP therapy. The study population showed a good level of health literacy, a low rate of precariousness, and more than two-thirds had good self-efficacy (based on a SEMSA-15 score > 2.78). Interestingly, there was no difference in precariousness between individuals with low or good self-efficacy even though other factors such as education level and profession did differ between patient subgroups based on SEMSA score (≤2.78 vs. >2.78). However, health literacy was significantly impacted by precariousness and self-efficacy, and was predictably lower in those with higher levels of precariousness and/or lower self-efficacy.

The rate of precariousness reported by study participants was 12.6%. To the best of our knowledge, SEMSAS is the first study to report precariousness in individuals starting CPAP. One previous analysis that included patients with OSA syndrome found that 43.7% reported deprivation based on the Evaluation de la précarité et des inégalités de santé dans les Centres d'examens de santé (EPICES) questionnaire score (36). Deprivation may differ from precariousness, limiting the ability to directly compare these findings. However, both studies were conducted in France and highlight the fact that precariousness and/or deprivation are likely to be important factors for a relevant proportion of individuals with OSA.

As described in the Methods section, the original SEMSA scale included 26 questions, but a shortened version was developed and validated (38) to improve clinical utility. It was this shorter version (SEMSA-15) that was used in the current study. Data on association between SEMSA-15 scores and adherence are only available from one previous study (as a secondary endpoint), where the self-efficacy subscale score was significantly correlated with mean CPAP usage at 1 month and a trend was found at 6 months (48). In addition, a number of previous prospective studies have reported an association between SEMSA-26 scores and CPAP adherence, although none had a follow-up period of longer than 3 months (28, 49–55). In addition, the SEMSA-26 score has been found to

TABLE 4 Health literacy item scores for the overall population and in patient subgroups based on DipCareQ index score and SEMSA-15 score.

HLQ item	All patients (n =302)	Baseline DipCareQ score			Baseline SEMSA-15 score		
		0–1 (n =264)	2–5 (n =38)	Value of p (ES)*	≤2.78 (n =93)	>2.78 (n =209)	Value of p (ES)*
Feeling understood and supported by healthcare providers	3.3 (3.0–3.8)	3.3 (3.0–3.8)	3.0 (3.0–3.5)	0.02 (0.42)	3.0 (3.0–3.5)	3.3 (3.0–3.8)	<0.01 (0.48)
Having sufficient information to manage my health	3.0 (3.0–3.3)	3.0 (3.0–3.3)	3.0 (2.5–3.0)	<0.01 (0.59)	3.0 (2.8–3.0)	3.0 (3.0–3.3)	<0.01 (0.27)
Actively managing my health	2.9 (2.6–3.0)	3.0 (2.6–3.0)	2.8 (2.2–3.0)	0.01 (0.45)	3.0 (2.6–3.0)	2.8 (2.6–3.2)	0.40
Social support for health	3.2 (3.0–3.6)	3.2 (3.0–3.6)	3.0 (2.4–3.4)	<0.01 (0.71)	3.0 (3.0–3.4)	3.2 (3.0–3.6)	0.04 (0.17)
Appraisal of health information	3.8 (3.5–4.0)	3.8 (3.5–4.0)	3.5 (3.3–4.0)	0.05 (0.45)	3.0 (2.6–3.0)	3.0 (2.6–3.2)	0.03 (0.23)
Ability to actively engage with healthcare providers	4.0 (3.6–4.2)	4.0 (3.6–4.2)	4.0 (3.4–4.2)	0.07	4.0 (3.6–4.0)	4.0 (3.6–4.2)	0.03 (0.15)
Navigating the healthcare system	3.8 (3.5–4.0)	3.8 (3.5–4.0)	3.5 (3.3–4.0)	0.05 (0.33)	3.8 (3.5–4.0)	3.8 (3.5–4.2)	0.13
Ability to find good health information	3.8 (3.4–4.0)	3.8 (3.6–4.0)	3.8 (2.8–4.0)	<0.01 (0.69)	3.8 (3.4–4.0)	3.8 (3.4–4.0)	0.06
Understand health information well enough to know what to do	4.0 (3.6–4.2)	4.0 (3.6–4.2)	3.8 (3.6–4.0)	0.07	3.8 (3.6–4.0)	4.0 (3.6–4.2)	0.02 (0.25)

Values are median (interquartile range).
*Effect size (ES) computed using Cohen D coefficient. DipCareQ, deprivation in primary care questionnaire; HLQ, health literacy questionnaire; SEMSA-15, 15-item self-efficacy measure for sleep apnea.

be higher in individuals defined as CPAP adherers (3.5 ± 0.52) or CPAP attempters (3.1 ± 0.7) compared with CPAP non-adherers (2.8 ± 0.2) (48).

Poor adherence to CPAP therapy remains a challenge that limits the clinical benefits of treatment in real-world settings. Identifying which variables and data are able to predict CPAP adherence is crucial both for clinicians and homecare providers. This is likely to best be achieved by collecting information at the time of CPAP initiation to allow identification of individuals that might need additional support to achieve appropriate levels of CPAP adherence during long-term therapy. Appropriate and personalized measures can then be implemented during the early stages of treatment, allowing both adherence and the clinical benefits of CPAP therapy to be maximized.

Recruitment and collection of baseline data in SEMSAS are now complete. Adherence data at 3- and 12-month follow-up are being collated, which will allow this to be correlated with the extensive baseline data collected to provide a comprehensive picture of factors associated with CPAP adherence. In addition, data on CPAP adherence are being collected daily by remote monitoring utilizing the cloud connectivity features built in to CPAP devices. This will allow additional and informative analysis of CPAP adherence trajectories rather than just at two specific timepoints during follow-up.

In conclusion, SEMSAS aims to answer specific questions to help improve knowledge about patient determinants of CPAP adherence, especially self-efficacy, precariousness and health literacy. A multidimensional evaluation of data from these assessments combined with clinical/demographic data will allow more in-depth understanding of sociological concerns that are associated with poor CPAP adherence and could limit access to healthcare. The study findings should help to facilitate the identification of individuals who will be nonadherent to CPAP therapy, and determine specific clinical thresholds for several questionnaires that might help to differentiate between those who will be adherent or non-adherent.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors under request.

Ethics statement

The studies involving human participants were reviewed and approved by French Comité de protection des personnes Nord Ouest III (ref 2020-68). The patients/participants provided their written informed consent to participate in this study.

Author contributions

TG: study conception, principal investigator, patient enrollment, interpretation of data, drafting of the manuscript, and data analysis and interpretation. EG: study conception and methodology, data management and data acquisition, and drafting of the manuscript. BD: study methodology, data acquisition and quality control, patient enrollment, and final check and approval of the manuscript. J-LP: study conception and methodology, and final check and approval of the manuscript. SB: study conception and methodology, data management, statistical analyses, and drafting of the manuscript. J-AM-F: final check and approval of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1148700/full#supplementary-material

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Phrenic nerve stimulation for treatment of central sleep apnea

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The prevalence of central sleep apnea (CSA) is rare in general population. However, CSA is prevalent in those with cardiovascular and cerebrovascular disorders. CSA may persist or even worsen with positive airway pressure therapy in some patients and phrenic nerve stimulation (PNS) offers an alternative treatment for patients with CSA. The device is implanted similar to a cardiac pacemaker and typically followed in the sleep clinic. Multiple studies have described the efficacy and safety of PNS. Improvements were seen in apnea hypopnea events, central events, arousals, and daytime sleepiness and maintained through 5 years. Safety demonstrated a 91% freedom from serious adverse events through 1 year. The physiologic approach and improvement in sleep metrics and quality of life with a strong safety profile make this therapy a good option for many patients with central sleep apnea.

KEYWORDS

central sleep apnea, neurostimulation, sleep disordered breathing, phrenic nerve, cardiovascular disease, heart failure

Introduction

Compared to obstructive sleep apnea (OSA), the prevalence of central sleep apnea (CSA) is rare in general population. Similarly, while there are many treatment options today for OSA, treatment options for CSA are few. Phrenic nerve stimulation (PNS) represents one of the newest treatment options for patients with CSA. The device is implanted by a cardiologist in the cardiac suite and programmed by sleep specialists. Clinical data demonstrates improvement in sleep metrics with safety similar to other neurostimulation systems. It is important for sleep clinicians today to understand where the benefit and risk of this therapy for this unique patient population.

In adults, CSA is prevalent in certain conditions (Javaheri and Badr, 2023), most commonly in those with cardiovascular and cerebrovascular disorders (Javaheri et al., 2017). Among cardiac disorders, left ventricular systolic dysfunction, heart failure with reduced ejection (HFrEF) is the most common (Figure 1). However, CSA can also be comorbid with symptomatic and asymptomatic left ventricular dysfunction (Lanfranchi et al., 2003), and atrial fibrillation (Sin et al., 1999). The association with CSA has been best documented in AF in association with HFrEF. In one study of 100 patients with HFrEF, 80% of those with AF had CSA (Javaheri et al., 1998). Importantly, in a long-term prospective study of 2,865 community-dwelling older men who underwent a baseline polysomnogram (PSG) and were followed for a mean 7.3 years, elevated central apnea index (CAI) and Hunter Cheyne-Stokes Breathing (HCSB) was significantly associated with increased risk of decompensated heart failure and/or development of clinical heart failure (Javaheri et al., 2016). Atrial fibrillation is associated with CSA not only in those with reduced ejection fraction, but also with those with preserved ejection fraction (Bitter et al., 2009).

Phrenic nerve stimulation for treatment of CSA

Whereas, continuous positive airway pressure (CPAP) is quite effective in the treatment of OSA, it is ineffective in a large number of subjects with CSA such those with heart failure (Javaheri and McKane, 2020) or those on opioids (Javaheri et al., 2014). In these individuals, CSA persists or may worsen with positive airway pressure therapy, whereas phrenic nerve stimulation (PNS) is quite effective in virtually eliminating central sleep apnea.

Following a pivotal randomized control trial (Costanzo et al., 2016) in 2017, the FDA approved a transvenous phrenic nerve stimulation (TPNS) device (remedē system, ZOLL Medical, Minnetonka, MN) for the treatment of CSA of various causes.

Historically, it is interesting to note that although PNS was approved by the FDA in 2017, this is not a new idea. In Sarnoff et al. (1948) demonstrated for the first time that artificial respiration could be effectively administered to the cat, dog, monkey, and rabbit in the absence of spontaneous respiration by electrical stimulation of one (or both) phrenic nerves (Sarnoff et al., 1948). In later experiments, these investigators showed that unilateral phrenic nerve stimulation is also equally effective in humans as they had exhibited in animal models (Wittenberger et al., 1949).

The system and the algorithm

The phrenic nerves pass over and come in close proximity with veins, both on the right (brachiocephalic) and on the left (pericardiophrenic vein) (Figure 2). Similar to cardiac pacemaker implantation, an electrophysiologist places the stimulation lead within the vein in close proximity to the phrenic nerve. The stimulation lead is typically introduced on the right side below the clavicle and then attached to the pulse generator, which is placed under the skin in the right pectoral area (Augostini et al., 2019). The procedure typically lasts between 2 and 3 h, is completed under conscious sedation and patients typically go home the same day.

The therapy is activated in the sleep medicine clinic ~6 weeks after implantation using a programmer similar to a tablet computer. The device collects information regarding position, breathing and activity at night and this information can be used to program the device (Figures 3, 4). Following the initial programming session, therapy is personalized over the next few months and then efficacy is confirmed with a sleep study (Figure 5). Typically, the device is programmed to lower the respiratory rate with a slightly longer and deeper breath.

This is in contrast to other diaphragmatic or phrenic nerve stimulation systems which increase both respiratory rate and tidal volumes. These systems are typically placed in the operating room under general anesthesia with electrodes placed touching the phrenic nerve. These systems are often bilateral and the batteries are external and rechargeable. The tidal volume and rates can be changed by the patient or family similar to a ventilator and they are designed to take the place of mechanical ventilation in the case of spinal cord injury or central congenital hypoventilation syndrome (Headley et al., 2021). In other words, they are designed to increase minute ventilation whereas the transvenous PNS (remede system) is designed to stabilize breathing (stabilize carbon dioxide) and indicated for CSA in adults (Schwartz et al., 2020).

Clinical studies

Multiple studies have described the efficacy and safety of PNS.

Feasibility and pilot studies

A proof-of-concept study (Ponikowski et al., 2012) was completed in sixteen patients with CSA. Overnight unilateral stimulation of phrenic nerve resulted in virtual elimination of CAI (27 to 1 events/hour of sleep, $P \leq 0.001$). There was also significant reduction in the apnea hypopnea index (AHI) with the median decreasing from 45 to 23 events/ hour of sleep ($P = 0.002$). There were no significant changes in obstructive apnea index (OAI); the residual events were primarily hypopneas. In concert with reduction in CAI, similar changes occurred in arousal index (32 to 12 events/hour of sleep, $P = 0.001$]. Oxygen desaturation index of 4% (ODI4%) decreased from 31 to 14 events/hour of sleep, $P = 0.002$]. The feasibility study was followed by a pilot study (Abraham et al., 2015) which demonstrated chronic efficacy at 3 months with a reduction in AHI from baseline of 49.5 +/- 14.6 events per hour of sleep to 22.4 ± 13.6 events per hour of sleep; $p < 0.0001$) with follow-up through 1 year (Jagielski et al., 2016). Additionally, improvements were noted in sleepiness (Epworth Sleepiness Scale improved 4.1 points from baseline) and quality of life compared to baseline (76% noted improvement in health) (Abraham et al., 2015).

Pivotal trial

In this trial (Costanzo et al., 2016), 151 eligible patients with moderate or severe CSAwere randomly assigned to the treatment ($n = 73$) or control ($n = 78$) groups at the time of implantation. Participants in the active arm received PNS for the next 6 months. All PSG were centrally and blindly scored. There were significant decreases in AHI, CAI, arousal index, % time in rapid eye movement (REM) sleep and ODI4% (Table 1). The difference between the treatment and control group demonstrated a 25 event/hour reduction in AHI and 23 event/hour reduction in CAI. Importantly, daytime sleepiness and patient global assessment were statistically improved compared to the control group. Following the six-month randomization period, all patients had therapy activated and were followed until the end of the trial at ~3 years.

In general, CSA is less prevalent in REM sleep than in non-REM (NREM) sleep (Orr et al., 2016). In the pivotal trial, the CAIs in NREM and REM sleep were 28 and 8/h of sleep, respectively. In order to determine the efficacy of PNS to improve CSA during REM sleep, we performed a separate assessment of patients from the pivotal trial. We compared changes in sleep apnea indices from baseline to 6 months in REM and NREM sleep for treatment (active TPNS therapy, $n = 50$) and control (inactive device, $n = 57$). The analysis was performed only in patients who had at least 5 min of REM sleep in both the initial and follow up PSG. Similar

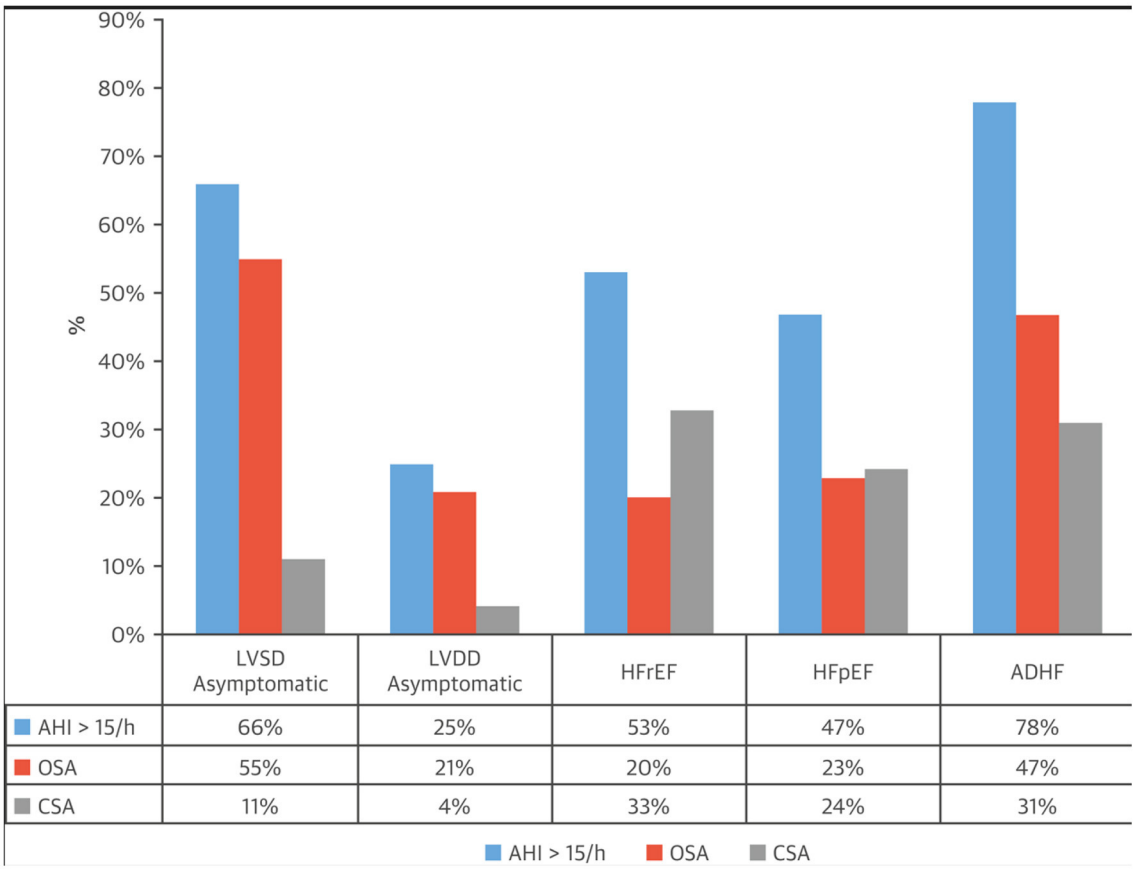

FIGURE 1
Prevalence of central sleep apnea in heart failure.

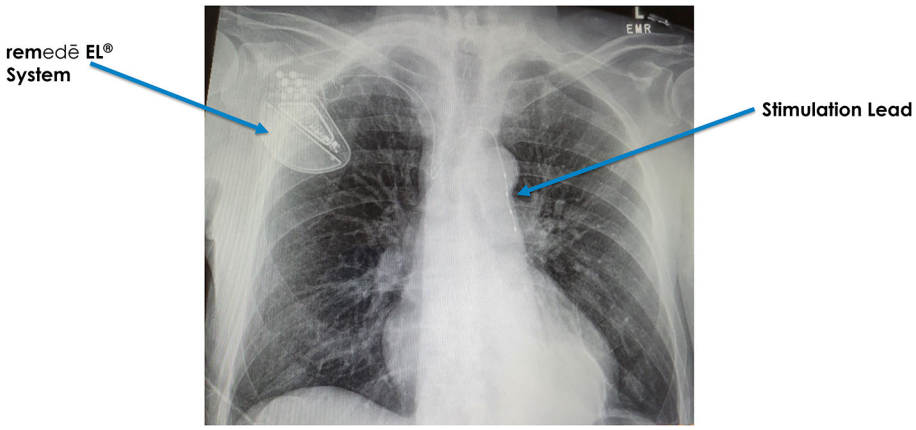

FIGURE 2
Transvenous phrenic nerve stimulation system.

to findings from the pivotal trial, we found the AHI decreased significantly during both REM and NREM sleep in patients with TPNS. Compared to baseline, the mean REM AHI decreased significantly from 28/h of REM sleep to 8/h in the active arm. The respective values in the control group were 20/h of REM at baseline and 25/h at 6 month follow up.

Also, similar to the data in the pivotal trial, the reduction in AHI was driven by reductions in central events. Compared to baseline, respective median values for REM CAI were 8 at baseline and 0 with treatment at 6 months.

This analysis suggests that although CSA is traditionally associated with NREM sleep, patients

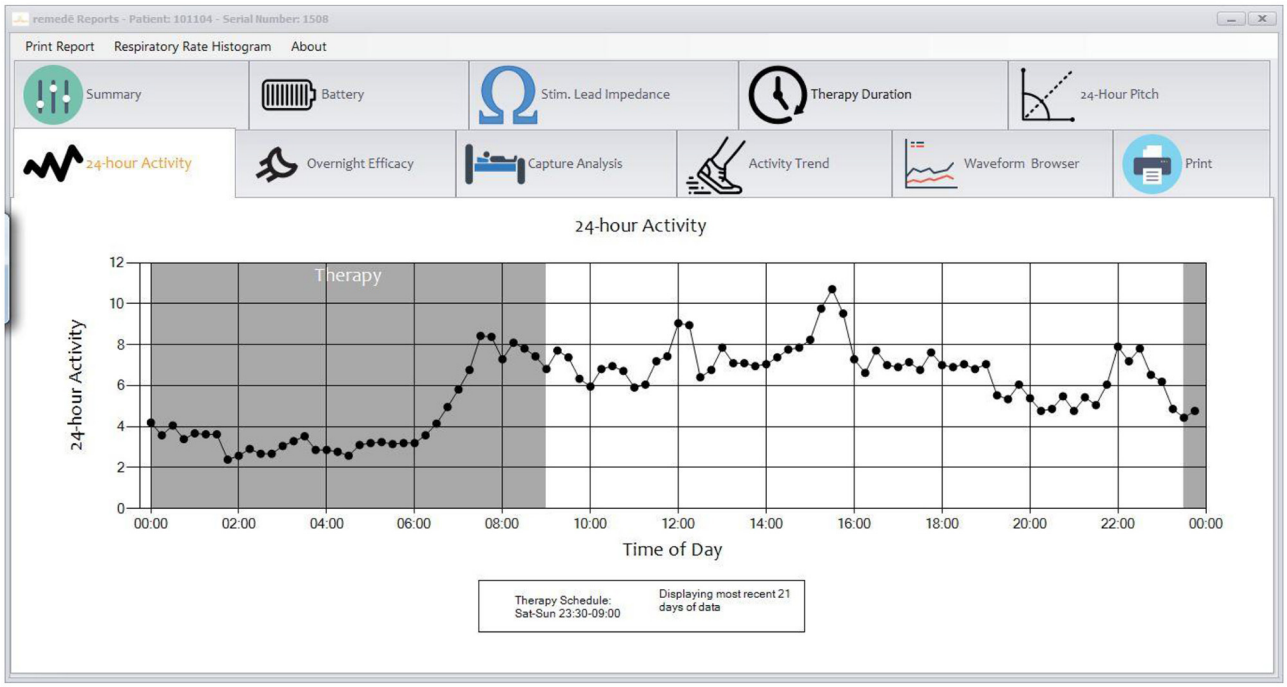

FIGURE 3
Sample diagnostic information from the remedē® system.

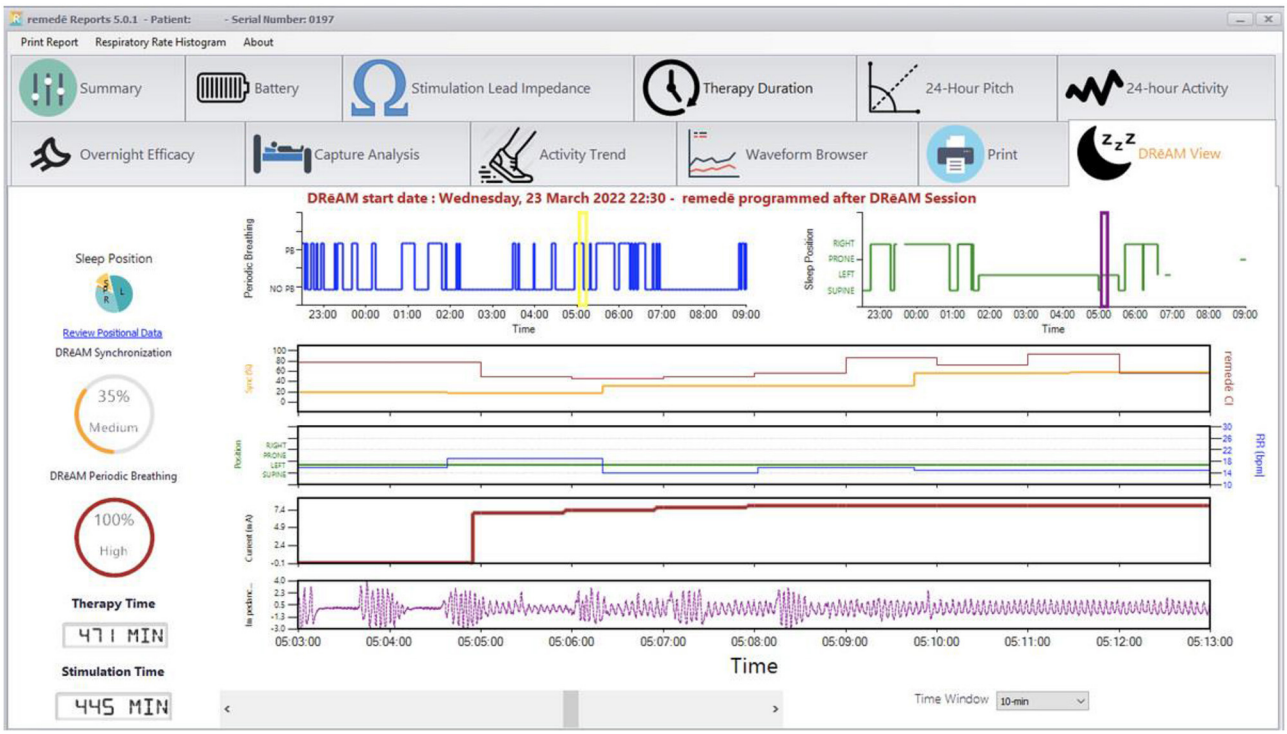

FIGURE 4
Sample diagnostic information: DREAM view screen.

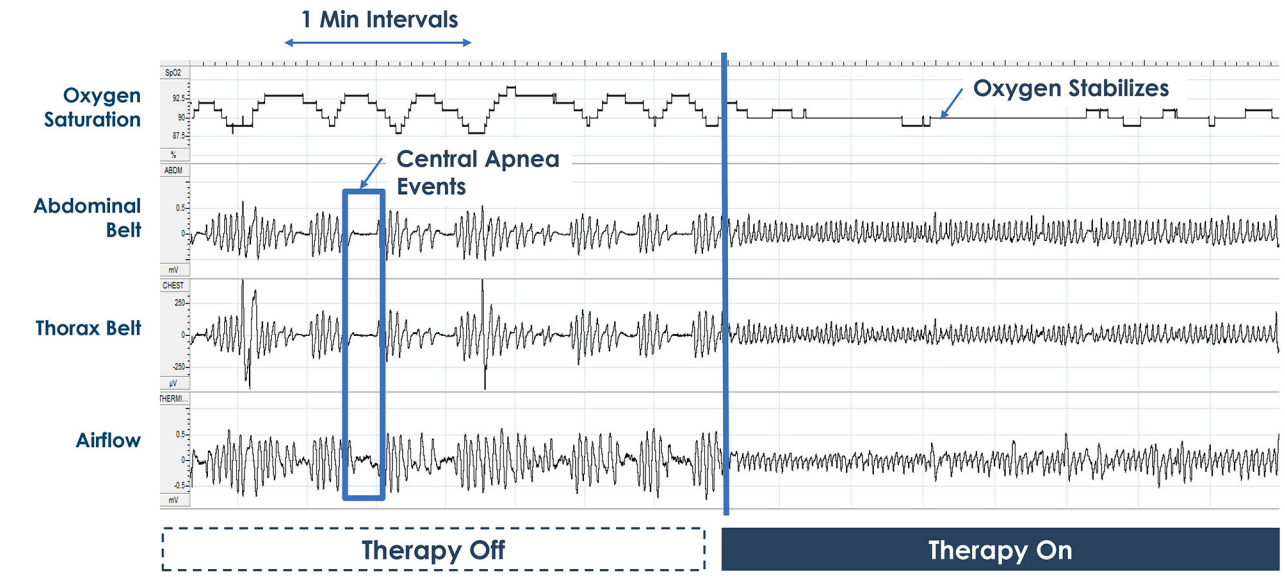

FIGURE 5
Example of therapy Off-On during overnight polysomnogram. Picture courtesy ZOLL Respicardia: This is an individual patient example and does not provide any indication, guide, warranty or guarantee as to the response other patients may have to the therapy. Individual results may vary.

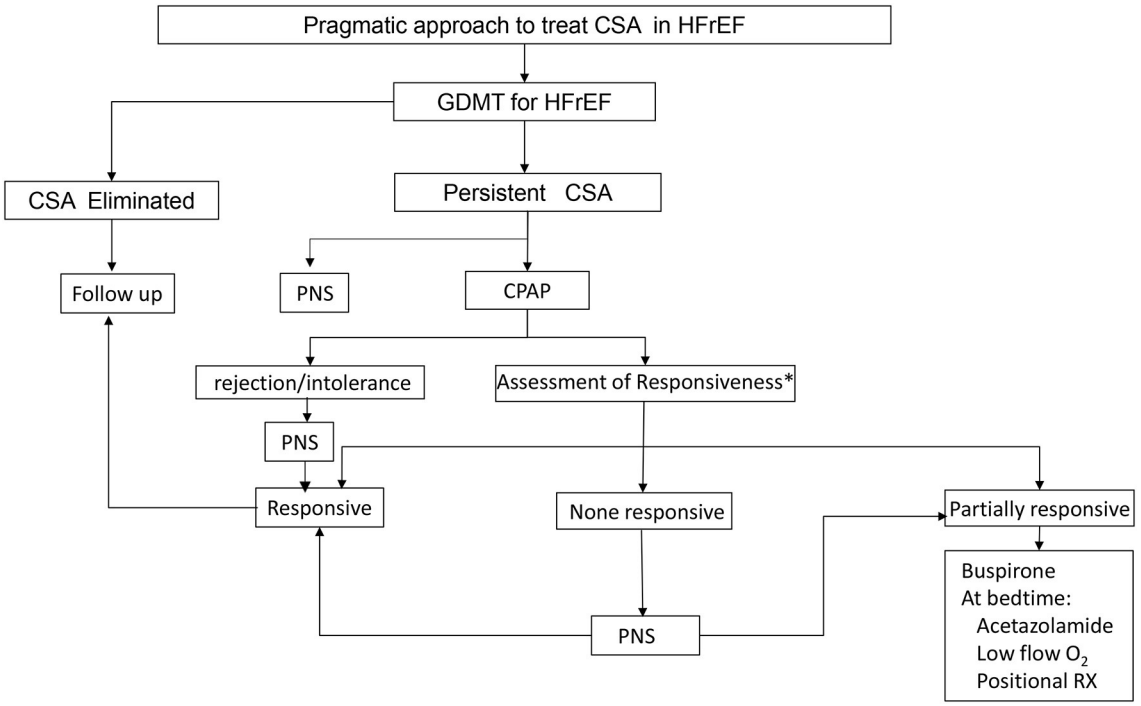

FIGURE 6
Proposed CSA treatment algorithm. Treatment should always start with guideline directed medical therapy (GDMT) and options for treatment include continuous positive airway pressure (CPAP), phrenic nerve stimulation (PNS), medications and oxygen.

with CSA have a significant, albeit lower, number of centrally mediated disordered breathing events in REM sleep, and PNS improves CSA in both REM and NREM sleep.

Long term studies

Efficacy and safety through 12 months (Costanzo et al., 2018b) were reported. Similar improvements were demonstrated

TABLE 1 Differences between treatment and control group in the remede® system pivotal trial (6 months data).

	Between group change (treatment versus control) $n = 132$ (change +/- standard deviation)	
Central apnea index (CAI)	−23 +/− 18	$P < 0.0001$
Apnea hypopnea index (AHI)	−25 +/− 18	$P < 0.0001$
Arousal index (AI)	−15 +/− 19	$P < 0.0001$
Percent of sleep in REM sleep	2 +/− 8	$P = 0.024$
Moderate or marked improvement in patient global assessment	55 (40–68)	$P < 0.0001$
Oxygen desaturation index (ODI) 4%	−23 +/− 18	$P < 0.0001$
Epworth Sleepiness Scale (ESS)	−3.7 +/− 5.0	$P < 0.0001$

TABLE 2 Serious adverse events with the remede® system through 12 months in the pivotal trial.

Serious adverse event	Number of patients ($N = 151$) (%)
Impending pocket erosion	2 (1%)
Implant site hematoma	1 (1%)
Implant site infection	2 (3%)
Extra-respiratory stimulation	1 (1%)
Concomitant device interaction	1 (1%)
Lead component failure	1 (1%)
Lead dislodgement	2 (3%)
Lead displacement	1 (1%)
Non-cardiac chest pain	1 (1%)
Elevated transaminase	1 (1%)

in the control group and the initial treatment group once activated including improvements in AHI, CAI, arousal index and oxygenation. Patient global assessment demonstrated a similar improvement in overall quality of life in 74% and a moderate or marked improvement in overall health in 58% of the former control group once therapy was activated, similar to the treatment group, at 6 months.

Additional long-term data was gathered in a subset of patients enrolled in a post-approval study through 5 years (Costanzo et al., 2022). Patients underwent an in-lab attended PSG at 5 years. Improvements in sleep metrics continued through the 5 years of the study as well as improvements in daytime sleepiness and included a 22 event per hour reduction in AHI with a median CAI of 1 event/hour (95% CI 0.5).

One additional investigator-initiated trial was completed by Fox et al. (2019) and demonstrated a similar safety and efficacy profile to the pivotal study. All patients enrolled had heart failure with reduced ejection fraction. AHI improved from 38 +/− 18 to 17 +/− 9 ($P = 0.01$) and time below 90% improved from 81 +/- 56 min to 28 +/− 43 min ($P < 0.01$). While no improvement in ejection fraction was noted, there was a 40-meter improvement in 6-minute hall walk test ($P = 0.035$).

Heart failure

There is particular interest of the treatment of CSA in patients with heart failure following the surprising results of the SERVE-HF study, which demonstrated increases in cardiovascular mortality with the treatment of CSA (Cowie et al., 2015). The subset of patients with HF was evaluated in a study by Costanzo et al. (2018a). This group was 64% of the overall study group in the Pivotal Study and had similar improvements in sleep metrics. In addition, an improvement in disease-specific quality of life was seen in the Minnesota Living with Heart Failure scale -6.8 ± 20.0 ($P = 0.005$) at 1 year compared to baseline (Costanzo et al., 2018a). There was a small improvement in left ventricular ejection fraction of 4.0% (interquartile range −1.0 to 8.0%; $P = 0.004$) and a positive trend in time to first heart failure hospitalization with rates of 4.7% (standard error = 3.3) in the treatment group and 17.0% (standard error = 5.5) in the control group ($P = 0.065$). There was no difference between the treatment and control group in mortality, but there was only 6 months of randomized data.

Idiopathic central sleep apnea

ICSA is a relatively rare disorder. Patients may present with insomnia, daytime fatigue, and sleepiness. In a small sub-study (Javaheri et al., 2020) of 16 patients with moderate to severe central sleep apnea (baseline AHI = 40, CAI = 25), PNS improved at 6, 12, and 18 months of therapy: the AHI decreased by 25, 25, and 23 events/h ($P < 0.001$ at each visit) and the central apnea index by 22, 23, and 22 events/h ($P < 0.001$ at each visit). Furthermore, the arousal index decreased by 12 ($P = 0.005$), 11 ($P = 0.035$), and 13 events/h ($P < 0.001$). Quality of life instruments showed clinically meaningful improvements in daytime somnolence, fatigue, general and mental health, and social functioning. The only related serious adverse event was lead component failure in one patient.

Safety of phrenic nerve stimulation

Safety of phrenic nerve stimulation has been studied with different systems for over 50 years (Sarnoff et al., 1948). Initial studies on the transvenous system found safety similar to other neurostimulation platforms, but with some lead issues related to dislodgement with the initial lead design (Abraham et al., 2015). The lead was redesigned for the pivotal trial to maintain better stability over time.

In the pivotal trail, 138 (91%) of 151 patients had no serious related adverse events at 12 months. Seven (9%) cases of related-serious adverse events occurred in the control group and six (8%) cases were reported in the treatment group (Table 2). Seven patients died (unrelated to implant, system, or therapy), four deaths (two

in treatment group and two in control group) during the 6-month randomization period when neurostimulation was delivered to only the treatment group and was off in the control group, and three deaths between 6 months and 12 months of follow-up when all patients received neurostimulation. Twenty-seven (37%) of 73 patients in the treatment group reported non-serious therapy-related discomfort that was resolved with simple system reprogramming in 26 (36%) patients but was unresolved in one (1%) patient. Complications between year 1 and 5 occurred in 5% of patients and were primarily related to lead issues. However, there were three episodes in two patients of interactions with cardiac devices. These resolved with reprogramming, but physicians should be aware of the possibility of interaction.

Advantage and disadvantages of PNS

In contrast to positive airway pressure devices which increase intrathoracic pressure and could result in adverse hemodynamic consequences, particularly in the setting of heart failure, PNS therapy is a physiological treatment mimicking normal breathing. Here we note that in the largest randomized clinical trial for the treatment of CSA, the SERVE-HF trial, there was a significant association with use of adaptive servo-ventilation (ASV) and cardiovascular mortality when compared to the control arm. The investigators hypothesized that one potential reason for this association was the increased intrathoracic pressure imposed by the device. PNS is devoid of this adverse side effect.

Another advantage of PNS is adherence to therapy. The therapy activates automatically at night as long as the patient is in a sleeping position. Notably, both in the CANPAP and the SERVE-HF trials, adherence to CPAP and ASV was about 3 to 4 h (Bradley et al., 2005; Cowie et al., 2015). Because, the burden of CSA increases in late hours of NREM sleep (Javaheri, 2000), full adherence to PNS provides additional benefit, compared to mask therapy. We note that residual hypopneas may remain after PNS. Changing the programming of the device over time can improve the number of events. If residual events are obstructive, low CPAP could be effective (Beyerbach et al., 2019).

Clinical implications

TPNS is now available at more than one hundred centers in the United States. Determining which patients are most appropriate for this therapy takes both the sleep metrics and patient co-morbidities. Specifically, patients with low ejection fractions have few therapeutic options and may be early candidates for TPNS. We have previously proposed the following flowchart for treatment of CSA (Figure 6) (Javaheri et al., 2020). Once implanted, patients will have several visits in the sleep clinic and a follow up sleep study to optimize the programming of the device. Understanding this follow-up pathway will be important to the prescribing physician.

TPNS is an implantable device, and the cost is high, like hypoglossal nerve stimulation, compared to other sleep apnea therapies. Large scale, long-term studies related to mortality are not yet available. However, the physiologic approach and improvement in sleep metrics and quality of life with a strong safety profile make this therapy a good option for many patients with CSA.

Author contributions

SJ was the lead author and developed the concept and outline. All authors contributed to the article and approved the submitted version.

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Conflict of interest

SJ and KD-M are consultants to ZOLL Respicardia. RG is an employee of ZOLL Respicardia. The authors declare that this study received funding from ZOLL Respicardia. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication, but they did fund some of the studies referenced in the article. SJ declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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Beyond CPAP: modifying upper airway output for the treatment of OSA

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Obstructive Sleep Apnea (OSA) is exceedingly common but often under-treated. Continuous positive airway pressure (CPAP) has long been considered the gold standard of OSA therapy. Limitations to CPAP therapy include adherence and availability. The 2021 global CPAP shortage highlighted the need to tailor patient treatments beyond CPAP alone. Common CPAP alternative approaches include positional therapy, mandibular advancement devices, and upper airway surgery. Upper airway training consists of a variety of therapies, including exercise regimens, external neuromuscular electrical stimulation, and woodwind instruments. More invasive approaches include hypoglossal nerve stimulation devices. This review will focus on the approaches for modifying upper airway muscle behavior as a therapeutic modality in OSA.

KEYWORDS

genioglossus, hypoglossal nerve, precision medicine, control of breathing, sleep disordered breathing, positive airway pressure

Introduction

OSA overview and underlying pathogenic mechanisms

Obstructive sleep apnea (OSA) is a common and heterogeneous condition that affects up to one billion individuals globally (1). OSA left untreated is associated with severe comorbidities, including diabetes mellitus (2), coronary artery disease (3), increased risk of stroke (4), congestive heart failure (5), atrial fibrillation (6), and possibly death (7). While continuous positive airway pressure (CPAP) is the gold standard, adherence is highly variable (8). The 2021 global CPAP shortage highlighted the need for different approaches to OSA management (9). Conventional approaches to those who are CPAP intolerant include positional therapy, weight loss, oral appliances, and upper airway surgery (10). Our lab and others are attempting to understand the pathophysiological drivers of OSA to personalize therapeutic options (11). The OSA traits (endotypes) will not be reviewed extensively here but include: (1) excessively collapsible upper airways, (2) inadequate muscle compensation, (3) ventilatory control instability (high loop gain), and (4) low respiratory arousal threshold (ArTH) (12). This review will focus on studied modalities for improving upper airway dilation as potential OSA treatments. We will examine the role of upper airway training and electrical stimulation of the upper airway muscles and nerves as therapeutic options for OSA (13). Notably, drug therapy for improving upper airway motor output is also an active area of investigation but is beyond the scope of this review (14–16).

Overview of the respiratory upper airway

The upper airway consists of 23 pairs of muscles, including dilators, protrudors, retractors, and the intrinsic muscles of the tongue (17, 18). These muscles are state-dependent, meaning that their activity level tends to decrease with sleep onset (19), especially with rapid-eye movement (REM) sleep (20, 21). Concerning OSA pathogenesis, genioglossus is the best studied of these muscles due to its ease of access [i.e., with electromyography (EMG) wires] (22).

However, multiple upper airway dilators and constrictors are important in the upper airway response to flow-limited breathing during sleep (23). Indeed, the superior, middle, and inferior pharyngeal constrictor muscles constrict and decrease airway caliber during times of increased airway volume (such as during inspiration), but have dilatory action when airway volumes are low (such as at the end of an apnea) (23). The pharyngeal retractors styloglossus and hyoglossus, while typically known for decreasing airway caliber on their own, may have a synchronous effect with genioglossus to promote upper airway patency (24). The peripharyngeal muscles as well as the intrinsic muscles of the tongue are also important in maintaining luminal patency amidst flow limitation (25, 26). Additionally, the muscles of the soft palate palatoglossus, palatopharyngeus, levator palatini, tensor palatini in addition to other muscle groups are important in combatting obstructive events of the upper airway (27).

Upon sleep onset, the upper airway relies on chemoreceptive cues, mechanical load, and lung volume afferent cues to drive firing patterns for each breath cycle (22). There is a negative pressure reflex, in which inspiratory negative pressure across the upper airway increases genioglossus output (28). This reflex is generally attenuated during sleep compared to wakefulness, but is augmented during supine sleep vs. recumbent (28, 29). Both mechanical loading and elevated pCO_2 increase upper airway dilator output, with an additive effect when these two stimuli are combined (22). In many cases of OSA however, the efficacy of upper airway dilators in maintaining pharyngeal patency is reduced (30). This loss of efficacy is partly related to a decrease in the state-dependent drive but also may emerge from an inadequate muscle output to compensate for an excessively collapsible upper airway (20). The importance of upper airway neuromyopathy has been debated, with data somewhat mixed regarding whether observed abnormalities are a cause or consequence of disease (31–35). There may also be muscle asynchrony contributing to the loss of pharyngeal patency in sleep (36). With consideration of the role of upper airway muscle function in sleep apnea pathogenesis, a number of strategies have been undertaken to improve upper airway performance in response to flow-limited breathing.

Attempts at improving muscular dilation of the upper airway

Myofunctional therapy for the treatment of OSA

While the mechanisms of OSA pathogenesis are heterogeneous, exercises for improving upper airway stability through muscle training and improvement in passive pharyngeal properties [such as the critical closing pressure (PCrit)] have been pursued in clinical research (37). The ideal training regimen, training method, and patient selection for improving OSA is yet to be determined. Still, there may be an improvement in sleep apnea severity, and daytime symptoms with dedicated upper airway training regimens often referred to as myofunctional therapy (MT), though the data is inconsistent (38). MT has been predominantly studied in mild to moderate OSA (39). The exercises prescribed are heterogeneous and the relative mechanisms for these exercises to combat OSA are uncertain. There have also been studies of MT in severe OSA, where MT appears less effective but may serve as a CPAP adjunct (40). Exercises are reported to target the soft palate, tongue, and external facial muscles (38).

A common combination of the above exercises is appended below (Table 1). Exercises are typically intensified over the course of a 6-week training period.

Benefits and limitations of myofunctional therapy

In some randomized controlled trials (RCTs), MT demonstrated improvements in polysomnographic measures of sleep, including AHI and oxygen saturation parameters (10). In a meta-analysis including observational studies, MT elicited a 50% decline in the AHI among adults and a 62% decline in the AHI among children (38). MT also demonstrated improvements in secondary outcomes, including subjective quality of life scores, Epworth Sleepiness Scale (ESS), snoring, and CPAP compliance (38). The mechanism(s) of MT on AHI reduction are heterogeneous and not fully delineated (10, 37). Notably, MT has also been used as an adjunct to improve CPAP adherence (41). However, a major limitation of MT is the lack of standardization. Generalizability between MT studies remains low due to variable inclusion criteria, follow-up protocols, exercise regimens, and training devices (10). Additionally, the mild severity of OSA within the available studies creates the possibility of regression to the mean explaining some of the positive reported results for MT. The ideal anatomy for MT benefit, i.e., based on Mallampati/Friedman scores, for instance, is unclear. The durability of effect of MT is also uncertain (39). Barriers to adherence with MT are potentially related to lack of patient engagement/understanding once they are in a home setting and practicing MT exercises independently (42). According to the European Respiratory Society guidelines, MT is not recommended as a treatment unless patients are reluctant to engage in surgical/mechanical strategies (43). Further research on MT should focus on determining which exercises yield maximal benefit, which patients benefit from MT, and which therapeutic adjuncts can and should be added for an individual based on their unique OSA traits.

According to the European Respiratory Society guidelines, MT is not suggested as a standard treatment for OSA [43]. The guidelines recommend patients use CPAP instead of MT (43). However, patients who are reluctant to engage in surgical/mechanical strategies may find improvements in their symptoms (43). These recommendations are

TABLE 1 Representative MT regimen prescribed to patients with mild-moderate OSA.

Category		Exercise name	# seconds	# repititions	# sessions/day
Tongue	1	Tongue Press	5	5x	2
	2	Stick Your Tongue Out	5	5x	2
	3	Stick Your Tongue Out and Down	5	5x	2
	4	Stick Your Tongue Out and Up	5	5x	2
Soft palate	1	Blowing with Resistance with Balloon	5	10x	2
	2	Say "Ahhh"	10	10x	2
Throat and neck	1	Ceiling Swallow	5	10x	2
	2	Going Up	10	10x	2
Jaw and lips	1	Lip Workout	10	10x	2
	2	Jaw Resist	10	10x	2
	3	Chewing			

The regimen advances and is modified over a 6-week period. Adapted from Guimaraes et al. (37). This is solely meant for illustrative purposes, and the ideal MT training regimen is unclear.

conditional and are based off a low quality of evidence. More research on MT is necessary to provide confident recommendations.

Upper airway training with woodwind instruments

Over the past 20 years, it has been noted that woodwind instrument playing may have a protective effect on OSA (44). In 2006, Puhan noted that playing the didgeridoo, an indigenous Australian instrument, improves the AHI compared to controls (44). This study prompted the investigation of other woodwind instruments for treating and preventing OSA (45). In a study comparing wind instrument musicians to string instrument musicians, no significant differences in sleep efficiency or subjective sleep quality metrics were noted (46).

Didgeridoo

The use of woodwind instruments such as the didgeridoo may be beneficial in the treatment of symptomatic OSA. In a study by Puhan and colleagues, didgeridoo practice showed significant improvement in AHI, ESS, and partner sleep disturbance scores (44). In a meta-analysis of the effects of musical interventions in OSA, the didgeridoo was the most therapeutic musical intervention in improving sleep-disordered breathing (45). This finding may be due to the unique nature of the didgeridoo requiring circular breathing (45). Circular breathing is the vocalization of a continuous tone while simultaneously inspiring through the nose. This procedure is performed by expelling air through the mouth and using the cheek muscles to create a reservoir of air. Notably, however, in other instruments requiring circular breathing, such as the bassoon, circular breathing in and of itself has yet to be shown to be effective in treating OSA consistently (47).

Puhan and colleagues, are the only research group to research the effects of the didgeridoo on OSA thus far to our knowledge (44). One major limitation of this study was the small sample size of 25 participants and the lack of a rigorous control group. The control group consisted of participants put on a waiting list. This approach was viewed as easier than having participants practice with a "sham" didgeridoo. A clear role of didgeridoo playing in OSA treatment is not defined (48).

Other woodwind instruments

Subsequent studies have separated instruments into single-reed, double-reed, high-brass, and low-brass instruments (48). Single reed instruments (clarinet, saxophone) include a single piece of cane that vibrates when sound is introduced. In contrast, double reed instruments (bassoon, oboe, English horn) have two pieces of cane that vibrate and a narrower aperture. Low brass includes tubas and sousaphones. High brass includes trumpets and French horns. Of the instruments noted, the double reed appears to improve AHI and daytime symptoms consistently, with more hours spent playing corresponding to greater AHI reduction (48). Ward et al. argued that the narrower aperture of double reed instruments and requisite air pressure were comparable to high-brass instruments (30–42 mmHg vs. 13–42 cmH_2O) and thus did not explain the differences in efficacy across the woodwinds. Additionally, benefit in OSA treatment was not seen in non-wind instrumentalists (48). Rather, they speculated that the differences in efficacy were attributable to the differences in muscle activation patterns across the instruments (48). Circular breathing does not have a clear and consistent role in improving the AHI (47). Although, the extent of circular breathing and requisite practice requirement of the didgeridoo may be greater than in other instruments and thus involve a more intensive circular breathing practice (48). While woodwind instruments may be helpful for sleep apnea,

which instruments to use and how to implement them remains uncertain (49).

Electrical stimulation of the upper airway

Electrical stimulation of the upper airway has included both external stimulation of upper airway muscles and direct stimulation of nerves supplying the upper airway. Current devices for external and internal (surgical) stimulation of the upper airway muscles and nerves, respectively, are shown in Figure 1.

External submental electrical stimulation

External stimulation of the upper airway dilator muscles has recently become a clinically significant modality in treating mild OSA. Devices like eXcite OSA and TESLA offer symptom relief for primary snoring and OSA (50, 51). External stimulation of upper airway muscles has come about through various approaches, predominantly focused on nighttime tongue stimulation.

The initial attempts at electrically stimulating the upper airway during flow-limited breathing were by Miki et al. (52). Using submental electrodes and a microphone over the cervical trachea, electrical stimulation of 15–40 V at a frequency of 50 Hz was applied when tracheal breath sounds were <15% of tracheal sounds during tidal breathing for 5 s (52). This study was in six patients and showed decreased sleep apnea severity and increased stage III sleep without associated arousals (52). This same group showed that direct stimulation of genioglossus in anesthetized dogs decreased upper airway resistance (53). Hillarp et al. later used submental electrical stimulation in a single patient during apneic events. The behavior of the upper airway was recorded using videoradiography and showed that tongue base obstruction improved with submental stimulation (54).

Edmonds et al. subsequently used a transcutaneous neuromuscular stimulation device (TENS) to assess the efficacy of concurrent submental and infrahyoid stimulation on OSA severity. No significant reduction in AHI was noted (55). Additional efforts entailing multi-site stimulation emerged in the following years. Guilleminault attempted simultaneous submental and transmucosal sublingual stimulation with a proprietary device without significant change in OSA parameters (56). Schnall also attempted simultaneous submental, paralaryngeal, and submucosal stimulation using a horseshoe shaped electrode while measuring pharyngeal resistance as the primary outcome measure. Only sublingual resistance improved (57).

In 1999, Wiltfang et al. applied daytime submandibular electrical stimulation to suprahyoid muscles by intra and extraoral electrodes via a transcutaneous electrical nerve stimulation (TENS) unit. After a 4-week training regimen (30 min twice a day), the researchers documented suprahyoid hypertrophy by ultrasound, reduced respiratory disturbance index from 13.2 to 3.9/h, and reduced oxygen desaturation index from 23 to 2.8/h. Despite these improvements, this study did not materialize into an exportable clinical protocol or novel device. Steier et al. used a commercially available Neurotrac stimulator to elicit submental stimulation of genioglossus during N2 sleep, with a resolution of upper airway occlusion when activated (58). This work ultimately culminated in the development of the transcutaneous electrical stimulation (TESLA) device. TESLA, a device that utilizes TES, delivers a continuous low-current electrical stimulation to the genioglossus during sleep, which causes increased airway patency. TESLA transmits an electrical current transcutaneously via dermal patches in the sub-mandibular area.

In an RCT, TESLA accounted for multiple positive outcomes. The AHI improved by a mean of 9.1 [95% confidence interval (CI) 2.0, 16.2] events/h, and the 4% oxygen desaturation index (ODI) improved by a mean of 10.0 (95% CI 3.9, 16.0) events/h (51, 59). TESLA exhibited a 100% response rate for mild OSA patients, while patients with moderate and severe OSA reported a 46 and 29% response rate, respectively. While it is still not understood which OSA patients are ideal candidates for TESLA, early studies have identified some features associated with higher success rates. Current inclusion criteria for TESLA include an AHI of 5–35 events/h, a BMI of <32 kg/m^2, CPAP intolerance, and low adherence to MAD (60). Adverse effects of TESLA include dry mouth, skin discomfort, and claustrophobia. No major adverse events were reported.

During sleep, the TESLA system included external stimulation of the "upper airway dilators" via 4 x 4 cm patches on the anterior neck. This system appeared to reduce RDI, but which muscles are activated with this program is unclear (59).

There is also the Kalinix device, but limited data have been reported beyond a congress abstract with 20 patients. The authors noted that 52% of individuals had a reduction in AHI, but the exact change is unreported. Inclusion criteria were adults with AHI 15–65 events/h and BMI < 32 kg/m^2. No serious adverse events were noted. Follow-up studies have not yet been reported (61).

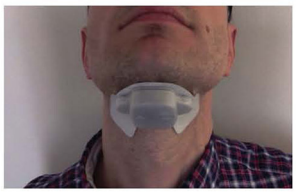
Day-time electrical stimulation

Most of the previously mentioned stimulation devices involved transcutaneous stimulation during sleep and included a broad range of OSA severity. Transoral stimulation is a new modality treating mild OSA and simple snoring in individuals with a BMI < 35 kg/m^2 (62). EXciteOSA, formerly known as Snoozeal, is an oral device that activates the upper airway through electrical stimulation. It includes three components: a control unit, a washable mouthpiece, and a Bluetooth smartphone application. Four electrodes supply the tongue with electrical stimulation. Two electrodes lie on top of the tongue, and two sit below the tongue to generate vertical and diagonal stimulation patterns.

Patients have full control over the intensity of electrical stimulation using their smartphone. The device emits a series of pulse-bursts over 20 min. The frequency of stimulation changes in a defined sequence throughout the treatment cycle. Phase 1 of the treatment includes 20 min once per day, and phase 2 includes 20 min twice per week, though phase 2 of therapy is often individualized in clinical practice.

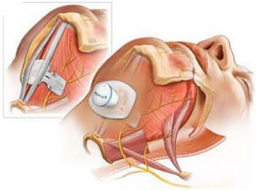
In the available clinical data, eXciteOSA showed significant improvements in objective and subjective indices of OSA. The AHI reported a mean reduction of 3.4 ± 5.0 events/h (95% CI 2.2–4.7) from 10.2 to 6.8 events/h ($p < 0.01$). The oxygen desaturation index decreased by 2.5 ± 4.6 events/h (95% CI 1.4–3.6) from 8.4 to 5.9

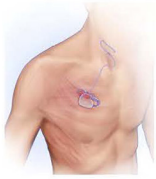
A Noninvasive Stimulation (External Stimulation)

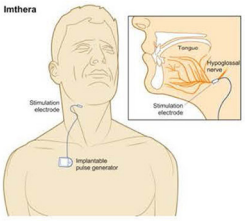


eXciteOSA	TESLA (Transcutaneous Electrical Stimulation for Obstructive Sleep Apnea)	Kalinix
FDA Status: Approved Strengths: • High adherence • Daytime use • Ease of use paired with app directions • 50% reduction in AHI Limitations: • Only studied for mild OSA • Requires daily use for at least 6 weeks	FDA Status: Not Approved Strengths: • At home use • Low cost, high safety Limitations: • 9% reduction in AHI • Potentially uncomfortable to wear for entire night • Most beneficial for those with mild to moderate OSA • Not necessarily beneficial for those with high BMI	FDA Status: Not Approved Strengths: • Light and portable • Ability to view results on screen • Adaptable to patient depending on sleep Limitations: • Only tested in Europe so far • Requires both daytime and nighttime use for best results • Device and cord sit on outside of body, possibly causing discomfort • Limited reported data

B Invasive Stimulation (Internal)







Genio	Inspire	Aura6000
FDA Status: IDE Approval Strengths: • No implanted battery or sensing leads • Single surgical incision Limitations: • Surgical intervention • Daily charging of external stimulator required	FDA Status: Approved Strengths: • FDA approved since 2014 • Well studied with large, prospective ADHERE registry being continually developed and analyzed Limitations: • Not as effective for patients who are significantly overweight (BMI > 32) • Not effective for patients with complete concentric collapse of soft palate	FDA Status: IDE Approval Strengths: • Single surgical incision • Does not require DISE Limitations: • Limited clinical data thusfar with pivotal trial ongoing.

FIGURE 1
(A) External stimulation devices which have been utilized in OSA treatment. Left to right, ExciteOSA, TESLA, and Kalinix devices. **(B)** Implantable upper airway stimulation devices, including Genio, Inspire, and the Aura6000 device. IDE, Investigational Device Exemption. Image re-use permissions granted where applicable (51, 86, 87).

events/h ($p < 0.01$). Mean ESS reduced from 8.7 to 5.3 (reduction of 3.4 ± 4.1; 95% CI 2.4–4.4; $p < 0.01$). Composite Pittsburg sleep quality index (PSQI) decreased from 7.3 to 5.9 (reduction of 1.4 ± 2.8; 95% CI 0.7–2.1; $p < 0.01$). However, further study is needed to identify the optimal patient population for this device. Additionally, it remains unclear how therapy should be modified (if at all) after the initial 6 weeks of treatment. A recent randomized controlled trial has completed enrollment with reportedly favorable results, but the results have not yet been made available to the public. Possible side effects include drooling, tongue tingling, and tooth discomfort (50).

It has been suggested that improving tongue endurance may not influence OSA. In one study evaluating the effects of a six weeklong tongue endurance program, no improvements in OSA severity were detected (63). The exercise regimen did however produce improvements in daytime sleepiness.

Surgical approaches to upper airway stimulation—hypoglossal nerve stimulation

Hypoglossal Nerve Stimulators (HGNS) are surgically implanted devices that apply electrical stimulation to the hypoglossal nerve to control the movement of the tongue. HGNS is an effective tool to treat OSA because it allows for control of the genioglossus and hence pharyngeal volume. We will include multiple HGNS devices on the market and in development in this review, including the Inspire device, Apnex, Genio, and Aura6000.

Inspire

Inspire became the only FDA-approved HGNS after the STAR trial in 2014. The initial feasibility study of this model however, dates back to 2001 (64). The Inspire device is surgically implanted into the upper chest, commonly on the right side, and innervates the medial branch of the ipsilateral hypoglossal nerve. Inspire contains three components: a respiratory sensing lead, an impulse generator, and a stimulation lead. The respiratory sensing lead detects the exact phase of the respiratory cycle activating the impulse generator during inspiration. The impulse generator sends an electrical impulse to the hypoglossal nerve through the stimulation lead. Upon electrical stimulation of the hypoglossal nerve, the tongue stiffens and protrudes. Inspire uses both respirophasic and a fixed stimulation pattern. Electrical stimulation strength is modulated with a remote control.

Benefits and limitations of Inspire

Observational studies have provided some evidence to establish Inspire as a clinically efficacious device in treating OSA (65). In the pivotal STAR trial, HGNS decreased AHI by 68%, from an average of 29.3 events per hour to 9.0 events per hour (65). The ODI score decreased by 70%, from 25.4 events per hour to 7.4 events per hour (65). Secondary outcomes, including the Functional Outcomes of Sleep Questionnaire (FOSQ) and ESS, also showed improvement (65). This trial was followed by a therapy-withdrawal study which randomly assigned responders to withhold HGNS temporarily. Results from this study showed responders taken off HGNS returned to baseline in both AHI and ODI. When HGNS was re-initiated, the AHI and ODI returned to post-treatment standards (65). The most comprehensive data set on HGNS is the ADHERE Registry, which includes patient-level data for individuals who have undergone HGNS. Analysis of this data set further confirms the significant therapeutic effects of HGNS on both objective and subjective measures of OSA (66). This registry now includes nearly 5,000 patients with longitudinal data.

Patient selection for Inspire is based on criteria informed by the STAR trial (65). Indications for implantation include moderate to severe OSA with CPAP intolerance or refusal. Patients must have a BMI < 32 kg/m^2; <25% central/mixed apnea events, and an AHI between 15 to 65/h (65). Contraindications for HGNS include a complete concentric collapse of the soft palate (65). Candidacy requirements for HGNS devices are still evolving.

HGNS appears well-tolerated, but 1/3 of patients have been deemed non-responders long-term (66). To optimize patient selection for HGNS, Op de Beek examined OSA endotypes and noted that those with a higher arousal threshold, greater muscle compensation, and lower loop gain had a higher chance of HGNS success (67). Conversely, patients with low muscle compensation and mild collapsibility were noted to have lower HGNS success rates (67). Additionally, higher baseline AHI, lower BMI, and older patient age appear to be associated with a greater reduction in AHI with HGNS (68). These results suggest diagnosing the non-anatomical characteristics of OSA may play a critical role in prescribing HGNS (67).

From an anatomic perspective however, complete palatal and complete tongue base collapse, but not complete lateral pharyngeal wall collapse as assessed by drug-induced sleep endoscopy (DISE) are associated with greater AHI reduction following HGNS implantation (69). Additionally, tongue morphology during stimulation is important for maintaining airway patency (70). Tongue protrusion and maintenance of tongue shape is associated with increased airflow, whereas anterior movement with increases in tongue height are associated with decreased airway patency (70). Lastly, both the extrinsic and intrinsic muscles of the tongue appear to be activated by HGNS, with the milieu of muscles activated depending on cuff position, voltage intensity, and pattern of stimulation (71). Thus, there is tremendous complexity underpinning patient selection, therapy optimization, and non-anatomic traits in generating an optimum response to HGNS.

Apnex

One of the initial HGNS device studied was the Apnex device (72). This device has a single stimulation lead and two respiratory sensing leads (73). Cuff placement is on the main branch of the hypoglossal nerve, distal to the branches innervating tongue retractors (determined intraoperatively through stimulation). This device was reported to be well-tolerated and significantly reduced AHI, particularly in those with a BMI < 35 kg/m^2 (73). This device, however, is no longer actively studied and is not clinically available.

Genio

Genio is a bilateral HGNS device produced by Nyxoah (74). Genio provides stimulation to both branches of the hypoglossal nerve (65). This device requires a single midline submental incision with placement of paddled electrodes over bilateral distal medial hypoglossal nerve branches. The preferential selection of the distal branches reportedly activates genioglossus alone without the recruitment of adjacent muscles (74). An external, submental stimulator is placed on an adhesive, disposable patch to activate the cuffs (74). The stimulator must be recharged daily but has the advantage of not having an implanted battery. The Genio does not have respiratory sensing leads and delivers stimulation via adjustable, pre-programmed rates and duty-cycles in order to match the patient's breathing frequency. The BLAST OSA study was pivotal for this device (74). Inclusion criteria were adults 21–65 years old, AHI 15–65 events/h, BMI < 32 kg/m^2, and fewer than ten central events/h on PSG (74). This study did not meet its primary endpoint of an AHI reduction of 15 events/h, but AHI was significantly reduced from 23.7 ± 12.2 to 12.9 ± 10.1 and ESS from 11.0 ± 5.3 to 8.0 ± 5.4 (74). Quality of life metrics and bed-partner-reported snoring were also considerably reduced. No serious adverse events were reported (74).

In a study comparing unilateral HGNS and bilateral HGNS, no significant differences were detected in the AHI or ESS between the two treatment groups (75). This evidence suggests bilateral HGNS may be as a safe and effective as unilateral HGNS.

Aura6000

The Aura6000 is an emerging technology from LivaNova (previously under ImThera). The Aura6000 does not have a respiratory sensing component and assessment for concentric collapse by DISE is not part of the clinical workflow (76). The Aura6000 electrodes are placed in an unfasciculated portion of the hypoglossal nerve, targeting multiple muscle groups in the fatigue-resistant components of the posterior tongue (77). The rate of serious adverse events appears to be comparable to Inspire (25). The inclusion criteria for ongoing studies include adults over 22 with AHI 20–65/h and CPAP refusal or intolerance. Exclusion criteria include BMI > 35 kg/m^2, comorbid pulmonary, cardiac, or renal disease, and detailed PSG exclusion criteria, most notably, the presence of central or mixed apneas in >25% of AHI events (78). Based on the recent THN3 trial, data at 12–15 months for enrolled participants suggest that AHI is reduced by 42.5% percent within their cohort (25).

Ansa cervicalis stimulation

Stimulation of the ansa cervicalis as a therapeutic target to treat OSA can be used alone or in combination with HGNS (79). The ansa cervicalis is a nerve plexus innervating the infrahyoid strap muscles including the sternothyroid muscle. When activated, these muscles create caudal displacement of the hyoid bone, resulting in a stiffened upper airway (80, 81). In a small clinical study, stimulation of the ansa cervicalis increased inspiratory airflow in patients with severe OSA during DISE (79). Ansa Cervicalis Stimulation (ACS) increases pharyngeal volume by increasing caudal traction of the upper airway (82).

ACS may help overcome incomplete responses to HGNS (83). The combined effect of tongue protrusion and tracheal traction is likely synergistic (80). Early data on ACS are limited by small sample size, low diversity of study population, and lack of data accounting for end-expiratory lung volume (79). However, it has been shown that ACS decreases PCrit and Popen (when nasal pressure exceeds surrounding tissue pressure), with a significantly greater improvement in Popen with bilateral vs. unilateral ACS (84). It is challenging to compare HGNS and ACS due to different stimulation patterns. Despite these limitations, ACS has shown robust improvements in airway collapsibility and should be further investigated.

Summary and future directions

There is a rich history of improving upper airway output as a therapeutic modality in OSA (52, 78). Efforts have included MT, woodwind instruments, external stimulation devices, and direct nerve stimulation of varying regions of the hypoglossal nerve and the ansa cervicalis. A comprehensive consensus statement on non-PAP therapies was issued by the European Respiratory Society in 2021. Notably, the quality of evidence for many non-PAP interventions appears to be poor (43). Each intervention has improved OSA with routine use, but it is unclear which patients and endotypes benefit from each modality (85). We anticipate that the future of OSA therapy will include tailoring interventions to OSA traits and patient preferences, which will allow for optimum therapeutic engagement. Despite being a relatively young field, with <50 years of history, tremendous progress has been made in the application of bench physiology to the bedside in the management of OSA. Improving upper airway mechanics is just one approach, but considerable nuance is involved in a task as seemingly simple as stabilizing the pharyngeal airway. Similar granularity is required in addressing the other endotypes as well. As such, the future of our field includes precision medicine toward unique combinations of endotypic traits, multiple lines of concurrent therapies, and therapeutic adjustments as individual patient physiology evolves (13). We view this challenge with great excitement and believe tremendous opportunities to individualize patient care in OSA lie ahead.

Author contributions

All authors contributed substantially to the development of the manuscript, its editing, and final manuscript preparation.

Conflict of interest

AM was funded by the NIH. He reports income from Merck and Livanova related to medical education. He is the Global PI for Osprey and receives income from Livanova for this role. ResMed provided philanthropic support for UC San Diego.

He has no personal income from Signifier. BN is the Medical Director for Hypoglossal Nerve Stimulation at VA San Diego, but receives no industry funding or additional clinical funding for this role.

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.

Publisher's note

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The role of the WatchPAT device in the diagnosis and management of obstructive sleep apnea

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Obstructive sleep apnea (OSA) is a common condition affecting an estimated 936 million individuals worldwide, leading to a considerable demand for diagnostic services. Polysomnography, the current gold standard for diagnosis, is resource intensive and inconvenient for patients and healthcare providers. The WatchPAT is an unobtrusive device for home OSA diagnosis. It utilizes peripheral arterial tomography in conjunction with heart rate, oximetry, actingraphy, and respiratory movements for the diagnosis of OSA. It has good correlation with polysomnography for OSA diagnosis and also reports sleep time and sleep staging. The WatchPAT device has reported sensitivities of 81–95%, specificities of 66–100%, positive predictive values of 79–96%, and negative predictive values of 92% for the determination of the apnea–hypopnea index (AHI). It has also been studied and its use validated in a variety of patient populations, including children, older adults, pregnant women, and those with comorbid medical conditions. The device has also been adopted for use in screening for cardiac arrhythmia and central sleep apnea, although neither use has become widespread. With the emergence of telemedicine and an increasing demand for sleep services, the WatchPAT device can be a useful aid in OSA diagnostics.

KEYWORDS

obstructive sleep apnea, WatchPAT, telemedicine, sleep disorders, central sleep apnea (CSA)

Introduction

Obstructive sleep apnea (OSA) affects an estimated 936 million individuals worldwide, of whom approximately 425 million individuals require treatment (Benjafield et al., 2019), leading to a considerable demand for OSA diagnostics. The current gold standard for diagnosis, polysomnography, has considerable drawbacks and is resource intensive. As a consequence, newer less invasive diagnostic modalities have emerged. One such modality is the WatchPAT (WP) device. The aim of this review is to discuss the WP device, its role in OSA diagnosis in various patient populations, and other uses for the device that have emerged.

Sources and search strategy

References used for this review were identified from PubMed and Medline searches. Search terms used included "WatchPAT," "Peripheral Arterial Tomography," and "PAT" in conjunction with specific disorders and other investigations, including "polysomnography (PSG)," "obstructive sleep apnoea," "sleep apnoea," "central sleep apnea," and "sleep staging."

Background

OSA is caused by recurrent episodes of upper airway collapse during sleep, which results in a reduction (hypopnea) or absence (apnea) of airflow, oxygen desaturation, and arousal. Arousals contribute to symptoms including sleep fragmentation, unrefreshing sleep, and excessive daytime sleepiness. It is then graded in severity on the apnea-hypopnea index (AHI) according to the average number of hypopneas and apneas during sleep. OSA is associated with increased rates of road traffic accidents (Terán-Santos et al., 1999), workplace accidents (Garbarino et al., 2016), cardiovascular disease (Peppard et al., 2000; Punjabi et al., 2009), and diabetes (Wang et al., 2022), among others.

Polysomnography (PSG) is the current gold standard for OSA diagnosis. It measures sleep time, stage, and arousals using an electroencephalogram, airflow using a thermistor, respiratory efforts with chest and abdominal bands, oxygen saturation, body position, leg movements, and snoring, with or without video monitoring. PSG can be performed with direct monitoring in a sleep laboratory (Type 1 study) or unattended at home or in the laboratory (Type 2 studies). However, polysomnography has significant drawbacks. It is labor intensive, intrusive for patients, and expensive for the health care provider.

Given the limitations of inpatient PSG, home sleep apnea testing (HSAT) has become commonplace and has been further accelerated by the COVID-19 pandemic. HSAT is broadly considered under two clinical pathways: the multiple access outpatient pathway and the telemedicine pathway. Under the multiple access pathway, the patient attends an outpatient appointment, then returns to pick up their HSAT device, returns the device, and attends a final appointment for results. The telemedicine pathway involves telemedicine consultations and direct receipt of the testing device by the patient at home. Home sleep apnea tests (HSATs) have proved popular and may be either Type 3 studies, which measure at least two respiratory variables (respiratory effort, flow), oxygenation saturation, and a cardiac variable, or Type 4 studies, which measure only one or two parameters, generally oxygen saturation and heart rate. The American Academy of Sleep Medicine (AASM) guidelines state that an HSAT should incorporate at least the following: nasal pressure, chest and abdominal movements, oximetry or peripheral arterial tomography with oximetry and actingraphy (Kapur et al., 2017).

WatchPAT technology

The WatchPAT device uses peripheral arterial tonometry (PAT). PAT technology is based on the variations in peripheral vascular resistance during sleep and arousals due to fluctuations in sympathetic nerve activity. During non-REM sleep, sympathetic activity is lower, with a consequent reduction in blood pressure and heart rate (Somers et al., 1993). During REM sleep, this activity increases above the levels observed during wakefulness, with blood pressure and heart rate increasing in tandem (Somers et al., 1993).

Arousals from sleep result in bursts of sympathetic activity, which in turn result in blood pressure surges and tachycardias (Schnall et al., 1999). These hemodynamic changes lead to increased peripheral vascular resistance. Our fingertips contain dense vascular beds with high contractions of sympathetic alpha receptors. Apnea- or REM sleep-induced activation of the sympathetic nervous system leads to the activation of these receptors, with resultant peripheral vasoconstriction, increased vascular tone, and decreased blood flow at the fingertip (Schnall et al., 1999). This can be detected by finger probe polysomnography. Studies have demonstrated a good correlation ($r = 0.82$) between PAT-detected apneas and those detected with EEG during PSG in both adult and pediatric populations (Pillar et al., 2002, 2003; O'Brien and Gozal, 2007).

Obstructive sleep apnea can be detected and diagnosed using PAT technology in conjunction with oximetry, heart rate, actingraphy, and respiratory movements (Penzel et al., 2004) (Figure 1). Additionally, WatchPAT technology allows for better assessment of sleep stages, including total sleep time, rather than total recording time, which is frequently used by HSAT (Hedner et al., 2011).

The WatchPAT and sleep staging

The vast majority of home sleep studies do not record sleep itself, as they do not have access to EEG data. Instead, they rely on recording time. The WatchPAT device utilizes actingraphy (Hedner et al., 2004) and a PAT signal to distinguish between waking time, sleep, REM, and non-REM (NREM) sleep (Herscovici et al., 2007), of which the latter is further subdivided into light or deep sleep (Bresler et al., 2008). Traditionally, NREM sleep has been classified into four stages by PSG: stage 1 (N1), drowsiness; stage 2 (N2), light sleep; and finally stages 3 and 4 (N3 and N4), deep sleep. Instead, the WatchPAT divides NREM sleep into light sleep (stages 1 and 2) and deep sleep (stages 3 and 4).

The WatchPAT then combines PAT signal and actingraphy to develop an automatic sleep-stage detection algorithm, using the PAT software package (Medical, 2002b). However, it is important to appreciate that the evidence for WP sleep staging is weaker than that for the gold standard, PSG. In a large multicenter study, researchers compared PSG and WP sleep staging and found only moderate agreement on the sleep stage (Cohen κ coefficient = 0.475) (Hedner et al., 2011). A smaller study, designed to assess the efficacy of the WatchPAT-200 (WP-200) in the diagnosis of OSA, found low agreement between PSG and light sleep (ICC = 0.495, $p < 0.001$), very low agreement for REM sleep (ICC = 0.237, $p = 0.044$), and no agreement for deep sleep ($p = 0.514$) (Ceylan et al., 2012).

Diagnosis of OSA by WatchPAT

There are currently three generations of the WatchPAT device: WatchPAT-100, 200, and 300 (WP-100, WP-200, and WP-300, respectively), as well as a disposable model, WatchPAT-ONE. All generations utilize PAT, oximetry, heart rate, and actingraphy, with various firmware and hardware upgrades in each generation. The most recent model, WP-300, contains an updated snoring, and body position sensor to monitor chest movements and diagnose central sleep apnea (Medical, 2020). Multiple studies

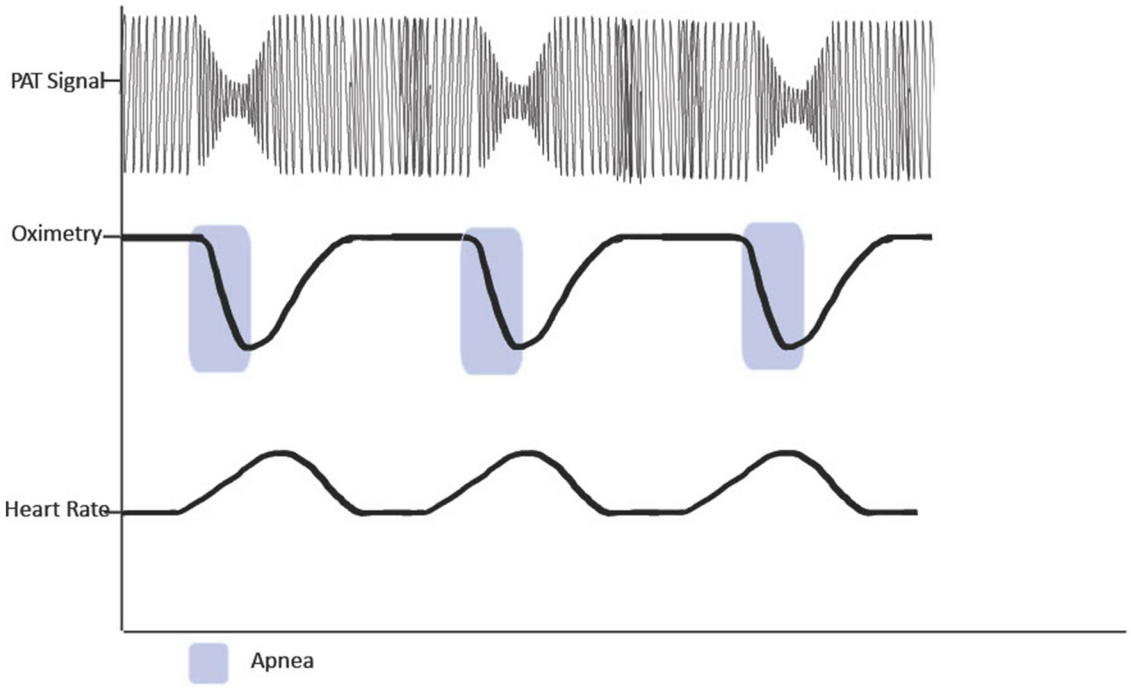

FIGURE 1
Figure demonstrating reduction in PAT signal following apnoic events.

have compared most devices with PSG, either by carrying out simultaneous PSG and WP studies or with studies on separate nights and in-lab and at-home studies. We have outlined in the following section the data relevant to OSA diagnosis for each generation of WP device in comparison to polysomnography for the diagnosis of obstructive sleep apnea.

At present, we know from several studies that the WP-100 has excellent correlation for AHI (Zou et al., 2006; Choi et al., 2010), respiratory desaturation index (RDI) (Bar et al., 2003; Penzel et al., 2004; Zou et al., 2006; Hedner et al., 2011), and oxygen desaturation index (ODI) (Penzel et al., 2004; Zou et al., 2006), with a reported sensitivity of 100%, a specificity of 83%, a positive predictive value (PPV) of 95%, and a negative predictive value (NPV) of 100% for the diagnosis of OSA compared to PSG (Choi et al., 2010).

Similarly, in a comparison with PSG, the WP-200 has been reported to have an excellent correlation for AHI (Pang et al., 2007; Ceylan et al., 2012; Onder et al., 2012; Weimin et al., 2013; Körkuyu et al., 2015; Gan et al., 2017; Tondo et al., 2021), RDI (Ceylan et al., 2012; Yuceege et al., 2013), ODI (Ceylan et al., 2012; Onder et al., 2012; Yuceege et al., 2013; Tondo et al., 2021), and mean oxygen saturations (Onder et al., 2012; Yuceege et al., 2013; Körkuyu et al., 2015). It also has a reported sensitivity of 81–95%, a specificity of 66–100%, a PPV of 79.4–96%, and an NPV of 92% for AHI (Ceylan et al., 2012; Weimin et al., 2013; Tondo et al., 2021). For RDI, a sensitivity of 89%, a specificity of 77%, a PPV of 82%, and an NPV of 86% are reported (Yuceege et al., 2013) (Table 1).

The most recent WatchPAT device, WP-300, uses a finger probe for oximetry and polysomnography and a chest probe to record snoring, body position and respiratory effort. No data on the WP-300 have yet been published.

A cost-effectiveness study using an unspecified WP device found that the telemedicine pathway was more expensive for the healthcare provider but significantly cheaper for patients, indicating that a telemedicine service with WP devices would be acceptable to the patient population (Di Pumpo et al., 2022). Use of the WP device rather than full PSGs in traditional outpatient services has been shown to reduce time to OSA diagnosis and treatment, leading to overall cost savings (Phua et al., 2021).

OSA treatment and WatchPAT technology

The WP has also been examined in the assessment of patients with OSA receiving continuous positive airway pressure (CPAP) therapy, which is the mainstay of treatment for individuals with OSA and excessive daytime sleepiness, or OSA and hypertension (Patil et al., 2019). One study compared simultaneous in-laboratory PSG and WP-100 assessment of patients on CPAP therapy, demonstrating good agreement between the WP and PSG for residual RDI (sensitivity of 86% and specificity 47% for RDI >5) (Pittman et al., 2006). An additional, non-inferiority study compared standard PSG diagnosis and titration of CPAP therapy with WP-100 in two separate groups. CPAP adherence and clinical outcomes were similar in both groups (Berry et al., 2008). Given the scarcity of PSG availability, many sleep centers use limited sleep studies (LSS) for the assessment of CPAP efficacy. One

TABLE 1 Summary of studies comparing WatchPAT and polysomnography.

References	WP device	Comparison device	Study population	AHI	RDI	ODI	Mean saturations	Sleep time
Bar et al. (2003)	WatchPAT-100	Level 1 PSG	N = 102 (No gender breakdown)	-	R = 0.88, $p < 0.001$	-	-	-
Ceylan et al. (2012)	WatchPAT-200	Level 1 PSG	N = 51 (No gender breakdown)	AHI < 15: Sensitivity 0.93 Specificity 66 PPP 0.794 NPV 0.85 AHI < 30 Sensitivity 0.88 Specificity 0.8 PPV 0.71 NPV 0.92	ICC = 0.961, CI 0.858–0.951, $p < 0.001$	ICC = 0.877, CI = 0.794–0.928, $p < 0.001$	-	-
Choi et al. (2010)	WatchPAT 100	PSG	N = 25 (84% men)	R = 0.94, $p < 0.001$ Sensitivity 1 Specificity 0.83 PPV 0.95 NPV 1	-	-	-	-
Gan et al. (2017)	WP-200	PSG	N = 20 (90% men)	R = 0.94, $p < 0.0001$	-	-	-	R = 0.6228, $p < 0.0034$
Hedner et al. (2011)	WP-100	PSG	$n = 228$ (No gender breakdown.)	-	ICC = 0.87, $p < 0.005$	-	-	ICC = 0.79, $p < 0.01$
Körkuyu et al. (2015)	WP-200	Level 1 psg	$N = 30$ (83.8%)	R = 0.802, $p < 0.001$ PPV 0.96	-	-	Mean WP 93.1%, PSG 92.6%, $p < 0.001$	r = 0.246, $p = 0.184$
Onder et al. (2012)	WatchPAT-200	Level 1 PSG	N = 59 (64% men)	Group 1: r = 0.92 $p < 0.001$ Group 2: R = 0.94 $p < 0.001$	-	Group 1: R = 0.97 $p < 0.001$ Group 2:r = 0.99 $p < 0.001$	Group 1: R = 0.89, $p < 0.001$ Group 2: R = 0.96, $p < 0.001$	Group 1: R = 0.62, $p = 0.003$ Group 2: R = 0.24, $p = 0.23$
Pang et al. (2007)	Unspecified	Level 1 PSG	N = 37 (33%)	R = 0.9288, $p < 0.0001$ AHI > 5 Sensitivity 0.94 Specificity 0.8	-	-	-	R = 0.5815;, $p = 0.005$
Penzel et al. (2004)	WP-100	Level 1 PSG	N =21 (No gender breakdown.)	R = 0.89, $p < 0.01$	R = 0.89, $P < 0.01$	R = 0.87, $p < 0.01$	-	r = 0.15
Tondo et al. (2021)	WP-200	PSG	N = 47 (62% men)	R = 0.86, $p < 0.001$ Sensitivity 0.81, Specificity 0.73	-	0.93, $p < 0.0001$	-	-

(Continued)

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TABLE 1 (Continued)

References	WP device	Comparison device	Study population	AHI	RDI	ODI	Mean saturations	Sleep time
Weimin et al. (2013)	WP-200	Level 1 PSG	N = 208 (72%)	R = 0.92, $p < 0.001$ For AHI > 5 Sensitivity 0.96 Specificity 1	-	-	-	-
Yuceege et al. (2013)	WP-200	Daytime PSG	N = 90 (100% men)	-	Sensitivity 0.89 Specificity 0.77 PPV 0.82 NPV 0.86	R = 0.923, $p < 0.0001$	R = 0.76, $p < 0.0001$	-
Zou et al. (2006)	WP-100	At home PSG	N = 106 (56% men)	R = 0.9, $p < 0.0001$	R = 0.88, $P < 0.0001$	R = 0.92, $p < 0.0001$	-	Mean difference 0.2 ± 1.1 h

study compared LSS with WP analysis for residual AHI on CPAP; interestingly, the WP device detected a higher rate of residual Sleep Disordered Breathing (SDB) than the LSS (Schöbel et al., 2018).

Limitations of WatchPAT in OSA

Although all these studies report high correlations between WP and PSG, with a proportion reporting high sensitivity and specificity, some have reported that the WP can underscore AHI at the mild range and overscore at the high range (Gan et al., 2017). A further study examined the correlation but also concordance for OSA diagnosis between the WP and PSG. Diagnostic accuracy was high in the moderate and severe OSA cohorts, with a sensitivity of 91%, a specificity of 61%, and negative and positive predictive values of 76 and 83% respectively. Conversely, of those assessed by the WP as having mild OSA, only 49.6% were deemed by PSG to have mild disease, with 20.4% having moderate or severe disease and 30.1% having no OSA (Ioachimescu et al., 2020). This suggests that further clarification is required in cases of high pre-test possibility or a negative test where symptoms are present. Additionally, in a meta-analysis of 17 studies comparing simultaneous PSG and WP, pooled specificities of 94, 92, and 74% and sensitivities of 44, 72, and 87% for AHI thresholds of 5, 15, and 30 events/h, respectively, were calculated (Iftikhar et al., 2022).

Importantly, in the vast majority of studies comparing WP and PSG, the majority of participants were men, with a mean 68% male majority in all studies, and some study populations containing 90–100% male participants (Yuceege et al., 2013; Gan et al., 2017). While this probably reflects the male preponderance in OSA, it does mean that the WP has been understudied in the female population; however, the results may not be generalizable.

It is also important to note that the WP device is not suitable for OSA diagnosis in all patients, and there are some contra-indications for its use. The manufacturer states that the device should not be used in adults taking short-acting nitrates or alpha blockers, those using a permanent pacemaker with atrial pacing and without sinus rhythm, or those with sustained non-sinus cardiac arrhythmia (Schnall et al., 2022).

Phentolamine, an alpha blocker, has been shown to induce peripheral vasoconstriction and decrease pulse wave amplitude during finger plethysmography, both in healthy controls (Grote et al., 2003) and in individuals with severe OSA (Zou et al., 2004). Although these studies were small, both strongly indicate that alpha blockers are likely to interfere with the diagnostic capabilities of a WatchPAT device. A specific study on the effect of nitrates on peripheral tomography in OSA has not yet been performed. Pharmacokinetic studies have demonstrated that both nitroglycerin and isosorbide dinitrate induce peripheral vasodilation and influence finger pulse plethysmography, which suggests that they would also interfere with the PAT signal (Schnelle et al., 1981; Bass et al., 1989). The manufacturers state that a wash-out period of 3 h may be adequate for doxazosin; however, this is based on a study where only five of the 106 participants used an alpha blocker.

The effect of cardiac pacing and cardiac arrhythmias other than atrial fibrillation on WatchPAT diagnosis has not been formally

evaluated, but the manufacturers state that they presume that it would interfere with the WP algorithms that derive AHI, among others. Although this recommendation is not evidence based, it would be prudent to avoid the use of WP in these cases, if possible.

Additionally, given that WP technology relies on vascular tone, conditions such as arterial stiffness or atherosclerosis may interfere with its diagnostic capabilities. Brachial-ankle pulse wave velocity (baPWV) has been used as a surrogate measurement for arterial stiffness and is a known predictor of cardiovascular disease (Kim et al., 2014). A comparative study of WP and PSG measured baPWV and found that participants with an elevated baPWV have a low correlation between WP-AHI and PSG-AHI. Notably, in those with a pulse wave velocity that the investigators determined as high, there was no correlation between WP and PSG AHI ($r = 0.4$, $p = 0.04$) (Kinoshita et al., 2018). Although this was a small study of 61, predominantly male, patients with a high prevalence of cardiovascular co-morbidities, it is still a reasonable assumption that, in a population at high risk of cardiovascular disease and arterial stiffening, with a high pre-test probability of OSA, a negative WP study may require further PSG clarification.

The WatchPAT has been used to good effect for OSA diagnosis across a range of conditions and research studies, including asthma, diabetes, congestive cardiac failure, myasthenia gravis, and following surgical interventions for OSA (Park et al., 2014; Yeh et al., 2015; Shinoda et al., 2019; Carey et al., 2023). Despite some critical studies, it has proved to be a good tool that has been widely adopted for the diagnosis of OSA. In those with a negative WatchPAT study and significant symptoms, PSG clarification may be needed; however, this is often the case with other HSATs.

OSA diagnosis in other patient populations

Pediatrics

SDB affects 1–3% of all children, causing, among other effects, sleep disruption, daytime cognitive impairment, and behavioral problems (Evans et al., 2023). SDB encompasses upper airway obstruction in children with otherwise normal development as well as in those with other underlying conditions. Full PSG is the gold standard for diagnosis of SDB, but as with adults, it is burdensome and costly. Moreover, some children may find PSG difficult to tolerate.

The WatchPAT device is currently approved for use in children from 12 years of age weighing >65 kg in America, Europe, and Japan (Medical, 2002a). The WP-200 has been studied in children aged 8 to 15 years. Compared to simultaneous Level 1 PSG, the WP had an excellent agreement for AHI (ICC = 0.89) and ODI (ICC = 0.87). The device used the same algorithm as that used for adults, which may under-detect respiratory events in the pediatric population (Tanphaichitr et al., 2018). In another study specifically addressing the diagnosis of OSA in adolescents (ages 13–17 years), the WP-200 had a sensitivity of 100% and a specificity of 96% for an AHI > 5 events/h compared to PSG (Choi et al., 2018).

The WP has also been studied in children under the age of 12 with symptoms suggestive of pediatric SDB (PSDB) but negative nocturnal pulse oximetry. Nocturnal pulse oximetry is often used as a screening tool for PSDB, as it is widely available, inexpensive, and simple to carry out. A study examined the use of WP rather than PSG following a negative pulse oximetry reading. WP detected PSDB in 35.7% of children with an RDI of >5. An AHI criterion of >1 was fulfilled by 60.7% of children (Serra et al., 2017). Given that all the population had previously had a negative pulse oximetry reading, the WP may be a more useful screening tool in this population. There are some disadvantages to WP device use in children. A pediatric finger probe is not available, and children under the age of five or those will smaller fingers will not be able to use it.

Pregnancy

SDB during pregnancy is associated with adverse outcomes, such as gestational hypertension, and is therefore important to detect. It is generally presumed to be related to gestational weight gain. PSG is inconvenient during pregnancy, so the WP would be a simple alternative. A study compared ambulatory PSG and WP-200 assessment of third-trimester pregnant women, some of whom were at high risk and some at low risk of SDB. Correlations between WP and PSG for total sleep time ($r = 0.76$, $p < 0.001$), AHI ($r = 0.76$, $p < 0.001$), RDI ($r = 0.68$, $p < 0.001$), and mean oxygen saturations ($r = 0.94$, $p < 0.001$) were all high; however, only low correlation was found for sleep stages ($r = 0.1$–0.32 for each sleep stage) (O'Brien et al., 2012). Additionally, WP had a sensitivity of 88%, a specificity of 87%, a negative predictive value of 70%, and a positive predictive value of 96% for an AHI >5 events/h (O'Brien et al., 2012). This suggests that the WP could be a useful tool for detecting SDB in pregnancy.

Patients with other medical conditions

The WatchPAT device has been examined in the diagnosis of OSA with a number of other conditions and co-morbidities.

For example, OSA is common in individuals with Down syndrome, with a reported prevalence of up to 78% (Giménez et al., 2018). A feasibility study into the utility of WatchPAT in a population of individuals with Down syndrome and signs and symptoms consistent with OSA found an OSA prevalence of 95%. Importantly, 69% of this study population found the WatchPAT device acceptable (Alma et al., 2022). Given that PSG is a burdensome investigation for any individual and those with intellectual disabilities often find some investigations difficult to tolerate, WatchPAT may provide a useful diagnostic tool in this population. As the study did not have a comparison group, the accuracy of the WatchPAT diagnosis in this population cannot be commented on.

For our growing elderly population, one study evaluated PSG and WatchPAT-200 in 56 individuals, comparing a younger age group (20–35 years) with an older group (50–65 years). Good agreement between PSG and WP was found for AHI and oxygen saturations in both groups, suggesting that WP can be reliably used in those populations. However, caution may still be needed for patients over 65 years old (Onder et al., 2012). As we age, vascular

stiffness increases, and vascular compliance reduces. Moreover, cardiovascular co-morbidities are more prevalent in the elderly population. These factors could all influence the ability of the WatchPAT device to diagnose OSA in the elderly population.

Chronic obstructive pulmonary disease (COPD) is a common condition that often overlaps with OSA. Given that COPD can itself lead to reduced oxygen saturation, many studies evaluating WP have excluded individuals with COPD. However, two studies in which the majority of patients had moderate COPD have directly compared the PSG and WP-200 analysis of individuals with COPD. The investigators found good correlation in AHI ($r = 0.85$, $p < 0.001$) between PSG and WP, including in those with moderate to severe disease, demonstrating that the WP device can be used to diagnose OSA in this patient population (Holmedahl et al., 2019; Jen et al., 2020).

Sleep apnea is a recognized risk factor for cardiovascular disease, including atrial fibrillation (AF). OSA is common in individuals with AF, with an estimated prevalence ranging from 49 to 62% (Gami et al., 2004; Stevenson et al., 2008), and it increases the rate of AF after electrical cardioversion (Mazza et al., 2009). Moreover, treatment of OSA leads to a reduction in the risk of AF recurrence (Qureshi et al., 2015; Shukla et al., 2015). Generally, studies examining WP have excluded patients with cardiac arrhythmia, owing to the concern that the arrhythmia may interfere with PAT amplitude and rate changes. In a study examining the usefulness of WP for the diagnosis of OSA in patients with AF, the authors found that WP is a suitable diagnostic tool for OSA in this population. AF does not appear to interfere significantly with the PAT signal or the time used for analysis. WP had a sensitivity of 88% and a specificity of 63% for the diagnosis of OSA compared to PSG, with an overall agreement in sleep staging of 62%, similar to that found in the general population (Tauman et al., 2020). An additional study used the WatchPAT-ONE disposable device to screen for SDB in a population with AF using a telemedicine model. Here, a prevalence of 55% for moderate to severe SDB was found by the WP device, again indicating that the WP is a useful tool for SDB screening in individuals with AF (Verhaert et al., 2022).

Other uses for the WatchPAT device

Diagnosis of atrial fibrillation

From the above findings, it is clear that the WatchPAT device is suitable for diagnosis of OSA in individuals with AF. As AF is common in patients with SDB, a team attempted to find whether the WP device could detect cardiac arrhythmias during a sleep study. Using the WP-200 device, they performed simultaneous WP and PSG analysis in a population suspected of SDB with co-existing congestive cardiac failure or AF. The ECG was scored manually on the PSG and blinded to the WP analysis. It is known that the PAT signal directly relates to ventricular contraction and, hence, can be used to detect the irregularly irregular pattern of AF. The WatchPat used a novel automatic algorithm, based on the PAT signal, and was found to have moderate sensitivity (77%) but high specificity (99%) for the detection of AF lasting longer than 6 min (Pillar et al., 2022). The results indicate that the WP device may be a useful screening tool for AF in a population being evaluated for SDB and could flag patients who need further investigation.

Diagnosis of central sleep apnea

Central sleep apnea (CSA) syndromes are characterized by SDB with associated decreased or diminished respiratory effort. Symptoms include excessive daytime sleepiness and nocturnal awakenings (Aurora et al., 2012). Given the symptom overlap with OSA, a proportion of patients referred for the assessment of OSA will actually have an element of CSA or a mixture of the two. The WP device detects CSA by combining PAT signal changes with respiratory movements derived from its snoring and body position sensor. A large study compared simultaneous WP-200 and PSG analysis of a population undergoing assessment for SDB. The study population was enriched with individuals with congestive cardiac failure, who have a high risk for CSA due to the Cheyne–Stokes breathing pattern. These investigators demonstrated moderate sensitivity (72%), high specificity (99%), and high correlation ($r > 0.8$) between PSG and WP (Pillar et al., 2020) in the detection of central apneic events, suggesting yet another use of WatchPAT technology.

Cognitive impairment and sleep disturbance

There is a strong relationship between Alzheimer's disease (AD) and sleep disturbance, and many patients with mild cognitive impairment (MCI) or AD report sleep problems. Performing PSG can be challenging in this population, due to the complexity of the equipment and also because patients are removed from their accustomed home environment. A study compared patient-reported sleep disturbance with WP sleep assessment in individuals with AD and MCI. Through this, it was found that AD patients had significantly reduced REM sleep with increased light sleep, compared to healthy controls and MCI. The authors noted that there was no correlation between subjective reports of sleep quality and objective sleep measures by WP, suggesting that WP may be a useful tool for objective sleep evaluation (Tadokoro et al., 2020).

Conclusion

Sleep apnea and its symptoms, including sleepiness and fatigue, are common in the general population. Additionally, the COVID-19 pandemic and the fatigue associated with post-COVID syndrome may lead to an increased demand for sleep services that are already stretched by pandemic-related disruptions.

The WatchPAT is an unobtrusive device for home diagnosis of OSA. It has good correlation with polysomnography, although the results should be interpreted with caution at the extremes of disease severity. Its use has been studied and validated in a variety of patient populations, including children, older adults, pregnant women, and those with co-morbidities. The device has also been adopted, though

not widely, in screening for cardiac arrhythmias and central sleep apnea.

Finally, the WatchPAT has been shown to decrease the time to OSA diagnosis and treatment and also has a cost-benefit for patients as part of a telemedicine service. It is clear that the WatchPAT could provide a cost- and time-effective solution in healthcare services where there is a high demand for services and limited access to PSG.

Author contributions

CC and IS drafted the article, revised it critically, and approved the version to be published. All Authors contributed equally to the manuscript.

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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Translation of obstructive sleep apnea pathophysiology and phenotypes to personalized treatment: a narrative review

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Obstructive Sleep Apnea (OSA) arises due to periodic blockage of the upper airway (UA) during sleep, as negative pressure generated during inspiration overcomes the force exerted by the UA dilator muscles to maintain patency. This imbalance is primarily seen in individuals with a narrowed UA, attributable to factors such as inherent craniofacial anatomy, neck fat accumulation, and rostral fluid shifts in the supine posture. Sleep-induced attenuation of UA dilating muscle responsiveness, respiratory instability, and high loop gain further exacerbate UA obstruction. The widespread comorbidity profile of OSA, encompassing cardiovascular, metabolic, and neuropsychiatric domains, suggests complex bidirectional relationships with conditions like heart failure, stroke, and metabolic syndrome. Recent advances have delineated distinct OSA phenotypes beyond mere obstruction frequency, showing links with specific symptomatic manifestations. It is vital to bridge the gap between measurable patient characteristics, phenotypes, and underlying pathophysiological traits to enhance our understanding of OSA and its interplay with related outcomes. This knowledge could stimulate the development of tailored therapies targeting specific phenotypic and pathophysiological endotypes. This review aims to elucidate the multifaceted pathophysiology of OSA, focusing on the relationships between UA anatomy, functional traits, clinical manifestations, and comorbidities. The ultimate objective is to pave the way for a more personalized treatment paradigm in OSA, offering alternatives to continuous positive airway pressure therapy for selected patients and thereby optimizing treatment efficacy and adherence. There is an urgent need for personalized treatment strategies in the ever-evolving field of sleep medicine, as we progress from a 'one-size-fits-all' to a 'tailored-therapy' approach.

KEYWORDS

obstructive sleep apnea, pathophysiology, phenotypes, precision medicine, personalized treatment

1. Introduction

Obstructive sleep apnea (OSA) represents a significant global health burden affecting an estimated 936 million adults globally with far-reaching consequences on individual and public health (1). OSA develops as a result of recurring upper airway obstruction (UA) during sleep leading to severely reduced or absent airflow (hypopnea or apnea). The disorder is typically

associated with snoring and intermittent hypoxia, and episodes are frequently terminated by brief mini-arousals resulting in fragmented sleep with reduced amounts of slow wave sleep (SWS) and rapid-eye-movement (REM) sleep (2). These changes in sleep architecture may result in unrefreshing sleep and excessive daytime sleepiness (EDS) (3).

Beyond the direct impacts on sleep quality, OSA is associated with numerous comorbidities. The intermittent hypoxemia and sleep fragmentation associated with OSA can trigger cellular and molecular responses that promote sympathetic excitation, systemic inflammation, and other abnormal responses, which may result in the development of comorbidities such as cardiometabolic and neuropsychiatric conditions (4). OSA is also a major risk factor for motor vehicle accidents, which appears to be largely a consequence of EDS (5). There is strong evidence that untreated OSA is associated with systemic hypertension, especially with a loss of the normal nocturnal dipping pattern of blood pressure (BP), with growing evidence of risk for cardiovascular disease (6). Overall, these factors also lead to a substantial economic toll arising from direct medical expenditures, productivity losses, and accident-related costs (7). Despite its high prevalence and significant health implications, OSA remains underdiagnosed and undertreated, emphasizing the urgency for effective management strategies.

However, not all patients with OSA as measured by the level of sleep-disordered breathing (SDB), have a clinically significant disorder. Moreover, there is increasing evidence that the current grading of OSA severity as measured by the apnea-hypopnea index (AHI, number of apneas and hypopneas per hour of sleep) is inadequate (8). Additional measures including the hypoxic burden during sleep, the level of daytime symptoms such as sleepiness, and relevant biomarkers such as nocturnal BP dipping are required to adequately assess the clinical significance of the disorder in terms of outcomes, comorbidity risk, and treatment indications (9–12).

The standard therapy of OSA over the past 3 to 4 decades has centered around continuous positive airway pressure (CPAP), which acts by overcoming the negative intrapharyngeal pressure during inspiration that is the most important causative factor in OSA. While highly effective, the device is cumbersome, and compliance is limited. Thus, other treatment options are highly desirable, which can be facilitated by a detailed understanding of the complex pathophysiology of OSA. Since aspects of pathophysiology vary between patients, in addition to phenotypes, such an understanding should facilitate a personalized approach to management, especially in the area of pharmacotherapy. This consideration represents the principal objective of this review.

This review provides an overview of the pathophysiological and phenotypic factors of OSA in the context of therapeutic interventions, discusses their effectiveness in targeting different pathophysiological traits, and underscores the need for a shift toward personalized treatment modalities for optimal patient outcomes. Moreover, with the rise of new computational paradigms and machine learning approaches to categorizing and clustering patient symptom profiles, the review provides an overview of the topic and stresses the significance of connecting these novel techniques with understandable and quantifiable physiological factors to facilitate personalized treatments. To this end, we conducted a non-systematic literature search on PubMed and included studies and articles published up until July 2023. Our selection of articles was primarily guided by their relevance to the themes of pathophysiology, personalized treatment, and digital medicine techniques for OSA assessment and management. We sought to integrate the insights from these diverse sources into a narrative discussion, enriching the understanding of the current state of translating physiological factors and phenotypes into personalized treatment in its various aspects. This review does not aim to be exhaustive but aims to illuminate key concepts and stimulate further investigation in the realm of OSA pathophysiology, phenotypes, and personalized treatment.

2. Pathophysiology

The pathophysiology of OSA is complex and multifactorial and stems from the interplay between anatomical and non-anatomical factors. The fundamental abnormality reflects an inability of the upper airway (UA) dilating muscles to overcome the negative forces that develop within the oropharynx during inspiration (Figure 1). The UA dilating muscles, contracting in a phasic manner that precede each inspiration, work to counteract the negative pressure generated in the UA during inspiration. This delicate balance can be compromised by any factor that escalates this negative pressure or diminishes the effectiveness of UA dilating muscle contractions, thereby leading to an increased risk of UA obstruction (2). A similar risk arises from a narrowed UA, as this amplifies the negative pressure in the oropharynx during inhalation, predisposing to closure. Anatomical factors that may contribute to such narrowing include craniofacial bony morphology, soft tissue accumulation in the neck from obesity or adenotonsillar hypertrophy, and variable factors such as fluid gravitating to the neck in the recumbent position. Moreover, non-anatomical factors such as diminished muscle responsiveness, heightened sensitivity to arousals, and a high ventilatory control system gain (termed loop gain), contribute significantly to the disorder's development and progression, which are also influenced by genetic, environmental, and lifestyle factors.

2.1. Upper airway narrowing

The majority of patients with OSA have a narrowed oropharyngeal airway, a finding that can be clinically assessed by the Mallampati score (13). Genetic factors play a major role in this narrowing (14). Defects in

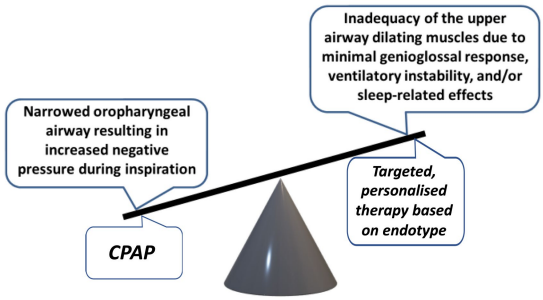

FIGURE 1
Balance of forces affecting the patency of the upper airway and potential for personalized treatment.

the bony and maxillofacial structures in the lower face and neck as well as malocclusions, i.e., misalignments of the teeth when the jaws are closed, significantly contribute to UA narrowing (15). Maxillofacial defects can include conditions such as micrognathia, where the lower jaw is undersized, or retrognathia, characterized by a receding jawline. Both these conditions can result in posterior positioning of the tongue, consequently predisposing to obstruction of the UA (16). These defects may be evident in children with the Robin sequence or Treacher-Collins syndrome who are especially prone to OSA because of bony changes to the lower face and/or mandible (17). Similarly, a high-arched palate or a long soft palate can further reduce the size of the UA, thus contributing to OSA. Moreover, malocclusions often present with a retruded mandible, which may cause posterior positioning of the tongue. Alternatively, malocclusions may lead to difficulties in breathing through the nose causing increased mouth breathing and increasing the likelihood of OSA (18, 19).

Furthermore, the accumulation of soft tissue in the neck due to obesity or within the UA due to adenotonsillar hypertrophy can precipitate OSA in susceptible individuals by reducing the size of the oropharyngeal lumen (2). Conditions such as heart failure and end-stage renal failure associated with fluid retention can also contribute to the development of UA obstruction and OSA. This is due to nocturnal redistribution of fluid to the neck region while in a recumbent position, subsequently increasing UA collapsibility by narrowing of the lumen and diminishing the efficiency of dilator muscle contractions (20, 21).

While nasal obstruction is a relatively minor factor in predisposing to UA obstruction, variable nasal obstruction such as with rhinitis, contributes to the pathophysiology of OSA (22, 23). Furthermore, intranasal corticosteroid therapy has been reported to benefit patients with rhinitis and mild to moderate OSA (24). The supine body position may also compromise UA patency (25), largely due to gravitational forces, which is evident in the clinical setting where the AHI is often highest in the supine position.

2.2. Upper airway dilator muscle function

Patency of the UA is dependent on contraction of the pharyngeal dilator muscles, especially the genioglossus, which stiffen the collapsible segment of the UA during inspiration (2). The phasic contraction of these muscles is co-ordinated with inspiration and precede contraction of the diaphragm by milliseconds (26). Contraction of these UA muscles is influenced by chemical stimuli, vagal input, changes in UA pressure, and baroreceptor activity (27).

The narrowed UA seen in OSA results in greater inspiratory negative pressure, which requires more forceful contraction of the UA dilating muscles to maintain oropharyngeal patency. There is evidence that dilating muscle contraction in OSA is greater than in normal subjects during wakefulness, but diminishes to a greater extent during sleep, which predisposes to occlusion (28), especially in REM sleep (29). Hence, the primary issue in OSA is inadequate muscle compensation to combat the heightened inspiratory negative pressure, and not necessarily a fundamental deficiency in muscle function. The effects of this insufficient response by UA dilating muscles are aggravated by the fact that these are skeletal muscles, whose performance sees a more pronounced drop during sleep compared to the diaphragm.

2.3. Respiratory control

Respiratory control is an integral aspect of OSA pathophysiology and its dysfunction contributes to decreased UA muscle activity in certain circumstances. OSA often presents with a pattern of frequently reoccurring apneas, highlighting the instability of respiratory control which shares similarities to periodic breathing. At the heart of this control is the coordinated activity of the key muscles, diaphragm and genioglossus as UA obstruction is most likely to develop when EMG activity of these muscles is at the lowest point of the respiratory cycle, thus acting as a critical physiological determinant of apnea onset (2). As the apnea progresses, EMG activity of the UA dilating muscles progressively increases reaching a peak at apnea termination. This is typically followed by several large breaths after which both EMGs decrease potentially predisposing to further obstruction (30).

The transition from wakefulness to non-REM sleep usually results in a minor reduction in ventilation even in healthy subjects. This is attributed to a reduced response to the carbon dioxide (CO2) stimulus that drives respiration. However, in OSA patients, this decrease may tip the balance toward an apneic threshold that is critically dependent on CO2 levels (31). This is exacerbated by post-apnea hyperventilation, resulting in CO2 reduction and predisposing to further apneas (30).

A vital component of unstable respiratory control is loop gain, which is a measure of the sensitivity of the feedback loop that modifies ventilation in response to respiratory disturbances. As such, loop gain may also affect the predisposition to apnea. A high loop gain, where the magnitude of the increase in ventilation following apnea is high, contributes to ventilatory instability, thereby predisposing to recurring apnea (30).

Apnea termination is often associated with cortical arousal, which is an important protective mechanism, but may predispose to further apnea by contributing to post-apneic hyperventilation (32–34). These respiratory-related cortical arousals may vary in intensity and represent a distinct pathophysiologic feature (35), which may be quantified by the arousal threshold, that can be assessed noninvasively by PSG (36). A low arousal threshold may be a contributing factor to recurring apneas and represents a potential therapeutic target in selected patients (37). The interactions of these multiple elements underline the central role of respiratory control in the pathophysiology of OSA.

2.4. Genetic contribution

Emerging research highlights the significant role of genetics in the pathophysiology of OSA. Studies have demonstrated a substantial genetic component to OSA and related traits, such as BMI, craniofacial structure, and sleep-related parameters. There is a strong heritability in the size of the oropharyngeal space, which is a major factor in the UA narrowing that is typical of patients with OSA (14). Recent advances in genomics have further enabled the identification of specific genetic variants associated with OSA (38, 39). Polymorphisms in several genes, including those involved in serotonin metabolism, inflammation, and obesity, have been linked to OSA susceptibility (38). Furthermore, gene–environment interactions, particularly with obesity, also play a crucial role in OSA risk. These findings underscore the complex, multifactorial nature of OSA, with genetic factors

interplaying with environmental and lifestyle factors in shaping disease onset and progression. While these advancements provide insights into the pathogenesis of OSA, there is still much to uncover, and ongoing research in this area is vital for refining disease risk prediction and uncovering potential targets for personalized treatment strategies.

2.5. Integrated pathophysiology and implications for treatment

Recently, there has been a surge in interest concerning the influence of non-anatomical factors on the development and progression of OSA (40). A study of subjects with and without OSA revealed that about one-third of the subjects in each group demonstrated the endotypes of either diminished genioglossus muscle responsiveness during sleep, low arousal threshold, or high loop gain, while 28% of subjects demonstrated a combination of multiple traits (41).

While the principal factor of increased UA collapsibility in OSA can be effectively reversed by CPAP therapy, a more comprehensive insight into the underlying pathophysiology provides the potential for additional management options in selected patients (Figure 1) (42). Inadequate UA dilating muscle compensation against increased collapsing forces may be improved by drug therapy that stimulates these muscles (43). The reduction in respiratory motor neurone output that is a physiological feature of sleep may be reversed by electrical stimulation of the hypoglossal nerve (44). A high loop gain may be diminished by acetazolamide (45) and a low arousal threshold may be increased by zolpidem therapy (46). These medications may have a role in selected patients where such factors are found to be contributing factors in the integrated pathophysiology of the disorder.

3. Clinical and pathophysiological phenotypes

3.1. Clinical phenotypes

The categorization of distinct clinical phenotypes is viable in populations suspected of having OSA (47). Furthermore, some pathophysiological traits that are frequently observed in OSA patients, such as loss of nocturnal dipping of BP, may influence the likelihood of associated comorbidity (48). As such, the findings of a diagnostic sleep study should be interpreted alongside these additional elements when assessing the clinical relevance of OSA for each patient. It's essential to tailor management strategies to individual phenotypes, considering not only the symptom profile but additional factors beyond the AHI such as acute systemic effects and associated relevant comorbidities in the decision-making process (40). However, understanding the underlying pathophysiological mechanisms and connecting them to observable characteristics is crucial when moving toward individualized treatment pathways.

Endotypes and phenotypes of OSA have been extensively studied (49). Phenotype refers to a combination of disease characteristics that can be used to distinguish certain categories of patients from others (50) and several cluster analyses have been reported that distinguish clinical subtypes (51). Early reports identified 3 symptomatic phenotypes of OSA, namely disturbed sleep, minimal symptoms, and EDS (52). More recent reports added the additional phenotype where upper airway symptoms were dominant (53). An important feature of such reports is that similar average AHI levels were evident across clusters, which indicates that clusters of clinical phenotypes cannot be differentiated by the AHI. Furthermore, specific pathophysiological endotypes identified by PSG predicted the risk of adverse cardiovascular outcomes (54).

There is some evidence that the sleepy OSA phenotype may be associated with a higher risk of comorbidity (40), although this relationship is not clear-cut. A report based on the Sleep Heart Health Study indicated that the excessively sleepy phenotype was strongly associated with prevalent heart failure and incident cardiovascular disease (55). However, the insomnia subtype, which was a distinct cluster in a report from the European Sleep Apnoea Database cohort study (ESADA), was more frequently linked with cardiovascular comorbidity than the sleepy phenotype (56). The phenotype of non-dipping nocturnal BP has a high diagnostic prediction for OSA as measured by the AHI (57).

Future research requires the identification of specific markers of OSA that predict clinical significance and risk of adverse outcomes, and which may more reliably predict response to targeted treatment (49, 58). Identifying the pathophysiological and endotypic connections would further the understanding of the underlying phenomenon to deepen the insight into the mechanisms through which the markers connect to outcomes.

3.2. Modern data analytical methods for phenotyping and the translation to treatment

Traditionally, the identified phenotypes are dependent on categorized or simplistic variables and metrics only considering a few aspects of the disorders. For example, by quantifying sleep disruption by the number of awakenings or the overall sleep architecture while connecting that to categories of questionnaire-quantified sleepiness (51, 59). However, there exists inherent variation in the quantified parameters and differences in their reporting. For example, there is always at least minor inter-scorer variability both in respiratory event scoring and sleep staging and major differences in scoring arousals from sleep (60). This variability is inherently propagated to all consequent analyses and assessments and may affect the identified phenotypes. Similarly, quantifying sleepiness based on questionnaires such as ESS is variable, especially noticeable between genders (61), and there can also be intra-individual differences depending on the timing of the questionnaire (62).

There are different ways to go beyond the current clinical practices in identifying disease characteristics. For example, in the sleep architecture, various methods to quantify sleep fragmentation and sleep microstructure have been presented (63–66). Meanwhile, there are possibilities to characterize respiratory events as well as nocturnal hypoxemia in more detail (10, 11, 67). Similarly, aside from only assessing sleepiness based on questionnaires, there are various objective measures as well as different tests to assess neurocognitive function and impairment which may provide more reliable outcome metrics. The major hindrance in adaptation is the massive workload

required to obtain a sufficient dataset for identifying phenotypes based on microstructures.

The rise of machine learning and artificial intelligence alongside increased computational capacities has given rise to different ways to utilize the entirety of the collected data without limiting it to a few simplified metrics (67). As an example, these developments form a major objective of Sleep Revolution project, funded by the European Union Horizon 2020 Research and Innovation Programme (Grant no. 965417), which seeks to transform current diagnostic methods for sleep-disordered breathing by using machine learning tools to facilitate automatic scoring outside traditional boundaries (68). By using these tools together with phenotyping, the project seeks to identify novel variables and analysis techniques that may more accurately identify patients with a clinically significant OSA syndrome, thus facilitating more personalized patient management (69). Similarly, as with biomarkers, there have been advances utilizing the patient characteristics and sleep recording data to develop markers, which can be termed data-markers, connected to disease characteristics, severity and risk of comorbidities (70). As an example, there have been promising approaches in identifying subgroups or clusters of patients based on observable characteristics. One way of summarizing the findings is a division into common themes as formulated by Zinchuk and Yaggi (51): (1) Subtype A, consisting of younger, obese males with severe OSA and classic symptoms, responding well to CPAP treatment; (2) Subtype B, which includes older, obese males with severe OSA, frequent comorbidities, and minimal symptoms, responding less effectively to CPAP; (3) Subtype C, featuring middle-aged, mildly obese females suffering from insomnia and moderate to severe OSA, with mixed responses to CPAP; and (4) Subtype D, which encompasses younger, nonobese males with severe OSA and primary upper airway symptoms, displaying the lowest hypoxemia and comorbidity rates and limited CPAP success. Overall, these approaches provide new pathways to targeted treatments.

However, while there have been promising approaches, these warrant further research and require major amounts of data, likely possible to obtain only through multi-institutional collaborative efforts. The major limiting factor in the adaptation of novel data-markers and data-analytical metrics to the clinics is the lack of reliability, generalizability, and especially the transparency of the results. If the obtained data-marker or phenotype cannot be rigorously connected to pathophysiological and endotypic aspects, it is unlikely to gain widespread use and reliability in clinical practice. While the modern data-analytical approaches may provide clearer connections between symptomology and measurable characteristics and even provide novel therapeutical targets, connecting these to the underlying factors and physiological effects giving rise to the observable characteristics would further promote the adaptation to clinics and therapeutics.

4. Personalized treatment

4.1. Continuous positive airway pressure

The fundamental goal of treatment in OSA is to maintain UA patency and thereby stabilize breathing pattern and ensure adequate ventilation. Continuous positive airway pressure (CPAP) is the gold standard in OSA treatment, consistently demonstrating high efficacy in mitigating the disorder's principal signs and symptoms when used appropriately. Its mode of action is delivering a positive air pressure via a mask to the UA, which effectively prevents airway collapse during sleep.

In the context of personalized treatment, CPAP's efficacy can occasionally extend beyond its primary anatomical target of airway obstruction. The therapy proves effective in treating non-anatomical or non-traditional traits involved in OSA pathophysiology, such as individuals with a high arousal threshold or high loop gain. Modern CPAP devices employ intricate algorithms to adjust pressure according to the user's individual requirements, thus facilitating more personalized treatment strategies.

4.2. Dental appliances

Although CPAP is highly effective in maintaining UA patency, the device is cumbersome and is often not well tolerated. Thus, alternative effective therapies are desirable, especially in patients with poor CPAP compliance. For example, mandibular advancement devices (MAD) are designed to push the lower jaw forward during sleep and these custom-fitted dental appliances enhance the UA size and reduce its propensity to collapse. MADs are especially suited to treat primary snoring and mild OSA (71), but are also reasonable alternatives in patients with more severe OSA who fail to tolerate CPAP.

In personalized OSA therapy, MADs primarily target anatomical contributors but can indirectly influence some non-anatomical traits as well. Their ability to adjust the level of mandibular advancement allows for patient comfort and therapeutic efficacy (72), enhancing treatment adherence and outcomes. MADs are also effective for treating bruxism alongside OSA (73, 74). They offer a promising step toward individualizing OSA treatment, with ongoing research set to further enhance their utility in this area. While reports comparing CPAP and MAD therapy found CPAP to be generally more effective in reducing AHI and EDS, the effects were similar in patients with milder OSA (75).

4.3. Pharmacotherapy

Several pharmacological agents have been evaluated that target different pathophysiological endotypes of OSA. While many such agents have been reported to benefit OSA in the form of reduced AHI, none are yet licensed to treat the disorder (76). Drug therapies that target pathophysiological traits such as UA collapsibility by increasing dilator muscle contraction, respiratory control abnormalities such as high loop gain, and low arousal threshold have each been identified to benefit OSA in selected patient populations.

Desipramine, a central nervous system norepinephrine reuptake inhibitor and a member of the tricyclic antidepressant (TCA) family, lessens the sleep-induced reduction of genioglossus activity and enhances pharyngeal stability in healthy individuals (77). It has been observed to lower the AHI in patients with OSA who exhibit insufficient genioglossus muscle adaptation (78). Another drug, atomoxetine, which also inhibits norepinephrine reuptake, in combination with an antimuscarinic agent, oxybutynin, has been

found to considerably decrease the AHI in patients suffering from OSA (43).

Hypnotics have long been recommended to avoid in patients with respiratory disease because of potential adverse effects on respiration during sleep. However, recent reports in the setting of OSA indicate a potential role for certain hypnotics such as zolpidem in selected patients where a low arousal threshold represents a significant pathophysiological trait (37, 79). However, as there are no published randomized clinical trials, no recommendations can be given on the clinical use of hypnotics in patients with OSA (80). Another more recent report indicated that zolpidem increases sleep efficiency and the respiratory arousal threshold without changing sleep apnoea severity and pharyngeal muscle activity (46).

4.4. Surgical approaches

Accumulation of soft tissue in the oropharyngeal region contributing to airway constriction can be medically or surgically addressed. Pediatric patients showing signs of adenotonsillar hypertrophy and OSA can improve with surgical intervention (81), while adults with central obesity and OSA can benefit from weight loss through methods such as bariatric surgery (82) or intensive dietary control coupled with medication (83). Liraglutide, a long-acting agonist of the glucagon-like peptide one receptor, has shown promising results in inducing weight loss and significantly decreasing AHI in OSA patients (84).

4.5. Other approaches and digital medicine

The diminished output of respiratory motor neurons triggered by sleep could potentially be countered by electrical stimulation of the hypoglossal nerve, offering an alternative treatment to CPAP, particularly for patients who struggle with compliance (44, 85). For those with high loop gain, acetazolamide may provide relief for OSA symptoms and carry the added advantage of decreasing blood pressure (45, 86). For individuals suffering from OSA who also have fluid overload, diuretic therapy might be beneficial by curbing the nocturnal upward shift of fluid (87).

The role of oxygen therapy in the management of OSA is uncertain and not advised in most cases, although a recent report suggests that oxygen supplementation may benefit OSA acutely, possibly by reducing the arousal response (88). Finally, positional treatments in cases where most of the respiratory events occur in supine position have long been recognized as a viable alternative (89).

Advances in digital medicine have begun to revolutionize the prevention and treatment of OSA. Telemedicine and remote patient monitoring, for instance, are making it easier for healthcare providers to diagnose and manage OSA. Patients can undertake sleep studies in the comfort of their homes using portable polysomnography devices, while apps and wearable technologies are providing insights into sleep pattern and other critical factors related to OSA (68). Moreover, cognitive behavioral therapy for insomnia (CBT-I) is showing promise in managing comorbid conditions often present in OSA patients, and has potential for digitalization and simple utilization alongside other treatment modalities (90, 91). Additionally, machine learning and artificial intelligence algorithms have the potential in the future to be utilized to understand factors behind limited adherence for CPAP and MAD devices as well as to optimize their settings, thus enabling a more personalized approach to OSA treatment. These digital health tools not only enhance the accessibility and convenience of OSA treatment but also offer the potential for more effective, tailored therapeutic interventions.

Overall, several potential treatment pathways have been identified (Table 1). However, targeting these to patients and choosing the optimal treatment pathway may require extensive knowledge and assessment of the pathophysiological characteristics and the individualized phenotype to match the established efficacy of CPAP (Figure 2).

5. Take-away messages and practical care points

Overall, successful management of OSA requires a comprehensive, personalized, and interdisciplinary approach. Below, we provide a few practical care points derived from our review, designed to assist in the decision-making process and enhance the management of OSA patients in a practical and applied manner:

1. **Comprehensive Evaluation**: OSA is multifactorial. A thorough evaluation of factors such as craniofacial anatomy, body mass index, neck circumference, and sleeping positions can provide valuable insights into a patient's risk of OSA.
2. **Recognition of Comorbidities**: Given the significant association between OSA and various cardiovascular, metabolic, and neuropsychiatric conditions, screening for these comorbidities should be an integral part of the patient's clinical evaluation.
3. **Phenotypic Consideration**: Understanding that OSA presents with different phenotypes can aid in the identification of patients who might not respond to conventional therapies. Awareness of these phenotypes can also help clinicians provide personalized treatment strategies.
4. **Alternative Treatments**: In patients who are non-compliant or non-responsive to CPAP therapy, consider other treatments such as dental devices, positional therapy, upper airway surgery, hypoglossal nerve stimulation, or pharmacotherapy.
5. **Proactive Follow-up and Management of OSA**: Regular follow-ups are necessary to assess the efficacy of the chosen treatment strategy and make adjustments if necessary. Also, patient education regarding the potential implications of untreated OSA and the benefits of treatment compliance can aid in improving therapeutic outcomes.
6. **Interdisciplinary Approach**: Clinicians should be encouraged to collaborate with experts from various disciplines, such as dietitians for weight management, psychologists for behavior therapy, or surgeons for potential surgical interventions, for a holistic approach to patient care.
7. **Research and Continuous Learning**: As the understanding of OSA pathophysiology and treatment options evolves, clinicians should make efforts to stay updated on the latest research findings and integrate them into their practice where relevant.

TABLE 1 Summary of the key findings and implications for personalized treatment of obstructive sleep apnea (OSA).

Key findings	Implications for personalized treatment
OSA is characterized by recurrent upper airway obstruction during sleep due to an imbalance between negative inspiratory pressure and the ability of the upper airway dilating muscles to maintain patency	Continuous Positive Airway Pressure (CPAP) and Mandibular Advancement Devices (MADs) can be tailored to individual needs, but suffer from low compliance
Identifying individual pathophysiological traits can inform personalized treatment approaches	Personalized treatment strategies have the potential to provide alternatives to CPAP therapy in selected patients
OSA is often associated with comorbidities such as cardiovascular disease, metabolic disorders, and neuropsychological conditions	Novel treatment strategies such as hypoglossal nerve stimulation, certain medications, and lifestyle modifications like weight loss can be employed based on the patient's unique pathophysiology
There are various phenotypes independent of the number of obstructions, which relate to symptoms and outcomes; however, linking these to underlying pathophysiology is vital to advancing our understanding of OSA	Ongoing research and advances in digital medicine techniques can further enhance the personalization of OSA treatment

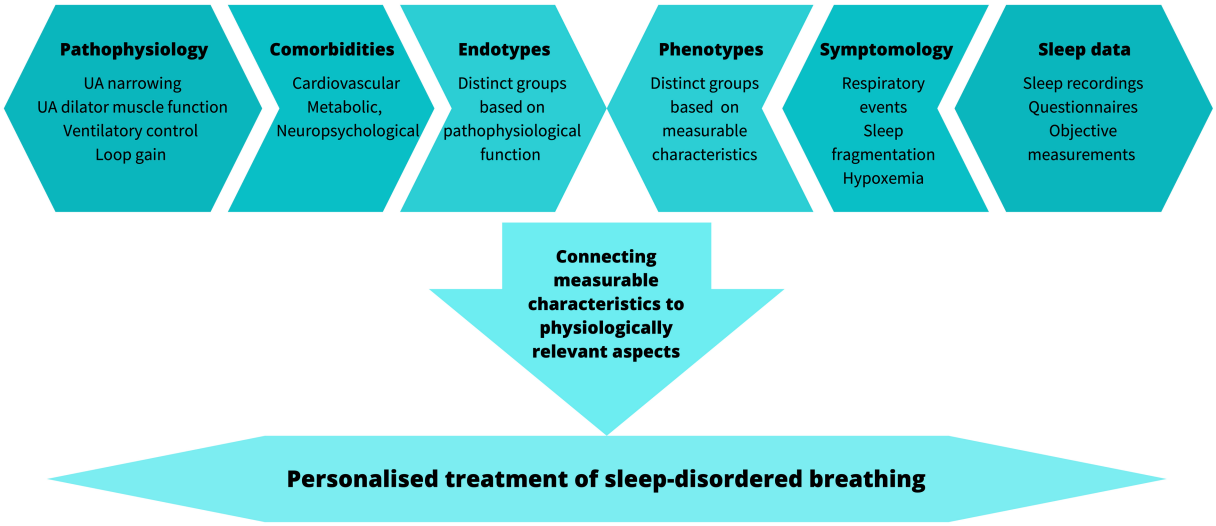

FIGURE 2
Factors to consider when translating pathophysiology and phenotypes to personalized treatment.

6. Conclusion and future directions

Despite extensive knowledge of the pathophysiological mechanisms and the adverse systemic effects of OSA, only limited benefit, if any, has been demonstrated from CPAP therapy in randomized trials designed to evaluate cardiometabolic benefit in patients with OSA. Many reasons can be considered for these negative outcomes including inappropriate patient selection such as inclusion of mainly non-sleepy patients, reliance on the AHI as the sole measure of disease categorization, inclusion of patients with pre-existing comorbidity, and inadequate CPAP compliance. Patient selection for such outcome studies should consider inclusion variables beyond the AHI that include symptomatic patients, and CPAP compliance should be factored into the outcome assessment (92).

Furthermore, it should be considered that some symptoms consistent with OSA such as sleepiness and fatigue could be a result of other factors such as lifestyle and disturbed sleep. New approaches to syndrome definition are required that consider different clinical OSA phenotypes in combination with endotypes and pathophysiological factors. New diagnostic approaches are needed that incorporate novel technologies to provide surrogates for sleep structure, to gauge exposure to systemic effects of OSA, and to identify specific biomarkers and data-markers for disease classification. While potentially useful markers could conceivably be derived from the PSG (93–96), the conventional sleep diagnostic test will likely require adaptation to facilitate ambulatory and multi-night diagnostic studies.

The ultimate goal is the development of diagnostic approaches that lead to the diagnosis of a clinically relevant OSA disorder that will include measures that give a more comprehensive insight into pathophysiological mechanisms in the individual patient. This approach should facilitate a more personalized treatment plan that goes beyond the simple question of CPAP or not (58, 97, 98).

Author contributions

WM wrote the first draft of the manuscript and designed the concept and structure of the review. HK wrote sections of the manuscript and contributed to the conception of the review. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Conflict of interest

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

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Feasibility of neck electrical impedance tomography to monitor upper airway dynamics during sleep

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Background: There is a lack of non-invasive methods for monitoring the upper airway patency during sleep. Electrical impedance tomography (EIT) is a non-invasive, radiation-free tool that has been validated to monitor lung ventilation. We hypothesized that electrical impedance tomography (EIT) can be used for monitoring upper airway patency during sleep.

Methods: Sleep was induced in 21 subjects (14 males, age 43 ± 13 years, body mass index 32.0 ± 5.3 kg/m^2) with suspected obstructive sleep apnea (apnea-hypopnea index: 44 ± 37 events/h, range: 1–122 events/h) using low doses of midazolam. Patients wore a nasal mask attached to a modified CPAP device, allowing variable and controlled degrees of upper airway obstruction. Confirmation of upper airway patency was obtained with direct visualization of the upper airway using nasofibroscopy ($n = 6$). The changes in total neck impedance and in impedance in four cranio-caudal regions of interest (ROIs) were analyzed.

Results: Total neck impedance varied in concert with breathing cycles and peaked during expiration in all patients. Group data showed a high cross-correlation between flow and impedance curves ($r = -0.817$, $p < 0.001$). Inspiratory peak flow correlated with simultaneous neck impedance ($r = 0.866$, $p < 0.001$). There was a high correlation between total neck impedance and velopharynx area ($r = 0.884$, $p < 0.001$), and total neck impedance and oropharynx area ($r = 0.891$, $p < 0.001$).

Conclusions: Neck EIT is sensitive and captures pharyngeal obstruction under various conditions. Neck EIT is a promising method for real-time monitoring of the pharynx during sleep.

KEYWORDS

diagnostic imaging, electric impedance, obstructive sleep apnea, structure collapse, electrical impedance tomography, nasofibroscopy

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive pharyngeal collapse during sleep, resulting in recurrent arousals and arterial oxygen desaturation (Young et al., 1993; Tufik et al., 2010). Upper airway collapse results from complex interaction of multiple factors, including respiratory control instability, insufficient pharyngeal muscle dilatory activity and upper airway anatomy (Haponik et al., 1983; Suratt et al., 1983; Schwab et al., 1995; Mezzanotte et al., 1996; Heinzer et al., 2005). In OSA patients, recurrent obstruction occurs in the upper airway between the soft palate, the palatal tonsils, the base of the tongue and the lateral pharyngeal walls (Kim et al., 2019). On the other hand, the dynamic mechanisms leading to upper airway obstruction during sleep are poorly understood. Imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), have provided detailed insights about the upper airway of patients while awake, but limited information during sleep (Abramson et al., 2010; Tang et al., 2012; Brown et al., 2013; Wang et al., 2014; Zhang et al., 2014). Direct visualization of the upper airway using drug-induced sleep endoscopy is an invasive method that has also provided only partial information regarding the dynamics of the upper airway during obstruction (Badr et al., 1995; Hewitt et al., 2009; Rodriguez-Bruno et al., 2009). Forced oscillation technique (FOT) is a non-invasive method to monitor upper airway patency, but the application requires a nasal mask and does not allow insights on anatomical behavior of the upper airway (Campana et al., 2012). Therefore, the monitoring of the dynamic upper airway collapse during sleep may provide a window of opportunity to better understanding the pathophysiology of OSA.

Electrical impedance tomography (EIT) is based on the concept that the injection of small amounts of electrical current (5–10 mA; 125 kHz) in a rotating sequence through pairs of surface electrodes provide electrical potentials that vary according to the shape and distribution of the anatomical area under study (Kim et al., 2019). EIT capacity to measure lung aeration (Victorino et al., 2004; Costa et al., 2009a) was validated previously since air has much higher impeditivity than tissues (Brown et al., 1985; Frerichs et al., 1999). Typically, 32 electrodes are positioned linearly around the thorax. This configuration is based on the Sheffield protocol (Brown and Seagar, 1987) and provides information regarding a total cross-sectional width of ∼7–10 cm (Costa et al., 2009b).

Kim et al. (2019) conducted a study with seven healthy participants and 10 patients with OSA under non sedated sleep, to determine whether EIT could identify upper airway narrowing or collapse. In that study, transient varsupsetneqqairway closure was induced by the swallowing maneuver, and EIT images were confirmed by simultaneous magnetic resonance imaging (MRI) scans. Obstructive hypopnea and apnea were detected successfully by EIT in 10 patients with OSA, and no significant changes in EIT data were observed in seven healthy participants during concurrent EIT and PSG tests. Authors concluded that EIT could be a useful real-time monitoring device for detecting upper airway narrowing or collapse during natural sleep, in OSA patients.

Another study applying EIT imaging technique to evaluate upper airway was conducted by Ayoub et al. (2019), with seven healthy subjects (six male and one female) with no history of witnessed apnea and ten male OSA patients. The subject was connected to the PSG and the 16-channel EIT device at the supine position. For EIT imaging, electrical currents of 1 mArms at 11.25 kHz were sequentially injected between chosen pairs of neighboring electrodes and induced voltages were measured between other neighboring electrode pairs. After removing the artifact components, they demonstrated the feasibility of the upper airway EIT imaging technique to characterize obstructive hypopnea and apnea events during natural sleep. In that study, during normal breathing, EIT images clearly showed that the upper airway was totally open and filled with the air. The air was replaced by conductive upper airway soft tissues during obstructive hypopnea and apnea events, which were successfully detected in the reconstructed EIT images (Ayoub et al., 2019).

In the same way, Ayoub et al. (2020) analyzed time series of reconstructed EIT images, providing quantitative information about how much the upper airway was closed during collapse and reopening. Ten OSA patients' data were studied, and the results showed that the EIT can compare the upper airway dynamics between obstructive apnea and hypopnea.

Our work, the first one that uses EIT technique in induced sleep, was designed to study neck EIT as a feasible method of monitoring upper airway patency during sleep.

This study applies EIT on the upper airway under the hypothesis that electrical impedance tomography can be a continuous upper airway imaging technique during sleep. To this end, we studied patients with a wide range of OSA severity. To obtain variable degrees of upper airway obstruction we used the method of critical closure pressure (Pcrit) determination, applying variable levels of nasal pressure during induced sleep. In a sub sample we directly visualized the upper airway anatomy using endoscopy.

Materials and methods

Subjects aged between 18 and 70 years suspected of having OSA referred to the Sleep Laboratory at the Heart Institute—Hospital das Clínicas were invited to participate. Subjects with previous upper airway surgery and significant heart or pulmonary disease were excluded. All participants underwent standard diagnostic overnight polysomnography (PSG) (Embla Systems Inc., USA) (Gamaldo et al., 2014). Subjects provided written informed consent, and the protocol was previously approved by the Hospital das Clínicas Ethics Committee (Protocol Number: 0748/11).

Neck electrical impedance tomography

EIT is a method of estimating impedance distribution (or variations of impedance distribution) inside a domain. This domain

Abbreviations: CPAP, continuous positive airway pressure; CT, computed tomography; EIT, electrical impedance tomography; FOT, forced oscillation technique; MRI, magnetic resonance imaging; OP, oropharynx; OSA, obstructive sleep apnea; Pcrit, critical closure pressure; PSG, polysomnography; RG, retroglossal; RP, retropalatal; V'Imax, inspiratory peak flow; VP, velopharynx.

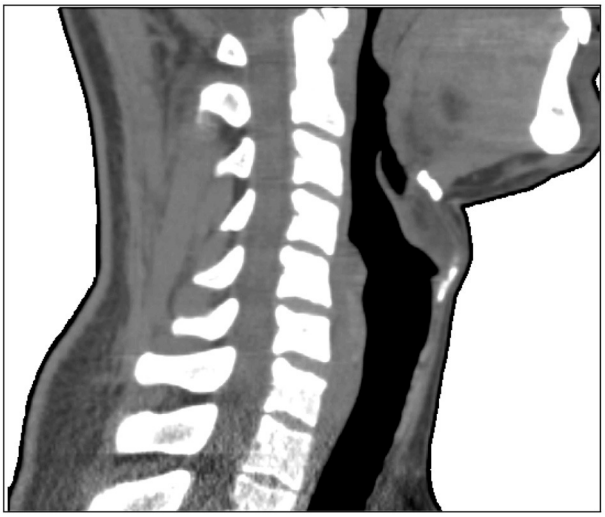

FIGURE 1
Sample CT-scan image of a volunteer, used to create a three-dimensional finite element mesh.

is discretized using the Finite Element Method (FEM). The vector of impedance of each finite element represents the variations of the impedance distribution in time. The problem of estimating the vector of impedance based on the injected current, measuring electrical potentials on the boundary of the domain and knowing the structure of the model may be classified as an inverse problem. The algorithm is a sensitivity matrix. Two different sets of measured voltages are required: the first set (V0) is the reference set of measurements, and the second set (V1) is related to the modified impedance distribution. An estimate of the normalized resistivity distribution may be computed using the Equation (1), where "B" is the inverse of the sensitivity matrix, and ρ is the impeditivity ($\Delta\rho = (\rho 1 - \rho 0)/\rho 0$) (Aya et al., 2007).

$$\Delta\rho = \mathbf{B}\Delta\mathbf{V} \quad (1)$$

Because the image formation problem of EIT is a difficult inverse problem due to its non-linearity, regularization methods are required. For this project, a Spatial Gaussian Filter was used for regulation, resulting in smooth images (Aya et al., 2007).

A three dimensional (3D) finite element mesh was created based on CT-scan images of a volunteer (Figure 1). The resulting mesh contained 62,500 tetrahedral elements and 11,700 nodes, and its total dimensions were 184 × 221 × 153 mm (height × length × width) (Figure 2A). Thirty-two electrodes were placed around the subject's neck circumference in a zigzag configuration, allowing the determination of impedance variation across a vertical length of 18.4 cm (Figure 2B). The electrodes were connected to an impedance tomography device (Enlight®, Timpel, Brazil), which generates 50 images per second.

For each set of measured voltages, impeditivity changes ($\Delta\rho$) were noted using the Equation (1) for all tetrahedral elements, and a cross-sectional image of the sagittal plane passing through the center of the mesh was created.

Small amounts of electrical current (5–10 mA; 125 kHz) were injected in a rotating sequence through pairs of electrodes, with one non-injecting electrode interposed between the injecting electrodes. These currents traveled through the neck following pathways that varied according to neck shape and the distribution of impeditivities, generating an electrical potential gradient at the surface, which was then transformed into a 3D image of the electrical impedance distribution within the neck. Surface electrical measurements were used to infer living tissue impeditivity. A low-pass filter (0.333 Hz) minimized perfusion interference. Image reconstruction was based on relative changes in impedance relative to a reference (first 300 frames of neck EIT), assuming that the shape of the neck did not change. Only regions of the upper airway in which the impedance changed over time were represented among the EIT images (Costa et al., 2009b). In this study the changes in total neck impedance and in impedance in four cranio-caudal regions of interest (ROIs) were analyzed. The total neck impedance value, as well as the ROI values, were obtained through the sum of the pixels values of the image (or the respective ROI).

Data acquisition during sleep

The subjects remained in the sleep laboratory in the morning immediately after diagnostic polysomnography (PSG). Sleep was induced using low doses of midazolam (Genta et al., 2011) with the subjects used a nasal mask connected to a modified CPAP device (Philips Respironics, Murrysville, PA) interposed by 2 pneumotachographs connected in series. The CPAP was initially titrated to overcome obstructive events and flow limitations during sleep (holding pressure). Pcrit was determined as previously described (Gleadhill et al., 1991). Briefly, once stable stage 2 was achieved at the holding pressure for at least 2 min, the CPAP was abruptly reduced by 1 cmH_2O during expiration and was held at this level for five breaths. CPAP was then returned to the holding pressure for 1 min before being dropped an additional 1 cmH_2O for another five breaths. This process entailed progressive CPAP decreases until obstructive apnea occurred. Flow and pressure curves were analyzed using custom-designed software (Matlab, The MathWorks, Natick, MA). Neck EIT data were stored in a computer that recorded neck impedance and pressure and flow measurements derived from the second nasal mask pneumotacograph. Neck EIT images and inspiratory peak flow (V'Imax) were analyzed using custom-designed software (LabVIEW, National Instruments Corporation). Pcrit determination allowed for neck EIT assessments under controlled levels of flow limitation.

Direct measurement of the upper airway

Sleep endoscopy was performed following Pcrit determination in a subgroup of patients ($n = 6$). An ultra-slim bronchofibervideoscope (2.8 mm diameter, Olympus® BF type XP160F) was inserted through a sealed port in the nasal mask. The distance between the tip of the scope and the area of interest was measured using a wire (marked in centimeters) that passed through the aspiration channel of the scope (Schorr et al., 2012). The scope's tip was placed one centimeter above the velopharynx (VP: retropalatal airway) and one centimeter above the oropharynx (OP: retroglossal airway). Images were digitally recorded during

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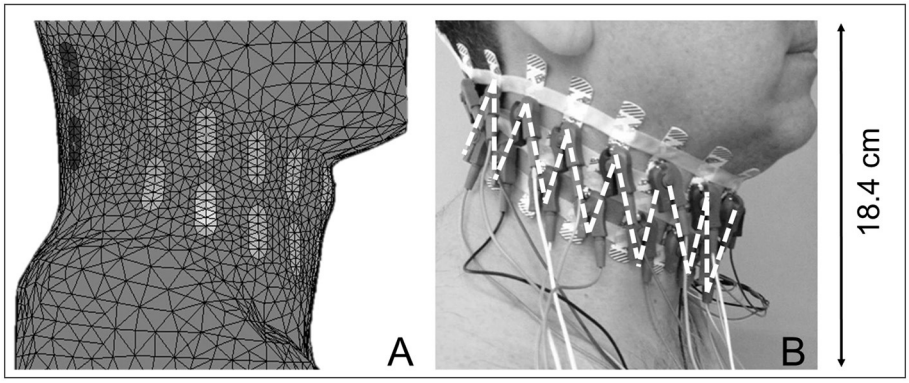

FIGURE 2
(A) Illustrates a finite element model of the neck. **(B)** Depicts a subject wearing 32 electrodes spanning his neck circumference in two equidistant bands, with 16 electrodes making up each band; the first strap is located near the level of the maxilla, and the second is immediately beneath the first. Small connectors were positioned in a zigzag configuration, as illustrated by the dashed lines. Neck EIT covers a vertical length of 18.4 cm.

TABLE 1 Baseline characteristics, sleep study, CPAP holding pressure and Pcrit of the population studied.

No. total of subjects	21		
	Male	Female	Total range
No. by gender, %	14 (67%)	7 (33%)	
Age, years	40 ± 13	50 ± 9	23–69
BMI, kg/m^2	32 ± 5	32 ± 5	24–43
Neck circumference, cm	42 ± 3	38 ± 2	36–50
AHI, events per hour	44 ± 37	44 ± 35	1–122
Min SaO_2, %	81 ± 10	82 ± 6	52–91
ESS	11 ± 5	14 ± 6	2–22
CPAP holding pressure, cmH_2O	13 ± 4	14 ± 3	5–20
Pcrit, cmH_2O	2 ± 5	4 ± 3	−4 to 10

Values are expressed as the means ± SD. CPAP, continuous positive airway pressure; Pcrit, critical closing pressure; BMI, body mass index; ESS, Epworth Scale; AHI, apnea-hypopnea index. The statistical analysis found no significant differences between genders.

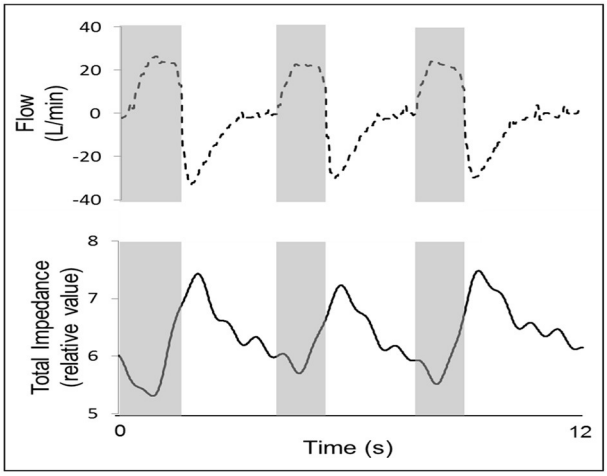

FIGURE 3
An example of one representative subject, showing that total impedance (solid line) varies during stable breathing (presented by a flow curve, dashed line). During measurements of the impedance during stable breathing, valleys occurred during inspiration (gray columns), and impedance peaks occurred during expiration. Because air is a poor conductor of electricity, the lower value of the upper airway cross-sectional area occurred during inspiration, and the higher value occurred during expiration. In this example, $r = 0.914$, $p < 0.001$. Flow data was acquired by the EIT machine a pneumotachograph connected in series with the airflow circuit, which saves the flow data synchronously with the impedance data.

five breaths under the following 3 different nasal pressures: with no flow limitation, with flow limitation and during obstructive apnea. At each level of nasal pressure, the images of the smallest VP and OP areas of one representative respiratory cycle were captured using specific software (Vegas Movie Studio HD Platinum 11.0, Sony Creative Software Inc.). The area was calculated by delimiting the lumen image (ImagePro Plus 4.5.0.19, Media Cybernetics Inc.) and comparing it with the same distance-magnification using millimeter paper (Isono et al., 2002). VP and OP areas were plotted against values of impedance valleys collected at the holding pressure, under flow limitation and during obstructive apnea.

Statistical analysis

Data were expressed as means ± SD (or medians when appropriate). Mann–Whitney *U*-test was used to detect the differences in the males' and females' baseline characteristics, sleep study, CPAP holding pressure and Pcrit. The relationship between flow and total impedance changes during stable breathing was tested using cross-correlation. We used the Fischer *r*-to-*z* transformation to transform these correlation coefficient values into weighted additive quantities. Spearman's rank correlation coefficient was applied to correlate V'Imax and impedance at each step of the pressure reduction during Pcrit determination. Also the Spearman's rank correlation coefficient was applied to correlate the mean impedance value in the impedance valley with the smallest VP and OP cross-sectional areas at nasal pressures

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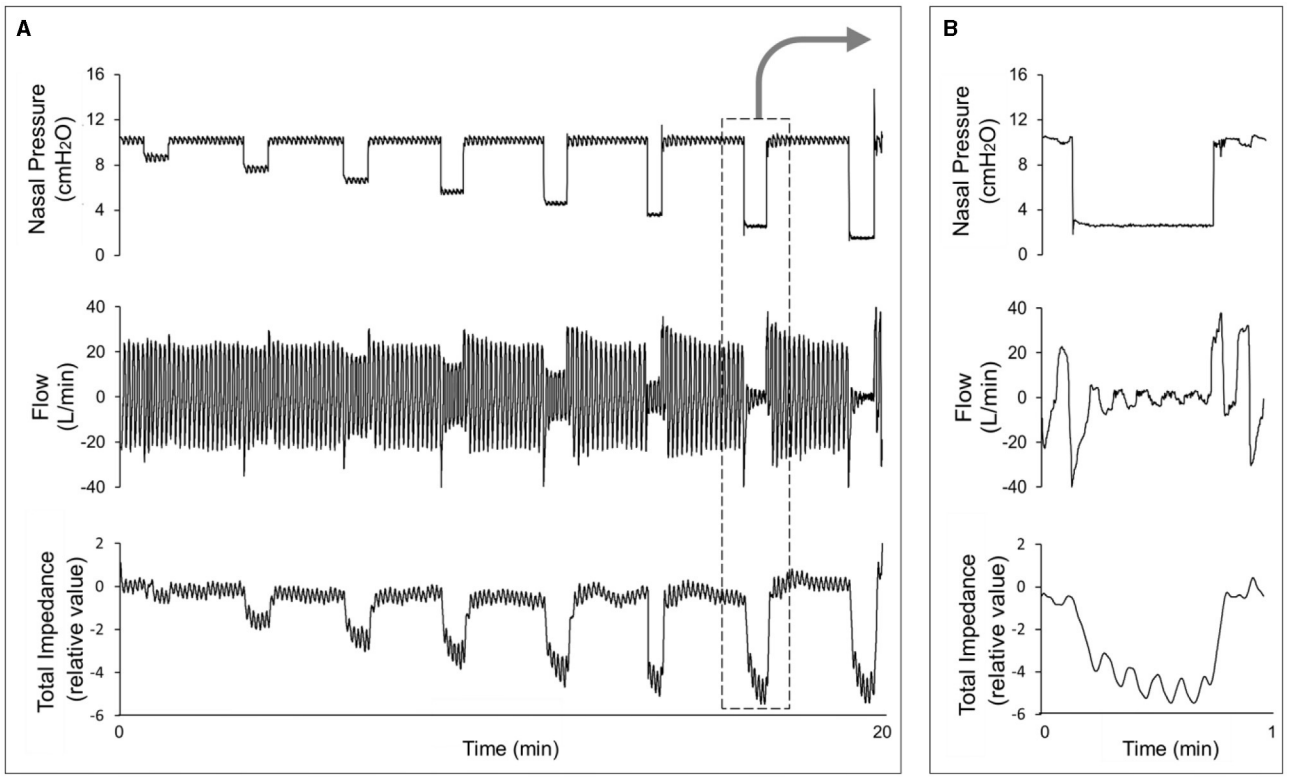

FIGURE 4
(A) Shows an example from a representative subject in whom we observed a flow decrease, followed by impedance variation, during CPAP reduction. **(B)** Provides a magnification of one step of the CPAP reduction (arrow), showing that the impedance also varies during the breathing cycle.

TABLE 2 **Delta between the impedance determined during stable breathing and impedance during severe flow restriction.**

	Delta	Range
1st ROI	−2.049 ± 1.240	−4.081/−0.497
2nd ROI	−3.286 ± 1.895*	−6.482/−0.907
3rd ROI	−1.980 ± 1.382	−4.803/−0.097
4th ROI	−1.684 ± 1.527	−3.776/+1.539

Group data for the delta between the mean impedance value at three consecutive inspiratory peak flows, during stable breathing and during severe flow restriction. The impedance delta was significantly higher in the 2nd region of interest (ROI) compared with the remaining ROIs ($p < 0.001$). The results are expressed as means ± SD. ROI: region of interest ($n = 21$). *$p < 0.001$.

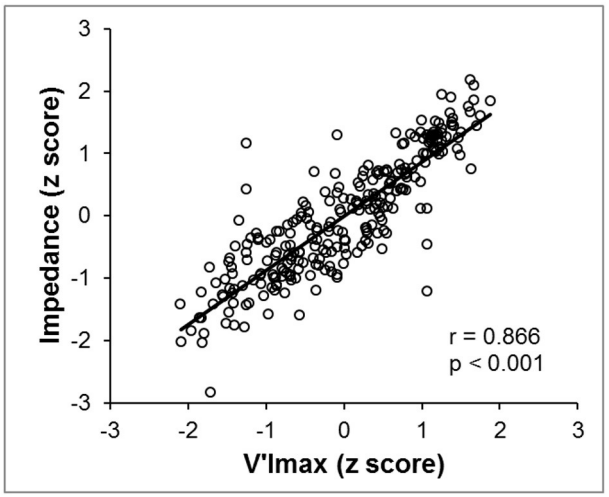

FIGURE 5
In all subjects, we observed a high correlation coefficient between the total neck impedance variation *z*-scores (*Y*-axis) and the V'Imax *z*-scores (*X*-axis). Data were acquired while the pressure was reduced until apnea occurred.

with no flow restriction, with flow restriction and during apnea. Because subjects' levels of nasal CPAP were different and because impedance is a relative value, the *z*-score transformation [*z*-score $= (x - \mu)/\sigma$, where x = sample value, μ = sample mean, and σ = standard deviation] was used to normalize and correlate the pooled data of V'Imax, neck impedance and pharyngeal area. Thereafter, we used a generalized estimation equation (GEE) model to determine in a subgroup of patients ($n = 6$) the numerical relationship between total neck impedance and the minimum VP and OP areas. The Kruskal-Wallis test was employed to identify differences in impedance variation between ROIs (delta between the mean impedance values at three consecutive peak inspiratory flow measurements) during stable breathing and severe flow restriction. The Wilcoxon test was used to define which ROI exhibited the higher delta value. Statistical significance was set at

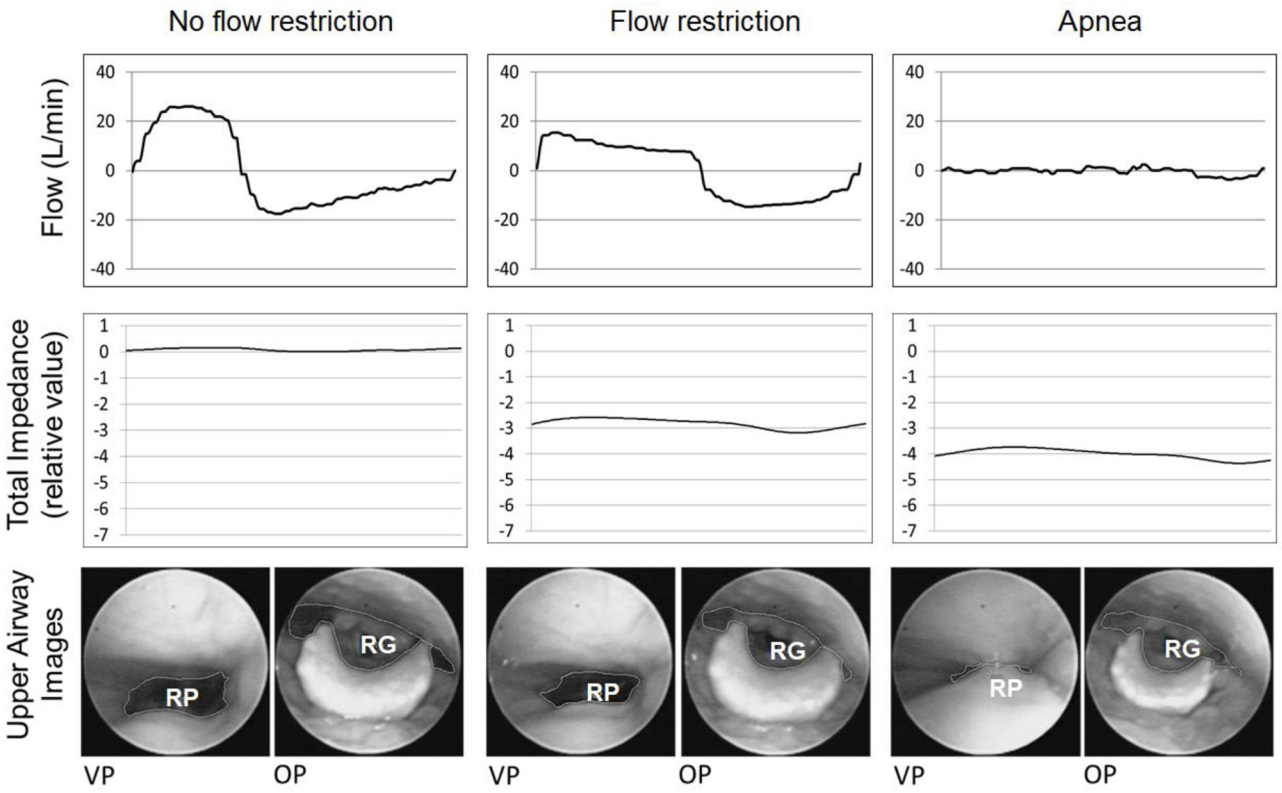

FIGURE 6
This figure shows an example of a representative respiratory cycle of one subject subjected to different CPAP levels. From left to right: no flow restriction, flow restriction and apnea. From top to bottom: flow curve (dashed line), total neck impedance (solid line), and upper airway images at the velopharynx (VP) and oropharynx (OP) areas. The impedance decreased progressively from no flow restriction to flow restriction and apnea. The chart scale does not allow us to visualize the impedance changes during the breathing cycle. RP, retropalatal; RG, retroglossal.

$p < 0.05$. SPSS 15.0 for Windows® was used (2006 SPSS Inc., Chicago, Illinois).

Results

Twenty-one individuals completed the study (Table 1).

Sleep was induced with a mean total midazolam dose of 2.5 ± 1.2 mg. In all subjects, the total impedance varied within the respiratory cycle during stable breathing, as shown in a representative example (Figure 3).

In all cases, the impedance valleys were close to the inspiratory peak flow, and the impedance peaks were close to the expiratory peak flow. During stable breathing, the group demonstrated an average cross-correlation between the flow and impedance curves of $r = -0.817$, obtained during stable breathing ($p < 0.001$). The mean time-lag was 0.48 ± 0.35 s (range: 0–1.52 s). During nasal pressure reductions, we observed that the total neck impedance decreased in proportion to the flow reduction on all occasions and in all patients, as observed in a representative subject (Figure 4).

Table 2 demonstrates that the delta between the average impedance values of three consecutives peak inspiratory flow measurements taken during stable breathing and during severe flow restriction was significantly higher in the 2nd ROI than in the 1st, 3rd, and 4th ROIs.

V'Imax and total neck impedance (expressed as z-score) were strongly correlated in the entire group ($r = 0.866$, $p < 0.001$) (Figure 5).

The minimum mean VP areas during stable breathing and severe flow restriction (six subjects that performed nasofibroscopy) were 20.52 mm^2 (3.59 SE, range of 12.90–37.18 mm^2) and 4.03 mm^2 (2.84 SE, range of 0.52–18.13 mm^2), respectively (Figure 6). The minimum mean OP areas during stable breathing and during severe flow restriction were 18.50 mm^2 (3.81 SE, range of 5.53–34.27 mm^2) and 5.19 mm^2 (2.36 SE, range of 0.78–15.06 mm^2), respectively. The GEE analysis indicates that there is a significant VP area effect when controlling for the impedance signal at retroglossal area ($p = 0.13$), with a prevalence ratio of 0.29. Also, the results indicate that there is a significant OP area effect when controlling for the impedance signal at retropalatal area ($p = 0.11$), with a prevalence ratio of 0.45.

The group data correlations among the minimum VP and OP areas and total neck impedance were 0.884 and 0.891, respectively ($p < 0.001$) (Figure 7). At Figure 8 it is possible to observe, in a

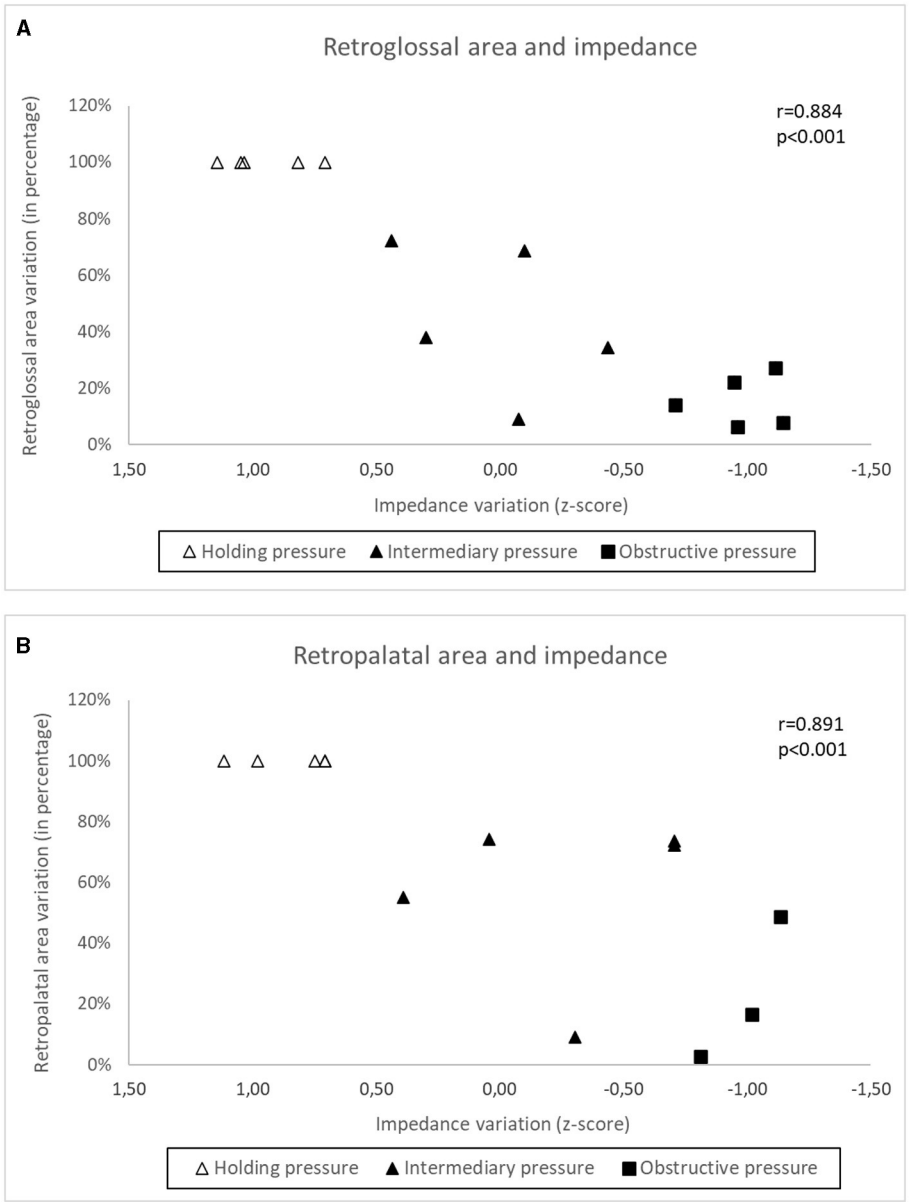

FIGURE 7
In a subgroup of subjects **(A)** shows the relationship between impedance variation and retropalatal area variation at the holding pressure (no respiratory flow restriction), intermediary pressure (~50% of respiratory flow restriction) and obstructive pressure (apnea). **(B)** Shows the same relationship between impedance variation and retroglossal area variation.

representative subject, that upper airway changes are also visible on the neck electrical impedance tomography image.

Discussion

This was the first study using EIT method in sleep induced patients. In our study, EIT consistently detected upper airway occlusion induced by applying variable levels of nasal pressure during induced sleep (method of Pcrit determination). There were no differences by gender in our study (regarding baseline characteristics, sleep study, CPAP holding pressure and Pcrit). Also, we didn't notice any sex-specific differences in male vs. female on impedance data acquisition.

Neck EIT was sensitive and varied in concert with the respiratory cycle (Figure 3). Neck EIT also decreased in concert with and in proportion to the level of CPAP reduction. The image of one representative patient (Figure 4) was confirmed via the demonstration of a close relationship between V'Imax and simultaneous neck impedance in all patients (Figure 5). Finally, the upper airway image obtained by direct visualization both on the VP and OP areas correlated with total neck impedance.

We placed the electrodes around the neck in two parallel rings in a zigzag configuration to obtain information from a wide region (that would encompass the pharynx). The zigzag electrode

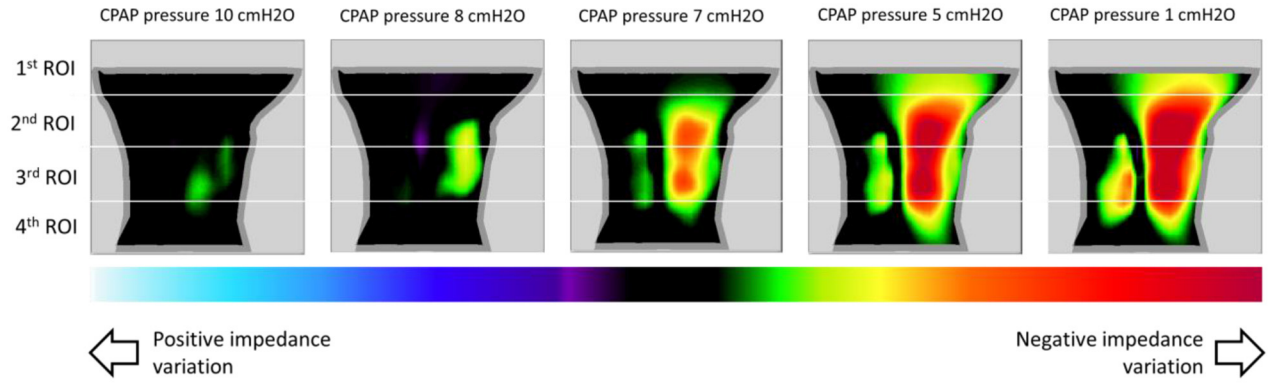

FIGURE 8
This figure shows images of impedance variation of the sagittal plane, in a representative subject, at different CPAP pressures (pressure of 10 cmH_2O was used as reference). The images show a decrease in impedance as the CPAP pressure decreases to Pcrit (1 cmH_2O). There is an artifact near the back of the neck, likely due to differences between the model's shape and the actual shape of the neck. Also, as showed in Table 2, we can observe that negative impedance variation was higher in the 2nd ROI (region of interest).

positioning allowed for the construction of a 3D finite element mesh that corresponded to a longitudinal area of 18.4 cm (~9.2 cm rostral and 9.2 cm caudal to the electrode center). Using this configuration neck EIT captured changes in pharyngeal patency cephalic to the electrodes positioned at the neck.

Total neck impedance was sensitive and varied in concert with the tidal volume during stable breathing. We found a strong inverse cross-correlation between the flow and impedance curves ($r = -0.817, p < 0.001$), indicating that impedance valleys (lowest upper airway cross-sectional areas) occurred during the inspiratory phase and that impedance peaks (highest upper airway cross-sectional areas) occurred during the expiratory phase (Figure 3).

These findings are consistent with previous studies of non-invasive continuous imaging of the upper airway during natural sleep, conducted for OSA patients, using the EIT technique (Ayoub et al., 2019, 2020; Kim et al., 2019).

In our study, the high sensitivity of neck EIT, which varied in concert with CPAP reductions, was self-evident in one representative example (Figure 4). Group data derived from all subjects demonstrated a high correlation coefficient between V'Imax and total neck impedance variation ($r = 0.866$). Therefore, the progressive flow restriction associated with progressive CPAP reduction was associated with progressive decreases in neck impedance (indicating a smaller cross-sectional area). This observation is consistent with those of previous studies that demonstrated strong correlations between CPAP levels and pharynx areas (Launois et al., 1993; Morrison et al., 1993; Isono et al., 2002). Additionally, Isono et al. (1997) demonstrated that variable and controlled levels of flow limitation correlate with upper airway cross-sectional area. The assumption that neck EIT correlates with upper airway patency was further confirmed via direct visualization of the upper airway. Also, at Figures 6, 7 we show the same relationship between impedance level, flow restriction and upper airway collapse.

Finally, the finding that the 2nd ROI (rather than the first and most cranial ROI) exhibited the largest variation in impedance during upper airway obstruction (Table 2) clearly indicates that EIT captured changes in pharyngeal patency cephalic to the electrodes positioned on the neck.

Limitations

Our new method has limitations. A virtual 3D finite element mesh was created based on CT-scan images from a single male volunteer. However, we studied a wide range of cranium, upper airway, soft tissue, and body characteristics (Table 1), and the signals were clear in all subjects. The method may also be applied using customized meshes according to individual biotypes. Additionally, the system only responds to changes in impedance; therefore, we are not able to provide absolute values for anatomical evaluations. Also, Kim et al. (2019) in their study concluded that changes in the upper airway size can be estimated with good accuracy, but shape estimation needs future improvements in the EIT image quality (Kim et al., 2019). We believe that electrical impedance may provide absolute values for anatomical descriptions in the future (Costa et al., 2009b).

Additionally, neck EIT images were obtained with the subjects in a stable position. Ayoub et al. (2019) found that EIT data from the lower face were contaminated by artifacts from respiratory motions, blood flows in the carotid artery and neck movements. In our study, EIT artifacts generated by body motion was limited to controlled conditions but is an important consideration that needs to be resolved in time to come

Although our method was able to assess impedance variations in different upper airway segments, the model of the electrical impedance tomography system in this study was built based on the anatomical characteristics of a single individual. This certainly limited our analysis to the comparison of different anatomical sites and made us prioritize the total impedance analysis. However, we demonstrated that the technique allows segmental evaluation, which we hope will be viable in the future.

Conclusion

Neck EIT is a sensitive method that varies with the breathing cycle and correlates with peak flow under flow limitation, indicating that neck EIT monitors

pharyngeal patency during sleep. Therefore, neck EIT is a promising non-invasive method that may provide insights on the dynamic of upper airway obstruction during sleep.

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 Hospital das Clínicas Ethics Committee (protocol number: 0748/11). 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

VP planned the project, recruited subjects, designed, and performed the study, performed statistical analyses, analyzed the data, and wrote the manuscript. EC planned the project, designed experiments, interpreted the results, and wrote the manuscript. VT, RA, FS, PS, and FM enrolled subjects and performed experiments. MG designed and performed experiments. PG, CC, and MA planned the project, designed experiments, and analyzed the data. GL-F planned the project, designed experiments, analyzed the data, and wrote the manuscript. All authors reviewed, revised, and approved the manuscript for submission.

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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.

The author PG declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Enhanced expiratory rebreathing space for high loop gain sleep apnea treatment

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The pathophysiology of sleep apnea goes beyond anatomic predisposition to airway collapse and includes additional factors such as arousal threshold and loop gain. High loop gain is a prominent feature in central and complex sleep apnea (with a mixture of obstructive and central features) where relative hypocapnia can lead to respiratory instability and periodic breathing. Existing therapies, including continuous positive airway pressure (CPAP) and adaptive servo-ventilators, often inadequately treat sleep apnea with high loop gain features. Enhanced expiratory rebreathing space (EERS) targets prevention of the hypocapnia that triggers central events in sleep by increasing dead space in amounts less than typical tidal volumes. This is accomplished by covering traditional exhalation ports on positive airway pressure masks and adding small additional tubing with distal exhalation and safety valves. This technique reduces carbon dioxide (CO_2) blow-off during arousals and the associated large recovery breaths, typically producing a maximal increase in resting CO_2 by 1–2 mmHg, thus increasing the CO_2 reserve and making it less likely to encounter the hypocapnic apneic threshold. Typically, the amount of EERS is titrated in response to central events and periodic breathing rather than aiming for a goal CO_2 level. Ideally CO_2 monitoring is used during titration of EERS and the technique is avoided in the setting of baseline hypercapnia. This method has been used in clinical practice at our sleep center for over 15 years, and retrospective data suggests an excellent safety profile and high rates of successful therapy including in patients who have previously failed CPAP therapy. Limitations include decreased effectiveness in the setting of leak and decreased tolerance of the bulkier circuit. EERS represents a simple, affordable modification of existing positive airway pressure modalities for treatment of central and complex sleep apnea. Areas of future study include randomized controlled trials of the technique and study of use of EERS in combination with adaptive ventilation, and pharmacologic adjuncts targeting high loop gain physiology.

KEYWORDS

complex sleep apnea, loop gain, periodic breathing, EERS, carbon dioxide, dead space

Introduction

It is now generally accepted that the pathophysiology of obstructive sleep apnea (OSA) involves non-anatomical traits, including high loop gain, an impaired negative pressure response, low arousal threshold, increased arousal intensity and sleep fragmentation. However, clinical guidelines and management of apnea has largely ignored the growing research data supporting the importance of considering an endotype/phenotype driven approach to optimized and personalized sleep apnea care. In those with hypocapnic central sleep apnea (CSA), there is little argument that high loop gain and hypocapnia is a key

destabilizer of sleep-respiration (Javaheri and Badr, 2023). The hypercapnic ventilatory response is in fact elevated in idiopathic CSA (Xie et al., 1994, 1995). In those with OSA, high loop gain will result in a tendency to hypocapnia. Yet, measurement or manipulation of carbon dioxide (CO_2) has largely remained confined to research laboratories. Here, we present the logic behind, the practical application of, and our results with the use of dead space plus positive airway pressure, a method we call Enhanced Expiratory Rebreathing Space (EERS).

Sleep apnea phenotypes and control of respiration—the importance of CO_2

There is increasing appreciation of the varied phenotypes of sleep apnea (Malhotra et al., 2020; McNicholas and Pevernagie, 2022). Although OSA, with an anatomic predisposition to airway collapse is the most commonly invoked mechanism, it has long been considered only a partial contributor (Remmers et al., 1978; Mezzanotte et al., 1996; Younes et al., 2007). While other factors such as failure of muscle recruitment/compensation can contribute to OSA (Younes et al., 2012, 2014), these factors fail to explain sleep apnea of a central nature, or, the common variant of a mixture of both obstructive and central disease (complex sleep apnea) (Gilmartin et al., 2005). Although the establishment of the diagnosis of treatment-emergent sleep apnea (TE-CSA) has raised awareness of pathophysiological "mixed" sleep apnea (ICSD-3), it oversimplifies the patterns of sleep apnea to an artificial "all or none" format where one physiology clearly dominates. In fact, TE-CSA merely reflects the consequence of targeting only the upper airway when breathing control instability is also present. In reality, the features of reduced respiratory effort and obstruction are often intertwined and evident to some extent across both diagnostic and titration sleep studies. Central events, with prolonged exhalation and reduced airway stenting can produce airway collapse and obstruction (Badr et al., 1995). Given this, the label complex sleep apnea may be more appropriate (Gilmartin et al., 2005; Morgenthaler et al., 2006). Thus, multiple pathophysiologic factors contribute to these different phenotypes, including a low arousal threshold and loop gain (Table 1) (Eckert et al., 2013).

The sleep-related arousal threshold describes the ease with which an individual can be triggered to arouse from sleep, with a low arousal threshold suggesting that even mild stressors (respiratory or non-respiratory) can lead to an arousal. Conversely, a high arousal threshold suggests that a high amplitude stressor is required to disrupt sleep. In the context of sleep apnea, a low threshold will lead to more frequent sleep wake transitions (Jordan et al., 2017) and seems to have consequences for tolerance of positive pressure therapy (Zinchuk et al., 2021). Targeting this factor underlies the principle of using sedatives to treat sleep apnea (Eckert et al., 2011; Edwards et al., 2016; Ahmad et al., 2023). However, trials examining monotherapy with sedatives to control sleep apnea have been inconsistent (Rosenberg et al., 2007; Carter et al., 2018). A high arousal threshold is a predictor of a positive response to hypoglossal nerve stimulation for sleep apnea, consistent with a role for the arousal threshold in modulating outcomes of sleep apnea (Op de Beeck et al., 2021).

Loop gain refers to the relation of a response to a disturbance, for sleep apnea the ratio of ventilatory response in reaction to a ventilatory stimulus. When the loop gain is higher than desirable, there is a disproportionately robust ventilatory response, and when lower than desirable, and over-damped system. A vigorous ventilatory response may seem advantageous compared to the alternative, a low loop gain leading to an insufficient ventilatory response, and hence a tendency to hypoventilation. However, high loop gain causes its own challenges given the control mechanisms governing respiration in sleep (Younes et al., 2001). Loop gain can be further classified as controller gain, mixing gain and plant gain. Controller gain refers to the sensitivity of the system to changes in chemical stimuli like carbon dioxide and is governed by central and peripheral chemoreceptors (Orr et al., 2017; Roberts et al., 2022). High controller gain suggests that a given change in $PaCO_2$ will result in a greater change in ventilation, while a low controller gain will generate a lesser response in ventilation for the same change in $PaCO_2$. In sleep apnea, intermittent nocturnal hypoxia sensitizes the carotid body and results in a steeper slope of the hypoxic ventilatory response and elevated controller gain (Tamisier et al., 2009). Plant gain refers to the efficiency of gas exchange within the respiratory system; it is dependent on the characteristics of the individual's cardiopulmonary systems. An individual without cardiopulmonary comorbidities will have a higher percentage of their lung volume participating in efficient gas exchange. A normal pulmonary system leads to more change in gas levels per change in minute ventilation than an individual with, for example, advanced chronic obstructive lung disease (COPD). The COPD patient has lower plant gain and is less likely to produce a large change in CO_2 for a given change in ventilation. In a system with high loop gain, a low efficiency of gas exchange can actually help prevent hypocapnia and hence the resultant overshooting of the ventilatory response. In addition, an "arousal gain" can be considered a modifier, with more vigorous arousals a result of greater effective controller gain. Mixing gain is most relevant in conditions like heart failure with a prolonged circulation time.

The control of ventilation is quite different in the states of wake and sleep. Inputs are much more numerous during wakefulness and include the peripheral and central chemoreceptor response to multiple molecules including oxygen, hydrogen ions, CO_2, nitric oxide and hydrogen sulfide; input from temperature and pain stimuli; lung stretch; emotional stimuli; and voluntary control of breathing (Del Negro et al., 2018). The influence of most of these inputs wanes with a transition to sleep. In the sleep state, voluntary and emotional stimuli are absent and respiration during non-rapid eye movement (NREM) sleep is largely governed by chemical drivers. Specifically, CO_2 becomes the key respiratory driver, such that hypercapnic respiratory response is the greatest determinant of ventilatory drive during sleep. The NREM CO_2 threshold is just a few mmHg lower than CO_2 values under eupnea. The CO_2 reserve, therefore, is the space where CO_2 may fluctuate without triggering ventilatory instability. CO_2 reserve is low in those with hypocapnic CSA, periodic breathing, or TE-CSA (Dempsey et al., 2004; Xie et al., 2011, 2013). The ventilatory response to hypercapnia and hypoxia are also more robust during wake as compared to sleep, with more substantial increases in ventilation in response to CO_2 increase or O_2 decrease.

TABLE 1 Relative contribution of pathologic features in different sleep apnea endotypes.

Sleep apnea type	Airway narrowing	Loop gain	Arousal threshold	Role for EERS
Obstructive	Significant	Average	Variable	No
Central	Minimal	High	Variable	Yes
Mixed	Significant	High	Low	Yes
Obesity hypoventilation syndrome	Mild to significant	Low	High	No

The changing inputs to respiration upon sleep onset result in an inherently unstable state. The loss of behavioral control, reduced respiratory drive, and reduced chemosensitivity make hypoventilation more likely, while decreased muscle tone increases obstruction; as a result, there is an increased risk for flow limitation. The mild retention of CO_2 after sleep onset offers some protection for respiratory stability as it increases the $PETCO_2$-PCO_2 apneic threshold difference. Progressive flow limitation causes a reduction in ventilation and a proportionate response dictated by the individuals' loop gain. In the situation of high loop gain, a robust respiratory response to this reduction in ventilation increases the risk of inducing hypocapnia below the hypocapnic apneic threshold and thus induction of a central apnea. A resulting apnea subsequently leads to CO_2 re-accumulation and therefore increased ventilatory drive, which is disproportionately high in the setting of high loop gain, generating an alternating cycle of relative hypo- and hypercapnia. Ultimately, this cycle can cascade to the point that periodic breathing is generated and maintained. The combination of both high loop gain and low arousal threshold can be particularly problematic, as the tendency to quickly arouse increases the frequency of transitions between wake and sleep, allowing for significant fluctuations in ventilatory drive and therefore the risk of over-ventilation in the setting of high loop gain. Even in patients with primary OSA, objective measurement of arousal threshold and loop gain suggest that about a third of patients have high loop gain and a third have low arousal threshold; this suggests that these factors are relevant across all forms of sleep apnea (Eckert et al., 2013). Although formal measurement of loop gain and arousal threshold is not typically utilized in clinical practice, features collected by typical polysomnography can hint at these characteristics (Table 2).

TABLE 2 Polysomnographic features suggestive of high loop gain and low arousal threshold.

Features suggestive of high loop gain	Description
NREM dominance of events	• Events cluster around sleep wake transitions when overventilation has maximal impact at inducing central events • Respiratory events markedly improved in REM vs. NREM sleep, ideally a supine-to-supine comparison
Periodic breathing	Cyclic under-shoot and over-shoot of ventilation creating a metronomic self-similar pattern
Oximetry banding	Series of self-similar events of consistent duration and oxygen desaturations produces a thick line on oximetry when viewed on the scale of the entire night
Treatment emergent central apneas	Increased ventilation triggers central events in the setting of low CO_2 reserve
Prolonged time between event onset and oxygen nadir associated with the event	Cardiac insufficiency leads to a mixing delay, an increased transit time of relatively deoxygenated blood to reach the peripherally located oximetry sensors
Features suggestive of low arousal threshold	**Description**
Elevated Spontaneous Arousal Index	Suggestive of easy arousal
Non-hypoxic sleep apnea	AHI3% significantly greater than AHI4%, suggestive fragmentation is not driven by gas exchange abnormalities
Elevated N1 sleep	Evidence of frequent sleep stage transitions
Persistent cyclic alternating pattern (CAP) of EEG despite optimal upper airway support	Indicative of frequent EEG arousals and arousability

Central apneas induced by relative hypocapnia during sleep are a well-established phenomenon. In the intubated and sedated ICU patient, alkalemia induced during a control mode of mechanical ventilation will result in apneas upon the transition to pressure support modes due to low levels of CO_2 and subsequent lack of respiratory drive. At high altitude, the reduced FiO_2 leads to increased minute ventilation based on the hypoxic respiratory response. This increased minute ventilation leads to hypocapnia below that achieved at sea level and thus central apneas and high attitude periodic breathing result (Masuyama et al., 1989; Khoo et al., 1996; Fowler and Kalamangalam, 2002; Lombardi et al., 2013; Pramsohler et al., 2019). In TE-CSA, the appropriate improvement in ventilation with treatment of obstruction leads to relative hypocapnia and induction of respiratory instability ("high altitude at sea level"). Patients with high loop gain, such as those with congestive heart failure and idiopathic CSA, lack the typical degree of hypoventilation with transition to sleep and the ventilatory response to CO_2 below eupneic values is more sensitive. This combination makes it more likely for these high loop gain CHF patients to reach the hypocapnic induced apneic threshold (Xie et al., 2002).

Despite the fact that central events induced by relative hypocapnia are a common feature of sleep breathing, traditional treatments of sleep apnea remain insufficient to treat sleep apnea phenotypes enriched for central events, whether due to primary CSA, or complex sleep apnea with a mixture of central and obstructive events. The CANPAP trial showed that continuous positive airway pressure (CPAP) leaves a substantial residual burden of central apneas in patients with congestive heart failure and fails to improve heart failure related outcomes (Bradley et al., 2005). Adaptive servo ventilators are designed for Hunter-Cheyne-Stokes respiration, a classic feature of high loop gain. These bilevel

machines are designed to adjust the pressure delivered relative to respiratory effort (inverse, anti-cyclic) in attempts to break the cycle of periodic breathing. Practically, the ability of these proprietary algorithms to successfully prevent periodic breathing may be brand-specific, as different models produce substantially different minute ventilations in the same individual (Knitter et al., 2019). Pathological pressure cycling imposes hemodynamic stress on the cardiovascular system (Gunn et al., 2018). Although studies suggest that adaptive servo ventilators are superior to CPAP for treatment of the respiratory features of complex sleep apnea, the impact on sleep quality and clinical outcomes is less striking (Morgenthaler et al., 2014). The expense of these machines and strict coverage criteria are challenges (Morgenthaler et al., 2021). The SERVE-HF trial demonstrated increased mortality in those with systolic heart failure, which severely undercuts the utility of the device in those patients at elevated risk for high loop gain (Cowie et al., 2015). Acetazolamide (discussed in more detail below) shifts the CO_2 response curve to the left and lowers the apneic threshold, improving respiratory stability. Supplemental oxygen has been demonstrated to have a positive effect on sleep apnea with high loop gain (Sands et al., 2018). However, oxygen monotherapy cannot overcome upper airway resistance. In addition, it can be difficult to qualify for in the context in the US insurance system, and self-pay has a significant long-term expense world-wide (Morgenthaler et al., 2021).

Introducing dead space/enhanced expiratory rebreathing space

Based on the physiology of hypocapnic induced central apneas, an intervention preventing hypocapnia would be a logical target. CO_2 modulation has been utilized as a strategy to stabilize periodic breathing and other chemoreceptor-associated breathing abnormalities for over 40 years. Berssenbrugge and colleagues first demonstrated in 1983 that hypoxia-induced periodic breathing could be eliminated by augmenting inhaled $FiCO_2$, resulting in a 3–6 torr increase in arterial $PaCO_2$ and normalization of breathing pattern, supporting the hypothesis that periodic breathing is due in part to transient oscillations in arterial CO_2 content above and below the CO_2 apnea threshold (Berssenbrugge et al., 1983). Dead space has been used to improve sleep-breathing and thus sleep in mechanically ventilated patients (Parthasarathy and Tobin, 2002), periodic breathing at high altitude (Lovis et al., 2012; Patz et al., 2013), idiopathic CSA (Xie et al., 1997), and heart failure (Khayat et al., 2003). The "dose" required to stabilize ventilation may not meaningfully improve sleep quality or arousals (Szollosi et al., 2004).

The first demonstration of the benefits of a low concentration of CO_2 that was "clamped" to just above the NREM sleep CO_2 threshold was in 2005 (Thomas et al., 2005). In that report, using an investigational device, a concentration of 0.5–0.8 (% CO_2) was sufficient to enable respiratory stability when combined with positive pressure airway support. This realization motivated the trial of a small amount of dead space (50–100 cc, vs. the 300–500 cc used in prior reports) with CPAP. The concept of Enhanced Expiratory Rebreathing Space (EERS) is the adaptation of dead space to concomitant use of positive pressure ventilation (Gilmartin et al., 2010). The EERS space is analogous to the "dead-space" in the native respiratory system, which accounts for the volume of air in each breath that does not interface with the gas-exchanging tissues of the lung (i.e., the volume of air contained within the conducting airways such as the mouth, trachea and bronchi). In the normal adult, anatomical dead space accounts for roughly 33% of the total tidal volume of inspired air (roughly 130–180 cc's per breath) and can be measured more accurately via the Fowler method, or single-breath nitrogen washout test. Other forms of dead space include alveolar dead space which is often secondary to disease (e.g., atelectasis, impaired pulmonary blood flow, or increased alveolar pressure) as well as apparatus dead space from respiratory equipment, such as that utilized in EERS circuitry.

Biological effects of EERS

EERS has a few possible effects to enable respiratory stability. First, by using EERS, loop gain is lowered through reduction in plant gain, by reducing the efficiency of CO_2 removal with ventilation. Second, by slightly raising baseline CO_2 (1–2 mm Hg), the likelihood of hitting the NREM CO_2 threshold is reduced, and the CO_2 reserve is therefore increased. Third, the greatest effect of EERS may be during intermittent arousal-induced ventilatory blow-off (a "shock-absorber" effect), preventing the major resulting fluctuations of CO_2 that inevitably occur. Finally, there may be effects at the level of cerebral blood flow. There is no change in mean heart rate or respiratory rate (Gilmartin et al., 2010).

Creating EERS

Native non-vented masks may be used, or "conversion" of a standard vented mask. It should be noted that some masks like the ResMed AirFit™ N20 has a non-vented configuration with a short stalk. EERS is achieved first by blocking the typical mask exhaust vents, for example by adding a compound such as silicone putty to block the vent holes and prevent normal CO_2 escape. This step converts a standard "vented" CPAP mask into a "non-vented" mask setup, and adds about 70 (nasal mask) to 100 (oronasal mask) cc's of dead space to the system. Additional EERS volumes are then added by inserting corrugated flexible tubing in 50 cc increments to the mask tubing, with the ability to add 50–150cc's total of EERS to the system. A swivel valve (we use the Philips Whisper Swivel II Exhalation Valves), which allows for continuous venting and thus represents the termination of the non-vented circuit, is added at the distal end of the EERS tubing and allows for exhalation of CO_2 (Figures 1, 2). In full-face mask setups, a safety valve (non-rebreathing valve) is added to prevent theoretical asphyxiation in the event of a power outage or machine malfunction, but could be considered optional in nasal-only. Most if not all current full-face masks come with an inbuilt non-rebreathing valve, and no added safety valve is required; as a default we use safety valves in nasal masks also. A patient with normal dexterity and mental status could also easily remove the mask in the event of power failure.

Patient selection

Adherence to positive pressure therapies is a significant predictor for symptomatic improvements in OSA, with usage >6 h nightly associated with decreased sleepiness, improvement in daily functioning, and normalization objective memory performance (Zimmerman et al., 2006; Weaver et al., 2007). In patients with high loop gain sleep apnea, there are some

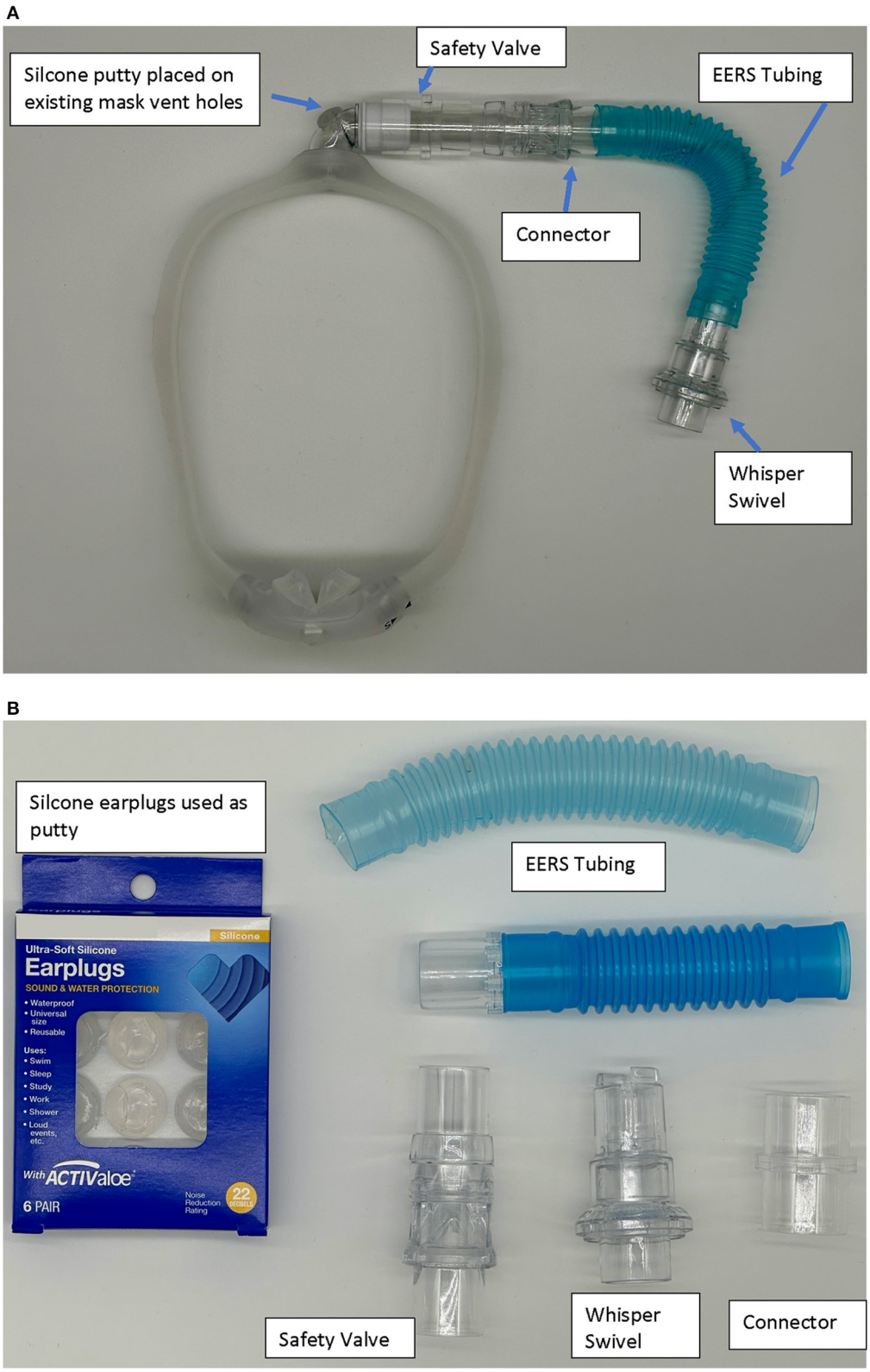

FIGURE 1 (Continued)

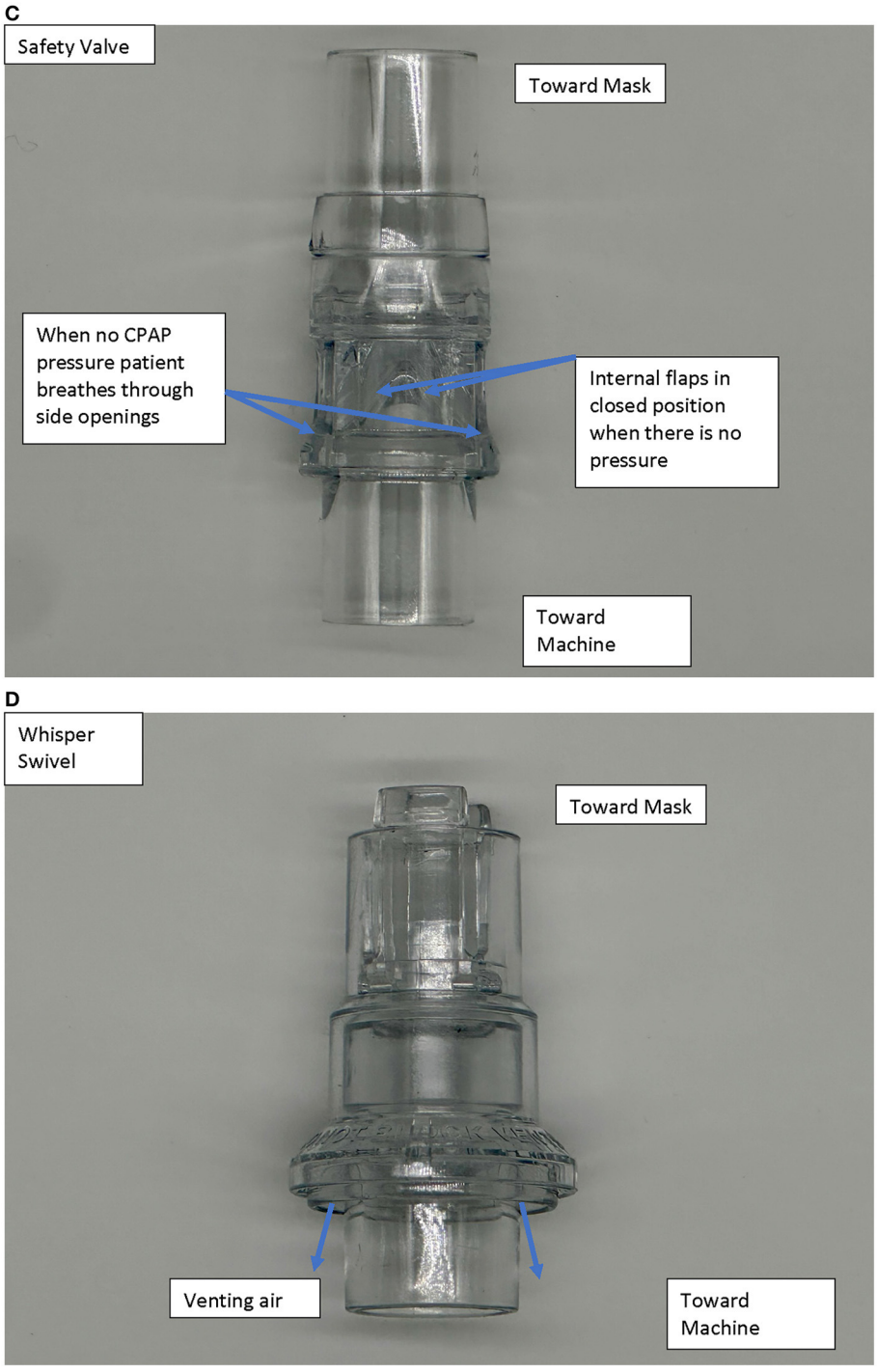

FIGURE 1 (Continued)
(A) Example of a nasal pillow mask set up with the nonvented, EERS modification. The model is a Dreamwear by Respironics-Phillips. **(B)** Description of parts used. Silicone ear plugs (typically CVS Health, or Mack's brand) are utilized to cover the standard mask vents. Other components—Whisper Swivel—332113—Respironics-Philips, Non-Rebreather Valve—NV-HC209—Fisher & Paykel, EERS tubing—PES-1680-(50,100,150) cc—Teleflex/Hudson, Flex Tube with 22 mm connector–PMS-6107—Portex, 22 mm Connectors—HUD1421—Teleflex/Hudson. The sequence is mask-safety valve (if nasal mask)-EERS-Whisper-standard CPAP (with connectors as needed). The connector and extra tubing allow both to connect to typical CPAP tubing and modulation of the amount of EERS. **(C)** The safety valve has a one wave valve that allows air to be entrained through side ports in the event of power loss with discontinuation of positive airway pressure. An alternative is the Hans-Rudolph non-rebreathing valve part numbers 115402 or 115401. **(D)** The Whisper valve serves as the exhalation vent in the series.

data that non-adherence rates are even higher than those with straightforward OSA (Ni and Thomas, 2023). Measurements of baseline unstable ventilatory control (i.e., high loop gain) have also been associated with elevated residual AHI and rates of CPAP non-response defined as residual AHI >5/h despite adequate control of obstruction, even when CPAP compliance

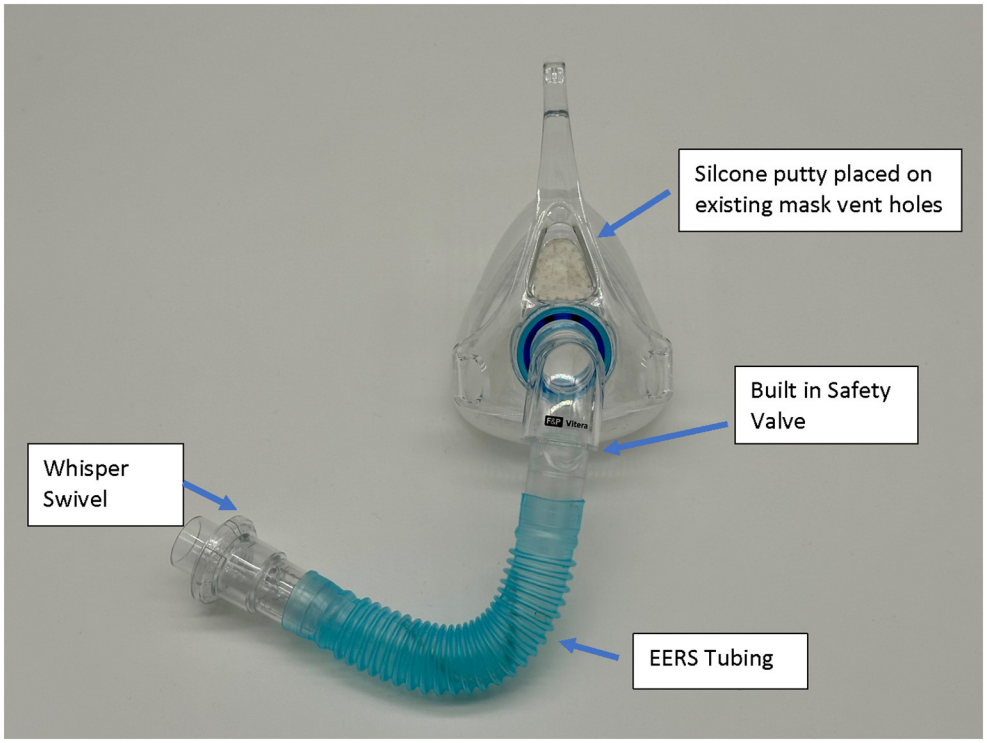

FIGURE 2
Example of a full-face mask set up with the nonvented, EERS modification. The model is a Fisher & Paykel, F&P Vitera™. The existing internal mask safety valve is utilized with the addition of connectors, EERS tubing, and Whisper Swivel Valve.

is maintained. This implicates that the measurement of loop gain is a potential *a priori* predictor of patients who would benefit from adjunctive therapies to standard positive airway pressure (Stanchina et al., 2015).

By identifying patients who would be suitable for EERS therapy prior to standard CPAP failure, there is the potential for improved long-term compliance and acceptance of CPAP therapy. In the original EERS paper, we reported that 80% of patients who were treated had given up therapy; we had a long-term "salvage" rate of about 50% at long-term follow-up. This is particularly important as CPAP therapy has been demonstrated to resolve central events related to loop gain over time in select patients (Kuzniar et al., 2008; Javaheri et al., 2009), but this relies on the establishment of successful and compliant CPAP use. Thus, EERS use has three global goals—enabling healing in those whose high loop gain features will resolve by improving short-term tolerance, long-term benefits in those who have persistence of control instability, and salvage of those who have already failed therapy (i.e., providing a "second chance" at therapy). As hypoxia is a key driver of acquired increases in loop gain, it is expected that those who have substantial hypoxia are likely to improve over time, while those who have minimal hypoxia and possibly genetically determined abnormality will have long-term persistence. Heart failure is an example of a condition where some patients do not have severe hypoxia yet can have overt periodic breathing; many patients however are hypoxic, and the combination of hypoxic and non-hypoxic mechanisms can markedly elevate loop gain.

There are currently multiple methods for identifying underlying high loop gain as a marker for standard CPAP failure and/or an indication for EERS. Besides overt CSA or TE-CSA, multiple morphological features on diagnostic polysomnograms can be used to detect likely underlying elevated loop gain including NREM predominance of respiratory events with stabilization during REM sleep, increased NREM sleep stage transitional instability, short-cycle (<30 s) self-similar events, and "banding" oxygen desaturations visualized on pulse oximetry (Thomas et al., 2004). Mathematical formulas to measure loop gain have been utilized routinely in the research settings or secondary analysis of clinical trial data (Sands et al., 2011; Stanchina et al., 2015; Joosten et al., 2017; Li et al., 2019). The Phenotyping Using Polysomnography (PUP) method is a promising, potentially scalable method, of estimating endotypes from existing polysomnograms by using changes in estimated minute ventilation to determine metrics of respiratory drive (Finnson et al., 2021). Objective measurement of respiratory self-similarity (respiratory events with clone-like timing and morphology) also aids in risk-prediction (Oppersma et al., 2021). Residual events after several months of CPAP use also is a useful marker of a person who may need therapy targeting high loop gain, though mechanical effects of an oronasal mask (Genta et al., 2020), high leak or sleep fragmentation may all contribute (Ni and Thomas, 2023). Current device algorithms for detecting residual apneas on CPAP therapy have been shown to have significant errors in detection, particularly with regards to the presence of short cycle (<30 s) periodic breathing (Ni and Thomas, 2023).

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Patient safety and monitoring

In our extensive clinical experience with over 1,000 active patients and over 10,000 patient years of use, the use of EERS has been demonstrated to be safe and well tolerated in general OSA populations, in addition to patients with significant comorbidities including heart failure with reduced ejection fraction (unpublished). Initiation of (or conversion to) a non-vented mask and addition of 50 cc EERS may be considered as empiric treatment (i.e., without in-lab CPAP titration with $ETCO_2$ monitoring) in patients without risk factors for hypoventilation (normal serum bicarbonate, normal pulmonary functions, body mass index $\leq$40 Kg/M^2, $\leq$20 min with oxygen saturation under 90%, absence of disorders known to cause hypoventilation, absence of opiate or baclofen use). This approach to empiric therapy was necessitated by the COVID-19 pandemic, and used successfully.

Biocalibration of CO_2

After the conventional setup for the polysomnogram recording, we routinely perform a "CO_2 biocalibration." With a NV mask, mainstream ET CO_2 sensor and no positive airway pressure, resting wake end-tidal CO_2 is measured, followed by the change in CO_2 with the addition of 50, 100 and 150 cc dead space. The sensor is placed at the mask outlet, and is able to capture the exhaled stream and provide a clear $ETCO_2$ "plateau" in most instances. This measurement is quite sensitive to leak around the edges of the mask, and thus a very good fit is necessary for accurate tracking during sleep. While we originally had a set of recommendations for starting EERS volumes based on these values, we have shifted to using this maneuver as a safety check for unexpected hypercapnia. If the $ETCO_2$ is $\geq$45 mm Hg, supervising on-call physician permission is required to use a non-vented mask. During titration, we tolerate a 5 mm Hg rise in $ETCO_2$ but this threshold is virtually never reached except in opiate-induced CSA, as positive airway pressure provides a natural continuous washout. In over 5,000 sleep laboratory titrations with end-tidal CO_2 monitoring, there has never been a single instance of induction of unexpected sleep hypercapnia in a patient with normal resting wake CO_2. In patients undergoing in-lab non-vented CPAP titrations with EERS, continuous real-time $ETCO_2$ monitoring is ideally utilized. With the non-vented configuration, end-tidal CO_2 levels are generally readily attainable, including a clean plateau signal. However, reliable $ETCO_2$ measurements can occasionally be limited by issues with mask fit and leak. Transcutaneous CO_2 monitoring is a non-invasive method for obtaining accurate skin-surface oxygen and CO_2 levels in the laboratory setting but is not critical if reliable $ETCO_2$ levels can be obtained. The minimum general recommendation is to measure resting wake CO_2 by any means including blood gas analysis prior to a non-vented titration.

How to titrate EERS and positive airway pressure—practice points

In-lab titration of EERS and positive airway pressure relies upon careful understanding of the individual patient's underlying physiology, and often requires balancing control of obstruction through increased positive airway pressure against potential worsening of respiratory instability as mean airway pressures increase. As patients can differ drastically regarding the level of obstruction and underlying loop gain, as well as important parameters such as baseline sleep consolidation and arousal threshold, titration is therefore unique to each patient and should be performed in a physiologic rather than algorithmic fashion. That being said, there are a few key principles which should serve to guide successful titration of EERS.

Typically, titration is started with a non-vented mask setup with CPAP pressures at the lowest reasonable pressure to address obstruction (e.g., 6–8 cmH20). The decision to start the titration with additional EERS (50–150 cc's) is individualized and is dependent on (1) perceived level of underlying loop gain abnormality, (2) starting CO_2 levels obtained prior to titration, and (3) the patient's tendency for prolonged sleep latency and poor sleep consolidation. This last point is important as adding additional EERS, as opposed to simply increased CPAP pressures, involves physically entering the room and making alterations to the patient's mask which will generate an arousal from sleep. No automated method to adjust EERS remotely currently exists. Regarding starting pressures, prior standard CPAP titrations can be useful to guide initial settings, with the understanding that standard titrations which do not address underlying loop gain often over-titrate in an attempt to stabilize breathing through increased pressures rather than CO_2 modulation.

As the titration progresses, pressures can be increased for clear flow-limitation and obstructive events, which typically predominate in REM sleep. Periodic (particularly short-cycle) obstructive events, especially in NREM sleep, should raise suspicion for high loop gain as a primary driver of the respiratory instability and aggressive up-titration of pressures should be avoided in favor of the addition of EERS if possible. It is often useful to intermittently and frequently review respiratory patterns in a 5–10 min window; this can help to visualize more subtle waxing and waning respiratory patterns seen as a result of high loop gain which can appear purely obstructive or even missed when viewing in a less compressed window (Figures 3–5).

Important aspects of the titration include stage/stability of sleep and body position. Both obstructive and high-loop gain physiology respiratory events are typically much more difficult to control in supine sleep. Therefore, an effort should be made to achieve respiratory stability in the supine position in both REM (typically predominantly obstructive requiring higher pressures) and NREM (typically predominantly loop-gain related and responsive to increased EERS). This balance is delicate and it is possible that respiratory control is unachievable in the supine position. If so, the titration can progress to avoidance of supine sleep utilizing the same principles, with non-supine sleep utilized as a primary therapeutic intervention.

Proof of efficacy and safety

Dead space has some documented efficacy in hypocapnic CSA, though a prospective randomized trial of EERS is yet

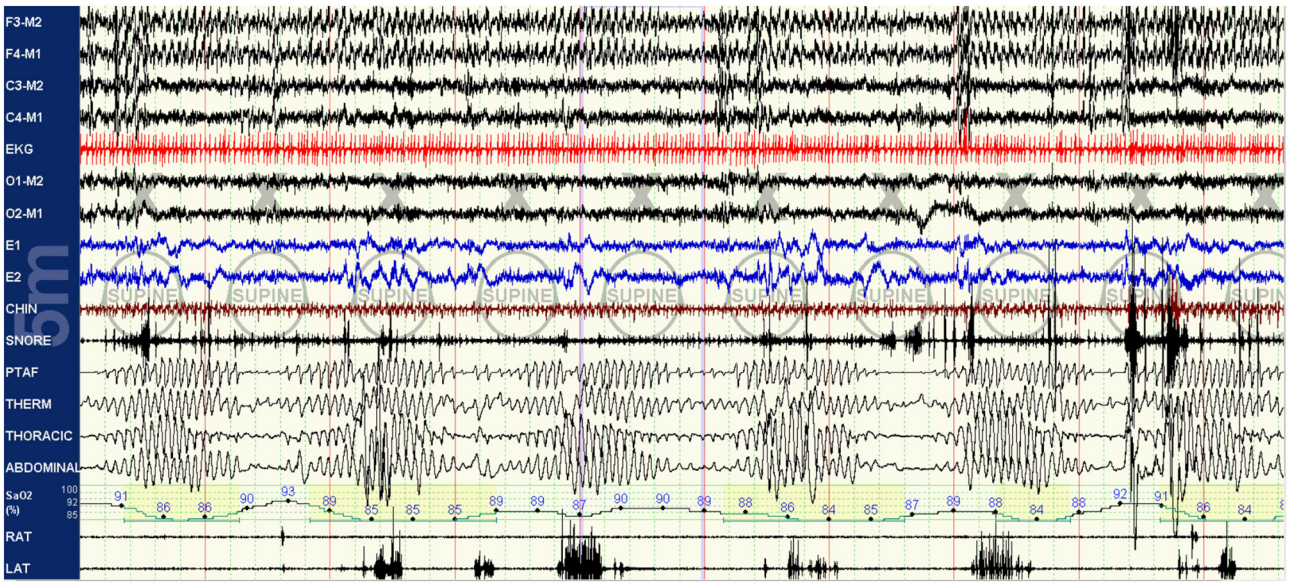

FIGURE 3
Baseline polysomnography: this baseline PSG of a patient with known sleep apnea demonstrates obstruction with clear high loop gain features including medium-cycle, self-similar waxing and waning respiratory events resulting in apneas and oxygen desaturations. Respiratory effort is present but minimal during apneic periods. The hypoxia nadir associated with an event actually occurs after the crescendo arm of respirations of the following cycle has concluded, indicative of a mixing delay.

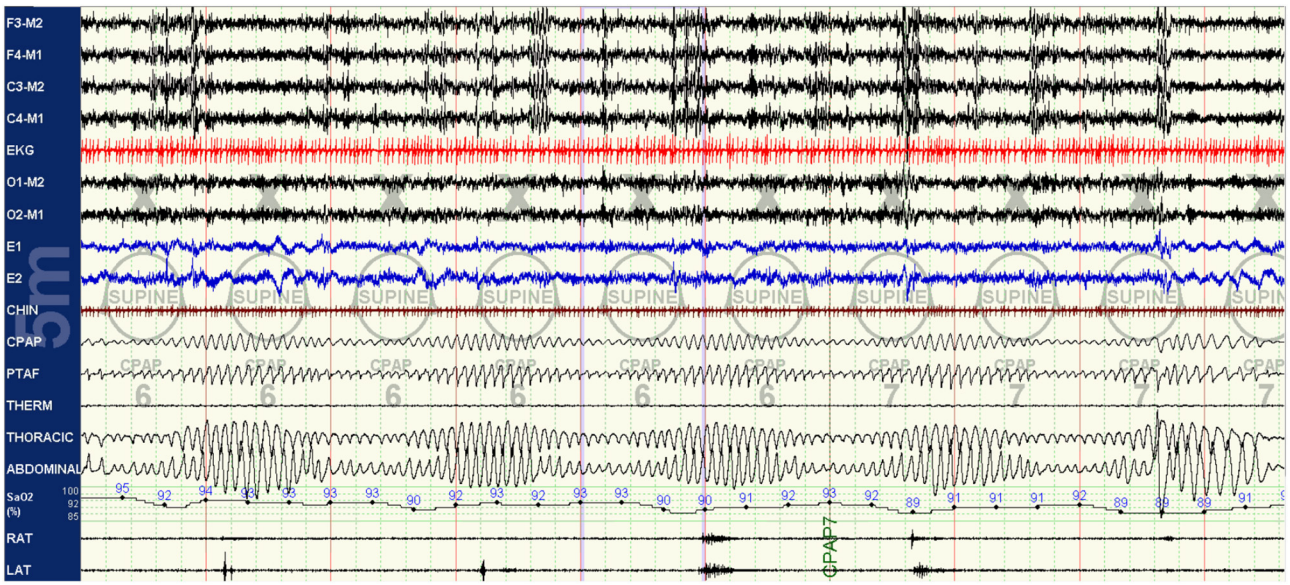

FIGURE 4
Standard CPAP titration: the patient was placed on standard, vented CPAP titration with no demonstrable improvement in breathing pattern with the use of positive airway pressure alone despite some improvement in obstructive physiology. The ongoing crescendo-decrescendo respiratory pattern and self-similar cycle suggest that the residual events are central rather than obstructive in nature despite the ongoing reduced respiratory effort. Despite guidance to score central hypopneas, the AASM scoring rules remains difficult for most sleep labs given the lack of use of esophageal balloon probes. Thus, identification of central hypopneas remains highly dependent on pattern recognition by the interpreting provider.

to be done. By using sub-tidal volume dead space with continuous wash-out with positive airway pressure, EERS enables an additive or even synergistic effect on respiratory control stability in sleep apnea care. EERS may be used with adaptive ventilation, a common practice in our center for patients that are difficult to control with either intervention alone. This combination typically reduces the range of pressure oscillations from the adaptive ventilator, improves tolerance, and reduces patient-ventilator desynchrony. Logically, EERS and standard bilevel ventilation would seem incompatible, but a rare patient

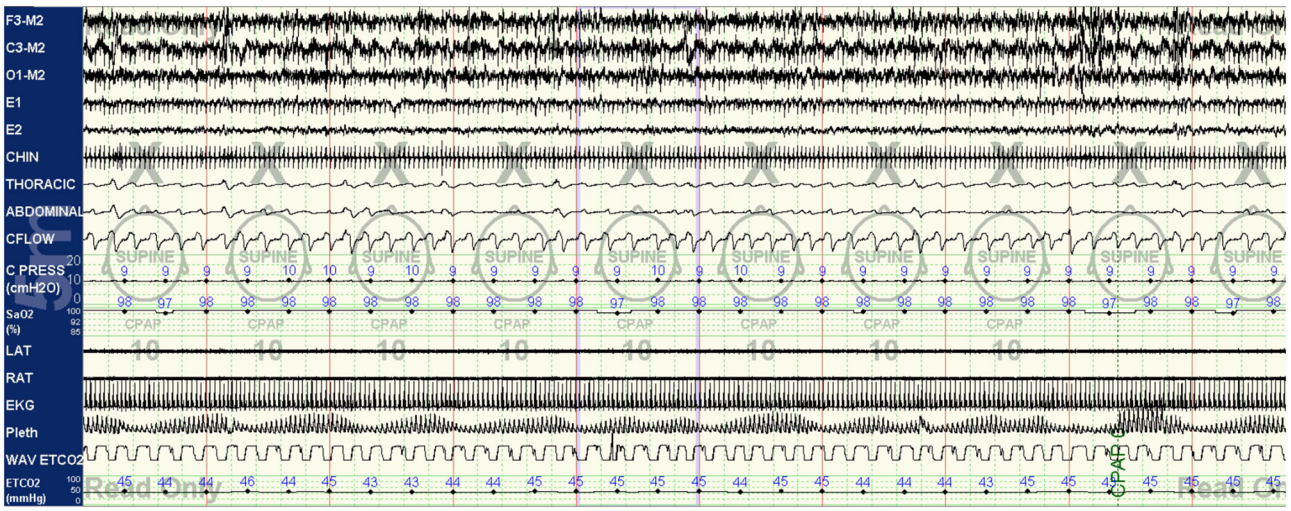

FIGURE 5
CPAP with EERS: the patient's CPAP titration is altered to include a non-vented mask and addition of EERS. With this change, breathing is immediately stabilized, with resolution of the crescendo-decrescendo respiratory effort of periodic breathing and normalization of oxygenation. The addition of EERS can allow successful application of higher CPAP pressures when needed to treat residual obstruction without augmenting instability. Of note, despite improvement in respiratory stability a cyclic pattern can still be observed in the plethysmogram signal, suggesting that the autonomic effects of the respiratory instability of high loop gain features are still not completely controlled. In some patients, cyclical arousals may persist despite stabilization of breathing. The serves as a testament to the complex multi-system integration of sleep physiology, with some components capable of demonstrating dissociated behavior.

may prefer the comfort of bilevel ventilation to CPAP. In a large-scale retrospective review of >200 patients with CPAP-refractory sleep apnea undergoing non-vented CPAP titration, control of disease was typically achieved when EERS volume was added to increase $ETCO_2$ during sleep by just 1–2 mmHg above wake eupneic levels (mean $ETCO_2$ 38.6 ± 2.9 mmHg at optimal therapy). Features of EERS titration vs. traditional CPAP titration from this retrospective review are summarized in Table 3 (Gilmartin et al., 2010). This study highlights the goal of EERS therapy in preventing nocturnal hypocapnia, rather than inducing hypercapnia, with EERS titrated for control of respiratory events rather than achievement of certain CO_2 levels. Modest overall increases in $ETCO_2$ with the addition of EERS additionally highlights the plausible mechanism of improved breathing control, which is likely secondary to reduction in plant gain and the amplitude of CO_2 oscillations during sleep, rather than large increases in arterial CO_2 levels.

Dead space has also been shown to efficacious in the treatment of CSA in patients with heart failure, with the addition of 400–600 cc of dead space alone resulting in improved sleep quality and respiratory stabilization, without detrimental effect on stroke volume or cardiac index as measured by transthoracic echocardiography, heart rate, or blood pressure (Khayat et al., 2003). Other data suggests that CO_2 modulation via dead space is effective in significantly reducing AHI in a majority of OSA patients with a wide range of chemoreflex gains, with improved control over other interventions such as hyperoxia and transient isocapnia (Xie et al., 2013). In clinical practice, the main limitations are excessive leak (site or total volume), mask fit (tightness) and amplification of borderline claustrophobia. While these are not unique to the use of EERS, the latter is less leak tolerant.

Patient barriers to use

The use of non-vented masking with EERS is highly reliant on an adequate mask seal, as significant leakage (even 20–30 lpm which is considered acceptable in standard CPAP application) may "wash out" rebreathing space and results in loss of breathing stability (Gilmartin et al., 2010), depending on the site of leak. Therefore, achieving adequate mask seal is paramount in successful therapy. Patients who demonstrate excessive leak should undergo mask fitting, with consideration of adjuncts such a chin strap or lip tape to prevent washout through the mouth.

A potential barrier to adequate mask seal is the EERS tubing itself; given the additional materials required to be added to the circuit, patients may need to alter their typical sleep position or utilize clips or other positional aids to ensure mask seal remains adequate for the duration of the night. Patients who are particularly sensitive to temperature and humidity fluctuations, including those with claustrophobia, may have more difficulty adjusting to the rebreathing space and comfort controls should be adjusted accordingly.

Finally, the dead space traps some moisture. Some patients may find that there is too much condensation in the rebreathing space. Adjusting humidification or even omitting humidification entirely are strategies to consider. The ambient humidity and temperature will also matter, as condensation ("rain out") is more common in winter months.

Pharmacologic adjuncts

In patients with significant respiratory instability, medications aimed at stabilizing breathing may be useful in conjunction with EERS. The most commonly utilized medication in this setting is

TABLE 3 Retrospective analysis of 204 patients with CPAP refractory sleep apnea treated with EERS between 1/1/04 and 7/1/06.

Measure	Diagnostic PSG	Standard Titration	EERS Titration	*p*-value
Sleep efficiency (%)	71.3 ± 18.2	66.9 ± 21.5	75.4 ± 14.9	<0.001
TST	222.4 ± 126.6	219.8 ± 105.2	308.5 ± 87.5	<0.001
Stage 1 (% TST)	21.6 ± 18	24 ± 19	20.3 ± 12.7	0.09
Stage 2 (% TST)	60.9 ± 16.8	56.7 ± 16.6	58.8 ± 13.1	0.05
Stage 3 (% TST)	5.8 ± 7.4	4.6 ± 6.5	5.5 ± 6.1	0.05
Stage 4 (% TST)	2.2 ± 6.3	1.2 ± 4.2	1.7 ± 4.2	0.10
REM sleep (% TST)	9.8 ± 9	13 ± 10.1	14 ± 9.5	<0.001
AHI 4% (/h of sleep)	36 ± 36.8	25.4 ± 59	4.1 ± 5.8	<0.001
RDI (/h of sleep)	69.8 ± 32.8	59.4 ± 33.9	30.7 ± 19.7	<0.001
CAI (/h of sleep)	3.8 ± 8.2	8.9 ± 11.1	1.5 ± 2.8	<0.001
Min O_2	88.7 ± 8.1	88.5 ± 4.8	92.7 ± 4.5	<0.001
PLM index	6.1 ± 15.7	2 ± 4.8	15.2 ± 19.2	<0.001

EERS titration finding	Value
$EtCO_2$ mean wake	38.1 ± 3.1 mm Hg
$EtCO_2$ minimum when respiratory control achieved (minimum 50ml EERS)	38.6 ± 2.8 mm Hg
$EtCO_2$ maximum for the study	42.1 ± 3 mm Hg
Throbbing headache on arousal	0
Headache attributable to mask straps	11 (5.4%)
Palpitations	0
Dyspnea	0

All patients' had in lab attended polysomnography for diagnosis, conventional CPAP titration, and further titration of EERS. Polysomnographic characteristics are displayed as well as CO_2 levels and reported complications (Gilmartin et al., 2010).
AHI, apnea hypopnea index; CAI, central apnea index; EERS, enhanced expiratory rebreathing spacel; Et CO_2, end tidal carbon dioxide; PLM, periodic limb movement; PSG, polysomnogram; RDI, respiratory disturbance index; TST, total sleep time.

acetazolamide, a carbonic anhydrase inhibitor initially used for the treatment of altitude sickness. The drugs shifts the CO_2 response curve to the left and lowers the NREM sleep apneic threshold. Acetazolamide has been demonstrated to reduce respiratory loop gain by approximately 40% in patients with OSA via reduction in plant gain, and reducing the ventilatory response to arousal (Edwards et al., 2012, 2013). In one study of 236 patients with high loop gain sleep apnea, the addition of 125–250 mg of acetazolamide to standard CPAP therapy resulted in a reduction in breathing related arousal index, AHI3%/AHI4%, and RDI when compared to CPAP alone (Ni et al., 2023), and is generally safe and well-tolerated. Other pharmacologic adjuncts for the treatment of high loop gain sleep apnea include zonisamide (Eskandari et al., 2014), topiramate (Westwood et al., 2012), sulthiame (Hedner et al., 2022) (all carbonic anhydrase inhibitors) as well as buspirone (Maresh et al., 2020; Giannoni et al., 2021), which could be considered for patients in whom acetazolamide is poorly tolerated or contraindicated. Oxygen can always be considered an additional adjunct, as it directly reduces chemoreflex gain (Franklin et al., 1997; Sasayama et al., 2009; Yayan and Rasche, 2016).

Considerations for home monitoring

In home settings, patients should be monitored for appropriate use of the EERS circuit. The increased complexity and need for after-market modification, combined with reduced familiarity of the technique with durable medical equipment (DME) providers means that there needs to be close collaboration with local DME companies. Practically this can increase risk for errors in application of the circuit for the patient. Compliance data is key to track with particular attention paid to markers of respiratory instability including residual central apneas and periodic breathing. However, positive airway pressure devices likely underestimate these patterns and manual review of the breath-by-breath waveform data can be particularly useful in EERS patients (Ni and Thomas, 2023). Given leak's ability to washout the effect of EERS this should be tracked and aggressively addressed on compliance data. Persistent optimal respiratory and symptom control despite substantial leak should raise the question of whether the EERS modification is still necessary and could trigger a trial return to a typical "vented" mask set up. A subset of patients with high loop gain, specifically those with substantial hypoxia, will have complete resolution of respiratory instability with successful therapy.

Conclusions

Sleep apnea has multiple endotypes and a substantial minority of patients have high loop gain and/or low arousal threshold which predisposes to respiratory instability and central apneas. This is often triggered by relative hypocapnia. Central and complex sleep

apnea remain difficult to control with existing positive airway pressure modalities. EERS represents an affordable, and relatively simple modification of existing positive airway therapy to modulate CO_2 and minimize the hypocapnia that can trigger central apneas. Retrospective data over more than 15 years of clinical use Suggest high rates of success in patients previously intolerant of CPAP and an excellent safety profile. This technique should be avoided in patients with baseline hypercapnia. As the technique typically only generates at most a 1–2 mmHg increase in CO_2 it is unlikely to evoke clinically significant hypercarbia or sympathoexcitation. In order to expand the use of EERS, multi-center, randomized control trials of EERS are desired. Further studies are also warranted to examine the combination of EERS with pharmacotherapy aimed at treatment of high loop gain.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

RT discloses: (1) patent and license/royalties from MyCardio, LLC, for the ECG-spectrogram; (2) patent and license/royalties from DeVilbiss-Drive for an auto-CPAP algorithm; (3) Unlicensed patent for a device which regulates inspired CO_2 when used with positive airway pressure, for treatment of central/complex apnea; and (4) consulting for Jazz Pharmaceuticals, Guidepoint Global and GLG Councils.

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.

Publisher's note

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New insights and potential clinical implications of the odds ratio product

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The odds ratio product (ORP) is a continuous metric of sleep depth that ranges from 0 (very deep sleep) to 2. 5 (full wakefulness). Its advantage over the conventional method recommended by AASM is that it discloses different levels of stage wake (sleep propensity) and different sleep depths within the same sleep stage. As such, it can be used to identify differences in sleep depth between subjects, and in the same subjects under different circumstances, when differences are not discernible by conventional staging. It also identifies different sleep depths within stage rapid-eye-movement sleep, with possible implications to disorders during this stage. Epoch-by-epoch ORP can be displayed graphically across the night or as average values in conventional sleep stages. In addition, ORP can be reported as % of recording time in specific ORP ranges (e.g., deciles of the total ORP range) where it produces distinct distribution patterns (ORP-architecture) that have been associated with different clinical disorders and outcomes. These patterns offer unique research opportunities to identify different mechanisms and potential therapy for various sleep complaints and disorders. In this review I will discuss how ORP is measured, its validation, differences from delta power, and the various phenotypes, and their postulated mechanisms, identified by ORP architecture and the opportunities for research to advance management of sleep-disordered breathing, insomnia and idiopathic hypersomnia.

KEYWORDS

sleep depth, delta power, in obstructive sleep apnea, insomnia, hypersomnia, validation, sleep architecture, precision medicine

Introduction

In contrast to evaluating sleep state in discrete stages (wake, NREM1-NREM3), assigned every 30 s, the odds ratio product (ORP) measures wake/sleep state on a continuous scale from 0 (very deep sleep) to 2.5 (full wakefulness) and makes this assessment every 3 s (1). The continuous nature of the ORP scale makes it possible to distinguish different wake states in the transition from full wakefulness to light sleep (Figure 1A), and different levels of sleep depth within the same conventional sleep stage (Figure 1B). In addition, measurement over 3-s intervals makes it possible to measure brief dynamic changes in sleep depth that cannot be obtained from the conventional staging approach.

Since its original description in 2015 (1). ORP was used in numerous studies to determine normative values and reproducibility (2), relation to conventional staging (1, 3, 4), differences in ORP between central and frontal electroencephalogram (EEG) derivations (4), differences from delta power as measures of sleep depth (5), changes in obstructive sleep apnea (OSA) and Insomnia (6–8), sleep changes with continuous positive airway pressure (CPAP) (6, 9), changes in response to sleep restriction and deprivation (5, 10), maturational changes in sleep and association with pediatric psychiatric disorders (11, 12), association with CPAP adherence (13), association with sleepiness and quality of life (2, 7, 13, 14),

underlying mechanism of poor sleep and its consequences in critically ill patients (15–17), response to traffic noise (18), association with traffic accidents (19), and dynamics of sleep recovery after arousal (8, 20).

Along with these studies, the reporting of ORP has evolved from simple description of its values in specific sleep stages or sleep disorders or as temporal changes across the night, to various patterns of ORP distribution within total recording time (7). This last development has changed ORP from being a simple descriptive tool of sleep depth to a way of understanding mechanisms of sleep complaints and disorders.

The above observations and developments have provided new insights into sleep physiology and pathology. However, virtually all published information was derived from retrospective studies. While the accumulated information is sufficient to formulate hypotheses about diagnoses and likely effective therapy of various sleep complaints, it is necessary to perform prospective studies to validate these hypotheses before ORP can be used clinically in patient management. In this review I will present the observations that form the bases for several proposed investigations, and what is needed to validate the retrospective observations. But first, some basic information about how ORP is measured, validation of ORP as a measure of sleep depth, and how ORP is reported, will be presented.

How is ORP measured?

ORP can be measured from any central or frontal electrode (1, 4). This feature makes it possible to measure ORP from reduced monitoring devices attached to the forehead. Although only one derivation is needed, it is always better to monitor two similar electrodes, one on each side. This allows detection of differences in ORP between the two sides. Such differences make it possible to identify and discard artifacts and to detect true differences in sleep depth between the two sides, with potential clinical implications (2, 15, 19). In addition, one electrode can serve as a spare if the other fails.

The method of calculating ORP was described in detail elsewhere (1). Briefly, fast Fourier transform is applied to all EEG values within non-overlapping 3-s epochs. Total power in each of 4 frequency ranges, within the 0.33–35.0 Hz frequency range, is calculated. Power in each frequency range is assigned a rank from 0 to 9 based on its location within the range of powers (in the relevant frequency) observed in 56 clinical polysomnograms (PSGs) representing a wide range of clinical disorders. The four ranks are concatenated into one 4-digit number (Bin number) that describes the powers in the different frequencies from left to right *relative to each other*. Thus, 4,179 refers to a 3-s epoch in which power in the slowest range is in the 5th decile of the range of powers observed in this frequency, while power in the next higher frequency is in the second decile, and power in the two highest frequencies are in their 8th and 10th (highest) deciles of their respective ranges [see Younes (3), for examples of EEG patterns with different bin numbers]. This approach is distinct from other spectral methods that rely on absolute power in selected frequencies, since absolute power is influenced by technical and biological factors unrelated to sleep depth [see, Normalized EEG power (2)]. The probability of patterns associated with each bin number occurring in epochs scored wake, or during arousals, is determined from a look-up table. This probability (0–100%) is divided by 40 (% wake epochs in development files) thereby converting the range to an ORP range of 0 to 2.5, where 0 refers to a pattern that never occurs during wake epochs or during arousals, while 2.5 refers to patterns that are never seen during sleep (1).

An important detail to note is that the slowest of the four frequency ranges used to calculate ORP (0.33–2.33 Hz) is different from the conventional delta range, which is wider (0.5–4.0, or 0.5–5.0 Hz) (21). For ORP, power in the fast delta range (2.6–4.0 Hz) is combined with power in the theta range (4.3–6.7 Hz) to provide the power in the second range used to calculate ORP. This has important implications to the EEG frequency that is most sensitive to sleep depth, as will be discussed in the section on ORP vs. Delta Power, below.

Validation

ORP correlates well with the visual appearance of the EEG (1, 7) (Figure 1), and decreases (deeper sleep) following sleep deprivation (10), and sleep restriction (5), while increasing as sleep progresses during the night (22). ORP increases transiently following application of brief noise stimuli whether or not they result in cortical arousal (18). However, the most compelling evidence is the finding that the correlation between ORP in a given 30-s epoch and probability of spontaneous arousal or awakening occurring in the next epoch is quite high (Figures 2A, B; $r^2 = 0.98$) (1, 5).

ORP vs. Delta power

Power in the delta frequency range (up to 4 or 5 Hz) is commonly used to evaluate sleep depth. However, other than its increase following sleep deprivation (23, 24), and decrease across the night (24), and during nocturnal sleep after daytime naps (25), there has been little information on the quantitative relation between delta power and sleep depth as defined by ease of arousing from sleep.

In a recent study (5), the relationships between delta power (0.33–5.67 Hz) or ORP and arousability, were compared in healthy young adults monitored overnight for 8 consecutive nights of which the first two served as baseline. Baseline results are shown in Figure 2B. The relationship between ORP in any given 30-s epoch and probability of arousal or awakening in the next 30-s epoch was, as described earlier (1), linear ($r^2 = 0.99$; Figure 2B). The relationship for delta power was strikingly different; arousability decreased as delta power increased but only over a very limited delta power range (0.0–300 μV^2), with no further decrease in arousability as delta power increased to 1,000 μV^2 or more (Figure 2B). The inflection point, at 300 μV^2, is generally the delta power at which the large delta waves (>75 μV^2, 0.5–2.0 Hz) begin to appear and stage N3 is scored (5). Further increases in average delta power (in 30-s epochs) simply reflect increasing number and/or amplitude of delta waves. These observations have important *clinical implications*:

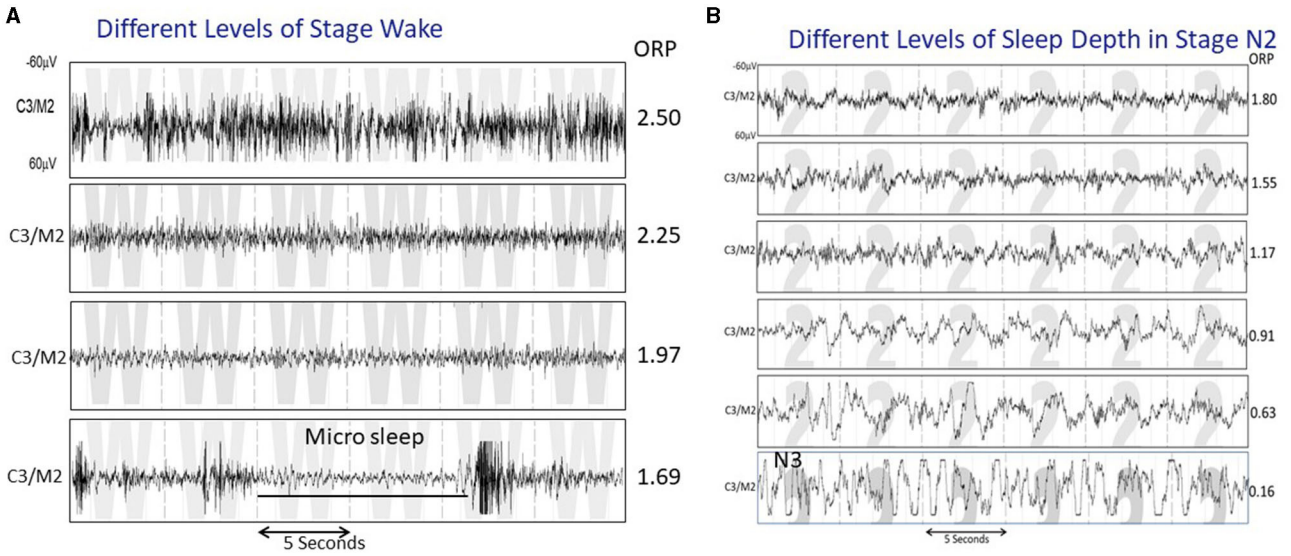

FIGURE 1
(A) Four 30-s strips of EEG tracings all staged as wake, illustrating various states between full wakefulness (top tracing) and near sleep. The ORP values reflect these differences. **(B)** Five 30-s strips staged as N2 but showing a variety of patterns that range from one that reflects very light sleep (top panel) to one that is very similar to stage N3 except that the total duration of delta waves is <20% of the epoch (From reference: Younes M, Azarbarzin A, Reid M, Mazzotti DR, Redline S. Characteristics and reproducibility of novel sleep EEG biomarkers and their variation with sleep apnea and insomnia in a large community-based cohort. *Sleep*. (2021) 44:145.).

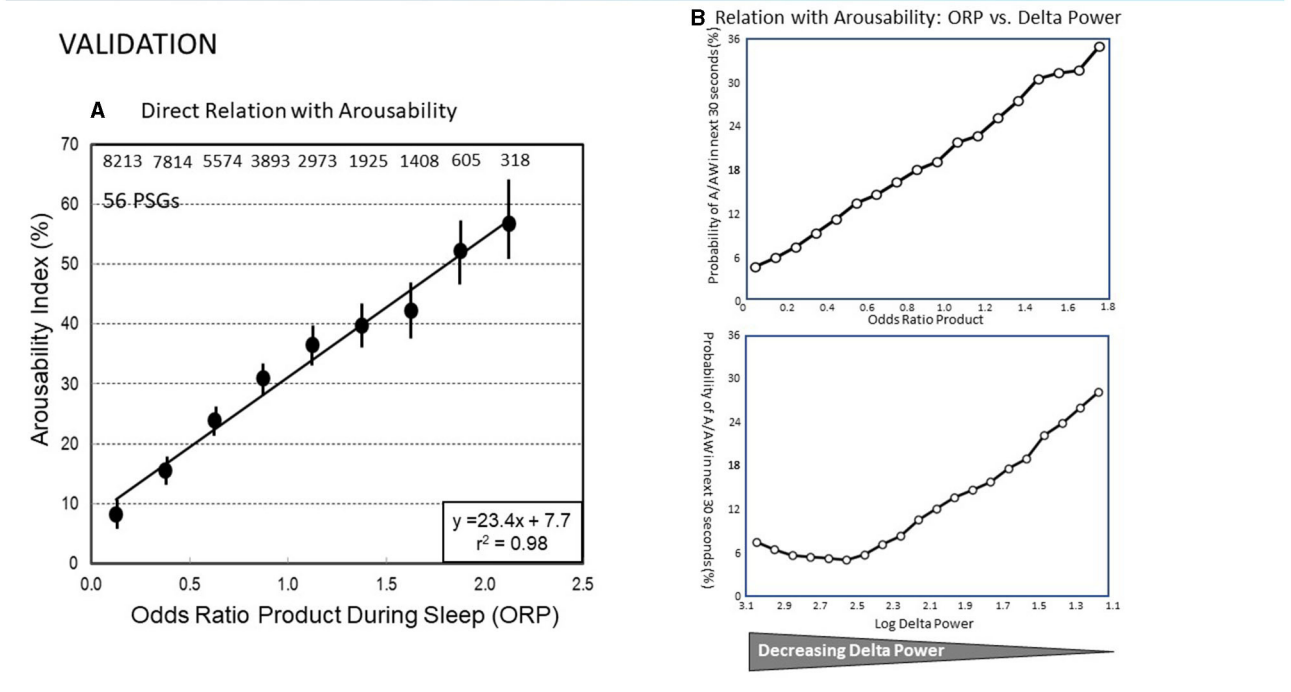

FIGURE 2
(A) Relation between average odds ratio product (ORP) in 30-s epochs during sleep and the probability of arousal or awakening in the next 30-s epoch (Arousability Index) in 56 polysomnograms (PSG) of patients with assorted sleep disorders. Numbers at top are number of 30-s epochs used at each ORP level (From reference: Younes M, Ostrowski M, Soiferman M, Younes H, Younes M, Raneri J, et al. Odds ratio product of sleep EEG as a continuous measure of sleep state. *Sleep.* (2015) 38:641–54.). Permission to be obtained if paper is accepted **(B)**, Top Panel: Relation between average ORP in 30-s epochs during sleep and the probability of arousal or awakening in the next 30-s epoch in 40 normal subjects. Bottom Panel: Relation between log delta power and arousal probability in the same sleep studies. Note that arousability decreases over a small range of delta power (From reference: Younes M, Schweitzer PK, Griffin KS, Balshaw R, Walsh JK. Comparing two measures of sleep depth/intensity. *Sleep*. (2020) 43:127.).

- Differences in delta power when delta waves are present do not reflect differences in sleep depth; rather they reflect density (number per minute) and amplitude of delta waves. Growing evidence points to a critical role of these delta wave characteristics in memory, cognition, sleep maintenance and mental health (26). Given that these characteristics can be easily measured in clinical sleep studies, reporting them, or simply reporting average delta power in stage N3, may provide important insights into mechanisms of various manifestations of clinical sleep disorders.
- Almost the entire change in sleep depth occurs before N3 is scored (Dotted vertical lines, Figure 4). Thus, absence of stage N3 need not signify absence of deep sleep.

ORP and conventional sleep stages

Figure 3A illustrates how 30-s epochs with different ORP levels are typically scored by expert scorers (Panel A), and Figure 3B the range of ORP in different visually scored sleep stages. When ORP is <0.25 two scorers agree that the patient is asleep almost all the time (white sections). When ORP is >2.25, they agree the patient is awake almost all the time (black zones). Percent of epochs scored wake by both scorers remains very low (<5%) until ORP of 1.00, but disagreement (gray zones) increases slightly as ORP approaches 1.00. Between ORP 1.00 and 1.75, disagreement between scorers occurs in a substantial fraction of epochs and for these three deciles collectively, the chances of disagreement, agreement on stage wake or sleep are almost random. Epochs in this range contain features of both stages to a sufficient extent that elicits disagreement between expert scorers. Accordingly, they are considered transitional. Between 1.75 and 2.25 epochs are most commonly scored wake by both scorers but in some epochs, sleep features (slowing, micro sleep) are sufficiently prominent to result in the epoch scored sleep by one or both scorers. Thus, ORP in this range reflects the extent to which visually appreciated sleep features exist in the epoch. Figure 3B shows results of ORP recorded in different stages in in the Sleep Heart Health Study ($n = 5{,}804$). There is a wide range of ORP in all stages but on averages ORP decreases progressively as stage progresses from wake to stage N3. The range of ORP in rapid eye movement sleep (REM) is very wide and on average higher than in stages N2 and N3. However, much overlap exists between stages.

How is ORP reported and how its results might be interpreted?

While the methods of reporting are extensively described here, the interpretations suggested in this section are mostly based on retrospective studies or logical extension of basic sleep findings in the literature. Interpretations provided here are intended to stimulate discussion and to suggest ideas for prospective research and not as a guide to management.

ORP can be reported in several ways with each offering different insights into the patient's sleep. Figure 4 illustrates four of these approaches. The figure shows results of 3 subjects, one with no sleep symptoms (Panel 4A) and two with symptoms of insufficient/non-restorative sleep (Panels 4B and 4C). The conventional hypnogram and conventional architecture data (above each panel) in all three cases were within normal limits:

A) Graphical approach (30-s epoch-by-epoch ORP graph, Figure 4): This display provides a bird's-eye view of the changes in wake propensity and sleep depth across the night, offering detail that cannot be appreciated from numerical summaries. It also serves a learning objective in that it confirms some of the advantages of ORP. For example, in the illustrated Figure 4, one can see that ORP varies widely within stage wake and stage N2 (any panel), and that REM ORP may be higher (Figures 4A, B) or similar to ORP in NREM sleep in different patients (Wide arrows). It is also clear that ORP during stage N2 can be as low as in stage N3 (1, 5), such that absence of stage N3 does not mean lack of deep sleep. It can also be appreciated that the rate at which sleep deepens following an awakening is different among patients (compare rates of decline at light arrows in panels 4B and 4C). A curious observer may also make new connections between certain patterns and clinical presentations that may result in new research hypotheses.

B) ORP in Different Sleep Stages (Figure 4, values at the bottom of each panel): These values compliment conventional stages by showing differences between patients, or in the same patient before and after interventions, that cannot be disclosed by conventional stages. Figure 4, and the following discussion, illustrate how the use of ORP can identify sleep abnormalities when a patient is symptomatic, but the sleep study is normal by conventional metrics. Thus, notwithstanding the similar conventional architecture among the 3 subjects of Figure 4, ORP_{WAKE} was low (less alert) in subjects B and C than in subject A and ORP_{NREM} and ORP_{REM} were highest (lighter sleep) in subject B and very low (deep sleep) in subject C (Figure 4). The obvious next question is: what are normal values in the different sleep stages?

Table 1 shows average and range of ORP in different stages according to demographic and disease categories (2). ORP in any stage ranges widely among individuals within any category, even in subjects with no OSA or insomnia, and there is almost complete overlap in the ranges among different subcategories, so that there is no clear demarcation between values in health and disease. This is likely because sleep depth (ORP during sleep) and propensity (ORP during stage wake) are to a large extent influenced by sleep pressure (5, 7, 10). In turn, sleep pressure may be high or low in different subjects because of sleep pathology (e.g., excessive sleep need in idiopathic hypersomnia and hyperarousal in insomnia, respectively) or because of different demographics (2, 7), and sleep history (5, 7, 10) in people who are otherwise normal (Table 1). Accordingly, actual values in individual patients are not very helpful in determining, *per se*, whether they represent pathology or physiology.

What is important in interpreting ORP in sleep stages is to note where the value falls within its respective range in the community at large. A high ORP_{NREM} within its range (e.g., patient B, Figure 4; 1.29 in a range of 0.50–1.36, Table 1) indicates that NREM sleep is very light. Absence of clinical sleep symptoms (insomnia, excessive sleepiness, non-restorative sleep…etc.) would suggest a physiologic reason and may be ignored. On the other hand, presence of sleep symptoms (e.g., patient B, Figure 4) would point to: (a) A disorder that interferes with progression to deep sleep (e.g., OSA, periodic limb movement (PLM) disorder, other somatic or environmental arousal stimuli); (b) A low sleep pressure state associated with

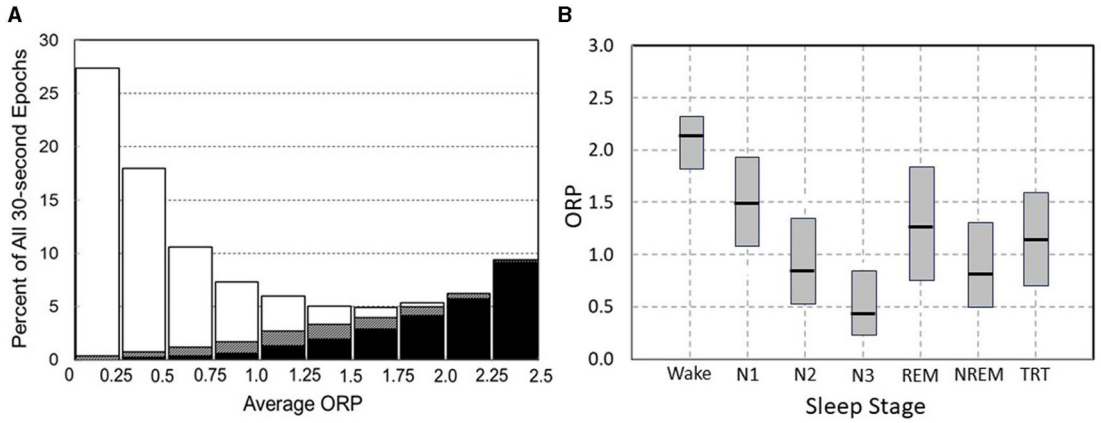

FIGURE 3
(A) Frequency distribution of 30-s epochs with different average odds ratio product (ORP). Within each bar white and black segments are epochs staged asleep and awake, respectively, by two expert technologists while hatched segments are epochs receiving a split awake/asleep decision (From reference: Younes M, Ostrowski M, Soiferman M, Younes H, Younes M, Raneri J, et al. Odds ratio product of sleep EEG as a continuous measure of sleep state. *Sleep.* (2015) 38:641–54.). **(B)** Range (median and 5 and 95 percentiles) ORP in different visually determined stages in 5,781 subjects of the Sleep Heart Health Study (SHHS) incorporation subjects with obstructive sleep apnea (OSA) (n = 2,504), insomnia (n = 419), insomnia + OSA (n = 403), and neither insomnia nor OSA (n = 2,455).

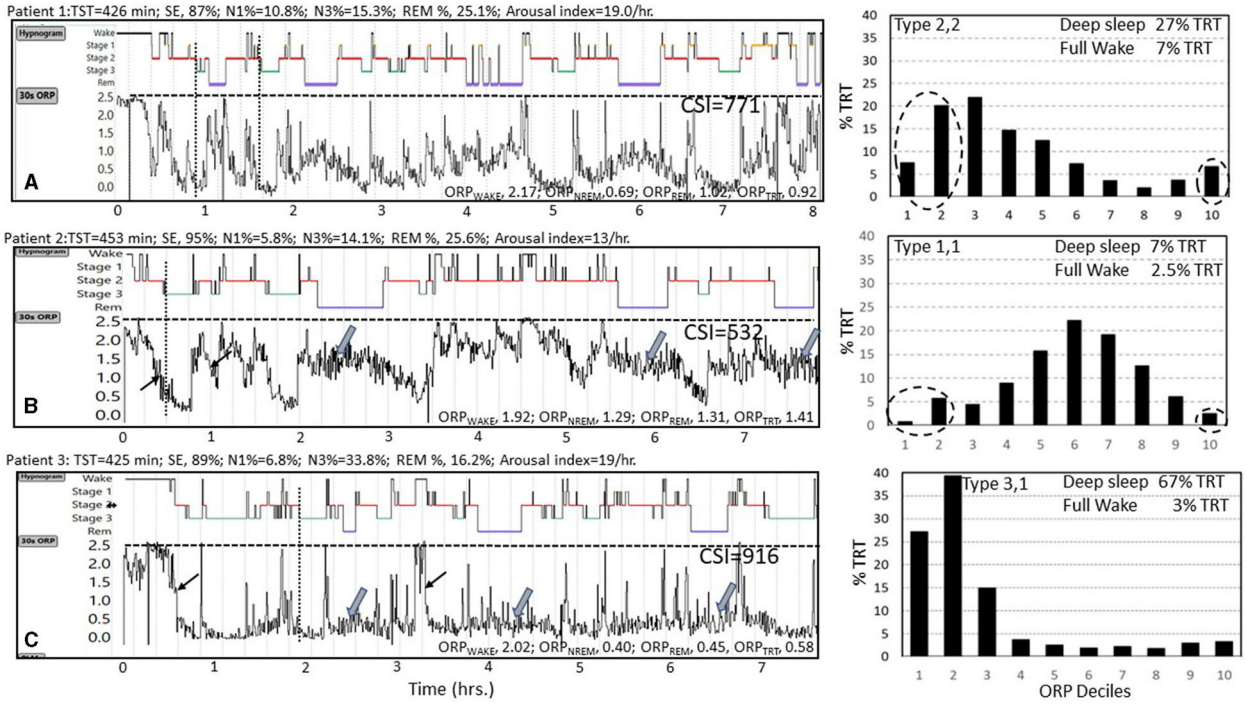

FIGURE 4
Data from three subjects **(A–C)** with normal conventional hypnograms illustrating substantial differences in their ORP metrics. Values above each panel are derived from the conventional sleep metrics showing that all values were within normal limits. TST, total sleep time; SE, sleep efficiency; N1%, N3%, and REM% are percent of TST in stages N1 and N3 of non-rapid eye movement sleep (NREM) and in rapid eye movement sleep (REM), respectively. Epoch by epoch odds ratio product (ORP) values are displayed as graphs below the hypnograms of the 3 subjects and as averages in different sleep stages and show substantial differences between the 3 subjects. ORP_{WAKE}, ORP_{NREM}, ORP_{REM}, and ORP_{TRT} are the average values of ORP in all epochs staged as Wake, NREM sleep, REM sleep, and total recording time, respectively. Note that the rate at which ORP decreases from full wakefulness to deep sleep differs between subjects [thin arrows in subjects **(B, C)**], and that ORP during REM sleep varies among subjects [thick arrows in subjects **(B, C)**]. CSI, integral of the difference between 2.5 (full wakefulness) and instantaneous ORP (Graph values) across total recording time, representing total units of wake suppression during the study. Note the marked difference between the three subjects. Histograms to the right show %TRT spent within each ORP decile with sleep depth decreasing from decile 1 (very deep) to decile 7 (transitional sleep) to full wakefulness (decile 10). Note the marked difference in the ORP histograms of the three subjects with subject A having a normal distribution, subject B having most epochs in transitional and light sleep while in subject C the distribution is markedly shifted to the left. See text for interpretation of these differences (Un-published data).

TABLE 1 Odds ratio product in different stages per demographics and disease categories.

Category	Number	ORP_{WAKE}	ORP_{NREM}	ORP_{REM}	ORP_{TRT}
All	5,781	2.12 (1.85–2.35)	0.83 (0.49–1.22)	1.28 (0.74–1.89)	1.14 (0.73–1.60)
Age (yrs.)					
40–55	1,533	2.07 (1.74–2.30)[a]	0.79 (0.48–1.16)[a]	1.18 (0.72–1.75)[a]	1.04 (0.67–1.46)[a]
55–70	2,399	2.13 (1.83–2.34)[b]	0.83 (0.52–1.24)[b]	1.30 (0.78–1.86)[b]	1.13 (0.74–1.58)[b]
70–90	1,849	2.15 (1.84–2.36)[c]	0.87 (0.52–1.31)[c]	1.35 (0.79–1.92)[c]	1.22 (0.79–1.68)[c]
Gender					
F	3,027	2.14 (1.85–2.35)[a]	0.82 (0.50–1.25)[a]	1.28 (0.74–1.88)[a]	1.12 (0.71–1.60)[a]
M	2,754	2.09 (1.77–2.32)[b]	0.85 (0.53–1.25)[b]	1.29 (0.78–1.83)[a]	1.15 (0.75–1.59)[b]
Race					
White	4,889	2.13 (1.83–2.34)[a]	0.84 (0.51–1.25)[a]	1.28 (0.76–1.86)[a]	1.14 (0.73–1.60)[a]
Black	512	2.10 (1.77–2.33)[b]	0.88 (0.57–1.29)[b]	1.38 (0.88–1.93)[b]	1.20 (0.80–1.65)[b]
Other	380	2.05 (1.74–2.29)[c]	0.77 (0.49–1.13)[c]	1.18 (0.72–1.79)[c]	1.04 (0.67–1.47)[c]
Disease category					
No OSA or Insomnia	2,454	2.13 (1.83–2.35)[a]	0.81 (0.49–1.22)[a]	1.27 (0.74–1.89)	1.10 (0.70–1.56)[a]
Insomnia	419	2.16 (1.86–2.36)[b]	0.85 (0.49–1.29)[bc]	1.31 (0.78–1.92)	1.18 (0.73–1.65)[bd]
Comisa	403	2.13 (1.78–2.34)[ac]	0.88 (0.53–1.36)[b]	1.30 (0.77–1.83)	1.21 (0.78–1.66)[b]
Mild OSA	1,557	2.11 (1.80–2.33)[c]	0.83 (0.52–1.22)[acd]	1.28 (0.77–1.83)	1.13 (0.75–1.57)[c]
Mod. OSA	482	2.10 (1.80–2.33)[c]	0.85 (0.53–1.26)[bd]	1.28 (0.79–1.85)	1.15 (0.73–1.64)[cd]
Sev. OSA	465	2.07 (1.70–2.30)[d]	0.93 (0.58–1.35)[e]	1.3 (0.84–1.86)	1.21 (0.80–1.63)[b]

*, values are means (5–95 percentile).
[a,b,c] values within the same category that do not share the same superscript are significantly different from each other ($p < 0.001$).
ORP, odds ratio product; REM, rapid eye movement sleep; NREM, non-REM; TRT, total recording time. Values in this table were derived from Tables 2, 3 of reference Younes et al. (2).

insomnia (hyperarousal) or related to lifestyle or use of stimulant drugs or drinks. These possibilities can be distinguished by other findings in the sleep study (e.g., OSA, PLMs, excessive wake time) or in the history (insomnia, lack of excessive somnolence, excessive napping, drugs, or stimulant drinks). Noting ORP in other sleep stages can be helpful in difficult cases. For example, high ORP_{NREM} associated with high ORP_{WAKE} suggests a low sleep pressure state, while an associated low ORP_{WAKE} points to a sleep disorder that interferes with progression to deep sleep (Patient B, Figure 4) (2, 8, 14).

By contrast, a low ORP_{NREM} (Patient C, Figure 4) could be normal, particularly in asymptomatic young adults (7). However, if associated with excessive somnolence or non-restorative sleep, it suggests a state of high sleep pressure due to insufficient sleep prior to the sleep study or excessive sleep need (certain types of idiopathic hypersomnia) (27). These can be distinguished from the sleep history.

Table 1 shows that on average ORP in all stages increases with age. ORP_{WAKE} is higher and ORP_{NREM} is lower in females, while the opposite is true in the black race. These differences are, however, small relative to the wide range in any category.

ORP_{WAKE} reflects the weighted average of ORP in all epochs scored wake. Thus, it is low when most wake epochs are in a drowsy wake state, indicating reduced vigilance (Figure 1A), and vice versa. Reflecting this, ORP_{WAKE} is higher in insomnia than in subjects with no insomnia while it decreases progressively with OSA severity (Table 1). By contrast, ORP_{NREM} is higher than controls (no OSA or insomnia) in the presence of both OSA and insomnia.

ORP_{REM} documents the variable background EEG in this stage, which visually ranges from a pattern indistinguishable from stage wake to one not that different from deep stage N2, without the spindles. Reflecting this range, ORP_{REM} is higher than ORP_{NREM} (0.74–1.89, Table 1) but the difference between ORP_{NREM} and ORP_{REM} varies widely from being minimal (Figure 4C) to being large (Figures 4A, B). The significance of these differences is not clear although the association of high ORP_{REM} with reduced REM time and increased REM fragmentation (28) may be relevant to abnormal dream states and mood disorders. Interestingly, ORP_{REM} is a strong trait (2) and, unlike other ORP measures, is not different between genders or disease phenotypes (Table 1).

In addition to the above uses of ORP in different stages, ORP_{NREM} was recently found to be a significant determinant of sleep improvement on CPAP (6) and adherence to CPAP (13), both outcomes are better when ORP_{NREM} is high before therapy.

Opportunities for research

- The most significant advantage of ORP over conventional staging is its ability to identify differences in sleep depth within the same conventional sleep stage (Figure 1). An

important clinical question is therefore whether clinical outcomes are improved when ORP in different stages is available to treating physicians investigating suspected sleep disorders. Specific questions may include: (A) Does ORP help identify abnormalities in patients with sleep complaints when conventional architecture is normal or inconclusive (e.g., using the approach described for interpreting differences in Figure 4)? (B) Does ORP help explain symptomatic improvement or deterioration following a given intervention (e.g., CPAP, or therapy for insomnia or depression …etc.) when conventional architecture did not change? For example, did ORP_{NREM} improve or deteriorate despite unchanged times in different sleep stages, or did ORP_{WAKE} increase or decrease, indicating change in sleep pressure, on therapy.

- Examining potential associations of ORP_{REM} with psychiatric disorders.
- Confirming the ability of ORP at baseline to predict sleep improvement on, (6) and adherence to, (13) CPAP.

C) Cumulative Sleep Index (CSI) (7): Given that ORP in full wakefulness is close to 2.5, the difference between 2.5 and ORP at any moment is a measure of "wake suppression" at that moment (Figure 4). CSI is the integral of these differences across total recording time (TRT) in minutes. Thus, a patient who remains fully awake throughout would have a CSI of 0 while a patient who was in very deep sleep throughout would have a CSI of 2.5*TRT. For a common TRT of 480 min, the maximum CSI is 1,200 min.ORPunits.

The advantage of CSI over total sleep time (TST) or sleep efficiency (SE) is that it takes into account different sleep depths during sleep and also includes reductions in ORP during stage wake (drowsy wake, Figure 1A). Thus, a minute with ORP of 1.8 during stage wake contributes 0.7 units to CSI when it does not contribute to TST or SE. Its advantage over ORP in total recording time (ORP_{TRT}) is that it incorporates differences in TRT. In practice CSI is calculated from [(2.5-ORP_{TRT}) * TRT] (7). When CSI is measured from sleep studies with unrestricted time in bed, it provides the total "units of sleep" needed by the subject to sleep enough (i.e., individual sleep need), particularly if the value is reproducible over several consecutive nights.

Normal values have not yet been properly established. However, the Sleep Heart Health Study (SHHS) provides preliminary data on this variable in that subjects were not instructed to wake up at any specific time. In SHHS subjects with no OSA or insomnia and with TRT >7 h (to avoid studies ending because of technical problems) TRT, TST, and SE ranged up to 541 min (≈9 h), 519 min (8.7 h), and 98.4%, respectively. In this cohort CSI averaged 651 ± 129 and was reported to decline with age (due primarily to declining ORP_{TRT}) and to be only marginally higher in women, and not affected by BMI (7). The most interesting finding here was that at any age the range of CSI varied widely with a SD of 121 units, representing a 90% confidence interval of 484 units (Figure 5A). After excluding 444 subjects with TST>7 h, who likely had excessive sleep pressure during the single study, the relation with age was essentially unchanged with the exception that the standard deviation (SD) decreased from 121 to 108 (Figure 5B). This wide variation of "sleep need" is particularly noteworthy as it is not consistent with the fairly narrow range of currently recommended sleep time (7–8 h).

CSI was recently used to investigate mechanisms of idiopathic hypersomnia (IH) (27). Figure 6 shows results from 3 patients from this study who underwent sleep studies with unrestricted duration in Dr. Robert Thomas' laboratory at Harvard University and represent the extreme range of the results. All three patients slept >10 h (Figure 6), had no OSA (apnea hypopnea index (AHI) 2.4, 0.9, and 0.5 h^{-1}), and only one patient had brief periods of PLMs (Figure 6A) (PLM index 26, 3, and 3 h^{-1}), thereby consistent with IH.

Arousal index was normal in all three (12, 22, and 21 h^{-1}) and although total sleep time (TST: 319, 395, and 474 min, in patients 1–3) and sleep efficiency (SE:70, 84, and 95%) were different among the three patients in the first 8 h, the differences were not informative regarding the reason for excessive sleepiness. The ORP tracings (Figure 6) clearly show that sleep was very light in patient 1, deeper in patient 2, and even deeper in patient 3 (ORP_{TRT}: 2.13, 1.12, and 0.48, respectively), thereby indicating that insufficient sleep in a typical time in bed (8 h) may be contributing to sleepiness in patient 1 but not likely in patients 2 or 3, unless sleep need is high (i.e., idiopathic hypersomnia).

CSI provides additional information to what can be gleaned from ORP values in that it is a quantitative index of how much sleep the patient obtained in the usual 8-h study vs. what he/she gets with unrestricted sleep. Thus, Patient 1 managed only 169 units of sleep at 8 h, well below the 90% CI observed in community dwellers (Figure 5). At the end of the unrestricted study CSI was 345, well below average sleep need (e.g., Figure 5). Given these findings, it may be reasonable to conclude that, rather than having excessive sleep need, this patient has decreased sleep need (e.g., hyperarousal) as evidenced by the low CSI after ad lib sleep, while this very modest sleep need cannot be delivered in 8 h due to the very poor sleep quality. Thus, pending validation studies, investigation and treatment of poor sleep to lower ORP might be the appropriate management strategy in this patient.

Patient 2 (Figure 6) had an average amount of sleep in the first 8 h (CSI 651) but he clearly needed more (1,022 at the end of the study). At his average ORP rate (ORP_{TRT} = 1.12), he needed an extra 4 h. However, his ORP during the first 8 h had still some room to improve (decrease). If ORP could be decreased to the same level as patient 3 (ORP_{TRT} = 0.48) patient 2 can potentially achieve his needs [1,022] within a normal time in bed (Patient 3 achieved 970 at 8 h).

At the extreme other end, patient 3 (Figure 6) had nearly the maximum CSI he could achieve in 8 h (970). There is no room to improve his sleep in order to decrease his required time in bed and treatment needs to focus on managing excessive sleepiness.

Following the same logic, it may be reasoned that excessive wake time in an 8-h study in a patient whose CSI during the study is average or high, may be due to the patient achieving his normal sleep need in a shorter than the recommended time in bed and spends the rest of bedtime awake. On the other hand, a low CSI under the same circumstances in a non-sleepy patient suggests low sleep pressure throughout, which may be a hyperarousal state (see ORP type 1,3, below).

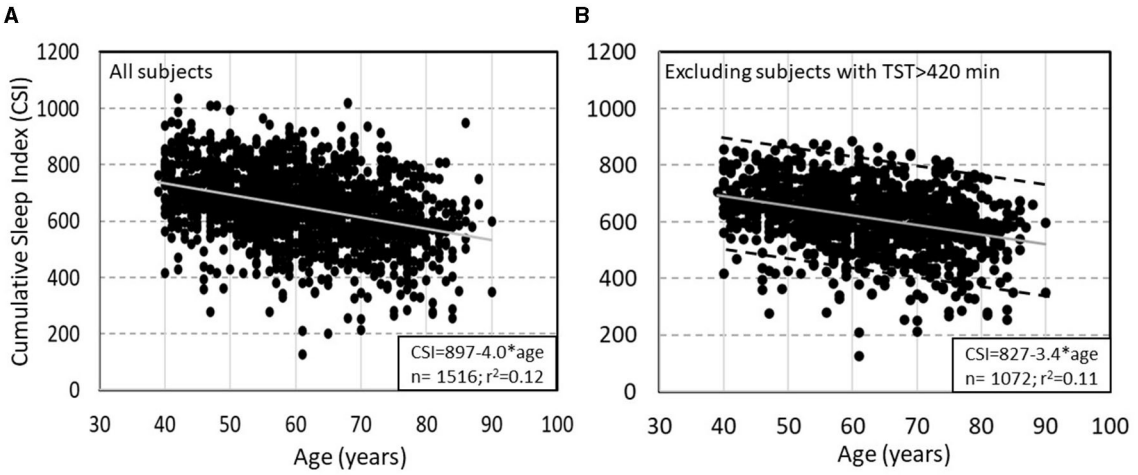

FIGURE 5
(A) Relation between Cumulative Sleep Index (CSI) and age in subjects of the Sleep Heart Health Study (SHHS) with total recoding time >7 h and no obstructive sleep apnea or insomnia. **(B)** Same relation after excluding subjects with >7 h of total sleep time. Dashed lines in panel B are ±2 SD from the main regression line (un-published data).

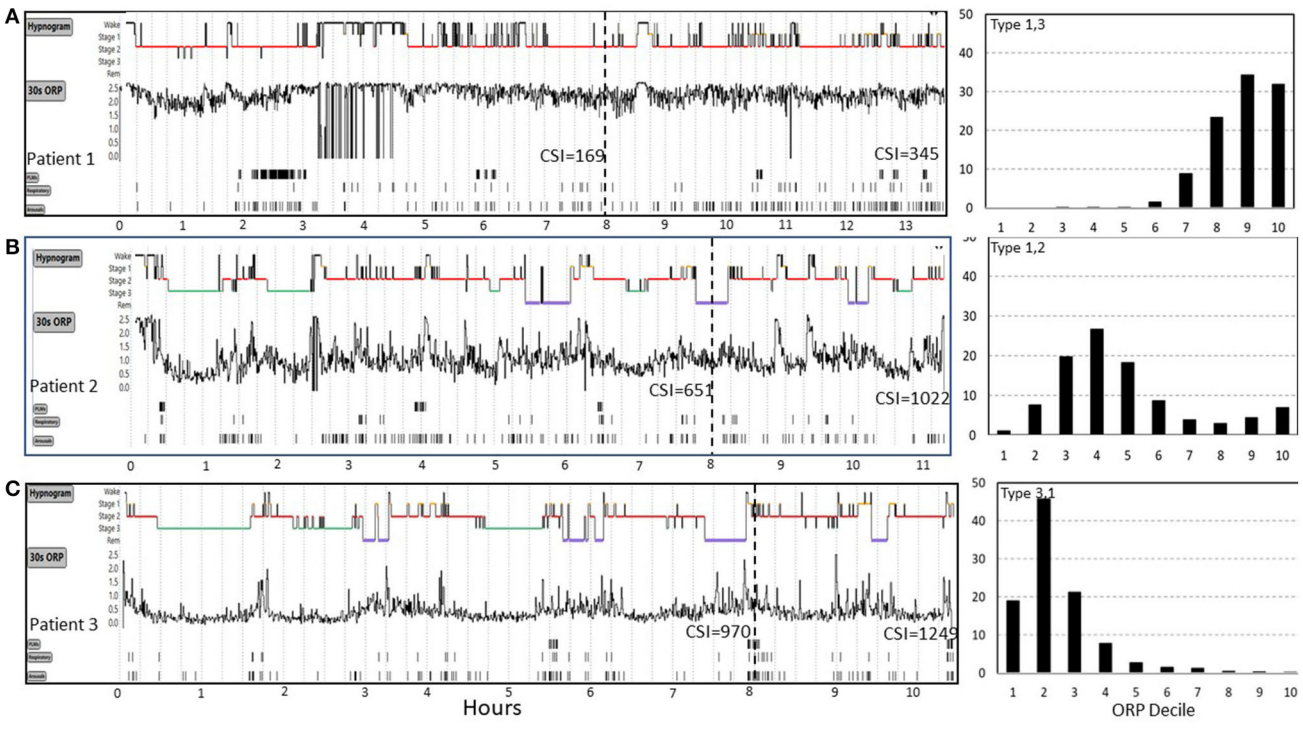

FIGURE 6
Range of odds ratio product (ORP) results in three patients (patients 1, 2, 3) with idiopathic hypersomnia represented in **(A–C)**. Cumulative sleep index values (CSI) values are shown at 8 hours and at the end of the study. Patient 1 had very high ORP (light/transitional sleep) throughout the 13 h study. His CSI was only 169 at 8 h and was still 345 after 13 h, both values are well below average sleep need (cf. Figure 5). CSI in patient 2 was normal at 8 h but increased well above mean ±2 SD (Figure 5B) after 11 h of sleep, indicating high sleep need. In patient 3 CSI was already well above average (970) at 8 h but increased further to 1,249 at 10.5 h, indicating extremely high sleep need. ORP histograms are shown to the right and illustrate marked differences despite the same clinical diagnosis. PLM, periodic limb movements. See text for potential implications of these different patterns on management (From an unpublished study by Dr. Robert Thomas, with permission from Dr. Thomas).

Opportunities for research

- The above interpretations and management suggestions assume that an increase of one unit of CSI has the same restorative function regardless of whether it is generated by more sleep time or more sleep depth. This is an assumption that needs to be proven. The easy availability of the quantitative CSI makes it possible to address this fundamental

question as well as other aspects of the restorative function of sleep.

- CSI provides an opportunity for determining personalized sleep need. Thus, measuring CSI in a subject who feels refreshed during a period of ad lib sleep on a sustained basis (e.g., vacation) would determine his/her total amount of sleep need. This would then represent the subject's sleep target needed under other conditions where he/she has non-restorative sleep, with the target reached through extension of regular time in bed or improvement in sleep depth via appropriate therapy, as the case may be.

D) ORP-related Sleep Architecture (The ORP Histogram): This is the most informative way of presenting ORP results (see Histograms in Figure 4). Rather than reporting % of time in different conventional sleep stages, percent of time in different ORP deciles is displayed as a histogram (7). The striking contrast between the three histograms in Figure 4, despite normal conventional architecture, illustrates the sensitivity of this approach. Such plots provide easy to recognize patterns that can be categorized, with the categories studied to determine their association with clinical outcomes. The patterns also allow caregivers to formulate hypotheses regarding the likely underlying mechanisms of the patient's complaints, which can be pursued by history or appropriate tests.

Based on susceptibility to arousal (Figures 2A, B) (1, 5) deciles 1 and 2 reflect the fraction of time spent in deep and very deep sleep (ORP <0.5), while decile 10 (ORP >2.5) reflects time in full wakefulness (Figure 1). In between these two extremes the different deciles represent (from left to right), decreasing levels of sleep depth (deciles 3 and 4; ORP 0.50–1.00, Figures 1, 2) and transitional sleep with features of both sleep and wakefulness (deciles 5–7, ORP 1.00–1.75). Epochs in deciles 8 and 9 (ORP 1.75–2.25) are usually scored wake but they contain some sleep features (e.g., theta waves or periods of micro-sleep that are <15 s; Figure 1A) and reflect drowsy wake states (7).

Categorization of these patterns is based on the relation between times spent in deep sleep and in full wakefulness in response to pure changes in sleep pressure (7). In response to a pure increase in sleep pressure, as in after sleep deprivation, the histogram shifts to the left, with deep sleep increasing and full wakefulness decreasing, while in response to decreased sleep pressure, as in later in the sleep period, the opposite happens (Figure 7) (7). This paradoxical relation between deep sleep and full wakefulness is put to use as follows:

The full ranges of % deep sleep (deciles 1 + 2) and % full wakefulness (decile 10) were determined in 3,585 subjects of the Sleep Heart Heath Study (SHHS) who had >7 h of total recording time (7). The mid-range (25^{th}-75^{th} percentile) for each variable (deep sleep and full wakefulness) was determined. Values in the lowest quartile of each range were assigned a rank of 1, values in the mid-range were assigned a rank of 2, and values in the highest quartile were assigned a rank of 3. A two-digit number was assigned to each PSG based on these two digits. Thus, type 1,3 describes a PSG with % deep sleep in the lowest quartile and % full wakefulness in the highest quartile, and so on. Nine types were, accordingly, categorized (1,1, 1,2, …3,3). Based on response to pure changes in sleep pressure (Figure 7), types with paradoxical relation between deep sleep and full wakefulness (e.g., 1,3 or 3,1) are consistent with low (type 1,3) or high (type 3,1) sleep pressure, respectively. When the two variables are both in the high or low quartile (e.g., 1,1 or 3,3), the type is not consistent with pure changes in sleep pressure.

In summary, assigning a two-digit number to ORP distribution makes it possible to easily appreciate the underlying pathophysiology. Thus, low first digit and high third digit (i.e., 1,3) signify a disorder associated with low sleep pressure across the night, and vice versa for type 3.1. When both digits are low (i.e., 1,1) the decreased amount of deep sleep is not due to low sleep pressure since there was little time in full wakefulness, and suggests a sleep disrupting disorder. And when both digits are high (i.e., 3,3) the excessive amount of full wakefulness is not due to low sleep pressure across the night (e.g., hyperarousal) since there was plenty of deep sleep. The other advantage is that these 9 patterns do not overlap (i.e., are mutually exclusive) which, unlike differences in times of conventional stages, limits the possible underlying mechanisms of sleep complaints.

The following section describes the clinical associations and likely mechanisms of the different ORP types (7), beginning with the most clinically relevant types. Table 2 gives an overview of the distribution of the different types in different clinical phenotypes in the SHHS, and Figure 8 shows the frequency of different types in different age groups in the same study (7).

Type 1,1 (Figure 4B, right): The low amount of deep sleep suggests either low sleep pressure or a disorder that interrupts progression to deep sleep. However, the low amount of full wakefulness does not support the existence of low sleep pressure (7). Accordingly, the most likely mechanism of this pattern is a disorder that interferes with progression to deep sleep and, likely as a consequence, may be associated with high sleep pressure (e.g., excessive sleepiness) (7). The following findings support this conclusion:

- This pattern is rare (2%) in community dwellers free of OSA or insomnia (7).
- Its frequency increases exponentially as OSA severity increases (3.1%, 3.5%, 5%, and 15.1%, respectively, with mild (AHI 5–15 h^{-1}), moderate (AHI 15–30 h^{-1}), severe (30–50 h^{-1}), and very severe (AHI >50 h^{-1}) OSA) (Table 2) (7).
- Its frequency is also very high in critically ill, intubated unsedated patients in the intensive care unit (33%) (17), where OSA is not a factor but other factors that preclude progression to deep sleep are in abundance (30).
- It is one of only three (of nine) ORP types in which CPAP improves sleep among patients with OSA (6).
- Among patients with OSA it is the ORP pattern associated with highest average ESS (11.3±5.4), highest frequency of ESS>10 (67.9%), and highest frequency of ESS >17 (15.5%) (6).
- Among all ORP types it is associated with the lowest mental [SF36(M)] and second lowest physical [SF36(P)] quality of life scores (7).

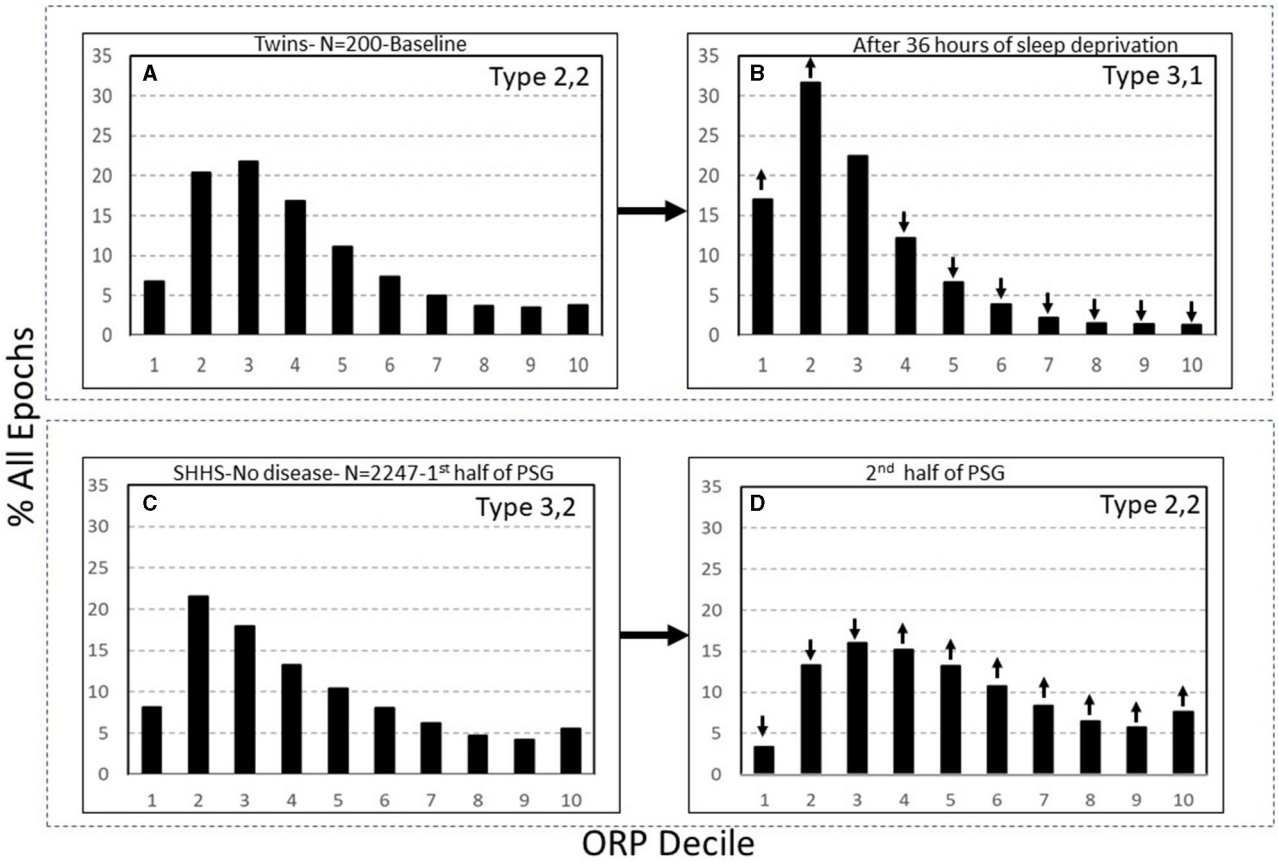

FIGURE 7
(A, B) Odds ratio product (ORP) architecture in 200 healthy participants in before and following 36 h of sleep deprivation. Note the remarkable leftward shift in the ORP distribution. **(C, D)** Comparison of ORP-architecture in the first and second halves of the night in Sleep Heart Health Study (SHHS) subjects with "No OSA or Insomnia." An opposite shift is evident. ↓ and ↑, significant increase or decrease relative the same decile in the reference panel ($p < 1E{-}10$ in all). PSG, polysomnogram (From reference: Younes M, Gerardy B, Pack AI, Kuna ST, Castro-Diehl C, Redline S, et al. Sleep architecture based on sleep depth and propensity: patterns in different demographics and sleep disorders and association with health outcomes. *Sleep*. (2022) 45:59.).

These observations support the notion that this pattern results from a disorder that interferes with progression to deep sleep that is frequently associated with excessive sleepiness, with OSA being the most recognized, but not the only, example of such a disorder. Thus, finding pattern 1,1 in a patient with sleep symptoms and no obvious sleep pathology that can account for it in the PSG (e.g., subject in Figure 4B) suggests the presence of other sources of frequent arousal stimuli (skin, musculoskeletal, gastrointestinal, …etc.).

Type 1,2: This type is similar to type 1,1 except that full wakefulness accounts for up to 12% of TRT instead of being <3.4% in type 1,1 (7). As in pattern 1,1, its frequency increases with OSA severity (Table 2) (6, 7), and it is one of the three types where sleep improves on CPAP (6). It is also associated with higher ESS and lower quality of life (7). Accordingly, it is considered to have the same underlying mechanism as type 1,1. It is, however, more common in the community, occurring in 9.7% of subjects with no OSA or insomnia, as opposed to 2% for type 1,1 (Table 2) (7). Thus, it is more likely to be encountered in patients with no OSA. It is still not clear, however, if it is associated with excessive sleepiness and poor quality of life if not associated with OSA.

Opportunities for research

- The long term impact of OSA on health outcomes is currently uncertain (60). It is likely that negative health outcomes occur in only a minority of patients such that they are obscured when diluted with a large number of patients who are not so affected. As a corollary, treatment of OSA may benefit only a subset of patients and this benefit is obscured when outcomes of therapy studies are performed on unselected patients. Currently, efforts are directed at identifying patients whose long term health outcomes are adversely affected and, by extension, who might benefit from CPAP or other OSA therapy. Conventional sleep study metrics, including AHI, are not very helpful in this regard (60). Recently, other markers such as hypoxic burden and presence of excessive somnolence have been associated with increased risk of cardiovascular events but the results have been inconsistent in different cohorts (29, 31–35). The discovery that only two ORP types, 1,1 and 1,2, are associated with poor sleep quality and associated excessive sleepiness, provides an opportunity to determine whether these two types selectively benefit from OSA therapy.

TABLE 2 Distribution of different ORP architecture types in clinical categories.

ORP type	Sleep heart health study								All
	"No disease"	Obstructive sleep apnea				Insomnia			
		Mild	Mod.[a]	Sev.[b]	V. sev.[d]	NSD[c]	SSD[e]	+OSA[c]	
1,1	30 (2.0)	30 (3.1)	13 (3.5)	7[a] (5.0)	11[d] (15.1)	6 (3.3)	0 (0)	10 (4)	107
1,2	147 (9.7)	118 (12.1)	53 (14.2)	29[b] (20.9)	18[b] (24.7)	26 (14.4)	5 (6.3)	29 (11.6)	425
1,3	131 (8.6)	88 (9.0)	40 (10.7)	15 (10.8)	16[b] (21.9)	9 (5.0)	23[d] (28.8)	43[b] (17.3)	365
2,1	168 (11.1)	106 (10.9)	37 (9.9)	16 (11.5)	3 (4.1)	21 (11.7)	3 (3.8)	23 (9.2)	377
2,2	406 (26.8)	266 (27.3)	102 (27.3)	40 (28.8)	13 (17.8)	64 (35.6)	9 (11.3)	57 (22.9)	957
2,3	177 (11.7)	128 (13.2)	54 (14.4)	16 (11.5)	4 (5.5)	10 (5.6)	31[d] (38.8)	38 (15.3)	458
3,1	201 (13.2)	104 (10.7)	39 (10.4)	11 (7.9)	5 (6.8)	20 (11.1)	1 (1.3)	21 (8.4)	402
3,2	219 (14.4)	114 (11.7)	36 (9.6)	5 (3.6)	1 (1.4)	23 (12.8)	3 (3.8)	20 (8.0)	421
3,3	35 (2.3)	19 (2.0)	3 (0.8)	0 (0)	2 (2.7)	1 (0.6)	5 (6.3)	8 (3.2)	73
Total	1,517	973	374	139	73	180	80	249	3,585

OSA, obstructive sleep apnea; NSD, normal sleep duration; SSD, short sleep duration; Mod., Sev., V.Sev., are moderate, severe, and very severe OSA, respectively. values are number of subjects with the type indicated; numbers in brackets indicate the percent of subjects in each clinical category with the type indicated. Differences between values in each category and the "No-disease" category were evaluated by the Chi-square test and their significance is indicated by superscripts in the column heading.
[a]$p < 0.02$; [b]$p < 0.0001$; [c]$p <$ 1.E-5; [d]$p <$ 1.E-10; [e]$p <$ 1.E-25. From Table 3 in reference Younes et al. (7).

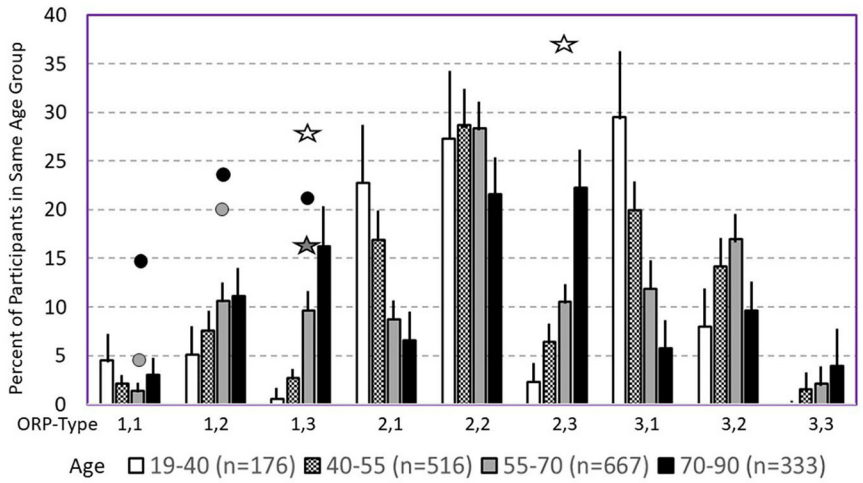

FIGURE 8
Prevalence of different odds ratio product (ORP) types in different age groups in the Sleep Heart Health Study. Lines are upper margin of error (95% confidence interval). Solid circles, values found in participants with severe (gray circle), and very severe OSA (black circles) in the different ORP types. White stars, values found in participants with insomnia and short sleep duration. Dark stars, values found in participants with insomnia plus OSA. All symbols are plotted against the 55–70 age group (gray columns) since average age in all clinical groups fell in this range. Where no symbols are shown above a given ORP type, the prevalence of the type is within the confidence interval of participants with no OSA or insomnia (From reference: Younes M, Gerardy B, Pack AI, Kuna ST, Castro-Diehl C, Redline S, et al. Sleep architecture based on sleep depth and propensity: patterns in different demographics and sleep disorders and association with health outcomes. *Sleep*. (2022) 45:59.).

- Similarly, given the myriad causes of excessive sleepiness, at least as measured by the Epworth Sleepiness Scale (ESS), presence of somnolence in a patient with OSA does not indicate that somnolence is caused by OSA (6). In fact, average ESS does not begin to increase until AHI is >45 h^{-1} and even then the increase is minimal (6). Determining if sleepiness in sleepy patients with OSA improves preferentially in those with ORP types 1,1 and 1,2 would be worthwhile.
- Given that the selective improvement in sleep on CPAP in types 1,1 and 1,2 was found in split sleep studies, additional prospective studies while patients are on long term CPAP are needed to confirm these findings.

Type 1,3 (Figure 9A): This pattern is most relevant to patients with excessive wake time (low sleep efficiency). The paradoxical relation between deep sleep (very little) and full wakefulness (excessive) in this type is consistent with low sleep pressure *across the night*. Given the multiple mechanisms of low sleep pressure, this pattern is ubiquitous, occurring in asymptomatic subjects and in association with various sleep disorders (Table 2) (7). In a large

community cohort (Sleep Heart Health Study; SHHS) pattern 1,3 was present in 365 of 3,585 (10.2%) of all subjects (Table 2). Of these, 131 (35.8%) occurred in subjects with no insomnia or OSA (7). Of the remaining 234 subjects with this pattern 202 subjects (87%) had concomitant OSA (Table 2) (7). Of these, only 43 (21%) also had concomitant insomnia (Table 2) (7), thereby meeting the criteria of COMISA (Comorbid insomnia and sleep apnea) (36).

It should be pointed out that the frequency of type 1,3 in patients with mild, moderate, and severe OSA is not significantly different than that of subjects with no OSA and that even in very severe OSA (AHI >50 h-1), the number of patients with this type (16, Table 2) exceeded that expected from values in no OSA (6, Table 2) by only relatively few patients (10), several of whom had insomnia symptoms but in whom symptoms were less frequent than 3 times per week. Thus, the extra patients with type 1,3 (n = 10) may have been examples of COMISA. Furthermore, in a separate study on patients with insomnia and excessive wake time, there was no difference in ORP in any sleep stage between those with and without mild-moderate OSA (8), and in a separate study, wake time remained high, albeit somewhat lower, in patients with type 1,3 and insomnia when treated with CPAP (6). Accordingly, when type 1,3 and OSA coexist, the excessive wake time likely reflects a state of low sleep pressure, independent of OSA.

Consistent with earlier findings that wake time increases with age (37, 38), type 1,3 increases dramatically in frequency with age in asymptomatic subjects, from <2% (95% percentile) in those <40 years to 20% in those over 70 years (Figure 8) (7). The increase in wake time with age is primarily in the ORP range of full wakefulness (decile 10), with much smaller increases in drowsy wakefulness (deciles 8 and 9) (7), suggesting that the excess wake time in older people is due to age-related decrease in sleep pressure (or need) rather than to age-related diseases that impair sleep (7). It follows that finding this pattern need be of concern only if associated with insomnia or if the patient is young even in the absence of insomnia, where it may indicate a disorder of low sleep pressure, for example a latent hyperarousal state or excessive napping.

In summary, the above findings suggest that OSA is not causally related to excessive wake time when the two conditions coexist except possibly in very severe OSA. Even when the associated OSA is severe, it is possible that the low sleep pressure in this pattern may be contributing to OSA severity, rather than the other way around (8). By correcting upper airway instability CPAP use in such combined cases is associated with improved sleep depth but is not expected to normalize wake time (6).

The relation between type 1,3 and insomnia is complex. Of 365 subjects with this pattern in the SHHS, only 75 (20.5%) met the accepted definition of insomnia (Table 2) despite the excessive wake time (Table 1) (7). On the other hand, the frequency of type 1,3 in subjects with COMISA (17.3%) and in those with insomnia and short sleep duration (Insomnia SSD; 28.8%, Table 2), was significantly higher than in those without insomnia (8.7%) or in those with paradoxical insomnia (Insomnia with normal sleep duration (NSD); 5%, Table 2), suggesting a causal relation between the excessive wake time in this type and the patient's symptoms.

For the entire SHHS cohort type 1,3 was associated with the lowest SF36 (P) and the third lowest SF36 (M) (7). These associations persisted after adjusting for age, gender, body mass index (BMI), AHI, and insomnia. In addition, type 1,3 was associated with significantly lower SF36 (P) and SF36 (M) in subjects with no OSA or insomnia after adjusting for age, gender, and BMI (7). Thus, this type is the most consequential with respect to quality of life, whether or not it is associated with OSA or insomnia. Type 1,3 was also associated with higher risk of hypertension and all-cause mortality in the same study (unpublished observations).

It is worth noting that despite the progressive increase in frequency of types 1,1, 1,2, and 1,3 with OSA severity (Table 2), other types not associated with poor sleep, sleep improvement on CPAP, or reduced quality of life (Types 2,1 to 3,3, see below) are also seen in OSA (Table 1). These types accounted for 75.8%, 71.6%, 63.3%, and 38.3% of all patients in mild, moderate, severe, and very severe OSA, respectively (Table 2) (7).

Opportunities for research

1) Further studies are needed to determine if long term CPAP use improves clinical outcome in patients with mild-moderate OSA associated with excessive wake time since the impairment in sleep depth at this level of severity is minimal (6).

2) Sleep in Critically Ill Patients: It is well-known that sleep is very poor in critically ill patients in intensive care units (39–42). Independent of critical illness, poor sleep adversely affects several organ functions that are critical for recovery and liberation from mechanical ventilation (immune function (43, 44), respiratory control (45), neuroendocrine and metabolic function (46–48), cardiovascular responses (49), mental health (50, 51). It is therefore likely that poor sleep contributes to poor outcome in such patients (30, 52). An important question, therefore, is whether normalization of sleep improves clinical outcomes in these patients. Critically ill patients are routinely administered different kinds of sedatives to help them sleep. However, whether these sedatives result in normal sleep or simply act as CNS depressants is not known.

ORP was recently used to study sleep in critically ill patients (15–17). In one study, those with little or no time in full wakefulness during 15 h of monitoring were less likely to pass a weaning trial (15). In another study on un-sedated stable patients prior to extubation, ORP types 1,1, 1,2, and 1,3 were present in 68% of patients, by contrast to a frequency of 25.8% in the general community (17). Of these three types, type 1,1 was the most frequent (33.0%) followed by type 1,3 (22.0%) (17). Furthermore, these abnormal ORP patterns were found with similarly high frequency (77%) among a separate cohort of intensive care unit (ICU) survivors, with little improvement 6 months after discharge (17). These findings strongly suggest that poor sleep in critically ill patients, prior to attempted extubation, is largely due either to arousal stimuli that preclude progression to deep sleep (types 1,1 and 1,2) or to a hyperarousal state (type 1,3), and that these abnormalities persist even months after discharge (17).

In a third study, the impact of *mild* sedation with propofol and dexmedetomidine on ORP architecture was studied (16). These two agents caused a leftward shift in the ORP distribution toward the normal pattern in all patients, with pattern becoming normal or almost normal in most patients. On average, ORP

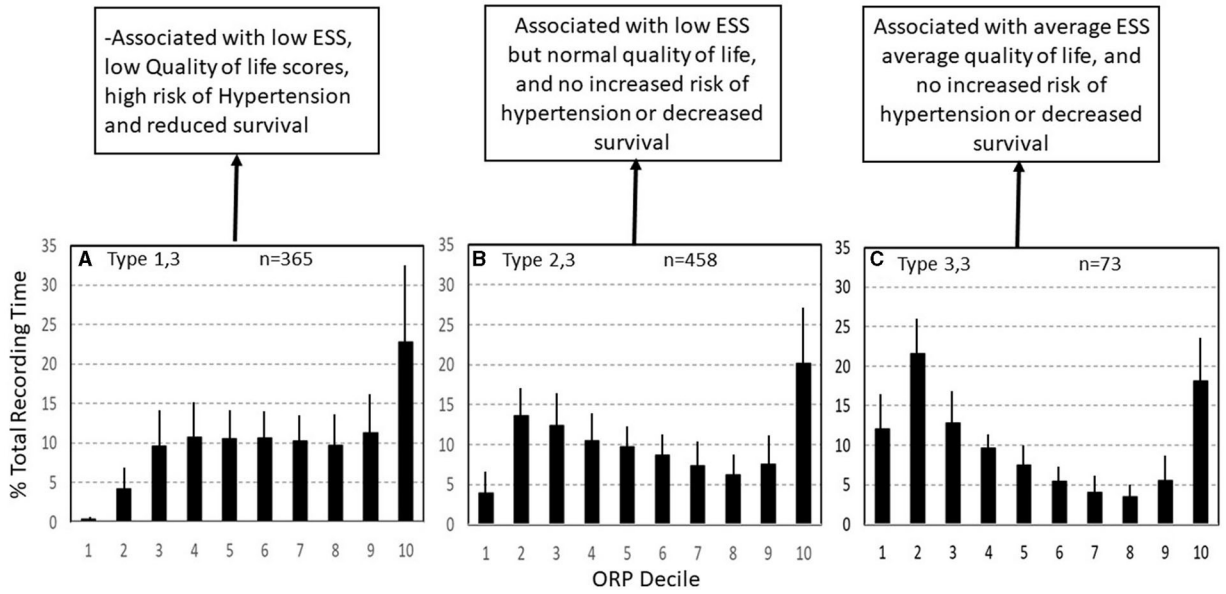

FIGURE 9
Three ORP types found in subjects with excessive time in full wakefulness (decile 10). In type 1,3 **(A)** there is little deep sleep. In type 2,3 **(B)** time in deep sleep is normal, and in type 3,3 **(C)** time in deep sleep is above average. Types 1,3 and 2,3 are the most common types in insomnia with short sleep duration. ESS, Epworth Sleepiness Scale (From reference: Younes M, Gerardy B, Pack AI, Kuna ST, Castro-Diehl C, Redline S, et al. Sleep architecture based on sleep depth and propensity: patterns in different demographics and sleep disorders and association with health outcomes. *Sleep*. (2022) 45:59.).

architecture approached normal distribution. Importantly, apart from normalizing ORP distribution, the spectral pattern of the EEG at any given ORP was indistinguishable from that in natural sleep outside the ICU, suggesting that these agents, in appropriate doses, are capable of producing normal sleep rather than CNS depression (16).

Collectively, these three studies indicate that poor sleep in the ICU is mostly related to abnormal arousal stimuli, or a hyperarousal state, and that sleep can be normalized by the appropriate kind and amount of sedation. Also given that ORP can be measured and displayed in real time (53) it would be feasible to control the sedative dosage using ORP feedback. It would be of great interest to determine whether, using such feedback, clinical outcomes improve by implementing a sustained period of sleep (e.g., corresponding to normal total sleep time) with some variation in sleep depth to simulate the different sleep cycles seen normally, and adjusted to coincide with nighttime to maintain a normal circadian rhythm.

Type 2,3 (Figure 9B): As in type 1,3, type 2,3 is characterized by excessive time in full wakefulness (Figure 9B) and a high frequency in insomnia SSD (38.8%) but not insomnia NSD (Table 2). Therefore, the excessive time in full wakefulness likely contributes to insomnia symptoms. Type 2,3 is the most frequent type in insomnia SSD (Table 2). However, in marked contrast to type 1,3, type 2,3 is associated with normal amount of deep sleep (sum of deciles 1 and 2; 17.6 ± 4.9% vs. 4.6 ± 3.2%, $p < 0.0001$; Figure 9B). It is also not associated with reduced quality of life, (7) or hypertension or mortality (unpublished). These findings, along with a normal (average) ESS (6, 7) and no associated poor health outcome suggest that this type occurs in people who obtain enough restorative sleep but stay in bed longer than they need to Younes et al. (7).

Type 3,3 (Figure 9C): As its 2-digit number indicates, this type is associated with high amounts of deep sleep as well as full wakefulness (Figure 9C). Its frequency was very low in all age groups in subjects with no OSA or insomnia in the SHHS (Figure 8) and its frequency did not increase with OSA severity and/or insomnia (Table 2). ESS and quality of life are average (7). The location of the fully wake time within the sleep study is highly variable and may consist of one long period early, late or in mid-region, or multiple shorter periods within sleep period time (Figure 10). This type suggests a circadian disorder or an individual who meets his sleep need in less time than time in bed (short sleeper). Multiple short awakenings may also be related to urination. Wake periods often start suddenly from deep or REM sleep (Figure 10), which may suggest a parasomnia. Enquiry about these possible causes would be appropriate in patients with this type.

Opportunities for research

Research in insomnia

At present, sleep studies are not recommended for patients with insomnia as they are felt to contribute little to clinical management and may exclude many patients with primary insomnia (54). The use of ORP in patients with insomnia has, however, identified several phenotypes that differ in health outcomes and likely underlying mechanisms and, potentially in response to therapy. These findings advocate for use of PSG in patients with insomnia, if only for research purposes.

Insomnia with Normal Sleep Duration: As expected we found no difference in conventional indices between insomnia with

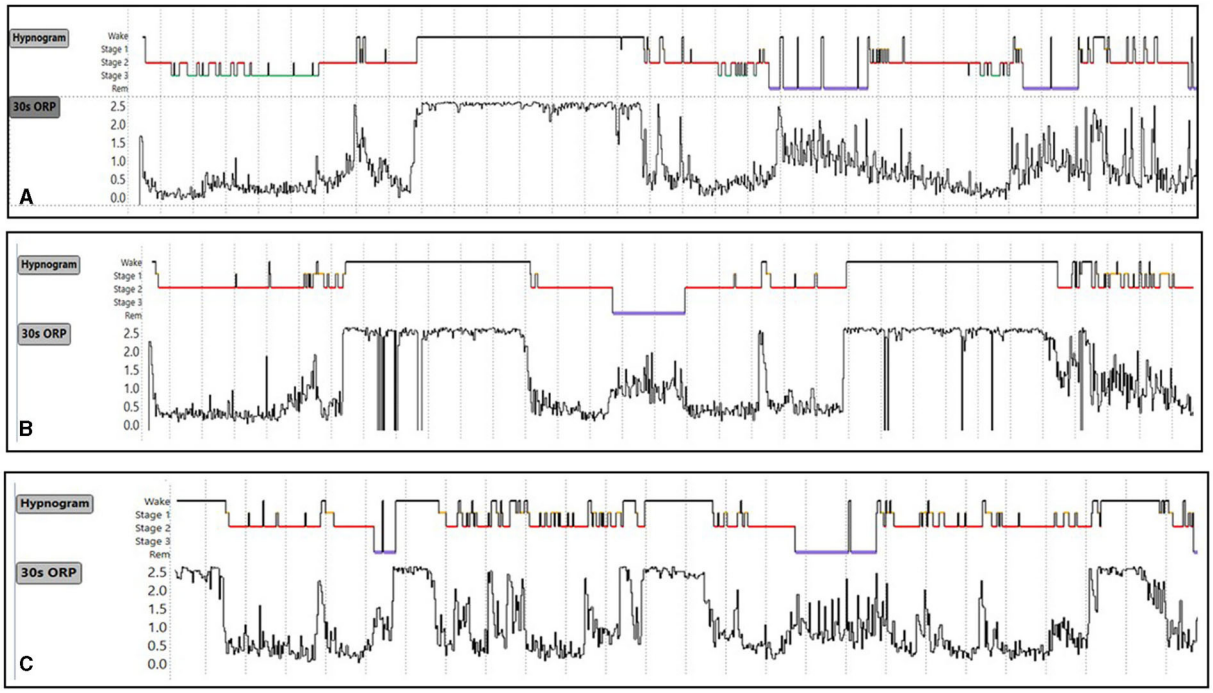

FIGURE 10
(A–C) Conventional sleep hypnograms and 30-s odds ratio product (ORP) results in three subjects with ORP type 3,3 [high amounts of deep sleep (ORP <0.5) as well as high amounts of full wakefulness (ORP >2.25)] showing the different locations of excessive time in full wakefulness within the sleep study. Unpublished data.

normal sleep duration and subjects with no insomnia (7). Also, apart from one interesting finding, there were no differences in ORP architecture between these patients and those with no insomnia (Table 2) (7). However, in marked contrast to insomnia with short sleep duration, time in full wakefulness (decile 10) was significantly lower than in patients with no insomnia (7). To the extent that less time in full wakefulness is suggestive of higher sleep pressure (Figure 7), this observation suggests that, notwithstanding the lack of difference in distribution of ORP types (Table 2), sleep may have been of lower quality in these patients. Further investigation into differences in sleep microstructure is warranted.

Insomnia with Short Sleep Duration: Vgontzas et al. reported that insomnia with SSD is the most biologically severe form of insomnia, being associated with a high risk of hypertension, diabetes, cognitive impairment, and mortality (55–59). The current findings indicate that ORP architecture in insomnia SSD includes several distinct phenotypes that share excessive wake time but differ in other respects: (a) ORP type 1,3 with poor sleep along with poor health outcomes (Figure 9A); (b) ORP type 2,3 with normal sleep quality and no adverse health outcomes (Figure 9B); (c) Type 3,3 with better than average sleep quality and no adverse health outcomes (Figure 9C); (d) Other uncommon types in which excessive wake time is preferentially in the drowsy wake state (deciles 8 and 9) (Table 2). Of these, except for type 1,2, which accounts for 6.3% of these patients and is associated with slight reduction in SF36 (M), these types are also not associated with adverse health outcomes.

Thus, it is possible that the adverse effects described by Vgontzas et al. (55–59) stem from the increased representation of type 1,3 in this insomnia category (Table 2). Also, given the different likely mechanisms of these various phenotypes (7), it is possible that response to insomnia therapy may differ among these phenotypes. It would be of considerable clinical importance to confirm these findings and to determine if these types respond differently to insomnia treatment modalities.

Types 3,1 and 2,1: Type 3,1 is the prototypical pattern of *uncomplicated* high sleep pressure (Figures 2C, 7B). Except for a lesser amount of deep sleep (19.8 ± 5.2% vs. 41.1 ± 9.7%TRT) type 2,1 shares all characteristics and associations as type 3,1. Thus, their frequency is highest in young adults (>24% of adults <40 years; Figure 8) and decreases progressively with age to <7% in subjects >70 years (Figure 8). On average, in the SHHS, they occurred with similar frequency in adults with no OSA or insomnia (13.2 and 11.1%, respectively; Table 2) and, reflecting the impact of severe OSA in preventing progression to deep sleep, frequency decreased as OSA severity increased, becoming uncommon (<7%) in very severe OSA (Table 2). Also as expected, their frequency is much reduced in insomnia SSD but not in insomnia NSD (Table 2). When associated with OSA, their presence indicates that sleep depth is not degraded by the disorder. This is supported by the fact that sleep depth does not improve, or deteriorates, when CPAP is used (acutely) in patients with OSA and this ORP type (6).

Reflecting the fact that most subjects with these two types have no sleep disorder or have OSA that does not interfere with progression to deep sleep (see above and Table 1), ESS is not significantly increased (6, 7). However, given their similarity with the pattern seen with sleep deprivation (Figure 7B), and their high frequency in patients with idiopathic hypersomnia

(Patient 3, Figure 6), (27) occurrence of type 3,1 in subjects with excessive sleepiness (e.g., Figure 4C), and particularly in older individuals, would suggest that the patient may not be getting sufficient sleep because of poor lifestyle or excessive sleep need (idiopathic hypersomnia; see Cummulative Sleep Index, CSI; above), and such disorders need to be excluded before discounting insufficient sleep as the reason for excessive sleepiness.

Type 2,2 (Figures 2A, 6A, D): This is the most common type among subjects (in the SHHS) with no OSA or insomnia (26.8%, Table 1), and its frequency is nearly the same at all OSA severity levels and both insomnia types (Table 2). ESS and quality of life indices are average (7). The average amounts of deep sleep and full wakefulness argue against high or low sleep pressure. Accordingly, this type almost certainly reflects normal sleep. If associated with symptoms suggestive of a sleep disorder (sleepiness, non-restorative sleep, insomnia) the symptoms are not likely due to a sleep abnormality (7).

Type 3,2 (Figure 7C): This type differs from type 2,2 in having more deep sleep while the amount of full wakefulness is average, making it less likely that sleep pressure is high. It is most common in subjects with no OSA or insomnia (Table 2) and its frequency decreases as OSA severity increases and in insomnia SSD (Table 2). It is also not associated with increased sleepiness or poor quality of life (7), and when associated with OSA sleep depth is not responsive to CPAP (6). These findings suggest that this is a normal pattern.

In summary, there are four patterns that predominate in subjects with no obvious sleep pathology and their frequency either decreases or is unchanged in the presence of OSA or insomnia (Types 2,1, 3,1, 2,2, and 3,2). They are statistically not associated with excessive sleepiness or poor quality of life. Accordingly, such patterns likely represent normal sleep except when they are found under specific circumstances such as types 2,1 or 3,1 in an older subject or in a subject with objective excessive sleepiness. Type 2,3 also appears to be a normal pattern except for its frequent occurrence in insomnia with short sleep duration, where it may be a milder variant of type 1,3 or, pending investigations, simply reflect staying in bed longer than needed. On the other hand, types 1,1 and 1,2 always warrant investigation into possible sources of frequent arousals. Type 1,3 is also of concern, except in old asymptomatic subjects, as it may indicate a disorder of low sleep pressure (e.g., hyperarousal, excessive napping…etc.).

Conclusion

ORP is a continuous metric of sleep depth and wake propensity. It makes it possible to distinguish different wake states in the transition from full wakefulness to light sleep and different levels of sleep depth within the same conventional sleep stage. It has been extensively validated. It can be reported in graphic as well as numeric ways. When reported as percent of recording time spent in different ORP deciles the distribution patterns are distinct from each other and suggest different underlying mechanisms for patient symptoms. Using these patterns, different phenotypes have been found in patients with OSA, insomnia and idiopathic hypersomnia. These provide the bases for future research that could pave the way for improved management of these disorders.

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 review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/ participants or patients/participants legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

MY: Conceptualization, Writing—original draft, Writing—review and editing.

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Conflict of interest

MY developed, and has a patent on, the ORP Technology. The technology has been licensed to Cerebra Health in Winnipeg. He is a shareholder and receives royalties from Cerebra Health.

Publisher's note

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A new approach to streamline obstructive sleep apnea therapy access using peripheral arterial tone-based home sleep test devices

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Obstructive sleep apnea (OSA) is a prevalent condition that negatively impacts cardiovascular, metabolic and mental health. A high proportion of individuals with OSA remain undiagnosed and incur significant healthcare costs. The gold standard OSA diagnostic is in-lab polysomnography, but this is costly and time-consuming. Home sleep apnea tests (HSATs), including cardiorespiratory polygraphy and peripheral artery tonometry technology, provide an alternative. Advances in HSAT technology include non-invasive, easy-to-use medical devices that could allow unobtrusive, accessible, multi-night, cost-effective diagnosis and management of sleep-disordered breathing. One type of these devices is based on determination of peripheral arterial tone, and use photoplethysmography signals from the finger (oxygen saturation, pulse wave amplitude and pulse rate). The devices contain algorithms that use these data to generate the traditional metrics required by the American Academy of Sleep Medicine. They can be used to record sleep parameters over multiple nights at home, and can also provide information on total sleep time (TST) and sleep stages (including time spent in rapid eye movement sleep). The combination of objective measures (apnea-hypopnea index, oxygen desaturation index, respiratory disturbance index, TST) and subjective measures (symptoms and other patient-reported outcome measures) could facilitate the development of a personalized therapeutic plan for OSA patients. It is anticipated that the streamlined digital pathway facilitated by new peripheral artery tone-based technology could contribute to reducing the underdiagnosis of OSA, accelerating access to appropriate treatment, and the optimization of OSA therapy.

KEYWORDS

diagnosis, peripheral artery tonometry, precision medicine, sleep disordered breathing, telehealth, HSAT, night-to-night variability

1. Introduction

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing (SDB). It is characterized by partial or complete upper airway obstructions that are associated with intermittent hypoxia and transient arousals. The global prevalence of OSA in middle-aged adults has been estimated to be nearly one billion, with approximately half of these having moderate-to-severe disease with an indication for treatment (Benjafield et al., 2019).

OSA results in increased sympathetic activity, oxidative stress, inflammation, endothelial and metabolic dysfunction, and is associated with a variety of cardiovascular, cerebrovascular and metabolic diseases, and increased all-cause mortality (Nieto et al., 2000; Peppard et al., 2000; Kendzerska et al., 2014; Kent et al., 2015; Linz et al., 2015; Reutrakul and Mokhlesi, 2017; Xie et al., 2017; Mehra et al., 2022; Salari et al., 2022). Untreated OSA also contributes to occupational and traffic accidents (Bioulac et al., 2017; Hirsch Allen et al., 2020) and absence from work (Lallukka et al., 2014), and has a negative impact on cognitive function (Gnoni et al., 2023) and quality of life (Kerner and Roose, 2016; Vinnikov et al., 2017; Alomri et al., 2021; Legault et al., 2021).

A high proportion of individuals with OSA remain undiagnosed (Young et al., 1997; Kapur et al., 2002). This is relevant from a health system perspective because a person with OSA has been estimated to have double the annual healthcare costs than someone without OSA (Kapur et al., 1999). Furthermore, the diagnosis and treatment of OSA are associated with positive economic benefit (Wickwire, 2021; Mattila et al., 2022; Sterling et al., 2023).

2. OSA diagnosis

The current gold standard for diagnosing OSA is in-laboratory polysomnography (PSG). PSG is a costly and time-consuming process that requires highly trained personnel for set-up and scoring, and therefore has limited availability. PSG is essential in specific patient groups (e.g., those with comorbidities), but the majority of individuals do not require PSG for diagnosis of OSA. PSG is subject to the first-night effect and although it can be performed over multiple nights and at home, this is resource intensive and not feasible in the majority of cases, which limits its ability to detect night-to-night variability in SDB parameters (Newell et al., 2012). Therefore, there is a need for OSA diagnostic tests that are more widely available, cost effective and can be used for timely multi-night sleep testing, allowing healthcare professionals to take care of all individuals referred for evaluation or management of OSA. As a result, home sleep apnea testing (HSAT) has become a routine approach for individuals with suspected OSA. HSAT does not require supervision, is less expensive than PSG and allows replication of sleep patterns under "usual" conditions. Many PSG-validated HSAT devices are available (e.g., level 3 cardiorespiratory polygraphy) that provide adequate apnea-hypopnea index (AHI) estimation according to the American Academy of Sleep Medicine (AASM) criteria for sleep apnea diagnosis (Kapur et al., 2017; Rosen et al., 2018). However, use of total recording time rather than total sleep time (TST) to calculate respiratory indices may lead to important underestimation of event rates (Escourrou et al., 2015; Massie et al., 2022a). According to the AASM practical guidelines, both polygraphy and peripheral artery tonometry-based HSATs can be used for the diagnosis of sleep apnea (American Academy of Sleep Medicine, 2023). There are two Conformité Européenne (CE) mark and US Food and Drug Administration-approved, commercially available peripheral artery tonometry-based HSAT devices (NightOwl® and WatchPAT®).

2.1. Photoplethysmography and peripheral arterial tonometry for detection of respiratory events

Reflectance-based photoplethysmography (PPG) detects pulsatile changes in blood volume in peripheral tissues and has been defined as an important technology in sleep monitoring devices (Ryals et al., 2023). Peripheral artery tonometry refers to the determination of peripheral arterial vascular tone (the net balance between vasoconstriction and vasodilation) using PPG data. Peripheral artery tonometry measures pulsatile volume changes in the digital vascular bed that are densely innervated (Schnall et al., 1999; Zou et al., 2004). In the context of OSA, there is increased sympathetic nervous system activity near the end of a respiratory event (obstructive apnea). The associated release of norepinephrine increases tone in the peripheral arteries, resulting in vasoconstriction and a reduction in the volume of blood displaced between systole and diastole. By measuring this relative change in blood volume, sudden changes in peripheral arterial tone that occur in response to respiratory events can be detected (O'Donnell et al., 2002). These pulse wave amplitude drops have been shown to be an important biomarker of cardiometabolic risk and outcomes (Hirotsu et al., 2020; Strassberger et al., 2021; Solelhac et al., 2023).

Peripheral artery tonometry-based devices combine information on changes in arterial volume with oxygen saturation (SpO_2; both from the PPG signal) with data on peripheral arterial tone and heart rate (Yalamanchali et al., 2013; Massie et al., 2018; Van Pee et al., 2022; Lyne et al., 2023). During recording, a respiratory event is typically detected by analyzing the co-occurrence of one or more of the following events: oxygen desaturation; vasoconstriction (decreased peripheral artery tonometry signal); and increased pulse rate. Based on these data, peripheral artery tonometry devices contain proprietary algorithms that generate the traditional metrics required by the AASM Manual for the Scoring of Sleep and Associated Events (e.g., AHI, respiratory disturbance index) (American Academy of Sleep Medicine, 2023). The two currently available devices, NightOwl® and WatchPAT®, have different proprietary algorithms and technical specifications. Both have been validated against PSG (Zou et al., 2006; Massie et al., 2018; Van Pee et al., 2022), and generally show good agreement with PSG for parameters such as the AHI and OSA severity (O'Brien et al., 2012; Yalamanchali et al., 2013; Camilon et al., 2014; Choi et al., 2018; Ioachimescu et al., 2020; Van Pee et al., 2022). Furthermore, information on sleep (e.g.,

TST, time spent in rapid eye movement [REM] sleep, wake time) can also be estimated using peripheral artery tonometry-based devices (Hedner et al., 2011; Massie et al., 2018; Zhang et al., 2020).

2.2. Detection of central sleep apnea and REM sleep using peripheral artery tonometry-based devices

Although OSA is the predominant sleep apnea subtype, central sleep apnea (CSA) is another important form of SDB (Dempsey, 2019). The mechanisms underlying these two types of sleep apnea are different, because CSA is characterized by a lack of respiratory drive, while OSA result from a partial or complete obstruction of the upper airways. In PSG, cessation of respiratory drive or effort can be inferred from the abdominal and thoracic respiratory effort belts. This information is not currently available from peripheral artery tonometry-based devices, but could be detected using fingertip PPG data. The fingertip PPG signal inherently contains respiratory information because blood flow to body extremities is influenced by alterations in thoracic pressure throughout the respiratory cycle (Ryals et al., 2023). Therefore, the PPG signal amplitude oscillates in synchrony with the respiratory cycle. This amplitude modulation can be isolated to retain a signal representing respiratory effort. The respiratory effort signal can then be used to classify respiratory events as being of an obstructive or central nature. Use of PPG has recently been shown to provide useful data for the detection of CSA in individuals with suspected sleep apnea (Sommermeyer et al., 2012; Massie et al., 2023).

Approximately 10%−36% of individuals with sleep apnea have REM-predominant OSA (Alzoubaidi and Mokhlesi, 2016), whereby SDB events are more pronounced during REM sleep (Varga and Mokhlesi, 2019). These individuals are at high risk for common OSA comorbidities, including atherosclerosis, hypertension, metabolic syndrome and diabetes (Mokhlesi et al., 2014; Acosta-Castro et al., 2018; Ljunggren et al., 2022). In order to properly define this phenotype, it is essential to be able to classify REM sleep with sufficient accuracy. Vasoconstrictions and oxygen desaturations detected in peripheral artery tonometry and SpO_2 signal traces, respectively, show a different temporal pattern between REM and non-REM sleep (Lavie et al., 2000; Dvir et al., 2002; Herscovici et al., 2007; Choi et al., 2016). Furthermore, pulse rate low frequency power has been shown to increase in REM sleep (Chouchou and Desseilles, 2014). This means that PPG-based techniques can be used to detect REM sleep (Lavie et al., 2000; Zhang et al., 2020), although peripheral artery tonometry-based HSAT has lower sensitivity for REM detection than PSG (Massie et al., 2022b).

Overall, the ability of peripheral artery tonometry-based HSAT devices to detect REM sleep and their potential to differentiate between central and obstructive respiratory events increase the utility and application of these devices across a range of SDB types. They may also have clinical usefulness in individuals with comorbidities such as atrial fibrillation (Tauman et al., 2020; Jensen et al., 2023) and chronic obstructive pulmonary disease (Hansson et al., 2023).

2.3. Multi-night sleep testing

A key advantage of a peripheral artery tonometry-based approach is that it provides a convenient and low-cost option for multi-night testing. This is important because evaluating SDB over multiple nights provides a greater amount of data on respiratory parameters. This may help to achieve a correct diagnosis, and could allow evaluation of the evolution of sleep-related breathing disorders over time during the application of appropriate therapy. Peripheral artery tonometry devices are small, and therefore allow more natural (e.g., less supine) sleep due to the lack of cables compared with PSG. Furthermore, there is a large body of evidence showing that there is substantial night-to-night variation in sleep-related respiratory events, meaning that a single night of monitoring may be insufficient to allow reliable determination of sleep apnea severity at the individual level, resulting in misclassification in a substantial proportion of people (Punjabi et al., 2020; Roeder et al., 2020; Lechat et al., 2022). Furthermore, emerging evidence suggests that large night-to-night variability in sleep apnea severity (based on the AHI) is a predictor of uncontrolled hypertension (Lechat et al., 2023), and that sleep data from a single night of recording performed worse than multi-night testing with respect to cardiovascular risk prediction (Lechat et al., 2023). For data from multiple nights of sleep testing (at least three nights in total, including one night on the weekend), some experts believe that it is probably best to use the highest AHI value recorded to provide guidance regarding treatment initiation, rather than the average AHI. However, studies are needed to validate this approach. In summary, the multi-night monitoring capability of peripheral artery tonometry devices allows patient sleep trajectories over time to be determined in an accessible and acceptable manner, providing a clearer understanding of sleep habits and allowing better shared decision-making and more personalized therapy (Hrubos-Strøm et al., 2023; Lisik et al., 2023).

3. OSA diagnostic and management workflow using peripheral artery tonometry-based devices

HSAT workflow is simple and can be implemented remotely. However, a wider consideration is how new, multi-night, low-touch tools such as peripheral artery tonometry devices can be incorporated into the SDB patient pathway in a way that maximizes benefits for the patient (optimizing diagnosis and therapy), for healthcare professionals (time saving, reduced sleep lab workload, patient-centered management), and for the healthcare system (cost savings, resource optimization). As well as diagnosis, use of simple, compact HSAT devices could contribute to improving the efficiency of ongoing management of OSA therapies, including oral appliances and positive airway pressure therapies. An integrated and personalized diagnostic and therapeutic digital pathway can be facilitated by the use of objective diagnostic measures (AHI, oxygen desaturation index, sleep time, hypoxic burden), subjective measures such as symptoms and patient-reported

outcome measures, and the monitoring of therapy efficacy (Figure 1).

For healthcare professionals, HSAT with a device that uses peripheral artery tonometry (such as NightOwl® and WatchPAT®) is considered to be less time consuming, allowing more efficient patient management using a digital pathway without any loss of diagnostic accuracy. Having a solution that can be implemented remotely also allows more patients to be reached, especially those who do not have easy access to a sleep laboratory or sleep physician. In addition, the COVID-19 pandemic highlighted the value of being able to continue healthcare evaluations and treatment monitoring without face-to-face interaction between healthcare professionals and patients (Bouloukaki et al., 2023).

Accurate, multi-night sleep testing information is a key component that can help to drive much-needed personalized approaches to the diagnosis and treatment of sleep apnea (Arnardottir et al., 2022). While OSA may superficially be considered as a single disease, there are a variety of diverse clinical manifestations (or phenotypes) (Zinchuk et al., 2017; Duong-Quy et al., 2022). The presence of different OSA phenotypes means that a personalized, approach to the diagnosis and treatment of OSA is required to optimize clinical outcomes for individual patients (McNicholas and Korkalainen, 2023). The ability to detect different sleep apnea phenotypes such as REM-predominant OSA and CSA makes peripheral artery tonometry-based devices valuable tools for facilitating this type of personalized treatment.

Another important consideration is the patient experience, which is becoming increasingly recognized as a key measure of health system performance (Jamieson Gilmore et al., 2023). There are a number of features that would likely result in a good experience for individuals being investigated for SDB using peripheral artery tonometry-based devices. These include the ability to perform sleep testing over multiple nights in the home environment, simple device set-up, quick and reliable event analysis. This approach is also ideally suited to facilitate a P4 medicine approach to OSA—Predict; Prevent; Personalize; Participate (Lim et al., 2017). Early and effective diagnosis of OSA in otherwise healthy individuals would allow the implementation of lifestyle interventions and early treatment that could contribute to prevention of common OSA comorbidities (i.e., primary prevention) (Yim-Yeh et al., 2010), facilitate personalization of therapy options, and allow the individual to participate in the diagnosis and monitoring of their condition. Furthermore, simplicity and flexibility are important, especially for the disabled, the elderly and for people who are less familiar with new technologies.

4. Discussion

It has long been recognized that there is a lack of healthcare resources to meet the clinical demands of individuals with sleep apnea or suspected sleep apnea (Flemons et al., 2004; Pack, 2004). Nevertheless, effective and timely diagnosis of OSA plays an important role in preventing or limiting the negative health impacts of this condition. Peripheral artery tonometry-based wearable sleep testing devices that can be self-administered by the patient and scored automatically using validated artificial intelligence and machine learning-based algorithms have the potential to fill an important gap in healthcare service provision, improve access to diagnostic sleep studies and provide a cost-effective solution for sleep apnea diagnosis and monitoring.

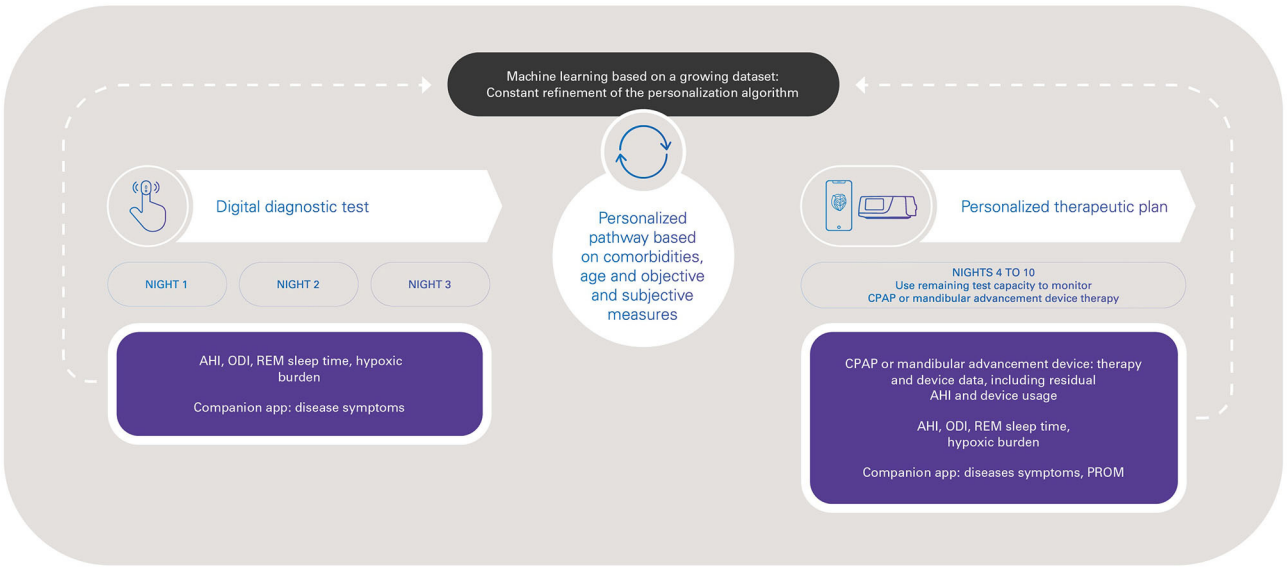

FIGURE 1
Toward a digital pathway for obstructive sleep apnea with peripheral arterial tone-based monitoring, from diagnosis to therapy management. AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; ODI, oxygen desaturation index; PROM, patient-reported outcome measures; REM, rapid eye movement.

Compared with conventional PSG, the benefits of peripheral artery tonometry-based wearable sleep testing devices include ease of performing evaluations over multiple nights. In addition, there will be savings in clinical staff time by avoiding complicated inventory, on-site desktop software updates, and cleaning and sterilization/disinfection procedures. However, these HSAT devices do not record a direct measurement of flow so it is not possible to distinguish between apneas and hypopneas (although both are counted), and there is no EEG-based sleep-staging (although information on sleep stages can be obtained by other means). Furthermore, there are some settings where use of peripheral artery tonometry may not be the most appropriate option. For example, device performance could be adversely impacted by alternations in the sympathetic response or impaired perfusion at the peripheral tissue, such as during treatment with adrenergic system modulators (e.g., alpha-adrenergic antagonists) (Zou et al., 2010) and in individuals with clinically relevant peripheral vascular disease. Thus, although alternative approaches to sleep apnea assessment might be more appropriate in these groups, use of peripheral artery tonometry-based devices to address the unmet need for better approaches to OSA diagnosis for the majority of individuals would allow in-demand sleep laboratory services to be prioritized for more complex individuals (Fietze et al., 2022).

4.1. Looking to the (not too distant) future

Sleep medicine is a rapidly developing field, but the prevalence of OSA is growing and the number of sleep specialists is inadequate to meet the increasing need. This highlights the need for initiatives such as new tools and telehealth to provide safe, effective clinical care to an expanding group of patients (O'Donnell et al., 2020). The move toward greater utilization of telemedicine solutions was accelerated during the COVID-19 pandemic due to lockdowns and social distancing requirements (Monaghesh and Hajizadeh, 2020). It makes sense to capitalize on this momentum to improve the diagnosis and management of SDB, and simple, wearable devices based on measurement of peripheral arterial tone, such as NightOwl® and WatchPAT®, can make an important contribution to this. For instance, peripheral arterial tone-based HSATs can provide primary care professionals with easy tools to diagnose OSA. These cloud-based multiple-night HSAT technologies can be beneficial for communities without major medical center for SDB management thus promoting equitable SDB identification, diagnosis, and treatment (Gueye-Ndiaye et al., 2023). Moreover, the technologies provide the possibility of OSA screening in large populations and enable new approaches for a simplified and automated OSA diagnostic procedure and treatment follow-up. HSATs, wearable technologies and advances in telemedicine may also help to strengthen inter-departmental collaboration, thus improving the overall care of patients with OSA (Mahoney, 2020; McNicholas and Pevernagie, 2022).

Overall, the possibility of integrating diagnostic, device therapy and patient clinical data is attractive, and facilitates a more holistic approach to patient management. New-generation wearable devices that record a variety of signals to provide information on sleep stage/quality, arousals, sleep position, and a variety of SDB metrics (such as hypoxic burden) (Trzepizur et al., 2022) will provide a more complete picture to inform clinical decision making throughout the patient journey. Better understanding of patient phenotypes will allow specific characteristics to be linked to treatment outcomes (Mazzotti et al., 2019). The variety of accurate data obtained from new connected devices could be used to inform both diagnostics and clinical decision making based on sleep-related breathing parameters, age, symptoms and risks (Hajipour et al., 2023), and in accordance with current clinical recommendations and guidelines (Patil et al., 2019; Randerath et al., 2021; Grote et al., 2023). The new capabilities provided by new technologies and innovations bring new capabilities, such as use of the same device to diagnose sleep apnea and then monitor therapy compliance and efficacy. For example, one currently available peripheral artery tonometry-based device (NightOwl®) has 10 nights of battery capacity. The ability to record over 10 consecutive nights could allow three nights for diagnostic studies (AHI, oxygen desaturation index, hypoxic burden and patient-reported outcome measures) followed by sevn nights to implement and monitor a personalized treatment plan, including assessment of changes in hypoxic burden and patient-reported outcomes (Figure 1). This could contribute to reducing the underdiagnosis of OSA, accelerating access to appropriate treatment, and optimization of OSA therapy.

Author contributions

DZ: Conceptualization, Writing—original draft, Writing—review and editing. SV: Conceptualization, Writing—original draft, Writing—review and editing. CE: Writing—original draft, Writing—review and editing. DE-T: Writing—original draft, Writing—review and editing, Conceptualization. FL: Conceptualization, Writing—original draft, Writing—review and editing. MA: Conceptualization, Writing—original draft, Writing—review and editing. IF: Writing—original draft, Writing—review and editing.

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FL and DE-T are employees of ResMed. SV is an employee of EctoSense, a ResMed subsidiary.

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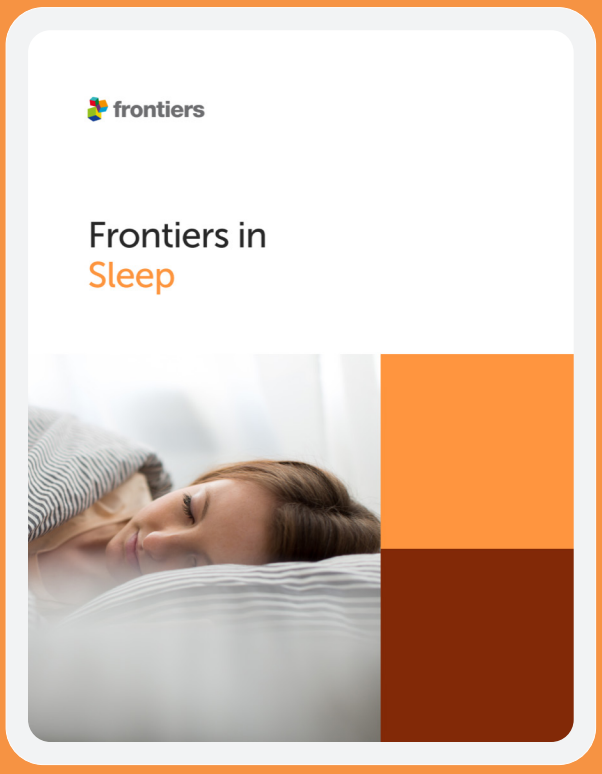

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