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Sleep problems: Diagnosis, biomarkers, interventions, and treatments

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Sleep problems: Diagnosis, biomarkers, interventions, and treatments

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Editorial: Sleep problems: diagnosis, biomarkers, interventions, and treatments

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KEYWORDS

diagnosis, biomarkers, interventions, treatments, personalized and precision medicine (PPM)

Editorial on the Research Topic
Sleep problems: diagnosis, biomarkers, interventions, and treatments

Sleep problems (SP) are highly prevalent among all age groups (1). Chronic SP are linked to increased risks of obesity, cardiovascular disease, diabetes, anxiety, depression, and impaired cognition. As a global issue that greatly impacts public health, SP warrants ongoing research and clinical attention (2). Accurately diagnosing specific sleep disorders via biomarkers could enable better-targeted, personalized medicine interventions and treatments. The current Research Topic represents a collection of papers investigating the complex physiological underpinnings of sleep to better diagnose and manage SP. In the current Research Topic, fifteen original articles, five review articles, and one research protocol article were published.

Two papers reported SP among university students. Zhang L. et al. showed that SP are also prevalent among university students. Their work aimed to create a prediction model (nomogram) that could be used to detect SP. Some intervention or preventive techniques, including quitting smoking and drinking, eating a healthy diet, avoiding midday naps, attending to chronic diseases, and managing worry and stress, may be very useful in improving sleep in university students. In the original article by Guo et al., the researchers used 24-h heart rate variability (HRV) as a biomarker to investigate the sleep quality and depression symptoms of medical students. The authors reported that SP were common among medical students and were associated with depressive symptoms. Students with SP had lower SDNN during the awake period and bedtime period and lower LF in the awake period. The use of HRV analysis may provide valuable information about SP and the different stages of sleep. During the different sleep stages, HRV patterns change, reflecting the varying activities of the autonomic nervous system.

Recent umbrella reviews and meta-analyses of self-reported psychological and behavioral symptoms (PBS) in medical students showed that a global analysis of all self-reported PBS combined yielded a pooled prevalence rate of 30%. The highest reported prevalence was for SP, affecting about 42%. Appropriately targeted assessment (perhaps using HRV) and intervention efforts are clearly warranted to decrease the SP of university students during their education (3).

Three papers focused on psychiatric populations. The meta-analysis by Hu et al. showed that persistent SP for seven more days worsened symptoms scores in patients with an existing major depressive disorder. This review suggests that persistent SP lasting over

a week would likely worsen symptoms or outcomes related to those health domains compared to more acute or transient sleep issues. The review by Fekih-Romdhane et al. bolstered the presence of disturbed sleep in young individuals at ultra-high risk (UHR) for psychosis, as demonstrated by subjective and objective sleep measurements such as polysomnography, sleep electroencephalograms, and actigraphy. The review discussed the potential mechanisms and processes underlying the association between sleep and psychosis and highlighted its complicated and multifaceted nature, which remains to be determined and understood. The review by Albanese et al. showed that among the various treatments proposed for treating nightmares in PTSD patients, those involving imagery rescripting appear to be the most effective. These techniques provide direct access to the traumatic contents and emotions of nightmares without overwhelming patients, and they enable healthcare workers to quickly detect and modify trauma-related negative beliefs.

Three papers focused on the diagnosis and management of SP in patients undergoing maintenance hemodialysis therapy (MHT). Xu et al. showed that in patients requiring MHT, older age, lower albumin, and calcium levels are all risk factors for SP. Lower albumin and calcium levels in these patients also correlating with SP is logically plausible, as nutritional deficiencies can affect sleep regulation. Albumin and calcium have important biological functions. In the same line of research, Tong et al. showed that SP were associated with declining renal function (the highest Cys-C, Q4) in postmenopausal women. The findings suggested that postmenopausal women should prioritize maintaining excellent sleep quality, which provides clinical evidence for the feasible early diagnosis and effective prevention of kidney disease progression, such as MHT, in postmenopausal women. Mohamed et al. highlight that collaboration between the family and healthcare workers are essential to improving the quality of sleep in patients undergoing MHT.

As a common and formal sleep disorder, OSA yielded three papers. Sun et al. found that using the slow-4 frequency range in OSA may be more specific. These findings imply that severe OSA patients exhibit frequency-related aberrant spontaneous brain activity, which could help us understand the pathology of OSA-related disorders and give us possible therapeutic targets for OSA patients. The study by Su et al. documented that despite considerable available OSA knowledge, medical residents have low confidence in OSA management. The authors suggested practical and small group teaching approaches that have the advantages of flexible time, short duration, and high participation, especially during clinical rotations. In a pediatric population, Lee et al. reported that a reduction in the overall obstructive sleep apnea (OSA) questionnaire score and the very low frequency (VLF) power of HRV mediated the improvement in the obstructive apnea-hypopnea index after adenotonsillectomy. These preliminary findings are innovative, and they point the way forward for further study into the impact of HRV-guided therapies on childhood OSA.

The study by Duong-Quy et al. highlighted that during COVID-19 SP, depression symptoms and fatigue in healthcare workers worsened among frontline healthcare workers. Earlier studies established that the COVID-19 pandemic has put great strain on the global healthcare system, necessitating the development of numerous field hospitals and isolation camps around the world. This temporary solution has resulted in the suspension of proper environmental conditions for patients and healthcare workers (4–6).

Belmon et al. suggested combining intervention mapping (IM) with the Health in All Policies (HiAP) for health promotion, which resulted in a comprehensive, evidence-based design for the implementation of a multi-sector integrated program to increase children's sleep health. Their blueprint document suggested that it be used to help build local (sleep) health promotion programs in other regions with distinct local governmental systems and cultures while keeping the policy environment in mind.

Niu et al. demonstrated high sensitivity and specificity and excellent diagnostic ability of the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), and Athens Insomnia Scale (AIS) questionnaires in screening for insomnia in stroke patients. The authors concluded that each of the three questionnaires has advantages and disadvantages when assessing insomnia.

Xiang et al. aimed to investigate the changes in features and related aspects of several GABAergic system indexes in the peripheral blood of individuals with insomnia. They found that serum GABA inhibitory activity may be altered in insomnia patients, and decreased expression levels of $GABA_A$ receptor α1 and α2 subunit mRNA may become a reliable indication of insomnia disorders.

While great strides have been made in understanding and treating SP, it remains an undertreated public health issue. A holistic, patient-centered approach combining multiple modalities tailored to the individual holds the most promise for optimal management of these conditions. Continued research to elucidate sleep-wake neurobiology and innovative technological solutions can help improve diagnosis, treatments, and quality of life for the millions affected by SP worldwide.

Author contributions

HJ: Conceptualization, Data curation, Investigation, Project administration, Resources, Writing—original draft, Writing—review and editing.

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SYSTEMATIC REVIEW
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Meta-Analysis of Sleep Deprivation Effects on Patients With Depression

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Objective: Depression is a common disorder with a high recurrence rate. Since the effect of sleep deprivation on depression in existing studies were inconsistent, the present study aimed to reassess the effects of SD on patients by performing a meta-analysis of updated research.

Methods: PubMed, Embase, the Cochrane Library, and Web of Science were searched for articles before January 20th, 2021. Data on participant characteristics, SD characteristics, adjunctive method and tests for depression were extracted. A comprehensive analysis was conducted to assess the effect of SD on depression and subgroup analysis was used to determine the sources of heterogeneity.

Results: In total, 8 articles were included. An SD time of <7 days slightly worsened depression levels [0.24 (−0.21, 0.69); I^2 = 0%; P = 0.43], a time of 7–14 days had antidepressant effects [−1.52 (−2.07, −0.97); I^2 = 19.6%; P = 0.288], and a time of more than 14 days also worsened depression [0.76 (0.12, 1.40); I^2 = 43.7%; P = 0.169].

Conclusion: SD may serve as an effective antidepressant measure in humans when the time was 7–14 days, while a time of <7 days and more than 14 days worsened depression.

Keywords: sleep deprivation (SD), depression, meta-analysis, patients, review

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INTRODUCTION

Depression is a common, debilitating, and potentially lethal disorder that can affect people of all ages (1). More than 300 million people worldwide suffer from depression. The World Health Organization (WHO) ranks depression as the single largest contributor to global disability, accounting for "years of life lived with a disability" in 13.4% of women and 8.3% in men (2, 3). In its most severe form, depression can lead to suicide. Nearly 800,000 people die by suicide each year, and it is the second leading cause of death in the 15–29 year-old age group (4).

Most people with depression have tried at least one antidepressant medication, but medication effects do slowly manifest, and side effects such as insomnia and anxiety can lead patients to try different medications or refuse medication altogether (5, 6). Furthermore, 30–40% of patients are resistant to available antidepressant medications commonly prescribed for major depressive disorder (7).

As a result of difficulties encountered when treating depression, there is an urgent need to find non-pharmacologic therapies. In clinical practice, many non-pharmacologic therapies have attracted special attention, such as sleep deprivation (SD) (5), bright light therapy (BLT) (8), cognitive behavioral treatment (CBT) (9), and repetitive transcranial magnetic stimulation (rTMS) (5). Among these, SD therapy may have rapid antidepressant effects (10). Some clinical studies have shown that SD is an effective treatment for patients with depression (11, 12). Total sleep deprivation (TSD) for one entire night has been found to improve depression symptoms in 40–60% of patients (13). Unfortunately, the therapeutic effects of SD are transient, and depressive symptoms can even return after a subsequent full night of sleep (5, 14).

Some results have indicated that patients who use a combination of antidepressants and SD have a significantly lower tendency to relapse after a full night of sleep than those who do not use this method (15). Many researchers have attempted combining antidepressants with SD, BLT, or CBT to form integrated antidepressant treatments, which have been shown to have positive effects (16, 17). Therefore, it was hypothesized that certain combinations of depression therapy can enhance the therapeutic effects of SD.

Despite a recent meta-analysis (5), comprehensive aggregated data are lacking. The literature on SD lacks randomized controlled trials and has shown inconsistent results. The literatures included by Boland et al. (5) were published relatively early and new relevant articles may have been published in recent years. Michael Ioannou et al. reported a meta-analysis including randomized controlled trials, cohort studies, and case series, which led to low Evidence-based Medicine Grade (18). In that particular article, SD was not the singular variable in the intervention, and the primary outcomes were depressive symptoms, quality of sleep, health-related quality of life, and so on. Thus, too many variables may lead to greater heterogeneity. This article, by performing a meta-analysis, included RCT articles to examine and update the effect of SD on depressed patients by assessing the change in depression scores before and after SD.

The present study aimed to explore the effectiveness of SD for depression levels. The antidepressant effects of SD are primarily reported in humans, yet the time of sleep deprivation has not been standardized across studies, which may yield inconsistent results. Thus, this study explored whether SD treatment for patients with depression requires a more specific treatment course.

Abbreviations: BDNF, brain-derived neurotrophic factor; BLT, bright light therapy; CBT, cognitive behavioral treatment; HAM-D, Hamilton Rating Scale for Depression; PICOS, participants, intervention, comparison, outcome, and study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSD, partial sleep deprivation; RCT, randomized controlled trials; rTMS, repetitive transcranial magnetic stimulation; SD, sleep deprivation; SMD, standard mean difference; SSRIs, selective serotonin reuptake inhibitors; SPA, sleep phase advance; TCA, tricyclic antidepressive agent; TSD, total sleep deprivation.

METHODS

Literature Search Strategy

Studies related to the effects of SD on depression in patients were identified by searching four electronic databases, i.e., PubMed, Embase, the Cochrane Library, and Web of Science. The databases were searched for articles before January 20th, 2021. Keywords included the following: ("sleep deprivation" OR "sleep curtailment" OR "sleep restriction" OR "sleep loss") AND ("depress*") for patients in the title or abstract.

Six authors in pairs, removed duplicates and screening the records, ensuring that all records were independently evaluated by two authors. Mesh in PubMed and EMTREE in Embase were used, and a secondary or supplementary search was then performed. In total, 10,873 records meeting both search criteria were obtained. Articles were screened in duplicate and excluded by keyword (case reports, reviews, and meta-analyses). Then, studies were selected for inclusion or exclusion according to the title and summary. Additionally, relevant original studies cited in the selected articles were also eligible for inclusion. Final inclusion was determined by reading the full text of the studies.

Inclusion Criteria

All studies included in this article met the criteria described by the participants, intervention, comparison, outcome, and study design (PICOS) according to recommendations by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Participants: Human patients were aged between 12 and 80 years and had been diagnosed with depression based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) criteria, regardless of depression type (e.g., bipolar or unipolar) and gender. In addition, patients with serious organic diseases or mental and somatic comorbidities as well as pregnant women were excluded. Intervention: Sleep deprivation as an intervention. Comparison: The only difference between the experimental group and the control group was that the experimental group had sleep deprivation while the control group did not. In a word, except for sleep deprivation, the rest of the interventions were the same in both groups. As long as such an experimental design was met, we could include the article regardless of how many combination therapies it had. Outcomes: Outcomes were depression assessment tools, such as the HAMD, Beck Depression Inventory (BDI), and Montgomery-Asberg Depression Rating Scale (MADRS). Study design: All included literature were randomized controlled trials.

Articles lacking either the full text or primary data findings that could not be resolved with the Engauge Digitizer tool were excluded.

Data Extraction and Quality Assessment

Each article was read in its entirety by two researchers to extract the data and record trial details in a standardized table containing the following information: author(s), year of publication, country, participant characteristics (e.g., sample size, age, gender, and sample type), SD characteristics (e.g., type

and timetime), adjunctive method (e.g., bright light therapy, cognitive behavioral treatment, and antidepressant drug), and patient outcome. Since the time of a single sleep deprivation and the frequency of sleep deprivation varied in the included articles, we used the concept of total sleep deprivation time including the total numbers of wake nights and recovery time. The time points for the assessment of depressive conditions were the baseline and after the total sleep deprivation intervention.

When no specific data were included (e.g., only graphs or figures), the authors were contacted and asked to provide the results of the experiments or the raw data. If this failed, data were estimated based on graphs or figures using a digital ruler called the Engauge Digitizer (19, 20). Primary data were estimated according to coordinate positions, and then statistical methods were used to calculate the mean and SD. The risk of bias was estimated independently by two researchers (J. Y. and T. M.) who extracted and appraised the data. They used the Cochrane Risk of Bias tool for patient studies (21). Inconsistencies between the two researchers were resolved through negotiation, and when this failed, a third professional was asked to judge the risk of bias.

Data Synthesis and Analysis

First, to assess the total effects of SD on depression, the selected trials were analyzed without considering characteristics and variables. Then, hierarchical analysis based on a significant variable (in this case, the time of SD) and its effects on patients was performed. Subsequently, subgroup analysis was used to determine the sources of heterogeneity. Subgroup analysis was performed according to the country and adjunctive method for the human studies. For each comparison, standardized mean differences based on Hedge's g were calculated as measures of the effect size, with values ranging from small (0.2–0.5), medium (0.5–0.8), and large (0.8 and higher), as per standard convention. This approach ignored differences in depression measurement tools so that the analysis was unified. The random effects model proposed by DerSimonian and Laird (22) was also used. Finally, publication bias was evaluated by funnel plots and Egger's test to quantify the bias.

The heterogeneity of effect size within each comparison was tested using Cochran's Q test and I^2 statistics. P-values of <0.05 indicated high heterogeneity. Data were presented as the effect size $\pm$ confidence intervals at 95%. Results were considered significant when the confidence interval range was lower or higher than zero. All calculations were performed using Stata software (version 13.1).

RESULTS

Study Characteristics

The search strategy resulted in 10,873 articles from PubMed and other databases (**Figure 1**). Redundant literature was eliminated, and articles were further screened for relevance according to keywords (e.g., case report, review, and meta-analysis). After these steps, a total of 6,980 articles on humans were analyzed according to the title and summary. After analysis of titles and abstracts, 36 articles remained and were screened by reading the full text. After excluding articles that lacked a control group or primary data, a total of eight studies (23–30) involving nine trials meeting the inclusion criteria were ultimately included in the present meta-analysis.

In the studies, TSD was applied in five articles, while partial sleep deprivation (PSD) was applied in three articles. No record of sleep curtailment, sleep restriction, or sleep loss was included. The included studies were conducted in Germany, the United States of America (USA), Turkey, Switzerland, and the Netherlands. All studies involved a combination of SD and other interventions. For instance, six involved antidepressant drugs, and the other two involved either BLT or CBT (**Table 1**).

Study Quality

Most studies adopted a randomized control trial (RCT) method, in which most random sequence generations indicated a low risk of bias (22). Performance bias was not mentioned in most of the articles and was therefore a mostly unclear bias risk. Although the articles did not mention detection bias, the degree of depression was quantitatively measured by the depression scale; therefore, the tested factor had little influence, and the authors believed there was a low risk of detection bias. Two studies did not blind participants (27, 28), and other articles did not mention blindness. However, SD was not possible to blind a human being exposed to, which was considered a shortcoming of those studies. The final data for one study were unclear; thus, a high risk of bias was identified for the outcome of that study (30). Unclear bias accounted for the majority of other biases, since some literature only provided images instead of concrete data; thus, the data obtained through software processing may have had some impact on the results (**Figure 2**). Besides, egger's tests showed that there were no indications of publication bias (**Figure 3**).

Main Efficacy of the Meta-Analysis

Figure 4 shows the total effect of SD on depression. Nine trials (10 datasets) reported depression using the HAMD. The random effects meta-analysis elicited a summary effect size of −0.15 (95% confidence interval [CI], −0.80 to 0.50; $I^2 = 84.3\%$; $P = 0.000$) (**Figure 4A**). When analyzed according to the SD schedule (<7 days, 7–14 days, or >14 days), the forest plot showed that an SD time of <7 days slightly worsened depression levels [0.24 (−0.21, 0.69); $I^2 = 0\%$; $P = 0.43$]. Finally, a time of 7–14 days had significant antidepressant effects [−1.52 (−2.07, −0.97); $I^2 = 19.6\%$; $P = 0.288$], and a time of more than 14 days also moderately worsened depression [0.76 (0.12, 1.40); $I^2 = 43.7\%$; $P = 0.169$] (**Figure 4B**).

Heterogeneity Analyses

By performing subgroup analysis, sources of research heterogeneity were identified. These may have been related to the country in which the research was conducted, type of combination therapy employed, and depression tests that were used. Studies were divided into five subgroups according to country (**Figure 4C**). Studies from Turkey showed large antidepressant effect sizes [−1.77 (−2.35, −1.19); $I^2 = 0\%$; $P = 0.586$], while studies from Switzerland showed large effect sizes for worsened depression [1.07 (0.51, 1.63); $I^2 = 0\%$; $P = 0.845$]. The studies were also divided into four subgroups

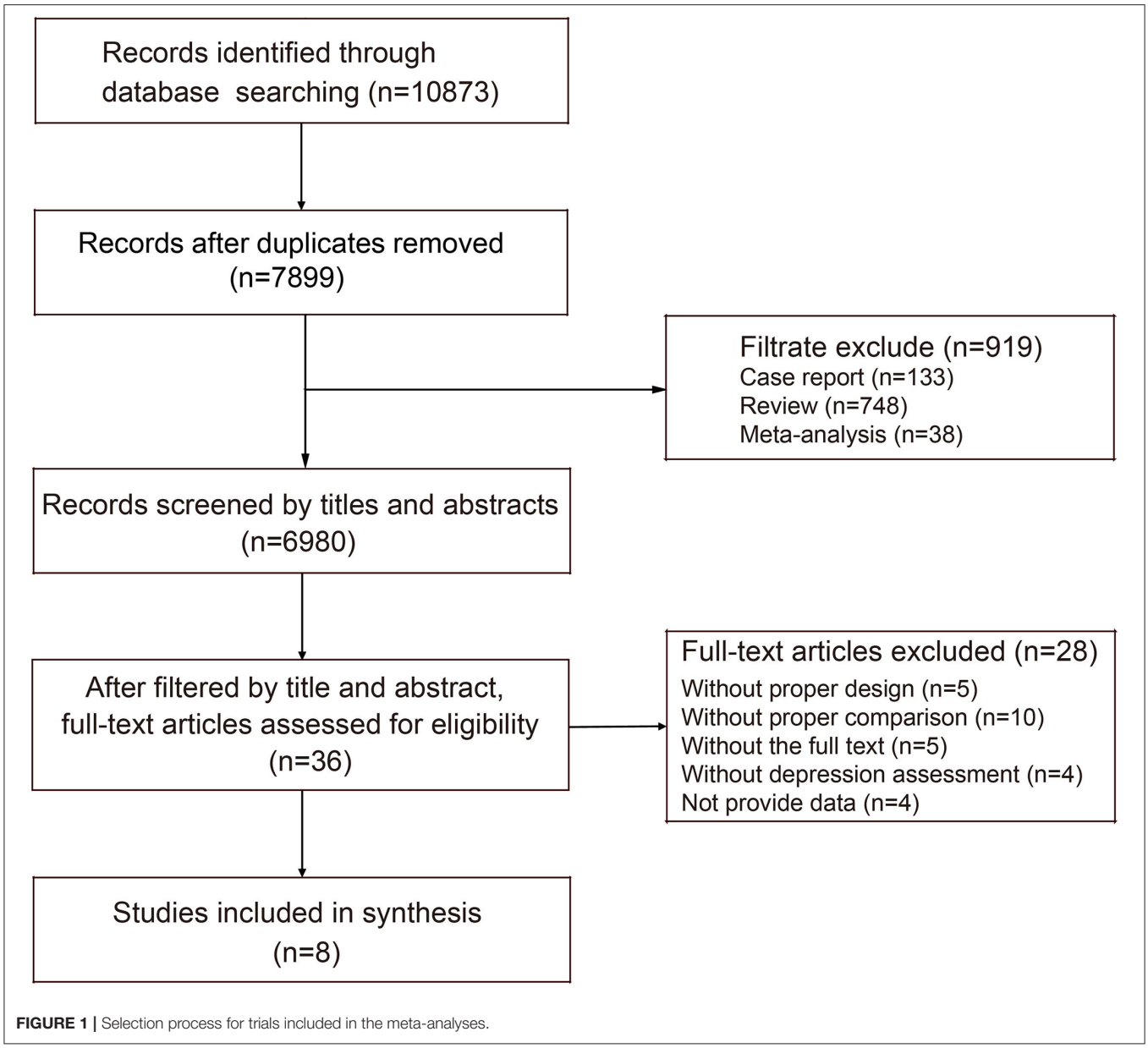

FIGURE 1 | Selection process for trials included in the meta-analyses.

according to the combination of therapies (**Figure 4D**). Studies that combined selective serotonin reuptake inhibitors (SSRIs) with SD showed antidepressant effects [−1.77 (−2.35, −1.19); I^2 = 0%; $P = 0.586$].

To investigate gender as a variable, a subgroup analysis was performed, and grouping was determined by the proportion of women in the total population. When the ratio was >0.8, the effect size was 0.31 (95% CI, −0.46 to 1.09; I^2 = 30.7%; $P = 0.230$). When the ratio was between 0.5 and 0.8, the effect size was −0.97 (95% CI, −1.69 to −0.26; I^2 = 71.6%; $P = 0.007$). When the ratio was <0.5, the effect size was 0.76 (95% CI, 0.12–1.40; I^2 = 43.7%; P = 0.169). After one paper was removed via sensitivity analysis (23), it was revealed that the heterogeneity of the 7–14-day group decreased from 66.6 to 19.6%, indicating that the effects of SD on depression were related to SD time in the studies.

DISCUSSION

All eight articles in this meta-analysis used RCT models, which helped to improve the rigor and significance of the review. Judging from the total results of the studies, the data were not as obvious as those revealed in previous meta-analyses and were highly heterogeneous (5). This was because new research was included, and digital software was used to address instances of incomplete data.

In the <7 days group, SD only occurred once with a time of <36 h and the results showed that SD slightly worsened

TABLE 1 | A table of the characteristics of the included studies.

Author(s)	Country	Intervention	Sample size	Age (mean, year)	Type of depression	SM	Combined with other interventions	Time	Depression scale
Elsenga et al. (25)	Netherlands	Clomipramine/SD	10	49.1 ± 13.6	Unipolar	TSD	Clomipramine	7 days	Hamilton interview ratings
		Clomipramine	10	55.6 ± 13.2					
Holsboer-Trachsler et al. (30)	Switzerland	Trimipramine/SD	14	50.43 ± 7.3	Bipolar	PSD	Trimipramine	28 days	HRS, MADRS
		Trimipramine	14	50.64 ± 8.50					
Kuhs et al. (23)	Germany	Amitriptyline/LSD	27	43.3 ± 13.6	Bipolar	LPSD	Amitriptyline	14 days	HAM-D, 10 Item
		Amitriptyline	24	46.0 ± 11.3					
Caliyurt et al. (27)	Turkey	LPSD/Sertraline	13	38.46 ± 12.03	Unipolar	LPSD	Sertraline	14 days	HAM-D, 21 Item
		Sertraline	11						
Kundermann et al. (26)	Germany	TSD+CBT	9	37 ± 2.7	Unipolar	TSD	CBT	21 days	HDRS
		CBT	10	37.4 ± 2.6					
Gorgulu et al. (28)	Turkey	TSD/Sertraline	19	40 ± 11.69	Unipolar	TSD	Sertraline	7 days	HAM-D
		Sertraline	22	33.27 ± 11.18					
Smith et al. (29)	USA	TSD/Paroxetine	7	69.0 ± 4.6	Unipolar	TSD	Paroxetine	36 h	HDS, 13 Item
		TSD/Placebo	6	68.6 ± 4.9					
		Paroxetine	3	71.4 ± 6.0					
Gest et al. (24)	Germany	Wake/BLT	25	16.2 ± 1.3	Unipolar	TSD	BLT	One night	BDI-II
		BLT	37	15.8 ± 1					

BDI-II, Beck Depression Inventory-II; BLT, Bright Light Therapy; CBT, Cognitive behavioral therapy; HAM-D, Hamilton Depression Scale; HAM-D, 10 Item, Hamilton Depression Scale (10-item); HAM-D, 21 Item, Hamilton Depression Scale (21-item); HDRS, Hamilton Depression Rating Scale; HDS-13, Hamilton Depression Scale (13-item); HRS, Hamilton Rating Scale for Depression; LPSD, late partial sleep deprivation; LPSD, late partial sleep deprivation; MADRS, Montgomery–Asberg Rating Scale; PSD, partial sleep deprivation; SD, sleep deprivation; SM, sleep manipulation; TSD, total sleep deprivation; USA, United States of America.

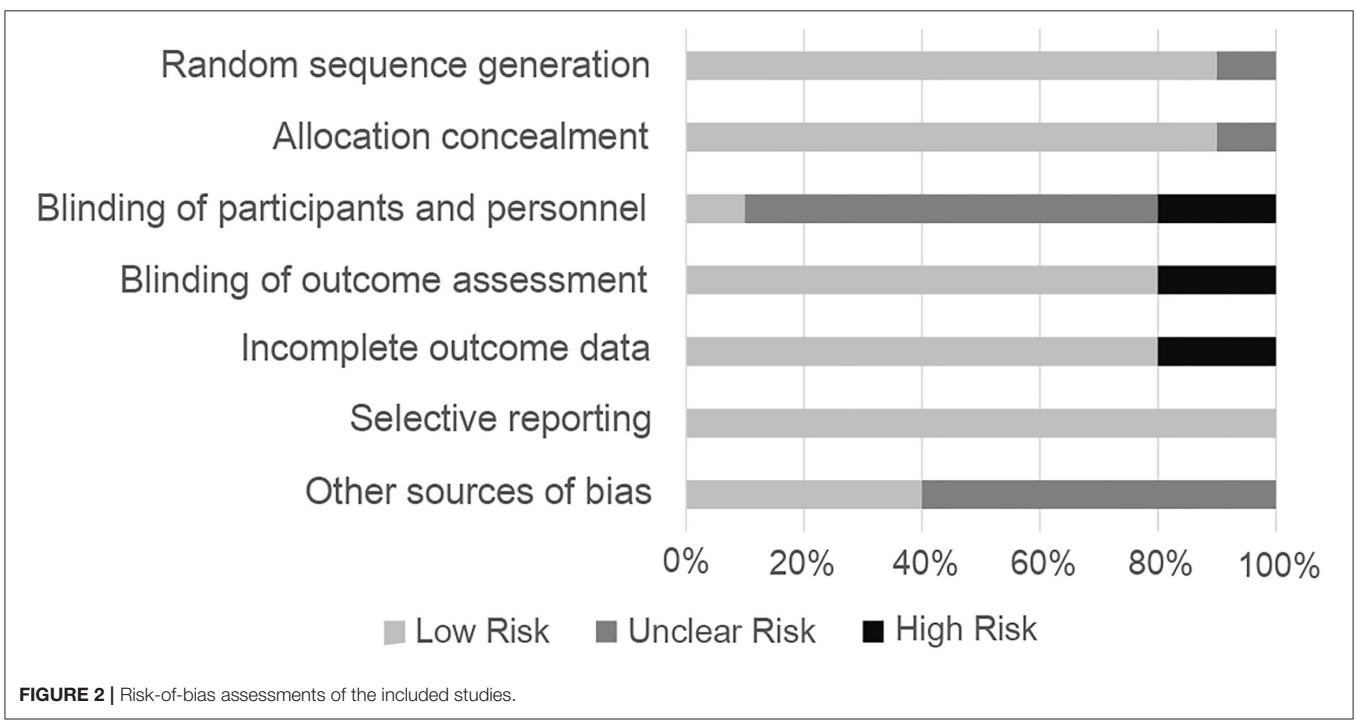

FIGURE 2 | Risk-of-bias assessments of the included studies.

depression. Several articles reported that depression symptoms returned immediately after SD and recovery, with some patients experiencing more severe depression than before (14, 15). The included studies in our study assessed depression after SD, therefore, it was likely that a recurrence of depression following short time of SD may be the cause of this outcome. Sleep loss, especially when chronic, can cause significant and cumulative neurobehavioral deficits and physiological changes, which may

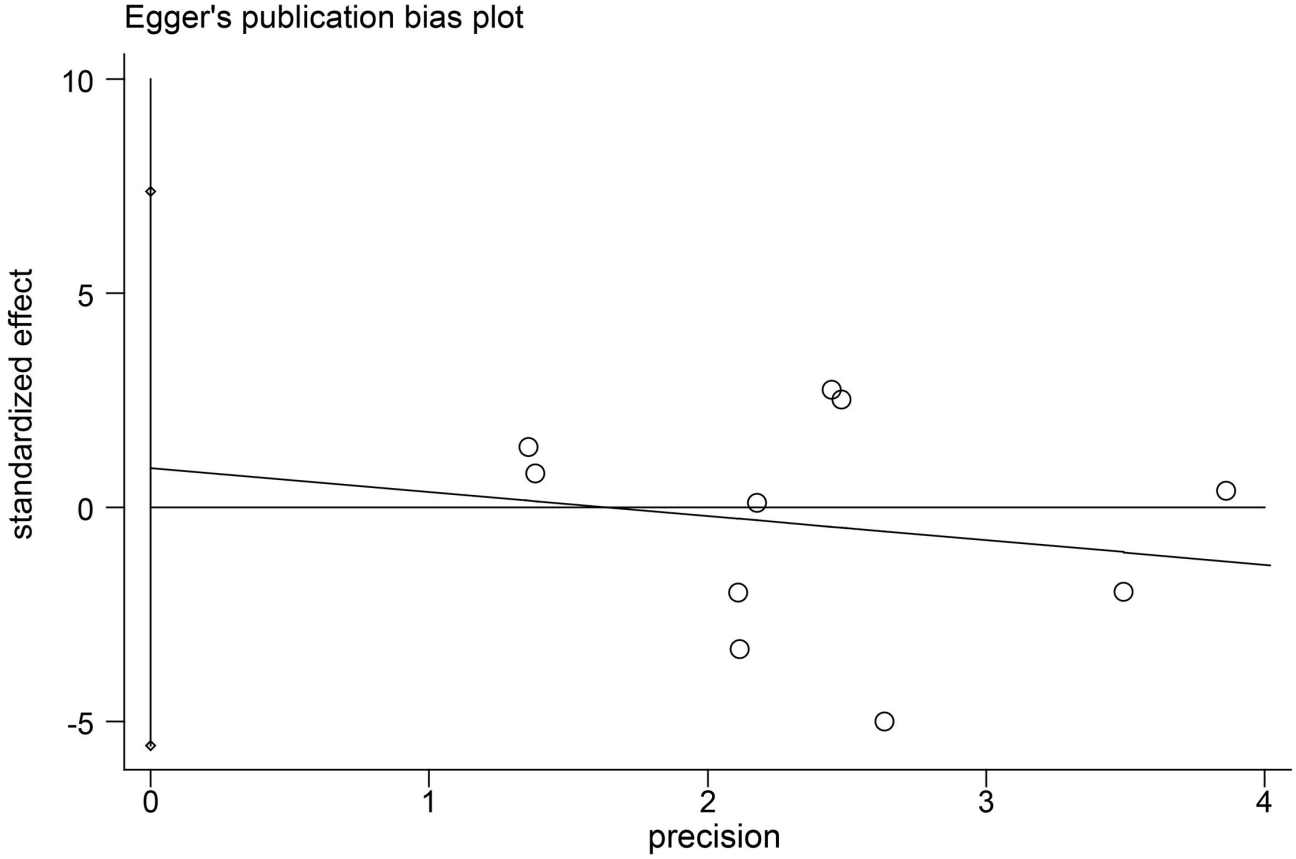

FIGURE 3 | Egger's test.

present as inattention, slowed working memory, reduced cognitive throughput, depressed mood, and perseveration of thought (31). Thus, prolonged and repeated SD may worsen depression, which could account for the increased depression in groups who were subject to an SD time longer than 14 days.

With 7–14 days of SD, interference of the first two conditions was slightly prevented, thus providing a better therapeutic effect. The heterogeneity of this group mainly originated from differences in sample type among the three articles (23). It has been debated whether the polarity of depression affects the response to SD. Studies indicated that in unipolar depressed samples, the response rate to SD was 50.6%, and in samples using a mixture of unipolar and bipolar depressed patients, the response rate was 53.1% (5). And in another meta-analysis, they found similar numerical yet not statistically significant effect sizes for patients with bipolar depression and non-elderly patients with unipolar depression (18). However, with the small amount of literature included in this study, it was impossible to clearly explore similar results. And in the future, it is a question worthy of discussion.

Given the large heterogeneity in the total dataset, sources of heterogeneity were explored for potential influences on variables. The first analysis was a subgroup analysis according to country. Different countries present different factors affecting the occurrence, treatment, and prognosis of depression, such as national health awareness, cultural and quality of education, medical research level, medical and social security, family economic income, social welfare, and social support systems (32, 33). In studies from Turkey, there was an antidepressant effect of SD [−1.77 (−2.35, −1.19); $I^2 = 0\%$; $P = 0.586$]. However, studies from Switzerland showed that SD worsened depression [1.07 (0.51, 1.63); $I^2 = 0\%$; $P = 0.845$]. These findings suggest that the effects of SD on depression may be related to ethnicity and nationality.

Although relatively few articles were included in this study, based on the available data, it was speculated that the treatment effects of SD on depression are more likely to be observed in studies conducted in the Turkish context. An adverse effect of SD was observed in patients from Switzerland in one paper, so additional studies are needed for verification. In light of the above, it should be noted that Turkey has low levels of economic and medical academic development and education, while Switzerland has high levels of the same indices. Depression levels in the Turkish studies may have been significantly related to the medical academic development. In consideration of the possible effects of different ethnic characteristics, further studies are needed to examine the effects of SD on depression across various ethnic groups.

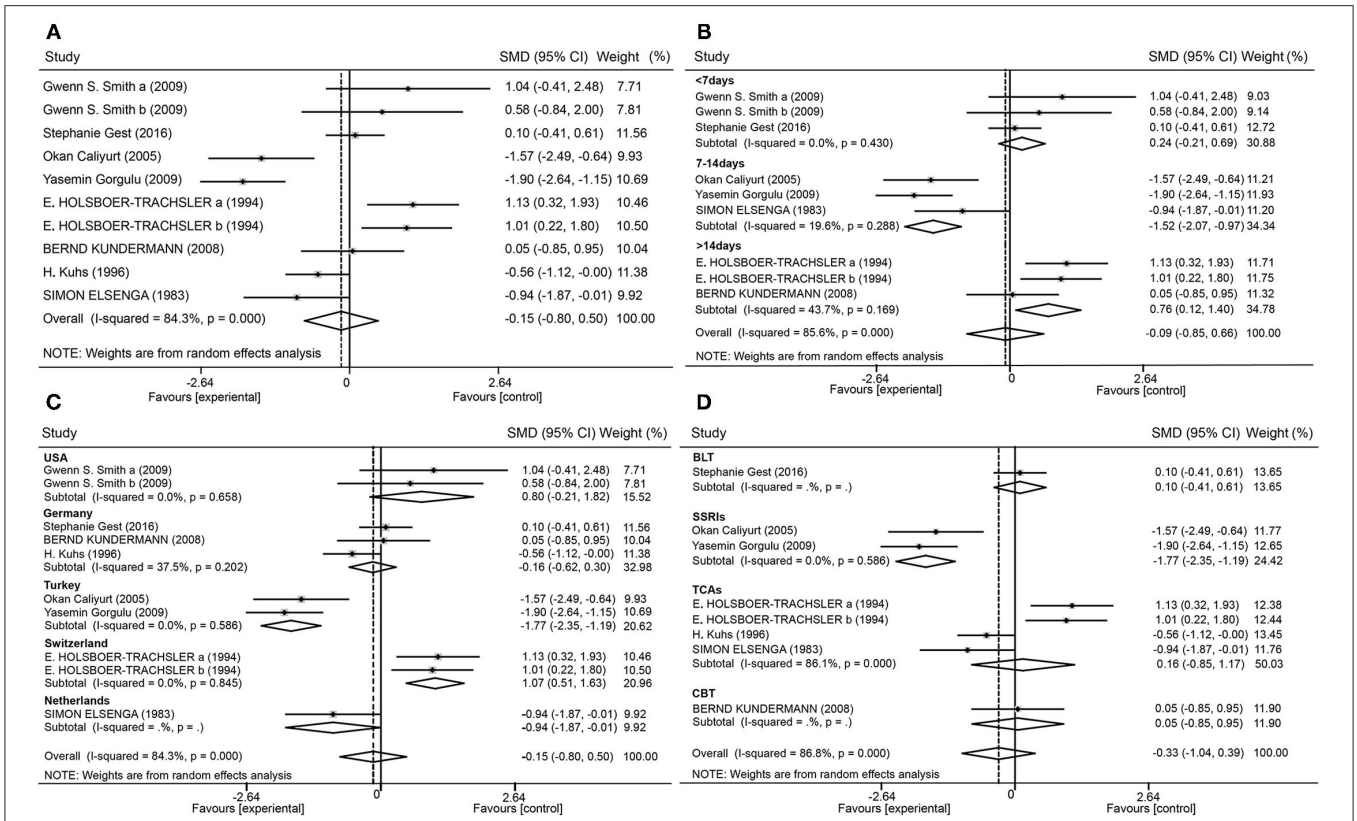

FIGURE 4 | Forest plot. Forest plot of the random effects model meta-analysis of SD effects **(A)**; and subgroup analysis of patients with regard to the time of SD **(B)**, the country **(C)**, and combined therapy **(D)**.

Another subgroup analysis was dependent on whether there was a combination of SD with other therapies. Combination therapy with BLT, CBT, and tricyclic antidepressive agents (TCAs), showed no significant effects of SD on depression. Three studies on SD combined with SSRIs showed antidepressant effects. After removing one study (29) with fewer than seven patients in each group, which may have affected the outcome, the effect size changed from [−0.58 (−1.94, 0.78)] to [−1.77 (−2.35, −1.19)], and heterogeneity changed from 84.3 to 0%.

It was suspected that heterogeneity was related to three aspects. (1) Patients in one of the studies were from the USA, and those in the other two were from Turkey. This correlated with the results of the above analysis, namely that the Turkish studies showed great antidepressant effect of SD and thus an overall effect was antidepressant. (2) One study incorporated paroxetine, while sertraline was used in the other two, so heterogeneity may have originated from the use of different SSRIs. The authors of one paper stated that although sertraline and paroxetine had comparable efficacy for major depression, patients who used sertraline showed lower recurrence rates than those who used paroxetine. Sertraline was somewhat better tolerated than paroxetine and induced lower side-effect profiles (34). (3) Finally, the time of SD in one study was <7 days, while the time was 7–14 days in the other two studies. Furthermore, TCA was not very effective but at the same time, two of the studies were conducted in Switzerland while the TCA studies not from Switzerland did indeed show small positive effects, which was related the above result that studies from Switzerland showed that SD worsened depression. Regarding the gender variable, an effect size between 0.5 and 0.8 was inconsistent with other figures, so it was suggested that gender was not an influential factor in the treatment effects of SD on depression.

In addition, it was worth mentioning that the article by Gest et al. (24) analyzed SD in adolescents. As far, there was very little evidence on chronotherapeutics (such as BLT and SD) in children and adolescents. However, since chronobiology in adolescents differed from that in adults (35) and the evidence for the effects of chronotherapy in children and adolescents were indeed mostly positive but of very low quantity (24, 36), such discrepancies may affect the results and longer-term studies of adolescents are needed. Furthermore, there was no information on sleep phase advance (SPA) in our article, which was also a relevant form of chronotherapy. SPA consists in manipulating the sleep–wake cycle by supporting sleep earlier than the patient's usual bedtime and wakefulness before the usual waking time. D'Agostino et al. (37) suggested that triple chronotherapy (SD-BLT-SPA) might be a safe and effective addition to conventional antidepressant interventions. Although SPA was not mentioned in the studies we included, future studies could try to combine SD, BLT and SPA in the treatment of depression and explore their effects.

The mechanisms of SD regarding depression treatment are complex and are thought to be based on monoaminergic neurotransmission, neuroplasticity, and gene expression. Brain-derived neurotrophic factor (BDNF) levels have been shown to be reduced in individuals suffering from major depressive disorder, and decreased levels are also negatively correlated with Hamilton Rating Scale for Depression (HAM-D) scores. Use of SD has resulted in faster treatment response and increased BDNF levels (28). One study (38) found that in patients who achieved an antidepressant effect after SD, the expression of specific circadian clock genes (e.g., RORA, DEC2, and PER1) increased. However, in patients that did not show this effect, a significant decrease in the expression of these genes was found (39).

Considering that the mechanisms underlying SD-induced or SD-inhibited depression are poorly understood, it is a natural choice to consider animal studies. Animal models are a cornerstone of human research, particularly in research on depression at the tissue, cellular, molecular, and genetic levels. However, no relevant meta-analyses have provided comprehensive results regarding animal studies of depression. Perhaps, we can look forward to animal-related studies that will allow us to compare the effects of sleep deprivation on animals and humans.

IMPLICATIONS

Based on this study's findings, confining the time of SD treatment to 7–14 days may be a clinically feasible way to enhance its therapeutic effects. Regarding combination treatment, SD in addition to SSRI medications was an option, but the time of SD, different medications and countries needed to be considered. Combined with clinical practice, TCAs yield more troublesome side effects and potentially lead to fatal overdose; thus, SSRIs may be safer (40). This study did not include papers with methods combining three or more therapies, so further investigation is needed.

LIMITATIONS

Aside from the abovementioned speculations, several limitations should be noted. The quantity of literature was small, which made the results less convincing and could also have compromised the power of the funnel plot. Second, the data derived using digital software were different from the actual study results, so there was a certain degree of data error. Third, included studies may differ in concern to SD protocols, such as the time of single SD and frequency of SD, which was typically a relevant issue in chronotherapy research and may then lead to heterogeneity.

CONCLUSION

This meta-analysis showed that SD may serve as an effective antidepressant measure in humans when the treatment time was 7–14 days. A time of <7 days slightly worsened depression, while a time of more than 14 days certainly worsened depression. These findings suggest that SD may be used as an intervention for depressed people within specific parameters. Additional high quality research with longer follow-up is needed to strengthen this evidence.

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

BH, MY, and CL wrote the protocol, managed the literature searches, analyzed data, and wrote the draft of the manuscript. ZL designed the study, wrote the protocol, and revised the manuscript. TL, TM, and FL managed the literature searches and analyses. TL undertook the statistical analysis. MY, CQ, and JZ modified the manuscript. All authors contributed to the article and approved the submitted version.

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Using 24-h Heart Rate Variability to Investigate the Sleep Quality and Depression Symptoms of Medical Students

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There have been numerous studies on the relationship between sleep and depression, as well as the relationship between sleep and depression, and heart rate variability (HRV), respectively. Even so, few studies have combined 24-h HRV analysis to study sleep quality and depressive symptoms. The purpose of this cross-sectional study was to investigate the relationship between depressed symptoms, sleep quality, and 24-h HRV in medical students. The particiants were all students at a medical university in Guangdong province, China. A total of 74 college students participated. They were asked to complete a questionnaire that included the Pittsburgh Sleep Quality Index (PSQI), the Beck Depression Inventory-II (BDI-II), the Positive and Negative Affect Scale (PANAS), and 24-h ECG monitoring. The results showed that 41.7% of the medical students had poor sleep quality, with higher levels of depressive symptoms and more negative emotions, and there was no difference in 24-h HRV indices between the low PSQI group and the high one. Correlation analysis showed that there was a significant relationship between sleep quality and depressive symptoms ($r = 0.617$), but the relationship between 24-h HRV indices and PSQI global scores, BDI scores were not significant. However, the correlation analysis of PSQI components and 24-h HRV showed that sleep disturbance was significantly negatively correlated with SDNN and LF in waking period ($r = -0.285, -0.235$), and with SDNN in sleeping period ($r = -0.317$). In general, the sleep disturbance in PSQI components can sensitively reflect the relationship between sleep quality and 24-h HRV of medical students. Individuals with higher sleep disturance may have lower SDNN during awake period and bedtime period, and lower LF in awake period. Twenty-four hour HRV has certain application value in clinical sleep quality monitoring, and its sensitivity and specificity in clinical application and daily life are still worth further investigation.

Keywords: sleep quality, depressive symptoms, positive and negative affects, 24-h heart rate variability, medical students

INTRODUCTION

Heart rate variability (HRV) is an important indicator of autonomic nervous system activity, and has been paid more and more attention for its objective, convenient, non-invasive, and sensitive characteristics. Heart rate variability is the fluctuation in time between successive heartbeats and is defined by interbeat intervals (1). Heart rate variability analysis methods mainly include time domain and frequency domain. Low HRV is thought to be a marker for a number of mental health problems, including the severity of psychiatric disorders such as insomnia, depression, and anxiety (2–10). Insomnia and depression were found to be independent risk factors for cardiovascular disease morbidity and mortality (11–13), suggesting that patients with depression and insomnia may have cardiac autonomic dysfunction. Poor sleep quality and mental disorders such as depression and anxiety disorder can be reflected by HRV (11–15). In terms of time domain indices, standard deviation of the NN (SDNN), root mean square of R–R-intervals, (RMSSD) or the ratio of adjacent R–R intervals to total R–R intervals (pNN50) was lower than that of normal control group. And in terms of frequency domain indices, the low frequency components (LF) and high frequency components (HF) are lower, while the LF/HF components are higher, among which the decrease of HF components is the most common. The parasympathetic nervous system is the branch of the autonomic nervous system responsible for critical restorative processes like "resting and digesting" (16). The effective functioning of this system has been associated with stronger phasic activity of vagus nerve efferent activity to the sino-atrial node of the heart, often termed *cardiac vagal control* (CVC).

Many studies have linked CVC to sleep. Although higher CVC during wakefulness (CVC_{wake}) (17–19) and higher CVC during sleep (CVC_{sleep}) (10, 20, 21) are both associated with higher sleep quality, some studies have found no significant relationship between CVC_{wake} and CVC_{sleep}, or found that CVC_{wake} but not CVC_{sleep} is associated with better sleep quality (21, 22). The relationship between CVC_{wake}, CVC_{sleep} and sleep quality remains to be further verified. Cardiac vagal control during wakefulness and sleep may be related to different sleep processes, and both of them may be predictors of sleep quality. Sleep is essential for normal brain function and mental health (23, 24). The maintenance and promotion of health is important to college student success. The study has shown that the phenomenon of sleep disturbance is not only common among Chinese medical students, but also higher than non-medical students and the general population (25), which may have a bad impact on their academic performance, physical and mental health, and quality of life (26). A recent meta-analysis of 43 studies involving a total of 18,619 students from 13 countries found that lack of sleep is a common problem among medical students, and they sleep an average of 6.3 h, <7 h of sleep advice, with 33 studies finding that more than half of the medical students report poor sleep quality (27). Sleep disorders can manifest as complaints of insufficient sleep, excessive sleep, or abnormal movement during sleep (28). Studies have shown that sleep disorders can lead to decreased immunity, decreased life adaptability, anxiety, depression, and other problems, and even cause a variety of physical diseases (29). College students are often characterized by irregular sleep time, insufficient sleep, and poor sleep quality (30, 31), and the sleep quality of medical students is still not optimistic (25, 32). Sleep disturbance is a risk factor for depression (33), and sleep quality index predicts future depression, anxiety, and stress scores in college students at both baseline and follow-up (34). Some research even reported that a complex bidirectional relationship between depression and sleep (35, 36). Sleep disturbance is receiving increasing attention as a public health issue.

Finally, The recordings and analysis of HRV can be as short as a few minutes or as long as 24 h. Each has its own advantages and cannot be replaced by the other. Long-term HRV recordings predict health outcomes heart attack, stroke, and all-cause mortality. Though the prognostic value of long-term HRV assessment, it has not been broadly integrated into mainstream medical care or personal health monitoring (1). Although there has been much research on the relationship between sleep problems and depression, a review of the literature found that there have been few current studies on the relationship between depression and sleep disorders combined with 24-h HRV analysis. The sensitivity and specificity of 24-h HRV in normal subjects and clinical samples required additional investigations, and the findings of previous studies on the relationship between CVC and sleep quality are extremely disparate. The purpose of this study was to explore the relationship between sleep quality, depressive symptoms and 24-h HRV among medical students. Our research hypothesis as follows: First, varied sleep quality can be reflected in 24-h HRV, and there are significant differences in HRV between groups with varying sleep quality. Second, CVC has a significant positive relationship with sleep quality in both the waking and sleeping phases.

MATERIALS AND METHODS

Participants and Procedure

Participants in this cross-sectional study were recruited from a medical university in Guangzhou, Guangdong, China, using a website link's recruiting information and experimental recruitment ads. The study was carried out from October 2020 to July 2021, and we received response from 80 potential participants. Our inclusion criteria were as follows: First, no history of mental illness, such as diagnosed depression, anxiety, or other mental diseases. Second, no history of heart illness, such as coronary heart disease, arrhythmia, cardiomyopathy, and so on. Third, no long-term smoking or drinking behaviors. A total of 76 participants were recruited for this cross-sectional study based on initial screening results.

Participants then arrived at the lab on time to complete a questionnaire containing the Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory -II, BDI-II), The Positive and Negative Affect Scale (PANAS), and wear a dynamic electrocardiograph to complete a 24-h dynamic electrocardiogram examination in school, with sensors connecting the electrocardiograph to the individual's sternum in the center. During menstruation, female participants were

not subjected to 24-h ECG monitoring. Four participants were excluded [one participant did not complete a 24-h ECG monitoring, one participant had a history of anxiety disorder, and two participants detected ventricular premature beat (VPB)]. Finally, data from 72 participants (31 males and 41 females, aged 19–34 years, $M = 23.90$, $SD = 2.39$) were included in the analysis, who were divided into low PSQI group and high PSQI group based on PSQI total scores. The study was approved by the ethics committee of Southern Medical University and all participants provided informed consent.

Measures

The Pittsburgh Sleep Quality Index

Subjective sleep quality was evaluated by the Chinese version of the PSQI, a widely used, self-report questionnaire that assesses sleep quality during the previous month (37). The Chinese version of the PSQI consists of 19 self-rated questions and five questions rated by the bed partner or roommate. The 19 items are grouped into seven component scores, each weighted equally on a 0–3 scale. The seven components are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. The component scores are summed to yield a PSQI global score (range: 0–21). A score above five would indicate poor sleep quality and higher scores indicate worse sleep quality (37). The Chinese version of the PSQI had satisfactory psychometric properties in previous studies (38), which is an effective tool to investigate and screen the sleep quality of medical students in China (39). In our research, the Cronbach's alpha was 0.774.

Beck Depression Inventory-II

The self-reported Beck Depression Inventory (BDI-II) (40, 41) was used to assess depressive symptoms among medical students. Beck Depression Inventory-II consists of 21 items, each of which is scored from 0 to 3. Responses were summed up to yield the total score, which could range from 0 to 63, with higher scores meaning higher levels of depressive symptoms (42). The Chinese version has good reliability and validity, with Cronbach's alpha 0.94 (43).

The Positive and Negative Affect Scale

The PANAS (44) consist of two 10-item mood scales and was developed to provide brief measures of PA and NA. Respondents are asked to rate the extent to which they have experienced each particular emotion within a specified time period, with reference to a five-point scale. Each adjective was rated on a scale from 1 = very slightly to 5 = extremely. A number of different time-frames have been used with the PANAS, but in the current study the time-frame adopted was "during the past week." In our research, the Cronbach's alpha was 0.925.

24-h ECG Monitoring

Holter recordings (Mobio® Portable Recorder, Chengdu Synwing Technology Co., Ltd., Chengdu, China) were used to obtain continuous 24-h ECG data. During testing, participants were asked to maintain their daily activities and to avoid drinking alcoholic beverages. Participants were asked to record the time when they slept and when they woke up. The bedtime ECG was defined as the recording obtained from the time at which subjects went to bed until the time they got out of bed, and the awake ECG as that obtained during the rest of day (10). All the subjects underwent ECG monitoring at school. ECG analytics software was used to process and analyze the collected data, and the time domain indices and frequency domain indices were obtained. Time domain measures of HRV include the mean heart rate and standard deviation of the normal interbeat intervals (SDNN), the root mean square successive difference (RMSSD) between adjacent normal interbeat intervals, and the percentage of adjacent intervals that varied by >50 ms (pNN50). Standard deviation of the normal interbeat interval is indicated to reflect overall HRV and RMSSD as well as pNN50 reflect parasympathetic activity (6). Frequency domain of measures HRV include high-frequency power (HF: 0.15–0.40 Hz), low-frequency power (LF: 0.04–0.15 Hz), and LF/HF ratio. Low-frequency power is thought to be modulated by both sympathetic and parasympathetic activities, whereas HF power is mainly modulated by parasympathetic activity. The LF/HF ratio was computed as a measure of the sympathovagal balance toward sympathetic activity (45, 46).

Data Analysis

Descriptive analysis and difference test between two independent samples were performed using SPSS 22.0. The collected demographic data, sleep quality index, depressive symptoms, positive and negative emotions, and 24-h HRV were analyzed by descriptive analysis. Since the variables in our study did not conform to normal distribution, Mann-Whitney U-test was used to test inter-group differences in depressive symptoms, HRV, as well as positive and negative emotions, as well as differences in HRV during wakefulness and sleep periods. Spearman rank correlation analysis was used to test the relationship between PSQI, depressive symptoms, and HRV, and to test the relationship between sleep quality index, depressive symptoms, and HRV during wakefulness and bedtime period, $p < 0.05$ was used to confirm statistical significance.

RESULTS

Demographic Data of the Total Sample and Descriptive Statisics

The age, sex ratio, height, weight, BMI [BMI (kg/m^2) = weight (kg)/Height^2 (m)], PSQI global scores, depressive symptoms, positive and negative emotions, and all 24-h HRV indices of the total study samples are shown in **Table 1**.

Differences in Depressive Symptoms, 24-h HRV and Positive and Negative Emotions Between Different Sleep Quality Groups

As shown in **Table 2**, the study divided the sample into two groups of participants, 42 of the 72 participants had good sleep quality (PSQI global score ≤ 5; Age, 24.07 $\pm$ 2.65), accounting for 58.3% of the total samples. Thirty participants had poor sleep quality (PSQI total score >5 points; Age, 23.67 $\pm$ 1.99),

TABLE 1 | Demographic data of the total sample.

Variable		*Mean*	*SD*
Age (years)		23.90	2.39
Male/Female	31/41		
Height (m)		1.65	0.08
Weight (kg)		56.53	8.90
Heart rate (beats/min)		74.57	6.77
BMI (kg/m^2)		20.65	2.30
PSQI global score		5.29	2.84
BDI-II score		8.26	8.61
PANAS			
Positive		30.07	6.57
Negative		21.39	7.16
HRV			
SDNN		170.09	34.74
RMSSD		45.02	14.93
pNN50		20.20	10.33
LF		1105.63	563.60
HF		849.81	581.01
LF/HF		1.60	0.89

PANAS, positive and negative affect scale; HRV, heart rate variability.

TABLE 2 | Differences of depressive symptoms, heart rate variability and positive and negative emotions in sleep quality group.

Variable	Low PSQI group ($n = 42$)	High PSQI group ($n = 30$)	p[a]
Age	24.07 ± 2.64	23.67 ± 2.00	0.719
Gender (male/female)	20/22	11/19	0.358
Height (m)	1.66 ± 0.08	1.64 ± 0.07	0.552
Weight (kg)	56.80 ± 8.39	56.15 ± 9.70	0.652
Heart rate (beats/min)	74.31 ± 6.84	74.93 ± 6.76	0.744
BMI	20.66 ± 2.19	20.64 ± 2.48	0.964
PSQI global score	3.48 ± 1.45	7.83 ± 2.29	0.000
BDI-II score	5.02 ± 4.51	12.80 ± 10.79	0.000
PANAS			
Positive	32.33 ± 6.48	26.90 ± 5.32	0.001
Negative	19.21 ± 5.23	24.43 ± 8.12	0.003
HRV			
SDNN (ms)	172.34 ± 33.83	166.96 ± 36.33	0.486
RMSSD (ms)	44.95 ± 14.83	45.12 ± 15.32	0.977
pNN50 (%)	20.21 ± 10.28	20.19 ± 10.57	0.991
LF (ms^2)	1130.27 ± 608.21	1071.13 ± 502.58	0.486
HF (ms^2)	823.16 ± 566.95	887.11 ± 607.91	0.623
LF/HF	1.59 ± 0.75	1.62 ± 1.07	0.652

[a]*Comparison between the two groups (non-paried): continuous variable (Mann-Whitney U-test). Low PSQI group indicated that the scores were below 5 and good sleep quality; High PSQI group indicated that the scores were above 5 and poor sleep quality. PANAS refers to the Positive and Negative Affect Scale. HRV refers to heart rate variability. Mean values (± SD) for the indices of each group.*

accounting for 41.7% of the total samples. There were no differences between the two groups in terms of age, gender ratio, BMI, or heart rate.There were significant differences in PSQI global scores (3.48 ± 1.45 vs. 7.83 ± 2.29, $p < 0.001$) and BDI-II scores (5.02 ± 4.51 vs. 12.80 ± 10.79, $p < 0.001$) between the low PSQI group and the high PSQI group. At the same time, the group with low PSQI experienced more positive emotions (32.33 ± 6.56 vs. 26.90 ± 5.32, $p = 0.001$) and less negative emotions (19.21 ± 5.23 vs. 24.43 ± 8.12, $p = 0.003$) in the recent period than the group with high PSQI.

Comparison of Heart Rate Variability of Different Sleep Quality During Awake and Bedtime Period

The overall mean and standard deviation of all HRV indices, and the mean and standard deviation of HRV indices during awake period and bedtime period are shown in **Table 3**. Mann-Whitney U-test was used to test whether there was a difference in HRV between the low PSQI group and the high PSQI group during awake period and bedtime period. The results showed that there was no significant statistical difference in HRV indicators between the group with low PSQI and the group with high PSQI ($p > 0.05$).

Correlation Analysis of Sleep Quality, Depressive Symptoms and 24-h HRV

The mean scores for the PSQI global scores, BDI-II scores, SDNN, RMSSD, pNN50, LF, HF, and LF/HF were 5.29 ($SD = 2.84$), 8.26 ($SD = 8.61$), 170.09 ($SD = 34.74$), 45.02 ($SD = 14.93$), 20.20 ($SD = 10.33$), 1105.63 ($SD = 563.60$), 849.81 ($SD = 581.01$), 1.60 ($SD = 0.89$), respectively. Spearman correlations were used to explore the relationship between sleep quality, depressive symptoms, and 24-h HRV, as shown in **Table 4**. The results found that there was a significant correlation between PSQI global scores and depressive symptoms ($r = 0.617$, $p < 0.01$), while there was no significant correlation between the indicators of 24-h HRV and the first two, so further analysis could not be carried out.

Correlation Analysis of Sleep Quality, Depressive Symptoms and HRV During Awake Period

Table 5 shows the mean and standard deviation of PSQI dimensions, PSQI global scores, BDI-II, and HRV indicators during awake period. Spearman correlations were used to explore the relationship between sleep quality, depressive symptoms, and HRV during awake period.We found that the score of Sleep disturbance is negatively correlated with SDNN and LF ($r_{SDNN} = -0.285$, $r_{LF} = -0.239$, $p < 0.05$), and positively correlated with BDI-II ($r = 0.372$, $p < 0.01$) during awake period. However, we did not find a significant correlation between LF, SDNN and BDI-II scores during awake period ($r = 0.040, -0.021$, $p = 0.740, 0.864$).

Correlation Analysis of Sleep Quality, Depressive Symptoms and HRV During Bedtime Period

Table 6 shows the mean and standard deviation of PSQI dimensions, PSQI global scores, BDI-II scores, and HRV indicators during bedtime period. We only found a negative

TABLE 3 | Heart rate variability characteristics and differences during awake and bedtime period.

Variable	Mean ± SD			p^a
	Total ($n = 72$)	Low PSQI group ($n = 42$)	High PSQI group ($n = 30$)	
Awake period				
Time domain				
SDNN (ms)	123.11 ± 29.71	125.09 ± 30.15	120.34 ± 29.36	0.398
RMSSD (ms)	36.52 ± 13.08	37.17 ± 13.90	35.62 ± 12.02	0.583
pNN50 (%)	14.50 ± 9.44	14.97 ± 9.69	13.85 ± 9.19	0.545
Frequency domain				
LF (ms^2)	971.36 ± 392.77	1004.30 ± 407.73	925.25 ± 372.69	0.253
HF (ms^2)	551.85 ± 449.87	554.94 ± 465.32	547.52 ± 435.14	0.936
LF/HF	2.39 ± 1.35	2.38 ± 1.11	2.39 ± 1.65	0.530
Bedtime period				
Time domain				
SDNN (ms)	116.21 ± 30.99	117.01 ± 29.29	115.10 ± 33.69	0.553
RMSSD (ms)	63.86 ± 24.83	63.38 ± 22.62	64.54 ± 28.03	0.950
pNN50 (%)	37.90 ± 16.44	37.22 ± 16.87	38.85 ± 16.05	0.564
Frequency domain				
LF (ms^2)	1312.82 ± 863.15	1215.85 ± 573.19	1448.59 ± 1151.89	0.855
HF (ms^2)	1614.01 ± 1320.89	1608.75 ± 1392.53	1621.3787 ± 1236.93	0.623
LF/HF	1.08 ± 0.72	1.03 ± 0.52	1.15 ± 0.95	0.855

[a]*Comparison between the two groups (non-paried): continuous variable (Mann-Whitney U-test). Low PSQI group indicated that the scores were below 5 and good sleep quality; High PSQI group indicated that the scores were above 5 and poor sleep quality. HRV refers heart rate variability. Mean values (± SD) for the indices of each group.*

TABLE 4 | Descriptive statistics and correlation analysis for PSQI global score, BDI-II score, and 24-h HRV.

Variable	*M ± SD*	1	2	3	4	5	6	7	8
1. PSQI global scores	5.29 ± 2.84	1							
2. BDI-II socres	8.26 ± 8.61	0.617**	1						
3. SDNN	170.09 ± 34.74	−0.122	−0.092	1					
4. RMSSD	45.02 ± 14.93	0.002	0.014	0.591**	1				
5. pNN50	20.20 ± 10.33	0.003	0.039	0.523**	0.970**	1			
6. LF	1105.63 ± 563.60	−0.090	0.010	0.606**	0.665**	0.576**	1		
7. HF	849.81 ± 581.01	0.068	0.036	0.582**	0.952**	0.920**	0.601**	1	
8. LF/HF	1.60 ± 0.89	−0.115	−0.021	−0.255*	−0.635**	−0.655**	0.034	−0.725**	1

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

correlation between Sleep disturbance scores and SDNN ($r = -0.317$, $p < 0.01$) during bedtime period, and a positive correlation between BDI-II scores ($r = 0.372$, $p < 0.01$). However, we did not find a significant correlation between SDNN and BDI-II scores during bedtime period ($r = -0.108$, $p = 0.37$).

DISCUSSION

This study found that (1) Correlation analysis found that the PSQI global scores was positively correlated with the BDI-II scores, that is, the lower the sleep quality, the higher the level of depressive symptoms. (2) Correlation analysis of PSQI components with 24-h HRV showed that higher LF during awake period is associated with higher subjective sleep quality (i.e., fewer sleep disturbances), and higher SDNN during awake period and bedtime period is associated with higher subjective sleep quality (i.e., fewer sleep disturbances). (3) 41.7% medical students had poor sleep quality, accompanied by relatively high levels of depressive symptoms, less positive emotions, and more negative emotions, which may be related to their heavy academic burden. (4) There was no statistical difference in 24-h HRV indicators between the low PSQI group and the high PSQI group in both awake period and bedtime period. These results suggest that sleep problems are common among medical students, that sleep quality is affected by depressive symptoms, and that cardiac autonomic control is closely related to sleep quality during wakefulness and sleep.

The results showed that the high quality of sleep (low PSQI global scores) group had lower levels of depressive symptoms and reported more positive emotions than the low quality of

TABLE 5 | Descriptive statistics and correlations for primary PSQI indices of sleep quality, BDI-II score, and HRV during awake period.

Variable	*M* ± *SD*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
PSQI component scores																
1. Subjective sleep quality	1.04 ± 0.72	1														
2. Sleep latency	0.85 ± 0.87	0.554**	1													
3. Sleep duration	0.79 ± 0.50	0.269*	0.158	1												
4. Habitual sleep efficiency	0.10 ± 0.34	0.157	0.091	0.121	1											
5. Sleep disturbance	0.96 ± 0.49	0.374**	0.339**	0.173	0.137	1										
6. Use of sleeping medication	0.14 ± 0.51	0.273*	0.341**	0.300*	0.095	0.230	1									
7. Daytime dysfunction	1.42 ± 0.95	0.511**	0.398**	0.204	0.187	0.330**	0.389**	1								
8. PSQI global scores	5.29 ± 2.84	0.769**	0.763**	0.396**	0.259*	0.535**	0.454**	0.774**	1							
9. BDI-II score	8.26 ± 8.61	0.555**	0.383**	0.191	0.147	0.372**	0.288*	0.663**	0.617**	1						
10. SDNN	123.11 ± 29.71	−0.046	−0.118	−0.106	0.032	−0.285*	−0.099	0.018	−0.127	0.040	1					
11. RMSSD	36.52 ± 13.08	−0.022	−0.016	−0.002	−0.039	−0.112	−0.112	−0.011	−0.035	0.040	0.667**	1				
12. pNN50	14.50 ± 9.44	−0.059	−0.024	−0.008	−0.042	−0.128	−0.100	−0.021	−0.057	0.027	0.645**	0.982**	1			
13. LF	971.36 ± 392.77	−0.093	−0.086	−0.082	0.085	−0.239*	−0.146	−0.026	−0.136	−0.021	0.608**	0.685**	0.665**	1		
14. HF	551.85 ± 449.87	−0.029	0.101	−0.017	0.030	−0.043	−0.128	−0.001	0.041	0.053	0.573**	0.930**	0.906**	0.680**	1	
15. LF/HF	2.39 ± 1.35	−0.037	−0.202	−0.034	0.106	−0.078	0.088	0.064	−0.119	−0.042	−0.308**	−0.694**	−0.670**	−0.114	−0.757**	1

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

TABLE 6 | Descriptive statistics and correlations for primary PSQI indices of sleep quality, BDI-II score, and HRV during bedtime period.

Variable	*M* ± *SD*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
PSQI component scores																
1. Subjective sleep quality	1.04 ± 0.72	1														
2. Sleep latency	0.85 ± 0.87	0.554**	1													
3. Sleep duration	0.79 ± 0.50	0.269*	0.158	1												
4. Habitual sleep efficiency	0.10 ± 0.34	0.157	0.091	0.121	1											
5. Sleep disturbance	0.96 ± 0.49	0.374**	0.339**	0.173	0.137	1										
6. Use of sleeping medication	0.14 ± 0.51	0.273*	0.341**	0.300*	0.095	0.230	1									
7. Daytime dysfunction	1.42 ± 0.95	0.511**	0.398**	0.204	0.187	0.330**	0.389**	1								
8. PSQI global score	5.29 ± 2.84	0.769**	0.763**	0.396**	0.259*	0.535**	0.454**	0.774**	1							
9. BDI-II scores	8.26 ± 8.61	0.555**	0.383**	0.191	0.147	0.372**	0.288*	0.663**	0.617**	1						
10. SDNN	116.21 ± 30.99	−0.047	−0.117	−0.053	0.064	−0.317**	−0.044	−0.131	−0.135	−0.108	1					
11. RMSSD	63.86 ± 24.83	−0.003	−0.006	0.063	−0.044	−0.101	−0.065	−0.046	−0.003	−0.032	0.631**	1				
12. pNN50	37.90 ± 16.44	0.000	0.069	0.063	−0.047	−0.062	−0.069	0.044	0.065	0.014	0.504**	0.917**	1			
13. LF	1312.82 ± 863.15	0.008	−0.038	0.039	−0.037	−0.215	0.059	−0.016	−0.025	0.035	0.758**	0.673**	0.556**	1		
14. HF	1614.01 ± 1320.89	−0.019	0.055	0.029	−0.023	−0.004	−0.075	0.007	0.052	0.025	0.522**	0.923**	0.892**	0.597**	1	
15. LF/HF	1.08 ± 0.72	0.048	−0.045	−0.060	−0.026	−0.201	0.072	0.015	−0.052	0.014	0.067	−0.484**	−0.574**	0.200	−0.564**	1

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

sleep (high PSQI global scores) group. It may be that the improvement or decrease of sleep experience has a direct impact on the individual's emotional experience, leading to an increase or decrease in the level of depressive symptoms. Studies have pointed out that depression patients experience less positive emotions and more negative emotions (47). Sleep disorders are closely related with depressive symptoms, and sleep insufficiency can lead to depressive symptoms (48). In this way, the individual will enter in a cycle that sleep quality decrease will lead to rising level of depressive symptoms and even for the onset of depression, in turn, the elevated level of depressive symptoms or the onset of depression will lead to the individual in a relatively long period of time remain depressed, thus affecting the quality of sleep. Therefore, if sleep problems do not improve, it can lead to increased levels of depressive symptoms and the onset of depression.

In addition, our results also show that there was a significant positive correlation between PSQI global scores and BDI-II scores. This is consistent with previous research (34). Sleep problems such as primary insomnia, shorten sleep duration, and hypersomnia have been linked to depression and its severity (35, 36, 49–52). These findings further support that individuals with poorer sleep quality have higher levels of depressive symptoms, which may be an important factor in reducing the success rate of treatment for depression, and there may be a complex bidirectional relationship between sleep problems and depression (35, 36). Therefore, more studies are needed to confirm whether the higher risk of depression is caused by sleep problems or the decreased sleep quality caused by the existence of depression, or the simultaneous occurrence of depression and sleep problems. Compared to people with depression, sleep problems, and the application of HRV are relatively easy to study in the general population, and future research could include the study of the biological factors to clarify the mechanisms of the link between depression, sleep quality and HRV.

Contrary to our hypothesis, the 24-h HRV indicators in this study failed to reflect the differences between groups of sleep quality of medical students. This result is in contrast to previous studies which found that SDNN, RMSSD, pNN50, as well as LF and HF were reduced in people with sleep problems compared with controls (10). The differences between these results may be caused by the following reasons. First, the sample size of our study may be small, with a total of 76 participants recruited. After excluding four participants who did not meet the inclusion criteria of the study, 72 valid data were obtained. However, compared with previous studies, the sample size of our study was relatively large, and we did not only recruit female participants (17). Secondly, the samples used in our study were not clinically diagnosed, and the diagnosis of sleep quality depends on self-report. However, for this study, PSQI has a good reliability (Cronbach' s $a = 0.75$), so it has little influence on the results of our study. Finally, the application of 24-h HRV may be more sensitive in clinical samples (4, 10). Even though our study samples met the criteria for grouping sleep quality statistically, no significant statistical difference was found after comparing various indicators of 24-h HRV between the two groups, which needs to be verified again in the comparison between large clinical and non-clinical samples in the future. Furthermore, stress and age might have an impact on an individual's sleep quality and depressive symptoms (53, 54). Individual stress levels were shown to be inversely connected to sleep quality, and depression was a prevalent condition in later life, which has been linked to disability and poor health outcomes over time. Future study should also focus on the role of these elements.

Alternatively, our study results provide a different finding to previous studies. There is a significant negative correlation between SDNN and LF during awake period and the dimension of PSQI, sleep disturbance($r_{SDNN} = -0.285$, $r_{LF} = -0.239$, $p < 0.05$), but the former two are not associated with depressive symptoms. We found a significant negative correlation between SDNN during bedtime period and the dimension of PSQI, sleep disturbance ($r = -0.317$, $p < 0.01$). SDNN reflects overall HRV and RMSSD as well as pNN50 reflect parasympathetic activity. Firstly, this indicates that the sleep disturbance in PSQI components can more sensitively reflect the sleep quality of medical students, and individuals with higher sleep disturbance may have lower SDNN in awake period and bedtime period, while LF in awake period is lower. Future research would need to replicate the results using larger samples, and the samples expanded to include different demographic groups so as to further analyze the sources of sleep quality problems and HRV characteristics of medical students. Provide targeted guidance for follow-up interventions. Second, the LF reflects a mixture of parasympathetic and sympathetic contributions (55) with greater sympathetic sensitivity (56). The HF is thought to reflect the variation in heart rate during the respiratory cycle (also referred to as respiratory sinus arrhythmia), and it has been suggested to be almost exclusively dependent on the parasympathetic activity, that is, with reductions in HF measures of HRV, we are assessing a reduction in vagal tone (57). Low frequency components and HF measures can be assessed using both long recordings (24 h) and short recordings (5 min). According to the results of our study, the sleep quality is related to the overall HRV. Low frequency components and SDNN druing awake period can jointly reflect the sleep quality, while SDNN during sleeping period can reflect sleep quality. The sympathetic nervous system is more sensitive to behavior that is uncertain, novel and threatening, and this response is often referred to as the sympathetic fight-or-flight preparation for action (58). This response to threat may be related to the well-known negative bias, in which negative information takes precedence over positive information in guiding behavior (59). Hence, LF, as an indicator of sympathetic nervous system, can sensitively reflect individual sleep quality. Although the balance of sympathetic and parasympathetic nervous system is the basis of maintaining human physiological function, the sympathetic activity is dominant during daytime arousal, while parasympathetic activity is dominant during night sleep, and the two are in an antagonistic and balanced state at any time (60, 61). Our results suggest that sleep should be mediated by both the sympathetic and parasympathetic nervous systems, rather than solely by the parasympathetic nervous system.

In any case, the relationship between sleep problems and depressive symptoms/depression is consistent with previous findings, but the relationship between 24-h HRV

and the former two or the use of waking and sleeping HRV indicators as indicators of sleep quality, depressive symptoms/depression needs further verification. Studies of sympathetic and parasympathetic nerves have shown that autonomic imbalances are precursors to disease development and other health-related risks (62–64). Thus, in order to improve the sleep quality of college students, in addition to enhance the pertinence and effectiveness of mental health education, psychological census should be conducted after the students enter school and psychological files should be established for them. The present study results suggested that the mindfulness intervention is effective for positive results of mental health, it can also reduce the physical symptoms associated with anxiety, self-perception stress levels, and relieve the symptoms of mental illness severity.

The limitations of this study are as follow. Firstly, this is a cross-sectional study, so it is still not know how is the dynamic relationship among depressive symptom, sleep quality and 24-h HRV. Future study need to address this issue. Second, depressive symptom and sleep quality are all assessed through a single source of self-report questionnaire. Relying on this subjective method can, therefore, be problematic. In future research, self-report approaches should be combined with clinical diagnosis and objective measures. Lastly, the participants surveyed in the current study were all medical students. Therefore, they are not sufficiently representative of the general population, and the extrapolation validity of this research is limited. Future study might focus on senior medical students as research subjects, or on medical students of all grades as research subjects for comparative studies. Simultaneously, data on recent stress levels, the time living under pressure, and resilience need to be gathered in order to further investigate and explain the association between sleep quality and 24-h HRV in medical students.

In conclusion, we found that sleep problems were more common among medical students and were associated with higher levels of depressive symptoms and more negative emotional experiences. Meanwhile, the results of our study provide supplementary explanation for the past research, we should not only pay attention to the relationship between HRV and sleep quality in the sleep stage, but also pay attention to the relationship between HRV and sleep quality in the wake stage. As a complex and comprehensive physiological process, sleep may not only rely on the role of parasympathetic nerves. The sympathetic or the whole autonomic nervous system also plays an indispensable coordinating role in sleep. This not only reminds us to pay more attention to the physical and mental health problems of medical students, but also to formulate targeted and effective prevention and intervention measures. Heart rate variability during awake and bedtime period may become effective applications for individual physical and mental health in the future. Future studies can further investigate the application value, sensitivity and specificity of 24-h HRV analysis in a large sample of normal population or a large clinical sample, so as to clarify the relationship between sleep quality, depressive symptoms and HRV indices. In terms of measuring instruments, future research may examine the differences in measurement outcomes between the patch dynamic electrocardiograph employed in this study and the smart wrist watch.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Academic Ethics Committee of Southern Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XG, TS, and HX collected and analyzed the data. XG and RX interpreted the data and wrote the first draft of the manuscript. ZX and XG generated the idea, designed the study, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Nightmare Rescripting: Using Imagery Techniques to Treat Sleep Disturbances in Post-traumatic Stress Disorder

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Besides affecting 8% of the general population, nightmares are one of the most frequent symptoms of traumatized individuals. This can be a significant factor in the treatment of post-traumatic disorders; indeed, several studies demonstrated its strong predictive and prognostic value. Sleep disorders, nightmares in particular, could be very distressing for individuals and need targeted interventions, especially if they are associated with a PTSD diagnosis. To date, the best technique for the treatment of traumatic sleep disturbances seems to be Imagery Rehearsal Therapy (IRT), an empirically supported method. Through a review of the literature on this matter, this article aims to outline the incidence and consequences of nightmares in PTSD, illustrate how IRT could prove useful in their treatment, and investigate its clinical applications.

Keywords: trauma, nightmares, post-traumatic stress disorder, insomnia, imagery rescripting, imagery rehearsal therapy

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Post-traumatic stress disorder (PTSD) is a mental health condition, which in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-5; (1)] has been included in a new category, "Trauma and Stressor Related Disorders." PTSD is characterized by the appearance of a wide array of symptoms after experiencing "death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence" [(1), p. 271], in the following ways: direct exposure to the event; witnessing the event; learning that a close one was exposed to a traumatic event; indirect exposure to details of the trauma.

PTSD diagnosis was added–not without many controversies–only in the third edition of the DSM [DSM-III; (2)], after noticing the development of post-traumatic symptoms among many veteran soldiers. However, it is possible to identify some descriptions ascribable to this disorder already at the beginning of the twentieth century, when many authors spoke of "war neurosis," "soldier's heart," and "shell shock" to describe the physio-psychological consequences of being exposed to war situations [for a historical overview, see (3)]. Shortly after the diagnosis of PTSD was introduced in the DSM, clinicians began to notice that there were other individuals–victims of sexual or physical abuse, for example–whose symptoms largely corresponded with those observed in soldiers. Today we know that the traumatic events that can give rise to PTSD are numerous and of various kinds. They produce lasting effects, which the DSM-5 describes as follows, dividing them into four clusters:

1) Re-experience of the traumatic event (intrusion symptoms) through distressing memories, dreams and nightmares, flashbacks, and dissociative reactions.
2) Avoidance of stimuli associated with the traumatic event.
3) Negative alterations in cognition and mood (e.g., amnesia, negative beliefs and expectations, distorted cognitions, feelings of detachment).
4) Marked alterations in arousal and reactivity (e.g., irritability, self-destructive behaviors, hypervigilance, difficulties in concentrating, sleep disturbances).

According to the DSM-5, in the United States PTSD affects ∼5% of men and 10% of women (1). In Italy, epidemiological studies show that about 56.1% of the general population is exposed to at least one traumatic event (with an average of 4 traumatic events experienced during the lifespan); the risk of experiencing PTSD following exposure to a traumatic event(s) is assessed to be between 0.8 and 12.2% (4). These data highlight the significance of a better understanding of the complex symptoms that are often associated with PTSD to develop targeted and effective intervention techniques.

SLEEP DISTURBANCES AND NIGHTMARES IN PTSD

Within the heterogeneous post-traumatic symptomatology, sleep disorders seem to occupy a particularly prominent place (5–8). "O memory, mortal enemy of my rest!," wrote Cervantes, enclosing–perhaps unconsciously–in these few words the struggle of those who, following a traumatic experience, continue to be haunted daily by the repetition of intrusive images, both during their wake and their sleep.

There are several studies [for a review, see (9)] that show how having experienced a traumatic event leads to difficulties in falling and/or staying asleep, as well as in having persistent and distressing nightmares. These consequences are part of a typical response to a traumatic event (10), so much that the DSM has always listed nightmares within the cluster B symptoms (re-experiencing), while a difficulty to falling asleep and/or staying asleep can be found among in Cluster D symptoms (arousal alterations).

Following the 1995 earthquake in Hanshin, Japan, Kat et al. (11) interviewed 143 people to study what effects the event had on them. The authors highlighted that sleep disturbances were the most common and frequently experienced symptom: 63% of the sample experienced it 3 weeks after the event, and 46% still 8 weeks later. Similarly, Goldstein et al. (12) and Kuch et al. (13) have highlighted the pervasiveness of these symptoms in trauma victims. Sleep disturbances were found in 97% of war soldiers and 95% of Holocaust survivors. Moreover, nightmares represented the major problem for both the former (94%) and the latter (83%).

Events such as the Oklahoma City attack and the World Trade Center attack have made it possible to study the dramatic impact of such incidents on the population involved, highlighting the essential link between trauma and sleep disorders. For example, more than 70% of Oklahoma City bombing survivors reported sleep disturbances 6 months after the event; ∼50% of the analyzed sample also reported experiencing distressing nightmares (14). After the terrorist attack of September 11th, Schuster et al. (15) investigated the reaction of 560 American adults and children. Despite the different ages of the individuals who made up the sample, the authors found similar reactions among all subjects: 11% of adult individuals and 10% of children reported significant difficulties both in falling and staying asleep due to the presence of disturbing nightmares.

Another line of research (16–19) mainly focused on investigating the content of nightmares of people diagnosed with PTSD, showing interesting results. Indeed, nightmares seem to be not only and necessarily a reproduction of the particular kind of traumatic event experienced by the subject (19) but also a reflection of the intense emotions associated with it. Even after some time has passed (in which nightmares tend to "become chronic"), the nightmares of patients suffering from PTSD seem to contain general traumatic themes, such as threatening or deadly circumstances (18, 20). Investigating the reactions of a sample of Vietnam veterans diagnosed with PTSD, Esposito et al. (20) found that the dream content of these patients included not only combat scenarios set in the past but also other kinds of threatening scenarios set in the present. Furthermore, Dagan et al. (21) have found that PTSD patient's dreams are characterized by more violence and aggressivity than those of the general population.

In light of these findings, it seems crucial to understand how the presence and persistence of nightmares and sleep disturbances affect the overall clinical picture of PTSD, giving rise to secondary implications that require targeted interventions. Inman et al. (22) compared a sample of 35 Vietnam veterans diagnosed with PTSD with a non-clinical sample of 37 patients suffering from insomnia. Although there was no significant difference between the two groups in terms of the total amount of sleep (an average of about 2.7 h per night in both groups), individuals suffering from PTSD showed more sleep-related anxiety symptoms, including fear of falling asleep, fear of the dark, waking up with covers torn apart, yelling/shouting in their sleep, psychomotor agitation during sleep, waking up in a confused and disoriented state, and trying to stay awake for most of the night. Hefez et al. (23) have shown that noncombat subjects suffer from the same sleep disturbances found in Vietnam veterans.

In addition to offering an important starting point for considering how nightmares and sleep disturbances represent not only a distressing symptom but also an essential maintaining factor of PTSD–as commonly observed in clinical practice–, these results raise another relevant question: can sleep disturbances and nightmares be considered a prognostic and predictive factor of posttraumatic stress disorder? Harvey and Bryant (24) have examined the predictive power of every posttraumatic symptom. Their study, conducted on adult trauma survivors at 1 and 6 months after a traumatic incident, highlighted how individuals who were suffering from nightmares at 1 month after trauma presented a PTSD diagnosis 6 months later in 33% of the cases; those who were suffering from sleep disturbances at 1 month after trauma were diagnosed with PTSD in 72% of the cases.

These findings suggest that the answer to our previous question is affirmative.

Koren et al. (25) have shown that sleep disturbances are a decisive prognostic factor in PTSD. The authors conducted a study on 102 adult patients who had survived motor vehicle accidents, administering them the *Mini Sleep Questionnaire* (26) 1 week after the traumatic incident and then 1, 3, 6, and 12 months later. Individuals who developed PTSD over time showed greater insomnia and sleepiness during the day than those who didn't develop it. Moreover, insomnia 1 month after the traumatic accident was not only predictive of PTSD later, but it also persisted until the end of assessment (i.e., 12 months after the trauma).

Recent studies (27–30) have observed a significant relationship between nightmares and suicidal behavior in patients with PTSD. The reason for this relationship is not yet completely understood. Littlewood et al. (31) proposed the association between nightmares and suicidal behaviors is due to the sense of defeat, entrapment, and despair inevitably experienced by those who continue to relive traumas in their dreams. Indeed, in their study, suicidal behaviors were higher in participants who experienced nightmares (62%), in comparison to those who did not (20%), regardless of comorbid insomnia and depression (31).

All the studies summarized above confirm the relevance of sleep disturbances and nightmares in PTSD and offer useful information for psychotherapeutic intervention. Indeed, it seems vital to find a specific intervention model for reducing the distress these symptoms cause. To date, the best technique for the treatment of traumatic sleep disturbances seems to be *Imagery Rehearsal Therapy* (IRT). In the following paragraphs, we will summarize how this approach was developed and why it is useful not only for reducing the distress caused by nightmares or other sleep disturbances but also for lessening the overall PTSD symptomatology.

IMAGERY REHEARSAL THERAPY: A SPECIFIC TREATMENT FOR NIGHTMARES

In light of the data reported in the previous paragraphs, it is important to develop a specific approach for treating sleep disorders–particularly nightmares–in patients with a PTSD diagnosis. Numerous authors with a cognitive-behavioral orientation have suggested using techniques that involve working with "mental images" (32–37). According to them, these techniques could represent the elective treatment for nightmares related to PTSD because they simultaneously allow the clinician to (a) have direct access to the content of the nightmare and to the emotions associated with it; (b) identify and modify negative cognitions related to the traumatic event; (c) reduce post-traumatic symptoms. Both Krakow et al. (38) and Davis and Wright (39) have identified, among the wide range of techniques for working with mental images, those that allow a more effective rescripting.

Imagery Rehearsal Therapy (IRT), a cognitive-behavioral procedure aimed at reducing the frequency and distressing impact of nightmares, was developed by Ian Marks in 1967 and subsequently perfected by Barry James Krakow and other psychotherapists interested in its use in the treatment of post-traumatic symptoms. This procedure, based on the work of Bootzin and Nicassio (40) and Howoritz (41), was developed within a theoretical framework that considers nightmares as a "learned" sleep disorder, which is, in turn, the result of distortions in the individual's mental images. From this perspective, nightmares are no longer considered solely as a post-traumatic symptom, thus treatable only through trauma-focused psychotherapy. Rather, they become a distinct phenomenon that, although originally connected with the trauma, tends to become chronic and to have a "life of its own," thus becoming a maintaining factor of PTSD and aggravating its overall symptomatology.

The IRT procedure consists of several sessions of variable duration, frequency, and number, depending on the specificity of the clinical case. In any case, the intervention is divided as follows:

1) *Psychoeducation*. The clinician offers the patient–and family members, if needed–detailed information about dreams and their association with traumatic experiences. In this phase, the patient is also given instructions on proper sleep hygiene and dysfunctional behaviors that maintain insomnia.
2) *Learning*. The aim of this phase is to help the patient "learn" how to cope with nightmares through the acquisition of techniques for working on his mental images to develop pleasant ones. Among the techniques proposed by Krakow (42), which the clinician will have to select on the basis of the patient's particular preferences, are the use of color, shapes, and movement as "basic tools" for constructing positive mental images (*visual sense*); *daydreaming*, which, if done with awareness, can encourage the emergence of positive images; and *self-talk*, through which the patient associates a positive word with a pleasant image or story. All these techniques help the subject to "stock up" on positive images that they can later take with them during *imagery practice*. This practice, which is the focus of the second part of the intervention, helps patients construct a new "script" of their dreams. In this second phase, the therapist also guides patients to manage their disturbing mental images and assesses their ability to do so. Working with disturbing mental images can indeed lead patients to experience intrusive mental images related to the traumatic event, which can be overwhelming and provoke dissociative phenomena. Therefore, the patient is provided with grounding and self-regulation techniques. Before moving to the next phase, the therapist must assess the patient's ability to manage any distressing element that may emerge.
3) *Selecting the disturbing nightmare.* Once the patient has acquired the techniques for working on his mental images and has acquired the necessary skills for managing potential dissociative responses, the target nightmare for the intervention is selected. This is usually the most emotionally disturbing or the most frequent one (these two aspects often coincide). In some other cases, the patient is asked

to start from a nightmare of lesser intensity so as to not feel overwhelmed.

4) *Re-evocation of the selected nightmare*. The patient is asked to write down the chosen nightmare and is encouraged to note all its details.
5) *Nightmare rescripting*. Using the skills learned during phase two, the patient can now make any changes they deem necessary on his nightmare. In this stage, which is at the heart of the IRT procedure, patients are offered the possibility of transforming their nightmare into a positive one–changing its theme, plot, ending, or any other part that they believe could help them in the rescripting. Interestingly, a study by Harb et al. (43) has shown that the majority of individuals (58%) created alternative endings. Others chose to insert new positive images without changing the ending (23%); a smaller percentage preferred to transform the threatening elements of the nightmare into less distressing images (13%). Finally, 10% of subjects decided to insert "reminders" (e.g., objects) that would help them be aware that they were simply dreaming, while 8% used distancing techniques (8%).
6) *Rehearsal*. The patient is invited to mentally rehears the rescripting of the selected nightmare for at least 10–20 min a day (preferably before going to sleep) until they obtain a significant reduction in the frequency of the nightmare. For this to happen, they should repeat only the new script without recalling the original nightmare (42). According to the rationale of the technique, the constant repetition of the new images created by the patient leads to a modification of the contents of the nightmare.

IRT works by progressively "inhibiting" the original nightmare, which is replaced with positive elements that can overcome the disturbing power of the unwanted contents of the dream. This leads to a change in the negative cognitions and feelings associated with the previous contents of the nightmare. We believe that this is the factor that makes the IRT such a helpful tool since it is plausible that such changes will be extended to other domains of functioning.

There are currently several variants of IRT, such as the Imagery Rescripting and Exposure Therapy (IRET) (44) and the Exposure, Relaxation, and Rescripting Therapy (ERRT) (45). These share with IRT not only the same rationale but also almost all the procedures listed above, even if with some modifications: IRET also uses relaxation techniques (e.g., progressive muscle relaxation) in the learning phase, while ERRT introduces "nightmare exposure" techniques, which are similar to imagery practice.

Currently, according to the American Academy of Sleep Medicine (AASM), IRT represents the treatment of choice (Level A) for PTSD-associated nightmares and nightmare disorder (5, 46). The present narrative review aims at describing and discussing the studies that analyzed the efficacy of IRT in the treatment of nightmares in post-traumatic populations (e.g., veterans, victims of sexual abuse). To this aim, a literature search was conducted using the following databases: Scopus, PsycINFO, PsycARTICLES, PubMed, Web of Science, and Google Scholar. The keywords for the search were: "nightmare," "nightmare disorder," "PTSD," "imagery rehearsal therapy," "nightmare rescripting," "sleep disturbance," "sleep disorder," "imagery rescripting," used in different combinations. Studies investigating the application of imaginative techniques to other psychopathologies (e.g., anxiety disorders) were not included.

CLINICAL APPLICATIONS WITH ADULT PATIENTS

War Veterans

In the adult clinical population, IRT seems to be particularly effective in reducing nightmares in war veterans who have developed PTSD (43, 44, 47, 48). To meet the specific needs of the veteran population, Long et al. (44) applied the IRET, a variant of the initial model. The authors investigated the effectiveness of the rescripting treatment, carried out over six sessions, on a group of 37 US veterans with PTSD and chronic post-traumatic nightmares (present for 10 years). Of the 33 individuals who completed the treatment, 15.2% reported that they had not subsequently suffered from distressing nightmares. 30.3% reported a significant increase in the amount of time dedicated to sleep, which became 6 h or more per night. Besides, 30 of the 33 patients (90.9%) reported general, albeit moderate, improvements in their sleep disturbances.

Other studies on the use and effectiveness of IRT and its variations with war veterans have focused on the peculiar qualities of their nightmares and how these could be modified by rescripting, analyzing the correlation between these elements and the positive outcome of treatment. Harb et al. (43) examined the characteristics of the distressing nightmares of 48 US veterans suffering from PTSD. The aim of the research was to outline if and how specific characteristics of the nightmares were associated with the treatment outcome. Compared to other survivors of traumatic events, war veterans presented significantly more "replicative" nightmares, characterized by reproductions of the original traumatic event or parts of it–such as bodily sensations, emotions, smells, or sounds. About half of the veteran's nightmares considered in the study (between 21 and 60%) contained scenarios, individuals, or objects characteristic of the original traumatic event(s). This study also highlighted that the vividness and intensity of the olfactory sensations in patient's nightmares were inversely related to their response to IRT treatment (patients with vivid and intense olfactory experiences tended to have a poorer response). Compared to other forms of sensory memory, smell is more closely connected to affects. The processing of olfactory stimuli involves the activation of primitive brain structures also implicated in fear and survival responses. Instead, a factor correlated with the success of the IRT was the patient's ability to incorporate a resolution of the central theme of the replicative nightmare in their rescripting, eliminating its most violent details. The most effective strategies in modifying the content of the nightmare and in resolving the distress it produced in PTSD patients were the conception of alternative endings, the insertion of resolving elements during violent scenes, the transformation of threatening objects such

as weapons into harmless objects, and/or the use of distancing techniques from the source of threat.

These results appear consistent with the literature on the cognitive-behavioral treatment of PTSD: the IRT seems to represent a form of cognitive restructuring of the meaning of the traumatic memory reproduced in the patient's nightmares. Long et al. (44) showed that the central themes of war veteran's nightmares revolved mainly around impotence (a feeling experienced by 90% of subjects and present in 27.1% of targeted nightmares), fear of death (experienced by 85% of subjects and present in 41.7% of targeted nightmares), and a feeling of lack of control and self-efficacy (present in 27.1% of targeted nightmares). The results of this study confirm that, during the rescripting phase, focusing on the central theme reported by the patient is associated with a positive treatment outcome. Indeed, the main themes present in the patient's new dreams, as well as the most effective elements in reducing their suffering, were related to the presence of positive, optimistic feelings (37.5%), a sense of security and peace (27.5%) and a feeling of greater self-efficacy (25%).

Moreover, the positive results of IRT seem to be long-lasting. Moore and Krakow (48) conducted a study on 7 soldiers who, after returning from their mission in Iraq, had developed distressing nightmares and sleep disturbances. At the end of the IRT treatment, they reported a significant reduction in the frequency of nightmares: at the 1 month follow-up, the mean number of nightmares diminished by 44%. Moreover, 64% of soldiers reported a significant relief regarding not only their nightmares but also their PTSD symptoms and insomnia, which diminished, respectively, by 41 and 34%.

The positive effects of IRT seem to last after the end of treatment, as confirmed by a study by Lu et al. (47). The study focused on 17 war veterans with a PTSD diagnosis, who were invited to participate in an IRT group training, with 6 weekly sessions of 90 min. Initially, contrary to what was expected, no significant results were found. However, during follow-up evaluations (at 3 and 6 months), the patients reported that the frequency and number of their nightmares were significantly reduced, that such nightmares were less distressing and that even their fear of being asleep considerably diminished. While no improvements in sleep quality or depression scales were found, a marked decrease in post-traumatic symptoms was observed.

These results suggest that the specific positive effects of IRT treatment may appear even after some time from its conclusion. Consistently with the results of other efficacy studies on IRT (49), the study by Lu et al. (47) shows how IRT can be effective in the treatment of distressing nightmares on veterans suffering from lasting PTSD symptoms, even after they have concluded other forms of treatment [see also (50)].

In another study, Ulmer et al. (51) treated 22 veterans with PTSD with a combination of CBT and IRT; the intervention consisted of 6 bi-weekly sessions for 12 weeks. The combined CBT/IRT intervention produced significantly greater improvements in nightmare frequency compared to usual care (51).

The limitations of the studies reviewed here are mainly of two types: the first concerns the non-representativeness of the sample, as this is often too small or restricted to a specific age range; the second concerns the fact that female subjects are excluded from these studies. Moreover, it would be interesting to extend the follow-up period to further support the long-term efficacy of IRT with war veterans.

Victims of Sexual Abuse

In addition to war veterans, IRT is also effective in reducing the distress caused by nightmares in subjects who have suffered sexual abuse, an experience that often leads to the development of PTSD. Davis and Wright (45) reported that sleep disturbances and nightmares are extremely frequent symptoms in victims of abuse; they can act as a maintenance factor for post-traumatic stress symptoms and/or lead to the development of depressive symptoms. Cognitive Behavioral Therapy (CBT), however, often does not involve interventions aimed at directly addressing this type of problem. According to Belleville et al. (52), although CBT typically leads to spontaneous improvement in sleep-related difficulties, these often resurface about 6 months after treatment ends. Therefore, the authors have highlighted the need to develop guidelines and standardized procedures for the treatment of sleep disorders in subjects suffering from PTSD. Thus, they have investigated through a randomized controlled trial the effects of IRT on sleep disturbances (e.g., insomnia, nightmares), as well as other PTSD symptoms, general functioning, and quality of life, comparing this treatment to the application of CBT alone. 42 adult subjects with a history of sexual abuse and a diagnosis of PTSD were thus recruited and then randomly assigned to the experimental condition (IRT+CBT) or the control condition (CBT only). Before starting CBT, the women assigned to the experimental group participated in 5 weekly sessions in which IRT was applied to their most disturbing nightmare. Subsequently, all subjects received 15 CBT sessions. The results of the study showed that even if at the end of treatment both groups showed a significant–and similar–decrease in PTSD symptoms, associated with an improvement in general functioning and quality of life, the group receiving the IRT showed a more substantial improvement in sleep quality and a greater decrease in the frequency of nightmares. The authors, therefore, concluded that IRT appears to be a valid technique for those patients who cannot benefit from long-term therapies or for whom sleep disorders represent a primary element to be addressed during treatment (52).

Similar results are also found in other studies, albeit less recent. Among these, there is only one other randomized controlled trial, conducted by Krakow et al. (53) on a sample of 114 adult women victims of sexual abuse and suffering from insomnia and other PTSD symptoms. The women were randomly assigned to an experimental group (*cognitive imagery treatment*) or a control group (*no imagery intervention, continuation of standard treatment*). The experimental group received three weekly group sessions: the first two lasting 3 h each, the last lasting 1 h. During the second session, the participants were asked to write down their most disturbing nightmare, modifying it "however they wanted"–according to

the model of Neidhart et al. (54). Soon after, the women were asked to use imagery rescripting to mentally visualize their new dream and to do so multiple times. At the end of the study, the women assigned to the cognitive imagery treatment group showed significantly fewer nightmares per week and better sleep quality than the control group; besides, their other post-traumatic stress symptoms lessened significantly more. The experimental group maintained these improvements even at follow-up (at 3 and 6 months), while the control group continued to show slight or no developments. Furthermore, the differences between the two groups were not mediated by variables such as the specific psychotherapeutic or pharmacological treatment previously received by each woman. The authors conclude that IRT is a technique that can be beneficial for victims of abuse, thanks to its many positive effects and its brevity. They recommend the use of IRT in the treatment of patients with post-traumatic symptoms or, more generally, patients suffering from sleep disorders. They also highlight the usefulness of IRT in cases where subjects are resistant to the idea of pharmacological treatment, while underlining the need for further studies to better understand the factors and mechanisms that make this technique effective in reducing traumatized subject's sleep difficulties and the disturbing emotional charge associated with their dreams (53).

Similar considerations can be found in a study by Germain et al. (33), which aim was to investigate if the increased sense of mastery may be among the main factors that explain the effectiveness of IRT in the treatment of post-traumatic nightmares. The authors applied the same procedure previously used by Krakow et al. (53). In this case, it was used during the treatment of 44 sexually abused women suffering from nightmares, insomnia, and other PTSD symptoms. The results showed that not only the new dreams produced with IRT were characterized by fewer negative elements, but that the subjects developed a greater sense of mastery regarding the negative elements of their nightmare, thus feeling more confident of being able to cope with them. According to the authors, this increased sense of mastery could prove useful in reducing not only sleep disorders but also other PTSD symptoms, such as intrusive memories, flashbacks, or the avoidance of stimuli and situations associated with trauma. In addition to the fact that it requires a relatively limited time to produce the first beneficial effects on traumatized subjects, one of the advantages of IRT is its simplicity, which makes it usable even in cases in which other interventions may prove less effective, for example with individuals with learning and intellectual disabilities.

Kroese and Thomas (55) conducted a case study on two sexually abused women with intellectual disabilities, showing that the rescripting of the most disturbing images characterizing their recurring nightmares (which were representations of the trauma they experienced) proved to be useful to modify the pathogenic beliefs relating to the victim's sense of helplessness. IRT also increased their sense of control and mastery over the traumatic situation represented in the dream–effects that, in line with previous research, seemed to generalize to other everyday situations.

Davis and Wright (45) have highlighted the usefulness of imagery rescripting in reducing PTSD symptoms not only in the adult population but also in adolescents. In their study, the participants (1 male and 3 females, all victims of sexual abuse) received a modified version of the technique, the ERRT. The participants were offered three sessions in total, lasting 2 h each. The results of the study once again confirm the usefulness of this technique: indeed, the rescripting of mental images characterizing the nightmare not only reduces sleep disorders related to PTSD but also has beneficial effects on post-traumatic symptomatology as a whole. However, the authors stress the need for further studies to shed light on the mechanisms underlying the effectiveness of the technique. The fact that IRT has also proved effective in a sample of adolescents, though, leads us to consider another population on which the use of nightmare rescripting seems to offer numerous benefits: that of developmental age.

CLINICAL APPLICATIONS WITH CHILDREN AND ADOLESCENTS

In a chapter of the volume "Innovations and Advances in Cognitive Behavior Therapy," Encel and Dohnt (56) highlight how, although nightmares and sleep disturbances are among the symptoms most frequently reported by children with PTSD, these rarely represent a direct target of cognitive-behavioral oriented therapies. Furthermore, post-traumatic nightmares in children often prove to be persistent and cause considerable distress: nightmares can damage the daily functioning of the child and aggravate their clinical picture (56). After highlighting the need for techniques specifically aimed at the treatment of nightmares in children, Encel and Dohnt suggest some changes to the IRT procedure that could make it more suitable for developmental age and underline the need for controlled studies to verify its efficacy in the treatment of sleep disorders in childhood.

Although thirteen years have gone by, such studies remain, to our knowledge, quite limited. Yet those conducted so far all suggest promising results. St-Onge et al. (57) conducted a randomized controlled trial to see if IRT could be useful for the treatment of prepubertal children suffering from frequent and chronic nightmares. They assigned 20 children (eleven boys and nine girls, aged 9 to 11) to an experimental group (*IRT*) or a control group (*waiting list*). After an initial psychoeducational session about sleep and nightmares, which was offered to all the subjects of the study, about 4 weeks later the children assigned to the experimental group participated in a second session, in which they were explained how to autonomously apply the IRT for the next 8 weeks. The use of IRT led to a significant reduction in the frequency of nightmares in the experimental group. This improvement was also maintained at the 9-month follow-up, thus confirming the usefulness and suitability of IRT with children. Similarly, Simard and Nielsen (58) found that administering a single session of IRT to a group of children (aged 6 to 11) with sleep disturbances, but without a PTSD diagnosis, led to a reduction in the distress caused by nightmares and to a decrease of other anxious and depressive symptoms.

The only study investigating the efficacy of imagery rescripting in a sample of children suffering not only from frequent and/or chronic nightmares but also from PTSD was conducted by Fernandez et al. (59), who have applied the ERRT on two girls of eight and eleven years of age respectively. Again, the results seem promising: the authors report an increase in sleep quality and a decrease in the frequency of nightmares in both girls, as well as fewer parental observations of behavioral problems in their children.

In conclusion, although further studies are needed (preferably randomized controlled trials with sufficiently large samples), it appears that IRT may be a useful technique to integrate into cognitive-behavioral treatment for children with nightmares and sleep disorders. Indeed, these symptoms often represent a problem of great importance during developmental age, especially with respect to the presence of a PTSD diagnosis; to date, however, there is a lack of proven techniques for their treatment.

DISCUSSION

Nightmares are a prominent symptom of PTSD and other stress-related disorders (5–8), and they often seem to resist classic trauma-focused psychotherapeutic interventions. Moreover, even if reduced, they tend to reappear in the follow-up assessments after several months (60, 61). Even when PTSD resolves, nightmares can persist (5, 46).

But what makes this symptom so central and "resistant" to treatment, and therefore so important to treat? Clinical practice offers interesting and useful observations on this matter, which found confirmation in the literature. Patients who suffer from frequent nightmares experience greater levels of insomnia; their resulting fatigue seems to contribute to the experience of dissociative phenomena, which are both more frequent and more intense in individuals suffering from nightmares and sleep deprivation. Several studies (62–65) have highlighted a correlation between dissociative symptoms and sleep disturbances: while insomnia induces dissociative symptoms (66), sleep improvement reduces them (63).

Furthermore, in clinical practice, we often observe that the presence of nightmares triggers vicious circles that not only act as a maintaining factor of PTSD but also, in more serious cases, aggravate its symptoms. This happens because the constant presence of nightmares leads patients to experience strong anticipatory anxiety before going to sleep. It is not uncommon to hear patients tell us of their abuse of alcohol or other drugs in the attempt of self-medicating, with the illusion that by using these substances, they will be able to cope with their anxiety and go to sleep "undisturbed."

Nightmares contribute to the maintenance of PTSD symptoms also because they sometimes prevent its treatment. Indeed, the insomnia experienced by traumatized individuals due to trauma-related nightmares and subsequent recurrent awakenings often leads them to have difficulties concentrating during the day. This can seriously inhibit their ability to carry out a wide number of activities–including psychotherapy. During the sessions, a patient suffering from sleep disorders may have difficulties in listening to the psychotherapist and actively participate in therapy precisely because of his/her fatigue. The fact that the presence of nightmares tends to exacerbate other symptoms of PTSD, hindering the success of psychotherapy, finds numerous empirical validations. Several studies (39, 67, 68) have highlighted this phenomenon, also suggesting that nightmares contribute to increasing the subject's general levels of psychological, above and beyond the severity of PTSD itself.

Finally, in clinical practice we often observe that nightmares play a central role in maintaining and strengthening the traumatized subject's pathogenic beliefs. Nightmares, especially if they are chronic, are indeed often experienced by such individuals as an uncontrollable and intrusive phenomenon, leading patients to tell themselves things like: "I am broken," "I have no hope of healing," "Things will never go back to the way they used to be," "This thing will haunt me forever," "I am no longer in control," "I am helpless," and so on.

We believe that this is the element that makes a specific model of treatment for nightmares effective and necessary: a specific intervention can indeed modify the patient's pathogenic beliefs related to trauma and, subsequently, foster a reduction of their PTSD symptoms and of their levels of psychological maladjustment (35). As we've seen, the reduction of PTSD symptoms correlates with the decrease in the perception of impotence gained through the application of techniques such as IRT (44).

These observations are also confirmed by recent studies (69, 70). Rosseau and Belleville (70) systematically reviewed the supposed mechanisms of action of existing nightmare treatments, revealing that an increased sense of mastery was the most often cited hypothesis to explain the efficacy of nightmare psychotherapies. Similarly, Kunze et al. (69) found that enhanced mastery (or self-efficacy) mediates the therapeutic efficacy of imagery rescripting (IR).

In summary, clinical observations and empirical data indicate that a treatment specifically aimed at reducing nightmares in trauma survivors is vital, since nightmares contribute to the development and maintenance of post-traumatic symptoms (71), while their treatment favors the resolution of PTSD.

CONCLUSIONS

Among the methods proposed for the treatment of nightmares in patients with PTSD, those involving imagery rescripting seem to be the most effective (32–39, 72). These techniques allow direct access to the distressing contents and emotions of nightmares without being overwhelming for patients, and they allow clinicians to quickly identify and modify trauma-related negative beliefs.

Rescripting-based therapy is generally thought to change the affective properties of a nightmare by altering its intrinsic meaning and by influencing the patient's ability to control distressing nightmare images (69). In nightmare disorder, this is very important because dreams are primarily hallmarked by a

lack of self-efficacy, powerlessness and uncontrollability. IR offers means to help patients express their unmet needs and inhibited responses (73).

Today, the treatment of choice for working on nightmares is Imagery Rehearsal Therapy (IRT). This method involves a psychoeducation phase, as well as the implementation of exposure and imagery rescripting techniques, and is effective in the treatment of both adults and children, and adolescents.

Since it shares the same theoretical principles of Imagery Rescripting (IwR) (73–75), which has recently been used for working on dream scenarios, it is important to conduct further studies to evaluate its efficacy in the specific treatment of nightmares on different clinical samples. This could lead to the development of an integrated intervention that may allow clinicians to intervene effectively even in cases in which there are linguistic communication barriers, as often happens when working with migrants, asylum seekers, refugees, and victims of torture, who need an intervention that can take these difficulties into account.

AUTHOR CONTRIBUTIONS

MA contributed to concept, design of the review, and wrote the first draft of the manuscript. ML, LC, and FM contributed to search for scientific papers. MA, ML, and LC wrote sections of the manuscript. FM contributed to manuscript revision, read, and approved the submitted version. All authors contributed to the article and approved the submitted version.

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Risk factors and prediction model of sleep disturbance in patients with maintenance hemodialysis: A single center study

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Objectives: This study aimed to explore the risk factors and develop a prediction model of sleep disturbance in maintenance hemodialysis (MHD) patients.

Methods: In this study, 193 MHD patients were enrolled and sleep quality was assessed by Pittsburgh Sleep Quality Index. Binary logistic regression analysis was used to explore the risk factors for sleep disturbance in MHD patients, including demographic, clinical and laboratory parameters, and that a prediction model was developed on the basis of risk factors by two-way stepwise regression. The final prediction model is displayed by nomogram and verified internally by bootstrap resampling procedure.

Results: The prevalence of sleep disturbance and severe sleep disturbance in MHD patients was 63.73 and 26.42%, respectively. Independent risk factors for sleep disturbance in MHD patients included higher 0.1*age (OR = 1.476, 95% *CI*: 1.103–1.975, $P = 0.009$), lower albumin (OR = 0.863, 95% *CI*: 0.771–0.965, $P = 0.010$), and lower 10*calcium levels (OR = 0.747, 95% *CI*: 0.615–0.907, $P = 0.003$). In addition, higher 0.1*age, lower albumin levels, and anxiety were independently associated with severe sleep disturbance in MHD patients. A risk prediction model of sleep disturbance in MHD patients showed that the concordance index after calibration is 0.736, and the calibration curve is approximately distributed along the reference line.

Conclusions: Older age, lower albumin and calcium levels are higher risk factors of sleep disturbance in MHD, and the prediction model for the assessment of sleep disturbance in MHD patients has excellent discrimination and calibration.

KEYWORDS

maintenance hemodialysis, sleep disturbance, sleep quality, factors influencing, prediction model

Introduction

Chronic kidney disease (CKD) is a global public health problem with increasing incidence and prevalence (1). According to statistical analyses, the prevalence of CKD in China is about 10.8%, and it is as high as 18.3% in some areas of China (2). When CKD progresses to the end stage, the main treatment options for patients are maintenance hemodialysis (MHD) and kidney transplantation. At the same time, MHD has become the main treatment for patients with end-stage kidney disease (ESKD) due to the serious shortage of donors for kidney transplantation. However, accumulating evidence indicates that sleep disturbance is frequently observed in MHD patients, and the prevalence rate is up to 49–98% (3–5). In addition, studies have found that sleep disturbance can lead to poor quality of life in MHD patients (6), as well as an increased risk of cardiovascular disease and all-cause mortality (7, 8). Unfortunately, sleep disturbance in MHD patients have not attracted the attention of clinicians, and lack of effective diagnosis and treatment (9). Therefore, more studies are needed to focus on sleep disturbance in MHD patients, in order to find better management strategies for the clinic.

Sleep occupies approximately one-third of human life span and is crucial for body health (10). However, the occurrence of sleep disturbance is common. Studies have found that sleep disturbance is a risk factor for of CKD (11), and is also related to the progression of CKD to ESKD (12). In MHD patients, there are various manifestations of sleep disturbance, including insomnia, restless legs syndrome (RLS) and sleep-related breathing disorders (4). As mentioned above, sleep disturbance has adverse effects on MHD patients. However, the mechanism of sleep disturbance in MHD patients is still unclear, and many phenomena are difficult to be explained by sleep itself. Therefore, it is important to explore the factors to improve sleep quality.

Currently, a series of studies have collected the demographic parameters and laboratory indexes of MHD patients to analyze the factors of sleep disturbance, and obtained different results. A study has found that gender, age, education level, diabetes history, blood phosphorus level and depression are associated with the sleep quality of MHD patients (13). Another study has confirmed that compared with MHD patients with good sleep, there are more males, lower serum parathyroid hormone (PTH) and 25-hydroxy vitamin D levels, and a higher incidence of depression in patients with poor sleep, while there is no significant difference in age between groups (14). Although both studies showed that gender and depression were associated with sleep disturbance in MHD patients, there were differences in age. In addition, a study has showed that old age and low serum selenium level are risk factors for sleep disturbance in MHD patients, and also found that high serum PTH level is associated with sleep disturbance in MHD patients (15). This contradictory result has blurred the role of serum PTH level in the sleep disturbance associated with MHD. Furthermore, studies have shown that diet regulation and melatonin can improve the sleep quality of MHD patients (16, 17). These lines of evidence suggest that there are many factors associated with sleep disturbance in MHD patients, and the role of some factors, such as age and PTH, needs to be confirmed by more studies.

In addition, few studies on factors influencing severity of sleep disturbance in MHD patients have been reported. However, a previous study has found that the severity of sleep disturbance in hemodialysis patients is positively correlated with the severity of depression and negatively correlated with the quality of life (18), which indicates that the severity of sleep disturbance can directly affect the prognosis of MHD patients. Moreover, no study has established a prediction model for the risk of sleep disturbance in MHD patients, which leads to the failure of early intervention. Therefore, exploring the influencing factors of the severity of sleep disturbance and developing a prediction model for the risk of sleep disturbance may be a key strategy to improve the sleep quality of MHD patients.

The purpose of this study was to explore the risk factors and to construct a risk prediction model of sleep disturbance in MHD patients, in order to provide strategies for the prevention and treatment of sleep disturbance in MHD patients.

Methods

Study participants

This was a single-center and cross-sectional study involving 193 MHD patients who underwent hemodialysis from April 2020 to March 2021 at the Blood Purification Center of the Department of Nephrology, The Third Affiliated Hospital of Soochow University. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University and registered in the Chinese Clinical Trial Register (clinical trial number: ChiCTR2100042093).

The inclusion criteria were (1) age $\geq$ 18 years; (2) regular hemodialysis therapy $>$3 months; (3) ability to complete questionnaires on sleep disturbance, anxiety and depression; (4) signed an informed consent form. The exclusion criteria were (1) the history of sleep disturbance before CKD; (2) the history of dementia, anxiety, depression, Alzheimer's disease or schizophrenia before CKD; (3) A history of trauma, surgery or infection within the past 3 months; (4) complicated with malignant tumor; (5) declined to participate.

All MHD patients enrolled in the study received blood purification 3 times per week (hemodialysis once weekly plus hemodiafiltration twice weekly or hemodialysis twice weekly plus hemodiafiltration once weekly). The low-flux polysulfone membrane dialyzer (B. Braun Diacap LOPS15, Germany) was

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TABLE 1 Clinical characteristics of MHD patients with or without sleep disturbance.

Variables	Total ($n = 193$)	Sleep disturbance ($n = 123$)	No sleep disturbance ($n = 70$)	t/Z/χ^2	*P* value
Age (years)	53.09 ± 11.68	54.80 ± 11.50	50.09 ± 11.46	2.744	0.007[a]
Male [*n* (%)]	127 (65.8)	77 (62.6)	50 (71.4)	1.545	0.214[c]
BMI (kg/m^2)	21.93 ± 3.26	21.98 ± 3.13	21.86 ± 3.51	0.242	0.809[a]
Primary diseases				2.984	0.394[c]
Chronic glomerulo-nephritis [*n* (%)]	40 (20.7)	24 (19.5)	16 (22.9)		
Diabetic nephropathy [*n* (%)]	26 (13.5)	18 (14.6)	8 (11.4)		
Hypertensive nephropathy [*n* (%)]	39 (20.2)	21 (17.1)	18 (25.7)		
Others [*n* (%)]	88 (45.6)	60 (48.8)	28 (40.0)		
Duration of dialysis				−1.161	0.246[b]
<3 years [*n* (%)]	40 (20.7)	22 (17.9)	18 (25.7)		
3–5 years [*n* (%)]	20 (10.4)	13 (10.6)	7 (10.0)		
>5 years [*n* (%)]	133 (68.9)	88 (71.5)	45 (64.3)		
Smoking [*n* (%)]	52 (26.9)	33 (26.8)	19 (27.1)	0.002	0.962[c]
Drinking [*n* (%)]	19 (9.8)	9 (7.3)	10 (14.3)	2.441	0.118[c]
Married [*n* (%)]	188 (97.4)	120 (97.6)	68 (97.1)	0.031	0.860[c]
High school or above [*n* (%)]	103 (53.4)	68 (55.3)	35 (50.0)	0.501	0.479[c]
Hypertension [*n* (%)]	163 (84.5)	104 (84.6)	59 (84.3)	0.002	0.961[c]
Diabetes mellitus [*n* (%)]	35 (18.1)	25 (20.3)	10 (14.3)	1.096	0.295[c]
Cardiovascular and cerebrovascular diseases [*n* (%)]	33 (17.1)	24 (19.5)	9 (12.9)	1.394	0.238[c]
Hb (g/L)	108.73 ± 18.47	108.75 ± 19.36	108.69 ± 16.92	0.022	0.982[a]
WBC (10^9/L)	5.75 (4.85–6.92)	5.86 (4.68–6.88)	5.63 (5.04–7.01)	−0.176	0.861[b]
RBC (10^{12}/L)	3.68 ± 0.66	3.71 ± 0.69	3.63 ± 0.62	0.762	0.447[a]
Hct (L/L)	0.33 ± 0.06	0.33 ± 0.06	0.33 ± 0.05	0.158	0.875[a]
PLT (10^9/L)	177.86 ± 58.66	175.54 ± 62.01	181.93 ± 52.44	−0.726	0.469[a]
TG (mmol/L)	1.60 (1.17–2.50)	1.62 (1.25–2.40)	1.60 (1.11–2.84)	−0.405	0.686[b]
TC (mmol/L)	4.11 ± 0.97	4.05 ± 0.97	4.21 ± 0.96	−1.098	0.274[a]
HDL-C (mmol/L)	0.90 (0.76–1.15)	0.87 (0.74–1.11)	0.98 (0.80–1.16)	−1.540	0.124[b]
LDL-C (mmol/L)	2.30 ± 0.74	2.25 ± 0.73	2.38 ± 0.76	−1.168	0.244[a]
Alb (g/L)	38.30 (36.30–40.15)	38.00 (36.20–39.60)	39.55 (36.78–41.43)	−3.303	0.001[b]
P (mmol/L)	1.97 (1.61–2.34)	2.11 (1.62–2.43)	1.89 (1.59–2.26)	−1.576	0.115[b]
Ca^{2+} (mmol/L)	2.28 ± 0.18	2.25 ± 0.18	2.34 ± 01.7	−3.497	0.001[a]
CRP (mg/L)	2.70 (2.20–3.40)	2.80 (2.20–3.60)	2.60 (2.10–3.10)	−1.628	0.103[b]
PTH (ng/L)	370.60 (197.35–609.25)	388.60 (199.50–614.20)	341.25 (185.08–591.45)	−0.525	0.599[b]
Cr (umol/L)	896.08 ± 186.95	891.84 ± 188.19	903.52 ± 185.87	−0.416	0.678[a]
BUN (mmol/L)	22.08 (18.11–26.30)	22.61 (18.10–26.30)	22.02 (18.51–25.43)	−0.549	0.583[b]
Anxiety n (%)	30 (15.5)	25 (20.3)	5 (7.1)	5.905	0.015[c]
Depression n (%)	34 (17.6)	27 (22.0)	7 (10.0)	4.390	0.036[c]

Alb, albumin; BMI, body mass index; BUN, blood urea nitrogen; Ca^{2+}, calcium; Cr, creatinine; CRP, C-reactive protein; Hb, hemoglobin; Hct, hematocrit; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MHD, maintenance hemodialysis; P, phosphorus; PLT, blood platelet; PTH, parathyroid hormone; RBC, red blood cell; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

[a] *Calculated by Student's t test.*

[b] *Calculated by Mann–Whitney U-test.*

[c] *Calculated by chi-squared test.*

used for hemodialysis and the high-throughput polysulfone membrane dialyzer (B. Braun Diacap HIPS15, Germany) was used for hemodiafiltration. Each blood purification treatment was ∼4 h and low molecular weight heparin was used for anticoagulation. The dialysate was bicarbonate with a flow rate of 500 ml/min, and the average blood flow velocity was 200–280 ml/min. Displacement volume using post-replacement was calculated by ∼30% of the ultrafiltration flow rate.

Data collection

Patients were informed of the study's objectives and instructed to complete questionnaires. The data collection instruments were structured questionnaires, the Hospital Anxiety and Depression Scale (HADS), and the Pittsburgh Sleep Quality Index (PSQI).

Demographic, clinical, and laboratory data

Demographic and clinical data were collected from face-to-face interviews conducted by trained nurses using structured questionnaires when MHD patients were awaiting hemodialysis treatment. The following information was recorded: age, duration of dialysis, gender, body mass index (BMI), primary diseases, smoking and alcohol consumption, marital status, educational level, history of hypertension, history of diabetes mellitus, and history of cardiovascular and cerebrovascular diseases. Venous blood samples were collected before the hemodialysis. The following laboratory parameters were measured: hemoglobin (Hb), white blood cell (WBC), red blood cell (RBC), hematocrit (Hct), platelet (PLT), C-reactive protein (CRP), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), albumin (Alb), creatinine (Cr), blood urea nitrogen (BUN), serum phosphorus (P), calcium (Ca^{2+}) and PTH.

Depression and anxiety

The HADS includes 14 items assessing depression and anxiety in general hospital patients. It was divided into depression subscale (HADS-D) and anxiety subscale (HADS-A). The two subscales each contain 7 items, with scores ranging from 0 to 3 points (19). The score for each subscale is computed by total score of the corresponding 7 items (0–21 points). The recommended cut-off is 8 points for anxiety or depression, with a higher score indicating more severe depression or anxiety. The HADS has acceptable reliability in Chinese (Cronbach's $\alpha = 0.776$) (20).

Sleep quality

The PSQI was used to assess the sleep quality of the subjects over the past month (21). The PSQI included 19-items that are composed of seven components: subjective sleep quality, sleep latency, total sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep drugs and daytime dysfunction. Each component was scored 0 to 3 points, with a score greater than 1 indicating a sleep problem in that component. The total scores of PSQI ranged from 0 to 21, with greater than 5 indicating sleep disturbance in the last month, and greater than 10 indicating severe sleep disturbance in the last month (15). The PSQI has acceptable reliability in Chinese (Cronbach's $\alpha = 0.713$) (22).

Statistical analysis

In the analysis of factors influencing, SPSS 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses and GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA, USA) was used for plotting. The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables with normal distribution were shown as mean ± standard deviation, and data with a skewed distribution were shown as medians (25–75% interquartile ranges); categorical variables were expressed as frequency (percentage). The differences between the two groups were evaluated by the Student's *t* test, Mann–Whitney U-test or chi-squared test. According to the actual clinical significance, variables with $P < 0.1$ in the comparison between groups were transformed and analyzed by univariate binary logistic regression analysis. Variables with $P < 0.5$ in univariate binary logistic regression analysis were further included in multivariate binary logistic regression analysis to obtain independent risk factors for sleep disturbance in MHD patients. A $P < 0.05$ was considered to be statistically significant.

The prediction model was developed using R software (version 4.1.2). The initial prediction model was established by using the variables with $P < 0.1$ in univariate binary logistic regression analysis and variables considered to be meaningful in previous studies, and optimized by two-way stepwise regression. A nomogram was developed based on the results of the two-way stepwise regression. The internal validation of the prediction model was carried out by 1,000 bootstrap resampling procedure. The discrimination and calibration of the prediction model were evaluated with the concordance index (C-index) and calibration curve.

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Results

Recruitment process and general clinical characteristics of MHD patients

Of the 236 MHD patients were enrolled, 43 were excluded from this study: 11 patients with hemodialysis therapy <3 months, 13 patients failed to complete PSQI and HADS, 6 patients with a history of sleep disturbance, 3 patients with a history of dementia, 2 patients with a history of depression, 1 patient had malignant tumor, 5 patients declined to participate, and 2 patients withdrew from the study (Supplementary Figure 1).

Table 1 shows the clinical characteristics of 193 ultimately enrolled MHD patients. All participants ranged in age from 27 to 79, with an average age of 53.09 ± 11.68 years. Male patients accounted for 65.8%, and the average BMI of all patients was 21.93 ± 3.26 kg/m^2. The main primary disease was chronic glomerulonephritis followed by hypertensive nephropathy and diabetic nephropathy. The duration of hemodialysis was <3 years in 20.7% of patients, and more than 5 years in 68.9% of patients. Smoking and alcohol consumption accounted for 26.9 and 9.8%, respectively. Almost all the patients were married and 53.4% had high school or above. Patients with hypertension, cardiovascular and cerebrovascular, and diabetes mellitus diseases were 84.5, 17.1 and 18.1%, respectively. Anxiety occurred in 15.5% of patients and depression in 17.6% of patients.

TABLE 2 PSQI score of MHD patients.

Dimensions	Total ($n = 193$)	Sleep disturbance ($n = 123$)	No sleep disturbance ($n = 70$)
Subjective evaluation of sleep quality (points)	1.19 ± 0.82	1.55 ± 0.75	0.56 ± 0.50
>1 point	49 (25.39)		
Sleep latency (points)	1.58 ± 1.09	2.07 ± 0.91	0.71 ± 0.82
>1 point	110 (56.99)		
Total sleep duration (points)	1.17 ± 1.07	1.59 ± 1.01	0.44 ± 0.75
>1 point	82 (42.49)		
Habitual sleep efficiency (points)	0.98 ± 1.15	1.45 ± 1.18	0.17 ± 0.42
>1 point	56 (29.02)		
Sleep disturbance (points)	1.06 ± 0.54	1.23 ± 0.49	0.77 ± 0.49
>1 point	32 (16.58)		
Use of sleep drugs (points)	0.67 ± 1.19	1.03 ± 1.34	0.04 ± 0.36
>1 point	45 (23.32)		
Daytime dysfunction (points)	1.33 ± 0.97	1.71 ± 0.93	0.66 ± 0.63
>1 point	75 (38.86)		
Total PSQI score (points)	7.98 ± 4.74	10.62 ± 3.86	3.36 ± 1.44
>5 points	123 (63.73)		
>10 points	51 (26.42)		

MHD, maintenance hemodialysis; PSQI, Pittsburgh Sleep Quality Index.

Sleep survey results in MHD patients

Table 2 shows the scores of PSQI in MHD patients. The average total PSQI score was 7.98 ± 4.74 points, with 123 (63.73%) patients > 5 points and 51 (26.42%) patients > 10 points. In addition, the average score of PSQI components in the sleep disturbance group was from high to low: sleep latency, daytime dysfunction, total sleep duration, subjective sleep quality, habitual sleep efficiency, sleep disturbance, and use of sleep drugs were 2.07 ± 0.91, 1.71 ± 0.93, 1.59 ± 1.01, 1.55 ± 0.75, 1.45 ± 1.18, 1.23 ± 0.49, and 1.03 ± 1.34 points, respectively.

Clinical characteristics of MHD patients in the sleep disturbance and no sleep disturbance groups

Table 1 shows the clinical characteristics of MHD patients with or without sleep disturbance. The age ($P = 0.007$) of MHD patients in the sleep disturbance group was significantly higher than those in the no sleep disturbance group. Conversely, Alb and Ca^{2+} levels ($P = 0.001$) were significantly higher in the no sleep disturbance group than those in the sleep disturbance group. In addition, anxiety ($P = 0.015$) and depression ($P = 0.036$) were decreased significantly in the no sleep disturbance group compared with the sleep disturbance group. It should be noted that CRP and PTH levels were higher in the sleep disturbance group compared with the no sleep disturbance group, although the differences did not show a statistical significance.

Supplementary Table 1 shows the univariate binary logistic regression analyses between sleep disturbance of MHD patients and clinical characteristics. Age and Ca^{2+} were transformed into 0.1* age and 10*Ca^{2+}, respectively. The higher 0.1 * age (OR = 1.435, 95% *CI*: 1.100-1.873, $P = 0.008$), anxiety (OR = 3.316, 95% *CI*: 1.208–9.106, $P = 0.020$), and depression (OR = 2.531, 95% *CI*: 1.040–6.164, $P = 0.041$) were risk factors for sleep disturbance in MHD patients. Conversely, lower Alb (OR = 0.827, 95% *CI*: 0.743–0.921, $P = 0.001$) and 10*Ca^{2+} levels (OR = 0.731, 95% *CI*: 0.607–0.880, $P = 0.001$) were associated with an increased risk of sleep disturbance in MHD patients.

The multivariate binary logistic regression analysis between sleep disturbance of MHD patients and clinical characteristics (Supplementary Figure 2). Higher 0.1*age (OR = 1.476, 95% *CI*:

1.103-1.975, $P = 0.009$), lower Alb (OR = 0.863, 95% *CI*: 0.771-0.965, $P = 0.010$) and lower $10*Ca^{2+}$ levels (OR = 0.747, 95% *CI*: 0.615-0.907, $P = 0.003$) were independent risk factors for sleep disturbance in MHD patients.

Clinical characteristics of MHD patients in the severe sleep disturbance and no severe sleep disturbance groups

Supplementary Table 2 shows the clinical characteristics of MHD patients with or without severe sleep disturbance. The age ($P = 0.005$) and TG ($P = 0.020$) of MHD patients in the severe sleep disturbance group was significantly higher than those in the no severe sleep disturbance group. In contrast, HDL-C ($P = 0.017$) and Alb levels ($P = 0.006$) were significantly higher in the no severe sleep disturbance group than those in the severe sleep disturbance group. Additionally, anxiety ($P < 0.001$) and depression ($P = 0.010$) were increased significantly in the severe sleep disturbance group compared with the no severe sleep disturbance group. It is worth noting that the duration of dialysis was longer in the severe sleep disturbance group compared with the no severe sleep disturbance group, although the differences did not show a statistical significance.

Supplementary Table 3 shows the univariate binary logistic regression analyses between severe sleep disturbance of MHD patients and clinical characteristics. Age was transformed into 0.1* age, and duration of dialysis was converted into grade variable. The higher 0.1 * age (OR = 1.493, 95% *CI*: 1.121–1.989, $P = 0.006$), the longer the duration of dialysis [3–5 years (OR = 3.769, 95% *CI*: 1.015–14.003, $P = 0.048$), >5 years (OR = 2.904, 95% *CI*: 1.059–7.963, $P = 0.038$)], anxiety (OR = 4.180, 95% *CI*: 1.861–9.385, $P = 0.001$) and depression (OR = 2.697, 95% *CI*: 1.246–5.838, $P = 0.012$) were risk factors for severe sleep disturbance in MHD patients. The lower HDL-C (OR = 0.212, 95% *CI*: 0.058–0.774, $P = 0.019$) and Alb (OR = 0.865, 95% *CI*: 0.778–0.963, $P = 0.008$) were associated with an increased risk of severe sleep disturbance in MHD patients.

The multivariate binary logistic regression analysis between severe sleep disturbance of MHD patients and clinical characteristics (Supplementary Figure 3). Higher 0.1*age (OR = 1.476, 95% *CI*: 1.076–2.023, $P = 0.016$), lower Alb (OR = 0.877, 95% *CI*: 0.778–0.989, $P = 0.032$) and anxiety (OR = 3.442, 95% *CI*: 1.204–9.839, $P = 0.021$) were independent risk factors for severe sleep disturbance in MHD patients.

The risk prediction model for sleep disturbance in MHD patients

Age, duration of dialysis, CRP, TG, HDL-C, Alb, Ca^{2+}, PTH, anxiety and depression were screened out to establish initial predictive model based on univariate binary logistic regression analyses between sleep disturbance or severe sleep disturbance and clinical characteristics, combined with variables considered to be meaningful in previous studies. Furthermore, age, CRP, Alb, Ca^{2+}, PTH and anxiety were screened by two-way stepwise regression. A collinearity test showed that no collinearity existed among these variables. Multivariate binary logistic regression analysis was conducted with the selected age, CRP, Alb, Ca^{2+}, PTH and anxiety as variables (Figure 1), and then the risk prediction model for sleep disturbance in MHD patients was developed, and a nomogram was constructed according to the parameters of the prediction model (Figure 2).

Taking the original data of the prediction model as the data set, the ROC curve for predicting sleep disturbance in MHD patients was plotted, and the area under the curve was 0.764 (Figure 3A). The 1,000 bootstrap resampling procedure was used for internal validation of the prediction model, and the C-index after calibration was 0.736. Subsequently, calibration curve plots indicated that the calibration curve is approximately distributed along the reference line (y = x), with a mean absolute error of 0.032 (Figure 3B), the Hosmer-Lemeshow test ($P = 0.434$), demonstrated that the predictive probabilities of the model fit the actual probabilities well.

Discussion

According to statistical analyses, CKD patients account for ∼9.1% of the global population, and the prevalence of ESKD is as high as 550 people per million (23). At present, hemodialysis is the main treatment for ESKD patients except kidney transplantation. However, complications caused by hemodialysis, especially sleep disturbance, are often ignored (24). Studies have shown that there are many factors associated with sleep disturbance in MHD patients, such as gender, diet, depression and serum PTH levels (14, 16). In this study, we found that age, Alb and Ca^{2+} were independent risk factors for sleep disturbance in MHD patients, and confirmed that age, Alb and anxiety were associated with the severity of sleep disturbance in MHD patients. In this regard, we developed for the first time a risk prediction model for sleep disturbance in MHD patients.

The incidence of sleep disturbance in 193 MHD patients included in this study was 63.73%, which is similar to previous study results (25). Meanwhile, it should be noted that the incidence of severe sleep disturbance in MHD patients is as high as 26.42%. In addition, we found that prolonged sleep latency was the most common form of sleep disturbance in MHD patients, followed by daytime dysfunction with less use of sleep drugs. Previous study has also found that sleep latency has the greatest impact on MHD patients, and fewer patients use hypnotic drugs (16). This may be due to the increased daytime sleep in MHD patients during hemodialysis, resulting

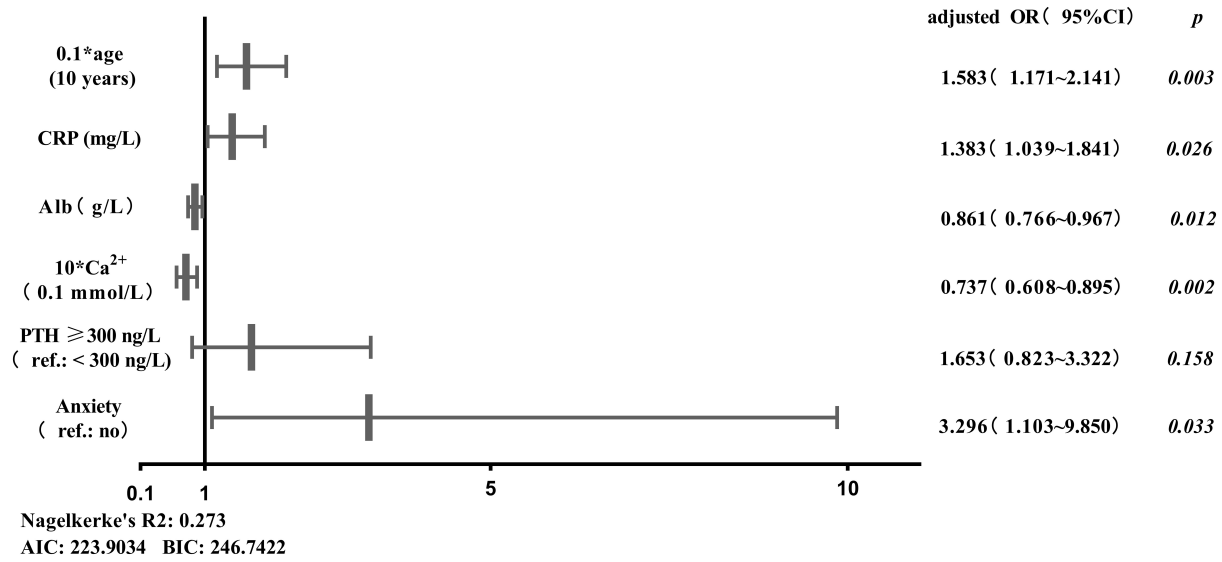

FIGURE 1
Binary logistic regression analysis between sleep disturbance of MHD patients and predictors. AIC, Akaike information criterion; Alb, albumin; BIC, Bayesian information criterion; Ca^{2+}, calcium; CRP, C-reactive protein; PTH, parathyroid hormone; Ref., reference.

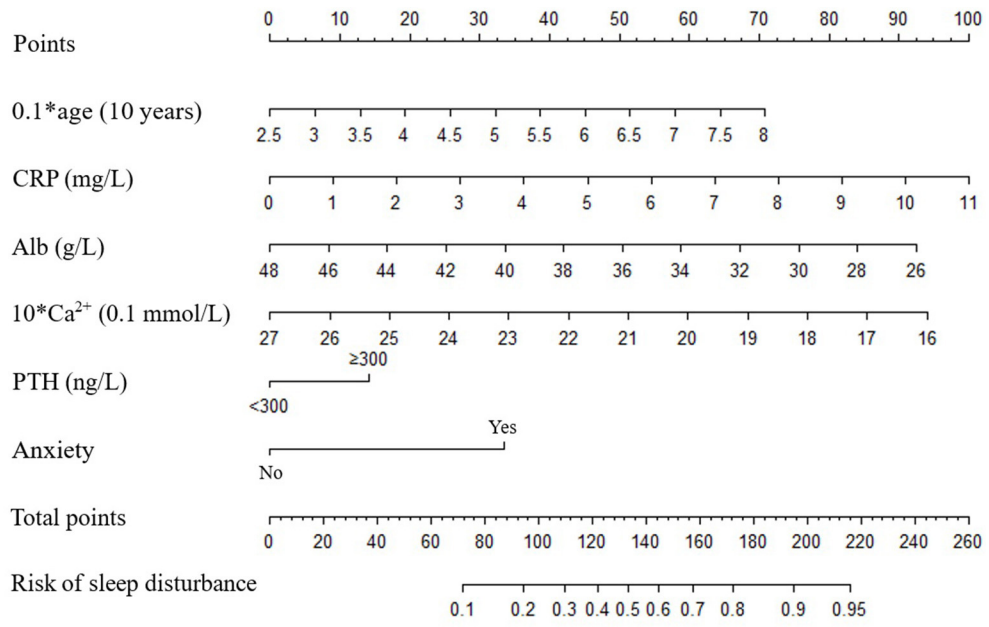

FIGURE 2
Nomograms predict the risk of sleep disturbance in patients with MHD. Alb, albumin; Ca^{2+}, calcium; CRP, C-reactive protein; PTH, parathyroid hormone.

in difficulty in falling asleep at night, and thus significantly prolonged sleep latency. Additionally, MHD patients have a high prevalence of depression (26), and depression is related to prolonged sleep latency (27), which may be another reason for prolonged sleep latency in MHD patients. Meanwhile, studies have found that the severity of RLS is positively correlated with PSQI score in hemodialysis patients, and the sleep latency of hemodialysis patients with RLS is significantly prolonged (28, 29). Therefore, improving RLS may be an important direction to shorten the sleep latency of MHD patients. Furthermore,

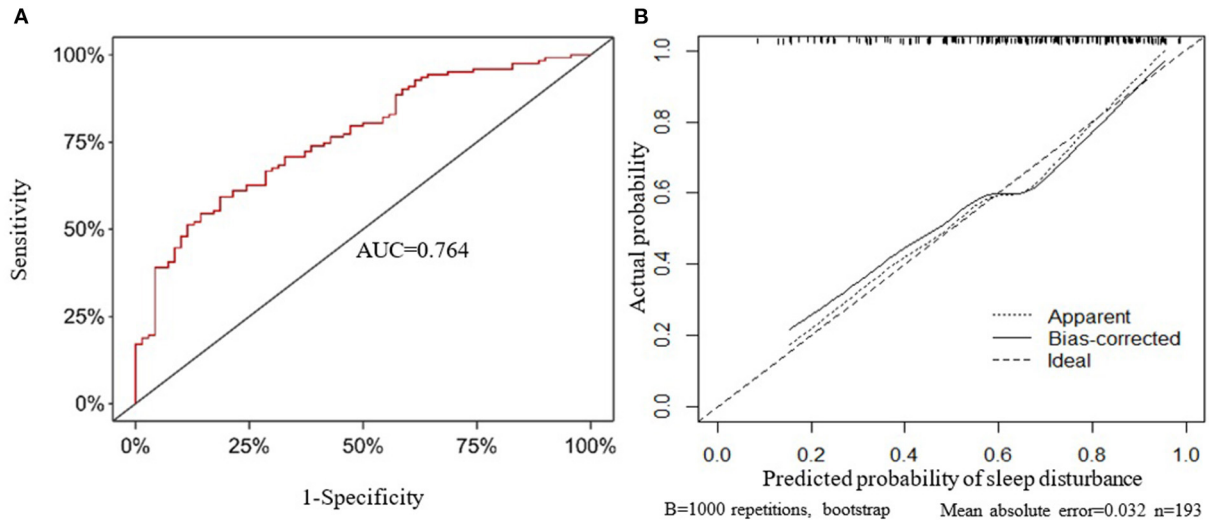

FIGURE 3
Internal validation of the prediction model. **(A)** The receiver operating characteristic curve. **(B)** Calibration curve. AUC, area under the curve.

the renal function of MHD patients is almost lost, and it is widely believed that most drugs are mainly metabolized through kidney, which may make MHD patients resistant to drug administration. Therefore, it is known that sleep disturbance is common and serious in MHD patients, and shortening sleep latency may be an important strategy to improve sleep quality in MHD patients.

The association between poor sleep quality and old age has long been recognized among the general population and has also been shown in MHD patients (30, 31). In addition, a study has confirmed that sleep disturbance in MHD patients is independently related to age (32), and this result has also been verified in this study. In the current study, we found the age of MHD patients in the sleep disturbance group was significantly higher than those in the no sleep disturbance group, and further statistical analysis suggested that age was an independent risk factor for sleep disturbance in MHD patients. Furthermore, this study found that age was associated with the severity of sleep disturbance, showing that the risk of severe sleep disturbance increased by 0.476 times for each additional 10 years of age. Additionally, the risk of sleep disturbance was increased with the duration of dialysis (33). Although the present study found there was no significant difference in the duration of dialysis between the sleep disturbance and no sleep disturbance group, our results suggested that the duration of dialysis may be a risk factor for the severity of sleep disturbance in MHD patients. These results demonstrate that elderly patients with long dialysis age are more likely to have sleep disturbance.

Alb in MHD patients with sleep disturbance was significantly lower than that in without sleep disturbance, and the incidence of severe sleep disturbance was significantly reduced with the increase of Alb. Ling et al. (34) also found that hypo-albuminemia was associated with poor sleep quality in MHD patients. Furthermore, a cohort study found that Alb level was positively correlated with total sleep time in MHD patients, and that regulating hypo-albuminemia could improve their sleep disturbance (35). In addition, it is important to note that vitamin D deficiency is thought to be a potential cause of sleep disturbance (36). A meta-analysis showed that vitamin D deficiency is associated with a higher risk of sleep disturbance, and subgroup analysis suggested that vitamin D deficiency not only reduced the sleep quality, but also affected sleep duration (37). Importantly, the association between vitamin D and sleep disturbance was validated in MHD patients. Hejazian et al. (38) showed that vitamin D deficiency was an independent predictor of sleep disturbance in MHD patients. It is well known that Vitamin D is closely related to Ca^{2+} metabolism in the body. Meanwhile, the results of the current study showed a significant difference in Ca^{2+} between the sleep disturbance and the no sleep disturbance group. Therefore, regulating Ca^{2+} and Alb levels may be an important strategy for improving sleep quality in MHD patients.

The relationship between blood lipid and sleep quality in MHD patients is still unclear. A clinical study suggested that increased TG is associated with increased risk of sleep disturbance in MHD patients (39). In addition, a study has found that MHD patients with poor sleep quality have lower HDL-C levels than those with good sleep quality (25). However, a recent study suggested that TG and TC levels were not associated with the sleep disturbance in MHD patients (15). Although the results of the current study suggested that HDL-C may be a risk factor for severe sleep disturbance in MHD patients, there

were no significant differences in TG, TC, HDL-C and LDL-C levels between the sleep disturbance and the no sleep disturbance group. These lines of evidence suggest that the role of lipid in sleep disturbance in MHD patients is ambiguous, and further studies will be needed to confirm the relationship.

Depression, anxiety and sleep disturbance are usually associated with a lower quality of life in MHD patients. Studies have found that depression is widespread in MHD patients and is a risk factor for sleep disturbance in MHD patients (26, 40). However, our study found that depression was not associated with sleep disturbance in MHD patients after adjusting for multiple covariates such as age, Alb and Ca^{2+}. Such inconsistent results may be related to the fact that fewer MHD patients with depression were included in this study. It has been well recognized that sleep deprivation can lead to anxiety (41), which in turn can contribute to decreased sleep quality (42). In addition, Dikici et al. (43) found that anxiety was associated with sleep disturbance in MHD patients. Meanwhile, the results of this study also showed that anxiety can significantly increase the occurrence of severe sleep disturbance in MHD patients. Therefore, although our data did not find that anxiety and depression were independent risk factors for sleep disturbance in MHD patients, the impact of anxiety and depression on sleep disturbance requires our attention.

Although a series of previous studies have focused on prediction models related to sleep quality, no study has discussed the risk prediction models for sleep disturbance in MHD patients. Li et al. (44) incorporated Hb, respiratory rate, diastolic blood pressure, delirium and cardiovascular diseases into the prediction model for assessing the risk of sleep disturbance in ICU patients, which provided clinical decision support for improving the sleep quality of ICU patients. Yang et al. (45) developed a prediction model to assess the risk of postoperative sleep disturbance in non-cardiac surgery patients, and then to provide reasonable prevention and treatment measures. In addition, a study has developed and verified the mathematical model for predicting sleep latency and sleep duration, providing a basis for developing personalized optimal sleep plans (46). This study was the first to explore the risk prediction model of sleep disturbance in MHD patients, in order to improve their sleep quality.

In the present study, age, CRP, Alb, Ca^{2+}, PTH and anxiety were used as predictors to develop a prediction model for sleep disturbance in MHD patients. As previously mentioned, age, Alb, Ca^{2+} and anxiety play important roles in MHD patients with sleep disturbance. The relationship between CRP and sleep quality has been demonstrated in multiple studies, with higher CRP levels indicating poorer sleep quality (47, 48). Furthermore, MHD patients are commonly associated with chronic inflammatory responses, and therefore often have elevated CRP levels. It is worth noting that CRP levels has been confirmed to be significantly negatively correlated with sleep quality of MHD patients (49). In addition, a clinical study has found that the incidence of sleep disturbance in MHD patients with hyperparathyroidism is significantly increased (50). Moreover, the sleep quality of MHD patients with hyperparathyroidism was significantly improved after parathyroidectomy (51). Therefore, although the current study did not find that CRP and PTH are the independent risk predictors for sleep disturbance in MHD patients, CRP and PTH were included in the prediction model based on previous evidence. Meanwhile, according to the actual clinical significance, age and Ca^{2+} were transformed into 0.1* age and 10*Ca^{2+}, respectively, and PTH was transformed into a categorical variable with a cut-off value of 300 ng/L. The internal validation of the prediction model was carried out by bootstrap resampling. The discrimination and calibration of the prediction model were evaluated with the C-index and calibration curve. In the present study, the prediction model has better discrimination and calibration. The C-index after calibration was 0.736, and the calibration curve was approximately distributed along the reference line ($x = y$).

There are some limitations in our study. First, this study had a single-center and cross-sectional design, which was not representative of the population and did not allow confirming causal relationship between sleep disturbance and risk factors. Further multicenter prospective cohort studies are needed to clarify the clinical value of risk factors in sleep disturbance in MHD patients. Second, our study developed a risk prediction model for sleep disturbance in MHD patients, providing a clinical guidance tool for improving sleep quality. However, this model has not been verified externally. In the future, external validation is needed to further improve the prediction efficiency of the model. Third, fewer patients with depression and anxiety were included in this study, which failed to adequately describe the relationship between depression, anxiety and sleep disturbance in MHD patients. Future studies should expand the sample size to further verify the interaction between depression, anxiety and sleep disturbance. Finally, our study relied on the scale to evaluate sleep quality, and we expect to use sleep monitoring devices such as polysomnography in the future, so as to provide better objective indicators for sleep monitoring of MHD patients.

In conclusion, sleep disturbance in MHD patients may be associated with age, Alb, Ca^{2+} and anxiety. In addition, we developed a risk prediction model for sleep disturbance in MHD patients, and early intervention with reversible predictors, such as CRP, Alb, Ca^{2+} and PTH, will contribute to the prevention and treatment of sleep disturbance in MHD patients. Subsequent studies should elucidate the exact pathogenesis of sleep disturbance in MHD patients and develop effective therapeutic strategies.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RX, LM, BZ, and RJ conceived the study. RX and LM performed the study and data analyses and drafted the manuscript. JN, YD, YS, and CY conducted the patient enrolment and collected the data. BZ and RJ revised 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.

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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.2022.955352/full#supplementary-material

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Prediction of sleep quality among university students after analyzing lifestyles, sports habits, and mental health

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The aim of this study was to develop and validate a prediction model to evaluate the risk of poor sleep quality. We performed a cross-sectional study and enrolled 1,928 college students from five universities between September and November 2021. The quality of sleep was evaluated using the Chinese version of the Pittsburgh Sleep Quality Index (PSQI). Participants were divided into a training (n = 1,555) group and a validation (n = 373) group. The training group was used to establish the model, and the validation group was used to validate the predictive effectiveness of the model. The risk classification of all participants was performed based on the optimal threshold of the model. Of all enrolled participants, 45.07% (869/1,928) had poor sleep quality (PSQI score $\geqq$ 6 points). Multivariate analysis showed that factors such as older age, a higher grade, previous smoking, drinking, midday rest, chronic disease, anxiety, and stress were significantly associated with a higher rate of poor sleep quality, while preference for vegetables was significantly associated with better sleep quality, and all these variables were included to develop the prediction model. The area under the curve (AUC) was 0.765 [95% confidence interval (CI): 0.742–0.789] in the training group and 0.715 (95% CI: 0.664–0.766) in the validation group. Corresponding discrimination slopes were 0.207 and 0.167, respectively, and Brier scores were 0.195 and 0.221, respectively. Calibration curves showed favorable matched consistency between the predicted and actual probability of poor sleep quality in both groups. Based on the optimal threshold, the actual probability of poor sleep quality was 29.03% (317/1,092) in the low-risk group and 66.03% (552/836) in the high-risk group ($P < 0.001$). A nomogram was presented to calculate the probability of poor sleep quality to promote the applicationof

the model. The prediction model can be a helpful tool to stratify sleep quality, especially among university students. Some intervention measures or preventive strategies to quit smoking and drinking, eat more vegetables, avoid midday rest, treat chronic disease, and alleviate anxiety and stress may be considerably beneficial in improving sleep quality.

KEYWORDS

quality of sleep, Pittsburgh Sleep Quality Index, university students, depression anxiety stress scales, prediction model

Introduction

Poor sleep quality is one of the severe health issues and is prevailing among teenagers who are vulnerable to the adverse effect of unsatisfactory sleep quality because of social or environmental shocks and their inclinations to stay up late (1). According to the available literature, up to 31.00–65.00% of university students had poor sleep quality (2–5). In particular, sleep problems can lead to various adverse outcomes, including a decreased academic performance (6), an increased risk for insomnia, high blood pressure (7), cognitive impairment, decreased quality of life, negative mental health condition (8), and even suicide ideation (9).

Several risk characteristics, such as grade (10, 11), stress (4, 12), physical activity (11), alcohol use (2), substance abuse (13), and severity of smartphone use (14, 15), associated with poor sleep quality were identified. These variables were able to guide doctors to roughly screen patients at a high risk of poor sleep quality. However, these variables could not accurately calculate the risk probability of having poor sleep quality, and thus early detection was difficult. Accordingly, this might result in not only inadequate diagnosis and therapeutic interventions but also overtreatment or improper administration of hypnosedatives (16). Thus, a valid tool that was able to cluster sleep quality was warranted before we could perform individualized healthcare. In addition, a model to evaluate the probability of poor sleep quality would be of great help to early detect the status, stratify risk, and treat this negative outcome individually. The currently available prediction models to predict the quality of sleep were particularly designed for elderly patients (16), rescuers (17), and caregivers (18). Nonetheless, data on prediction models for calculating the risk of poor sleep quality were extremely limited, especially among university students.

Therefore, the aim of this study was to investigate potential risk factors associated with poor sleep quality and further develop and validate a prediction model to measure the risk of poor sleep quality, especially among university students. This study hypothesized that significant variables associated with poor sleep quality could be identified and used to create a nomogram, which would accurately and individually evaluate the probability of suffering from poor sleep quality, especially among university students.

Materials and methods

Participants and study design

This study conducted a cross-sectional survey and analyzed 2,003 college students from five universities [Chongqing Normal University (Chongqing), Xiamen University of Technology (Xiamen), Harbin Sport University (Harbin), Sichuan Normal University (Chengdu), and North China University of Water Resources and Electric Power (Zhengzhou)] between September and November 2021 in China. University students voluntarily responded and completed the survey. The survey was distributed *via* instant communication tools, such as telephone messages and WeChat software, through a non-probability snowball sampling strategy (19). The survey consisted of the Student's basic information, lifestyles, comorbidities, mental health status, and evaluation of sleep quality. In addition, coronavirus disease 2019 (COVID-19) sporadic outbreaks were also reported by participants according to the real status of the great pandemic in their living city.

University students who were previously diagnosed with sleep problems in the hospital or did not want to complete the survey were not included in the analysis. **Figure 1** depicts the flowchart of participants, and a total of 1,928 university students were enrolled. To maximize data utilization, the majority of participants were used to develop the model. Thus, participants from the first four centers (n = 1,555) were employed as the training group, which was used to establish the model to predict sleep quality; participants from North China University of Water Resources and Electric Power (n = 373) were employed as the validation group, which was used to validate the predictive effectiveness of the model.

This study was approved by the Academic Committee and Ethics Board of the Xiamen University of Technology (no. 202001). Formal consent was obtained from all participants,

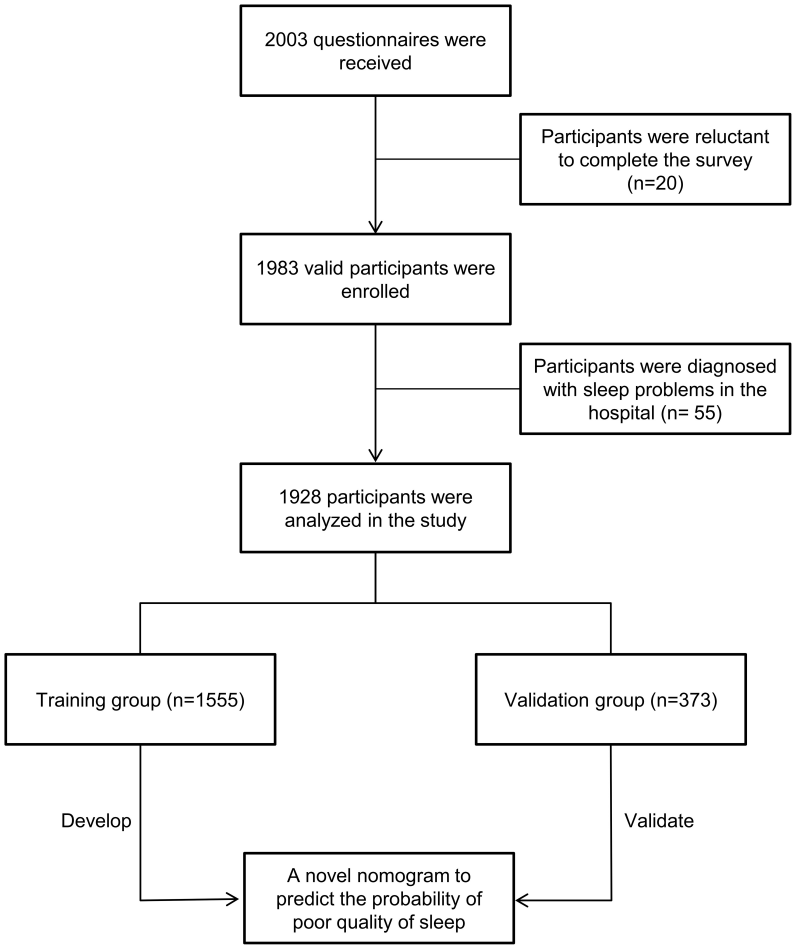

FIGURE 1
Patient's flowchart and study design. Based on inclusive and exclusive criteria, a total of 1,928 participants were enrolled and divided into a training group (n = 1,555) and a validation (n = 373) group.

and their identified personal information was not collected. This study was conducted in accordance with the Declaration of Helsinki.

Evaluation of sleep quality

The quality of sleep was evaluated using the Chinese version of the Pittsburgh Sleep Quality Index (PSQI). It was widely used among the Chinese population (20). It has 19 items and captures seven domains, namely, the subjective sleep quality, the sleep latency, the sleep duration, the habitual sleep efficiency, the sleep disturbances, the use of sleeping drugs, and the daytime dysfunction (21). Each domain has a score of 0–3, and the total score of PSQI, ranging from 0 to 21, was the combination of the seven domains. The PSQI score was the indicator variable to cluster participants with poor or good sleep quality. In detail, poor sleep quality was defined as participants with a total PSQI score of six points or above, while good sleep quality was defined as participants with a total PSQI score of less than six points (16, 22).

Potential risk features

The study evaluated 22 potential risk features for their ability to predict poor sleep quality, including basic information [gender, age (years), grade, and marital status], hobbies (smoking and drinking), living habits [having a habit of midday rest, monthly expense (¥), preference to low salt and fat food, preference to oil food, preference to barbecue, preference to red meat, preference to vegetable, and preference to fruit], sports habits [sedentary time per day (hours), frequency of sports per week, and sports type], comorbidities (chronic disease), COVID-19 sporadic outbreak in the local city, and mental health status (depression, anxiety, and stress).

All the above variables were reported by participants based on their actual conditions. Chronic disease was defined as

TABLE 1 Student's demographics, living and sport habits, and mental health.

Characteristics	Students (n = 1,928)
Gender	
Male	44.87% (865/1,928)
Female	55.13% (1,063/1,928)
Age [median (IQR), years]	19.00 (19.00, 20.00)
Grade	
First year	24.27% (468/1,928)
Second year	47.10% (908/1,928)
Third year	16.65% (321/1,928)
Fourth year	11.15% (215/1,928)
Delayed graduation	0.83% (16/1,928)
Marital status	
Single	76.56% (1,476/1,928)
Dating	22.61% (436/1,928)
Married	0.83% (16/1,928)
Smoking	
No	92.12% (1,776/1,928)
Abstain from smoking	2.96% (57/1,928)
Yes	4.93% (95/1,928)
Drinking	
No	81.64% (1,574/1,928)
Abstain from drinking	4.67% (90/1,928)
Yes	13.69% (264/1,928)
Having a habit of midday rest	
Yes	78.89% (1,521/1,928)
No	21.11% (407/1,928)
Monthly expense (¥)	
<2,000	78.89% (1,521/1,928)
≧2,000 and < 5,000	20.23% (390/1,928)
≧5,000 and < 10,000	0.41% (8/1,928)
≧10,000	0.47% (9/1,928)
Chronic disease	
Yes	4.10% (79/1,928)
No	95.90% (1,849/1,928)
Preference to low salt and fat food	
Yes	30.60% (590/1,928)
No	69.40% (1,338/1,928)
Preference to oil food	
Yes	25.83% (498/1,928)
No	74.17% (1,430/1,928)
Preference to barbecue	
Yes	28.99% (559/1,928)
No	71.01% (1,369/1,928)
Preference to red meat	
Yes	66.65% (1,285/1,928)
No	33.35% (643/1,928)
Preference to vegetable	
Yes	49.17% (948/1,928)
No	50.83% (980/1,928)
Preference to fruit	
Yes	57.47% (1,108/1,928)
No	42.53% (820/1,928)
Sedentary time (hours)	
<1	5.13% (99/1,928)
≧1 and < 3	18.36% (354/1,928)
≧3 and < 6	33.45% (645/1,928)
≧6	43.05% (830/1,928)
Frequency of sports per week	
0	21.27% (410/1,928)
1−2	36.41% (702/1,928)
3−4	21.06% (406/1,928)
≧5	21.27% (410/1,928)
Sport type	
None	21.27% (410/1,928)
Aerobic exercise	44.29% (854/1,928)
A middle between aerobic and anaerobic exercise	23.24% (448/1,928)
Anaerobic exercise	11.20% (216/1,928)
COVID-19 sporadic outbreaks in local city	
Yes	48.60% (937/1,928)
No	51.40% (991/1,928)
DASS-21 depression score [median (IQR)]	4.00 (0.00 10.00)
DASS-21 anxiety score [median (IQR)]	4.00 (0.00 10.00)
DASS-21 stress score [median (IQR)]	6.00 (0.00 12.00)
Quality of sleep[a]	
Poor	45.07% (869/1,928)
Good	54.93% (1,059/1,928)

IQR, Interquartile range; COVID-19, Corona virus disease 2019; DASS-21, Depression anxiety stress scales 21; PSQI, Pittsburgh sleep quality index.
[a]Indicates that poor sleep quality was defined as participants with a total PSQI score of six points or above.

participants with a diagnosis of chronic disease in a hospital, such as hypertension, diabetes, congenital heart disease, chronic kidney disease, chronic lung disease, chronic liver disease, and others. The frequency of sports per week was the number of sports that participants did each week, and the total time of each workout should be a minimum of 30 min. A COVID-19 sporadic outbreak was defined as at least one patient being diagnosed with COVID-19 during the last 2 weeks in the participant's local city. Depression, anxiety, and stress scores were evaluated using Depression Anxiety Stress Scales-21 (DASS-21) (23).

Establishment of the model

Participants in the training group were used to establish the model, and significant variables identified by the multiple logistic regression analysis were included in

TABLE 2 Multivariate analysis of characteristics for predicting poor sleep quality among university students in the training group.

Characteristics	Patients (n = 1,555, %)	OR	95% CI		*P*-value
			LL	UL	
(Intercept)		0.015	0.003	0.090	<0.001
Gender					
Male	632 (40.64%)	Reference			
Female	923 (59.36%)	1.301	0.988	1.711	0.061
Age [median (IQR), years]	19.00 (19.00, 20.00)	1.129	1.035	1.231	0.006
Grade					
First year	351 (22.57%)	Reference			
Second year	750 (48.23%)	1.205	0.883	1.644	0.239
Third year	271 (17.43%)	1.612	1.066	2.439	0.024
Fourth year	170 (10.93%)	1.236	0.730	2.094	0.431
Delayed graduation	13 (0.84%)	0.828	0.158	4.347	0.824
Marital status					
Single	1,187 (76.33%)	Reference			
Dating	356 (22.89%)	0.857	0.646	1.137	0.285
Married	12 (0.77%)	0.095	0.008	1.160	0.065
Smoking					
No	1,422 (91.45%)	Reference			
Abstain from smoking	45 (2.89%)	2.148	1.042	4.429	0.038
Yes	88 (5.66%)	0.997	0.567	1.753	0.991
Drinking					
No	1,256 (80.77%)	Reference			
Abstain from drinking	76 (4.89%)	1.433	0.820	2.505	0.206
Yes	223 (14.34%)	1.562	1.085	2.250	0.017
Having a habit of midday rest					
No	340 (21.86%)	Reference			
Yes	1,215 (78.14%)	1.443	1.080	1.928	0.013
Monthly expense (¥)					
<2,000	1,177 (75.69%)	Reference			
≧2,000 and < 5,000	363 (23.34%)	1.193	0.907	1.568	0.207
≧5,000 and < 10,000	8 (0.51%)	0.929	0.134	6.436	0.941
≧10,000	7 (0.45%)	1.020	0.120	8.634	0.986
Chronic disease					
No	1,487 (95.63%)	Reference			
Yes	68 (4.37%)	1.983	1.118	3.518	0.019
Preference to low salt and fat food					
No	1,086 (69.84%)	Reference			
Yes	469 (30.16%)	0.912	0.696	1.197	0.508
Preference to oil food					
No	1,153 (74.15%)	Reference			
Yes	402 (25.85%)	0.846	0.641	1.116	0.237
Preference to barbecue					
No	1,112 (71.51%)	Reference			
Yes	443 (28.49%)	1.258	0.960	1.650	0.097
Preference to red meat					
No	504 (32.41%)	Reference			
Yes	1,051 (67.59%)	1.011	0.782	1.306	0.935
Preference to vegetable					
No	793 (51.00%)	Reference			
Yes	762 (49.00%)	0.704	0.551	0.900	0.005
Preference to fruit					
No	636 (40.90%)	Reference			
Yes	919 (59.10%)	1.199	0.929	1.546	0.163
Sedentary time (hours)					
<1	81 (5.21%)	Reference			
≧1 and < 3	302 (19.42%)	0.731	0.409	1.305	0.289
≧3 and < 6	527 (33.89%)	0.747	0.428	1.305	0.305
≧6	645 (41.48%)	0.831	0.476	1.449	0.514
Frequency of sports per week					
0	366 (23.54%)	Reference			
1−2	615 (39.55%)	1.166	0.723	1.880	0.530
3−4	334 (21.48%)	1.371	0.841	2.236	0.206
≧5	240 (15.43%)	0.973	0.582	1.626	0.917
Sport type					
None	366 (23.54%)	Reference			
Aerobic exercise	655 (42.12%)	0.991	0.659	1.491	0.967
A middle between aerobic and anaerobic exercise	355 (22.83%)	1.153	0.755	1.761	0.511
Anaerobic exercise	179 (11.51%)	Not applicable			
COVID-19 sporadic outbreaks in local city					
No	646 (41.54%)	Reference			
Yes	909 (58.46%)	0.910	0.713	1.161	0.447
DASS depression score [median (IQR)]	4.00 (0.00 10.00)	1.018	0.989	1.049	0.223
DASS anxiety score [median (IQR)]	4.00 (0.00 10.00)	1.064	1.024	1.104	0.001
DASS stress score [median (IQR)]	6.00 (0.00 12.00)	1.071	1.038	1.104	<0.001

OR, odds ratio; CI, confident interval; LL, lower limit; UL, upper limit; IQR, interquartile range; COVID-19, coronavirus disease 2019; DASS-21, Depression Anxiety Stress Scale 21.

the model. The model was presented in the format of a nomogram, and the "regplot" R package was used to create the nomogram to calculate the risk probability of poor sleep quality and to promote the application of the model.

Validation of the model

Internal validation of the model was performed in both the training and validation groups. The predictive effectiveness of the model was evaluated using discrimination and calibration. In the study, discriminative ability was the model's capability to identify participants with poor sleep quality and those

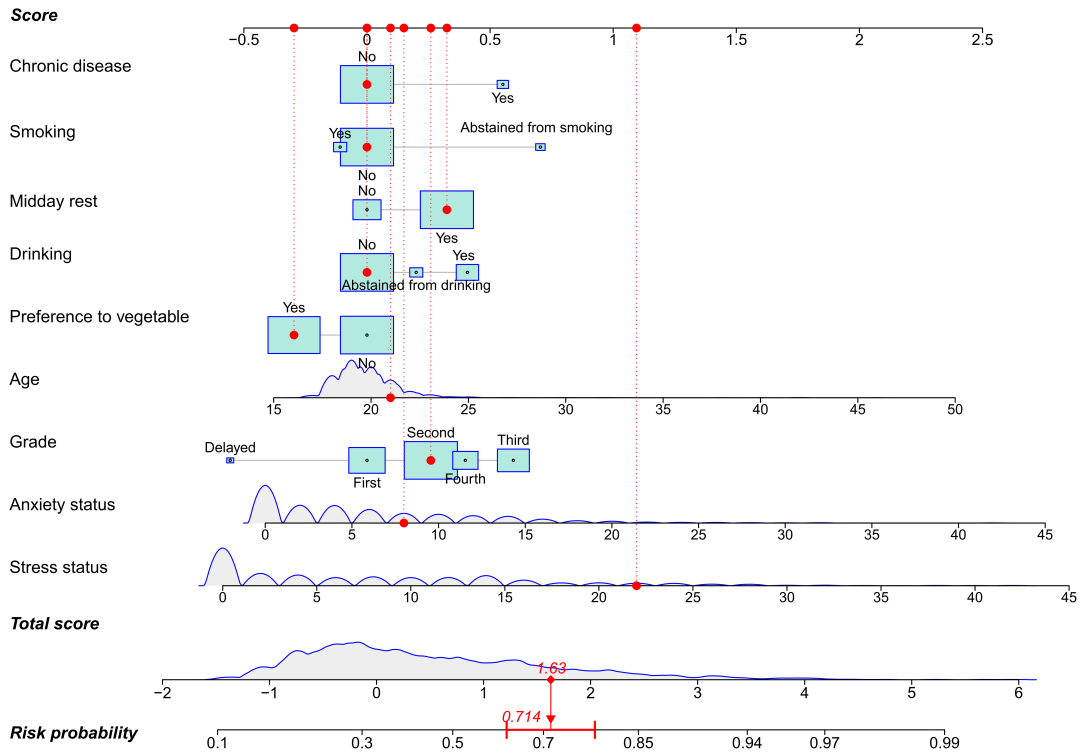

FIGURE 2
A nomogram to predict sleep quality among university students. The nomogram is comprised of nine features and three axes (score, total score, and risk probability axes). Each feature is able to obtain a score by referring to the score axis, the total score is the sum points of the nine features, and participant's risk probability can be calculated by drawing a line downward from the total score axis to the risk probability axis. In the nomogram, quantitative features are depicted as density curves to visualize distribution, and qualitative features including age, anxiety, and stress are presented as boxes. The size of boxes indicates proportions in each feature.

without poor sleep quality, and this metric mainly consisted of area under the curve (AUC) and discrimination slope. The calibrating ability was the model's capability to confirm the homogeneity between the actual and predicted probability of having poor sleep quality. In this study, calibrating ability was evaluated using the calibration curve and Brier score (24). A calibration curve was plotted using the Bootstrap method after applying 500 iterations. A Brier score is the mean squared difference between a patient's predicted probability and actual status (1 or 0 depending on whether the event is positive or negative). If the Brier score approaches 0.0, it usually indicates a perfect prediction. Decision curve analysis was used to assess the clinical usefulness of the model. In addition, the model's accuracy, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), precision, recall, and Youden index were also evaluated in the study.

Statistical analysis

Participants' sociodemographic characteristics were presented in proportions or median and interquartile range (IQR). According to the optimal threshold, all participants were divided into two risk groups, namely, a low-risk group (participants with a predicted probability of less than the threshold) and a high-risk group (participants with a predicted probability of threshold or above). The Chi-square test was used to compare the difference in the actual probability of poor sleep quality between the low-risk group and the high-risk group. A *P*-value of less than 0.05 was regarded as statistical significance (two-sided tests). All statistical analyses and data visualization were performed using R programming language software (version 4.1.2).

Results

Participant's demographics, lifestyles, and mental health

Among the total participants, the majority of them were female (55.13%, 1,063/1,928) and the median age was 19.00 (19.00, 20.00) years. The majority of participants were sophomore (47.10%, 908/1,928) and single (76.56%,

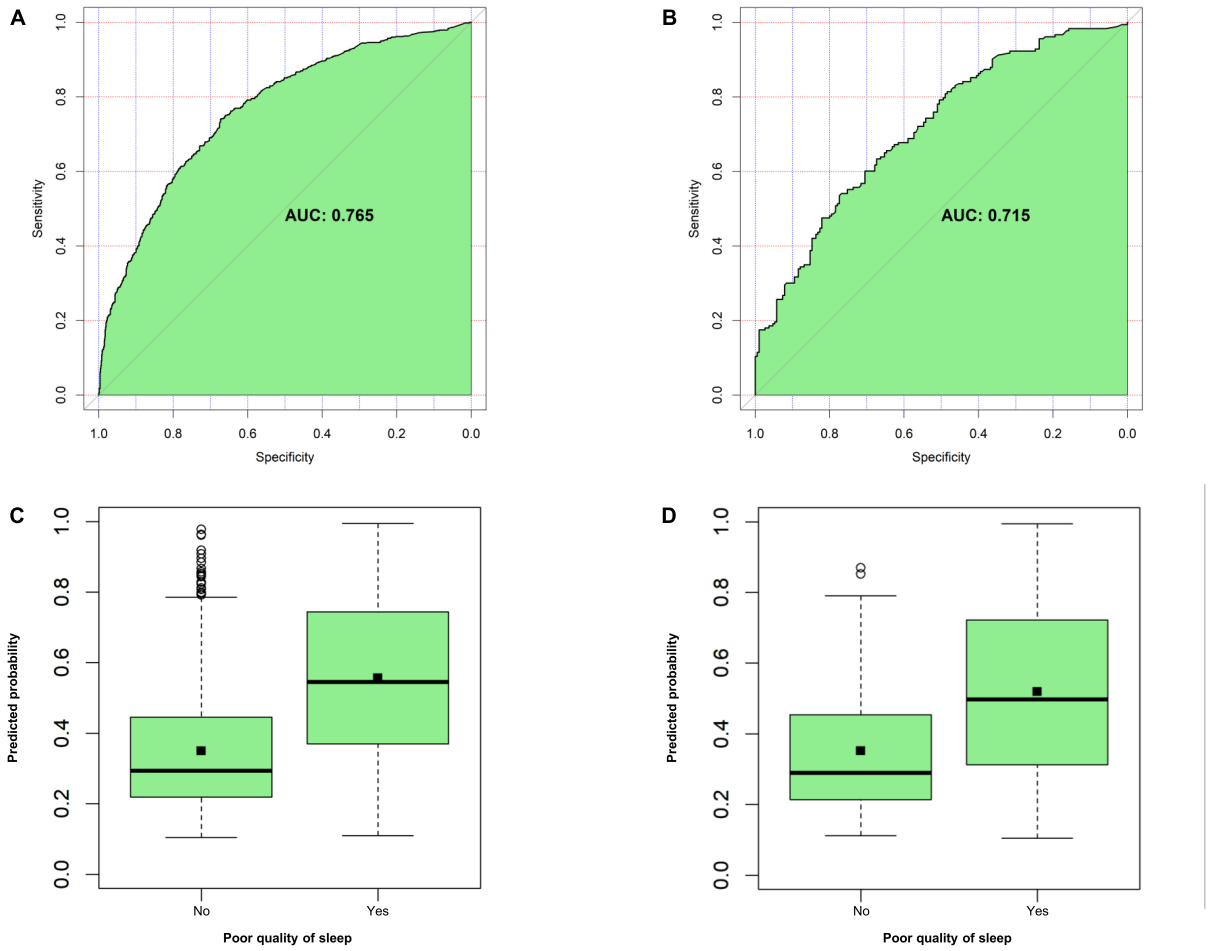

FIGURE 3
Evaluation of model's discrimination. **(A)** Area under the curve (AUC) for the model in the training group. **(B)** AUC for the model in the validation group. **(C)** Discrimination slope for the model in the training group (0.207, $P < 0.001$). **(D)** Discrimination slope for the model in the validation group (0.167, $P < 0.001$). A discriminative plot is plotted with an actual event (yes vs. no) against a predicted probability of poor sleep quality. Discrimination slope is the mean difference of predicted probabilities between participants with actual poor sleep quality and those without it.

1,476/1,928). Only a small fraction of participants were current smoker (4.93%, 95/1,928) or drinker (13.69%, 264/1,928). Of all the included participants, 78.89% (1,521/1,928) had a habit of midday rest, and 78.89% (1,521/1,928) had a monthly expense of less than 2,000 ¥. Furthermore, less than 5.00% of participants had previously been diagnosed and hospitalized for chronic disease. Notably, 48.60% (937/1,928) of participants were living in a city that had COVID-19 sporadic outbreaks. Based on the evaluation of DASS-21, the median depression, anxiety, and stress scores were 4.00 (0.00 10.00), 4.00 (0.00 10.00), and 6.00 (0.00 12.00), respectively, which indicated that the majority of participants were generally in a healthy mental condition. But, sleep quality was not satisfactory among those participants, and 45.07% (869/1,928) of them suffered from poor sleep quality (PSQI score $\geqq$ 6). Furthermore, Table 1 shows more details about the participant's food preferences and sports habits.

Development of the model

Multivariate analysis showed that older age ($P = 0.006$), a higher grade ($P = 0.024$), previous smoking ($P = 0.038$), drinking ($P = 0.017$), midday rest ($P = 0.013$), chronic disease ($P = 0.019$), anxiety ($P = 0.001$), and stress ($P < 0.001$) were significantly associated with a higher rate of poor sleep quality (Table 2), while preference for vegetables ($P = 0.005$) was significantly associated with better sleep quality. Thus, these nine features were all included to develop the prediction model. To promote the application of the model, a nomogram was created to evaluate the probability of poor sleep quality (Figure 2). An example of how to use the nomogram was shown as follows. A 21-year-old university student who was in the second year of school did not have a chronic disease and was not a current smoker or drinker. This student had a habit of midday rest and preferred eating vegetables, and the Student's anxiety and

TABLE 3 Predictive effectiveness of the model to predict risk probability of poor sleep quality among university students.

Prediction measures	Training group	Validation group
Brier score	0.195	0.221
$Brier_{scaled}$ score	0.208	0.115
AUC (95% CI)	0.765 (0.742–0.789)	0.715 (0.664–0.766)
Discrimination slope	0.207	0.167
Accuracy	0.703	0.657
Threshold	0.378	0.475
Specificity	0.673	0.768
Sensitivity	0.741	0.541
NPV	0.767	0.635
PPV	0.641	0.692
Precision	0.641	0.692
Recall	0.741	0.541
Youden	1.414	1.309

AUC, Are under the curve; CI, Confident interval; NPV, Negative predictive value; PPV, Positive predictive value.

stress scores were 8 and 22, respectively. Each feature could obtain a score by referring to the score axis, and the total score (1.63) was the combination of the nine features. By drawing a line downward to the risk probability axis, users could obtain the predicted probability of poor sleep quality (71.40%) and its 95% CI.

Predictive effectiveness of the model

The AUC of the model was 0.765 (95% CI: 0.742–0.789) in the training group (**Figure 3A**) and 0.715 (95% CI: 0.664–0.766) in the validation group (**Figure 3B**), and the corresponding discrimination slopes were 0.207 (**Figure 3C**) and 0.167 (**Figure 3D**). Models' accuracy, sensitivity, specificity, NPV, PPV, and other metrics are summarized in **Table 3**. Calibration curves demonstrated good consistency between predicted and observed probability in both training (**Figure 4A**) and validation (**Figure 4B**) groups, indicating excellent calibrating ability of the model. Decision curve analysis also showed favorable clinical usefulness in the training (**Figure 4C**) and validation (**Figure 4D**) groups.

Risk classification based on the model

The optimal cutoff value (43.00%) was obtained by calculating the round mean threshold of the training (37.80%) and validation (47.50%) groups. Therefore, this study defined that participants who had a predicted probability of 43.00% or above belonged to the high-risk group, while participants who had a predicted probability of less than 43.00% belonged to the low-risk group (**Table 4**). Based on the optimal cutoff value, the actual probability of poor sleep quality was 29.03% (317/1,092) in the low-risk group and 66.03% (552/836) in the high-risk group ($P < 0.001$), which indicated that participants in the low-risk group were 2.27 times more at risk of developing poor sleep quality than those in the high-risk group.

Discussion

Sleep problems are common among university students. In this study, we found that the incidence of poor sleep quality was up to 45.07%, and this number was consistent with other studies (2–5). Literature reported that 31.00–65.00% of university students suffered from poor sleep quality (2–5). To address this issue, it is necessary to accurately predict the probability of poor sleep quality, and thus appropriate interventions could be timely administered accordingly. This study successfully proposed a prediction model to evaluate the probability of poor sleep quality after analyzing 1,928 college students. A nomogram was created to promote the application of the prediction model. The prediction model had favorable predictive effectiveness in terms of calibration and discrimination.

This model was comprised of nine features, including age, grade, smoking, drinking, midday rest, chronic disease, anxiety, and stress, which were risk factors for poor sleep quality, and preference to vegetables, which was a protective factor for sleep quality. The results were in line with the currently available literature (2, 10–12, 25). For example, Xu et al. (10) reported that a high grade level, living in rural areas, depression, and anxiety might be negative impactors of poor sleep quality. Almojali et al. (12) found that a high level of stress and poor sleep quality were statistically correlated after analyzing 263 university students. Wang et al. (11) revealed that less exercise, skipping breakfast, and a higher grade were relevant to poor sleep quality. Li et al. (2) showed that for young people, alcohol use, gambling behaviors, and less frequency of sports per week were significant predictors of poor sleep quality. Alghwiri et al. (25) showed that pain and other systematic diseases were risk factors for predicting poor sleep quality after analyzing 1,600 university students.

In addition, the prediction model is gradually applied to evaluate sleep quality. For example, Chen et al. (16) developed the rapid classification scale for sleep quality to screen and subgroup poor sleep quality using four main variables, including sleep quality, hypnotic use, sleep onset, and lacking enthusiasm. But Chen's scale was designed specifically for older adults, and the young were not enrolled, which meant that this scale was not applicable to the young population. Sai et al. (17) investigated insomnia-related factors and further constructed a prediction nomogram to identify patients with insomnia in an early stage according to a cross-sectional survey and an analysis of 1,133 participants. These participants were rescuers working in a military unit. Zhou et al. (26) proposed a novel

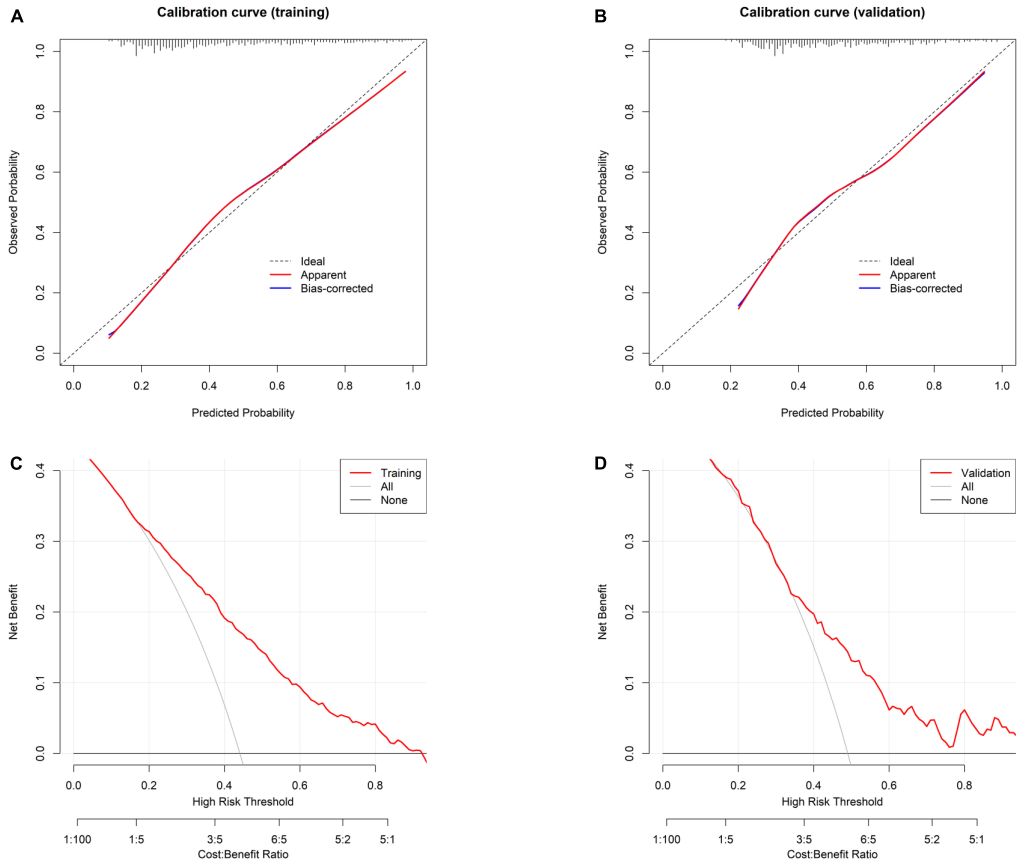

FIGURE 4
Evaluation of model's calibration and clinical usefulness. **(A)** Calibration curve for the model in the training group. **(B)** Calibration curve for the model in the validation group. Calibration curve is plotted with predicted probability against observed probability. A dotted diagonal line in the curve indicates perfect consistency between the predicted and observed probability. **(C)** Decision curve analysis for the model in the training group. **(D)** Decision curve analysis for the model in the validation group. Decision curve is plotted with different thresholds against net benefit. Larger space between the red line and the two reference (a treat-for-all line and a treat-for-none line) lines indicates better clinical usefulness.

framework to predict the quality of sleep according to the dynamic functional network connectivity after analyzing the fMRI data from human connectome project (HCP). Sadeghi et al. (18) achieved the sleep quality prediction with the help of physiological signals, including heart rate, electrodermal activity, body movement, and skin temperature, all of which were collected from a wearable device. The accuracy was about 75% for sleep quality among caregivers of dementia patients. The above scales generally had good accuracy, but the availability of information and population differences might compromise their applications to ordinary university students. This study included nine parameters, which were easily available, especially for university students. To the best of our knowledge, this model was the first to predict the poor sleep quality, especially among university students. This model was presented in the format of nomogram. In addition, risk stratification was achieved in the study, and it showed that participants in the low-risk group were 2.27 times more at risk of developing poor sleep quality than those in the high-risk group. Thus, more attention should be paid to participants among the high-risk group.

What can we do for participants in the high-risk group? On conducting the survey, COVID-19 is still prevailing. The great pandemic could affect the quality of sleep among university students due to lockdown, social distance, and stay-at-home orders, possibly because the negative mental health status that was aroused by the great pandemic was a significant contributor to poor sleep quality (27, 28). Luckily, with the normalization of preventing and controlling the great pandemic, its impact on sleep quality might be decreasing among university students. As depicted in this study, the feature (COVID-19 sporadic outbreaks in the participant's city) did not show any statistically significant association with sleep quality. But, considering the unexpected length and severity of the outbreaks, intervention measures to deal with the psychological health of university students were still warranted since good mental health status was remarkably beneficial to sleep quality. Furthermore, researchers also pointed out that some measures might be

TABLE 4 Risk classification based on the nomogram and corresponding predicted and actual probability of poor sleep quality among the entire cohort of university students.

Groups	Patients (n = 1,928)	Probability of poor sleep quality		P-value[a]
		Predicted	Actual	
Low-risk (<43%)	1,092	27.09%	29.03% (317/1,092)	<0.001
High-risk (≧43%)	836	66.05%	66.03% (552/836)	

[a]Indicates the P-value was calculated from the Chi-square test after a comparison between the low-risk and high-risk groups in the actual probability of poor sleep quality.

effective to boost sleep quality, such as predefined sports programs, sleep education programs, interesting entertainment, and avoiding the overuse of mobile phones (15). But a systematic review showed that the effectiveness of sleep education on sleep behavior and sleep quality needed more supportive evidence (29). Therefore, future studies on the approaches and contents of sleep education program are still needed. Regarding Chinese traditional medicine, a traditional herb, rosemary, might be helpful to reduce mental distress and improve sleep quality among university students based on a randomized clinical trial after analyzing 68 participants (30). This study further demonstrated that some measures to quit smoking and drinking, eat more vegetables, avoid midday rest, treat chronic disease, and alleviate anxiety and stress moods would also be great helpful to sleep quality.

Limitations

This study had certain limitations. First, this is a cross-sectional study in nature, and thus causalities between variables were unknown, although associations between variables could be analyzed in the study. Therefore, it needs further investigation on the causalities between quality of sleep and mental health. But we speculated that those variables can mutually affect each other. In other words, poor sleep quality can contribute to anxiety and depression and vice versa. Second, some variables, such as smartphone use severity (14, 15), were not taken into account when we initially designed this study, but it is relatively difficult to evaluate this variable due to no recognized criteria. Third, this model was not widely validated in other centers, despite favorable predictive effectiveness of the model.

Conclusion

Sleep quality is far from satisfactory among university students. The study develops a prediction model that can be a helpful tool to stratify sleep quality, especially among university students. More attention needs to be paid to participants in the high-risk group. Some intervention measures or preventive strategies to quit smoking and drinking, eat more vegetables, avoid midday rest, treat chronic disease, and alleviate anxiety and stress may be considerably beneficial in improving sleep quality.

Data availability statement

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

Ethics statement

This study was approved by the Academic Committee and Ethics Board of the Xiamen University of Technology (No. 202001). The patients/participants provided their informed consent to participate in this study.

Author contributions

LRZ, HZ, and MY: study design. LRZ, HZ, MY, YZ, and GC: data collection, analysis, and interpretation. LRZ, HZ, MY, CL, and LZ: drafting of the manuscript. All authors: critical revision of the manuscript and approval of the final version for publication.

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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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Aberrant amplitude of low-frequency fluctuations in different frequency bands and changes after one-night positive airway pressure treatment in severe obstructive sleep apnea

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Objective: This study was aimed to investigate the characteristics of the amplitude of low-frequency fluctuation (ALFF) at specific frequencies in severe obstructive sleep apnea (OSA) patients. A comparison was made between pre-CPAP treatment and one night after continuous positive airway pressure (CPAP) treatment.

Methods: 30 severe OSA patients and 19 healthy controls (HC) were recruited. The ALFF method was used to assess the local features of spontaneous brain activity and calculated at different bands (slow-5 and slow-4). A correlation analysis was performed to evaluate the relationship between the changes of the ALFF and polysomnography data.

Results: Compared with HC, in slow-5 frequency band, OSA patients showed significantly decreased ALFF in the left inferior temporal gyrus, and significantly increased ALFF in the left middle frontal gyrus, left inferior frontal gyrus, triangular part, right superior frontal gyrus, dorsolateral and right middle temporal gyrus. In slow-4 frequency, there was significantly decreased ALFF in the right inferior temporal gyrus, and significantly increased ALFF in the left precuneus, right posterior cingulate gyrus and right median cingulate besides the slow-5 difference band showed. Compared with pre-CPAP, we found that after CPAP treatment, ALFF signals in the left insula in slow-5 and left caudate in slow-4 increased, but the calcarine in slow-4 significantly reduced. Correlation analysis showed that the left angular slow-4 band change was positively correlated with the slow wave sleep change ($r = 0.4933$, $p = 0.0056$). The left cerebellum 6 slow-5 band change was positively correlated with the duration of the REM sleep change ($r = 0.4563$, $p = 0.0113$), and the left cerebellum 6 slow-4 band change was also positively correlated with the mean blood oxygen change in the REM ($r = 0.4591$, $p = 0.0107$) and NREM sleep ($r = 0.4492$, $p = 0.0128$).

Conclusion: We found that the use of slow-4 was more specific in OSA studies. These results suggested that the severe OSA patients have frequency-related abnormal spontaneous neural activity, which may contribute to a better understanding of the pathological basis of OSA-related diseases and provide a potential therapeutic target for OSA patients.

KEYWORDS

obstructive sleep apnea, CPAP, frequency band, restingstate functional magnetic resonance imaging, amplitude of low-frequency fluctuation (ALFF), brain function

Introduction

Obstructive sleep apnea syndrome (OSA) is a common sleep disorder characterized by frequent upper airway collapse during sleep, leading to intermittent hypoxemia, sleep fragmentation and changes in sleep structure (1, 2). OSA is associated with a range of harmful effects, including excessive daytime sleepiness, increased risk of work-related injuries and reduced quality of life. In addition, OSA is a multisystem chronic disease which often comorbid to various other diseases, such as heart disease, hypertension, cerebrovascular disease, reflux esophagitis, depression, anxiety, insomnia, etc. (3–6). To date, the underlying pathophysiological mechanisms associated with OSA are not fully understood.

Non-invasive neuroimaging techniques have been widely used to explore the pathophysiological mechanisms of various diseases, such as neurological and psychiatric disorders. Different neuroimaging techniques have been used to explore related structural, functional, and metabolic alterations in OSA patients (7–9). Many previous studies (10–13) using structural neuroimaging have suggested that OSA patients may have brain tissue damage. Resting-state functional magnetic resonance imaging (rs-fMRI) is an oxygen-dependent brain functional imaging method, which can give more accurate structural and functional relationships (14). As a reliable measure of rs-fMRI techniques, the amplitude of low-frequency fluctuations (ALFF) has been widely applied to assess spontaneous neural activity related to brain metabolism and brain function (15). Therefore, using rs-fMRI techniques such as ALFF measurement to conduct in-depth research on OSA patients and explore their brain changes has profound significance.

To date, most rs-fMRI studies have detected spontaneous low-frequency oscillatory (LFO) activity in a specific frequency band of 0.01–0.08 Hz. It is proposed that neural oscillations with different frequencies in the human brain may be sensitive to activity in different regions and can be used to reflect different physiological functions of brain activity (16). The rs-fMRI LFO can be divided into four different frequency bands [slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz)] (17, 18). However, only the traditional 0.01–0.08 Hz spectrum has been used to investigate OSA patients (19, 20). These researches (19, 20) reported that OSA patients had higher ALFF values in the right middle cingulate, left medial superior frontal gyrus, right anterior cingulate, right hippocampus, and right inferior occipital gyrus. The ALFF values were lower in the left inferior temporal gyrus and right cerebellum. In our study, the slow-5 and slow-4 bands were examined because they contain most of the traditional 0.01–0.08 Hz spectrum and there is minimal overlap with potential physiological noise frequencies. For example, Hoptman's study (21) showed that patients with schizophrenia were generally abnormal in the slow-4 band. Wang's study (22) also suggested that the brain's intrinsic activity patterns were sensitive to specific frequency bands such as slow-4 and slow-5 in Parkinson's disease patients. To our knowledge, no research has investigated the frequency-dependent ALFF in OSA patients. It would be necessary to differentiate the frequency bands to examine the ALFF in OSA patients.

Continuous positive airway pressure (CPAP) is the gold standard treatment for moderate/severe OSA patients (23). Previous studies have shown that brain damage may occur in OSA patients due to long-term sleep fragmentation and hypoxia, which can be ameliorated by CPAP. For example, brain structural imaging studies showed that after 3 months of CPAP treatment, partial white matter integrity was restored (24, 25), as well as the moderate improvements in mood, attention, and executive function. In addition, OSA patients treated for a longer period (6 or 12 months) had brain metabolite levels and brain volume changes in gray (26) and white matter integrity (24) in multiple regions of the brain which were similar to those of well-sleep people, suggesting that chronic brain damage in OSA patients can be reversed by CPAP treatment.

However, after one-night CPAP treatment, the proportion of slow wave sleep and REM sleep in severe OSA patients increased, the arouse index and apnea-hypopnea index (AHI) decreased significantly, and the blood oxygen saturation improved significantly. Furthermore, the next day, most patients' daytime sleepiness was alleviated and their attention and responsiveness improved significantly (27). However, there is no report on brain function related to such significant changes after one-night

CPAP treatment in severe OSA patients. Therefore, this study hypothesized that the brain regions of OSA patients are also altered after one-night CPAP treatment.

Method

Subjects

Thirty newly diagnosed, untreated male OSA patients and nineteen healthy controls (HC) were recruited for this study from the Sleep Medicine Center of West China Hospital, Sichuan University. In this study, all subjects were recruited based on the following criteria: (1) male, (2) OSA patients with AHI>30, HC AHI<5, (3) age 20-60 years. In addition, the following characteristics were excluded: (1) non-right-handed. (2) A history of neurological or psychiatric diseases (such as neurodegenerative diseases, epilepsy, brain trauma, depression, bipolar disorder) or other sleep disorders (such as insomnia); (3) MRI contraindications (such as metal implants); (4) shift work; (5) abuse of illicit drugs. All subjects underwent Epworth sleepiness scale (ESS) assessments before undergoing polysomnography (PSG). All subjects signed written informed consent forms for this study before data acquisition and the study protocol was approved by the Human Research Ethics Committee of West China Hospital, Sichuan University.

Polysomnography

All subjects were required to undergo PSG evaluation (Alice 6, Respironics, Orlando, FL, USA). According to the American Academy of Sleep Medicine guidelines, electroencephalography (EEG), electromyogram (EMG), electrooculography (EOG), electrocardiogram (ECG), oral and nasal airflow, snoring, thoracic and abdomen breathing movement, oxygen saturation (SaO_2) and body position were recorded. The subjects' tests were recorded by infrared cameras and continuously monitored by an experienced sleep technologist.

Continuous positive airway pressure (CPAP) treatment

On the following day, all OSA patients received CPAP treatment for one night (22:30-−6:30) after PSG evaluation. The treatment pressure of the ventilator was set at 4–20 cm H_2O, and the treatment pressure was set automatically.

fMRI data acquisition

All participants had functional and structural MRI images collected in our hospital using a 3.0 T MRI scanner (Siemens, Trio, Germany). MRI scans were performed the following day at 7:30–8:30 am after PSG or CPAP monitoring, so the patients underwent two scans and the controls only had one scan. Rs-fMRI data were acquired using an echo planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle = 90°, thickness = 5.0 mm, gap = 0.5 mm, field of view (FOV) = 240 × 240, matrix size = 64 × 64, slices = 30; a total of 6,000 rs-fMRI images were recorded. High-resolution T1-weighted MRI images of brain structures were obtained using a sagittal three-dimensional T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGR) sequence: TR = 1,900 ms, TE = 2.34 ms, inversion recovery Time (TI) = 900 ms, flip angle = 90°, thickness = 1.0 mm, gap = 0.5 mm, FOV = 256 × 256, matrix = 256 × 256, layers = 176.

Data preprocessing

We also evaluated the fMRI data for imaging or head motion-related artifacts before data preprocessing. Prior to ALFF analysis, DPARSFA (http://rfmri.org/DPARSF) and SPM12 (https://www.fil.ion.ucl.ac.uk/) based on MATLAB2018b (Math Works, Natick, MA, USA) were used to preprocess the fMRI data: (1) File format conversion from DICOM to NIFTI; (2) removal of the first 10 volumes; (3) slice timing and head motion correction; (4) T1 segmentation with the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) spatial normalization into the Montreal Neurological Institute (MNI); (5) regression of nuisance covariates including linear trend, white matter signals, cerebral spinal fluid signal, and Friston-24 parameters of head motions; (6) smoothing with a 6-mm full width at half maximum Gaussian kernel.

ALFF analysis

The mean square root of each voxel power spectrum was calculated as ALFF [slow-5 band (0.01–0.027 Hz), and slow-4 band (0.027–0.073 Hz)]. All ALFF maps were converted to z-maps by subtracting the global mean and dividing by the standard deviation. Subsequent statistical and correlation analyses were based on normalized ALFF plots.

Statistical analysis

Data were assessed for normality (Shapiro–Wilk test), and Student *t*-tests were performed to assess between-group differences on demographical and sleep data that were normally distributed. Mann–Whitney *U*-test was performed

to assess between-group differences in variables that were not normally distributed.

Whole-brain ALFF (slow-5 and slow-4) were compared between the OSA group and the control group using an independent sample *t*-test. Age, education level and head motion were imported as covariates. Whole-brain ALFF before and after CPAP treatment (slow-5 and slow-4) were tested using paired samples *t*-test. Head motion was imported as a covariate.

Whole-brain ALFF before and after CPAP treatment were correlated with sleep-related data, respectively, and regions with significant correlation results were selected as regions of interest (ROIs) and extracted (the results were presented in the Supplementary material). Then, we performed the changes between the mean ALFF values of brain regions before and after CPAP treatment in these ROIs and the changes between the sleep data before and after CPAP treatment for correlation analysis.

Results

Clinical characteristics

The demographic and polysomnography data are shown in Table 1. There were no significant differences in age, education, total sleep time (TST), and the time of REM sleep between the OSA patients and the HC groups. The OSA patients showed significantly higher Body Mass Index (BMI), ESS, AHI and the time of NREM sleep, but lower mean in SaO_2 (blood oxygen saturation) of REM sleep, NREM sleep and TST, slow wave sleep (SWS) compared with HC. After one-night CPAP treatment, the time of REM sleep, SWS, the mean SaO_2 of REM sleep, NREM sleep and TST increased significantly. AHI and the time of NREM sleep decreased significantly.

ALFF changes in specific frequency band

In the slow-5 frequency band, OSA patients showed significantly decreased ALFF in the left inferior temporal gyrus, and significantly increased ALFF in the left middle frontal gyrus, left inferior frontal gyrus, triangular part, right superior frontal gyrus, dorsolateral, right middle temporal gyrus compared to HC (Table 2 and Figure 1).

In the slow-4 frequency band, compared to HC, OSA patients showed significantly decreased ALFF in the bilateral inferior temporal gyrus, and significantly increased ALFF in the left precuneus, right posterior cingulate gyrus, right median cingulate, right middle temporal gyrus, right inferior frontal gyrus, opercular part, left middle frontal gyrus, left inferior frontal gyrus, triangular part (Table 2 and Figure 1).

ALFF differences between pre-CPAP and post-CPAP OSA patients

Paired sample *t*-tests were used to compare the difference in ALFF between pre-CPAP and post-CPAP OSA patients in the slow-4 and slow-5 frequency bands. Figure 2 showed significant differences of ALFF within different frequency bands. The detailed abnormal brain regions are shown in Table 3. We found that after CPAP treatment, ALFF signals in the left insula in the slow-5 and left caudate in the slow-4 increased, but the calcarine in the slow-4 significantly reduced.

Correlation analysis

As shown in Figure 3, the change of ALFF in the left angular of the slow-4 frequency band was positively correlated with the change of slow wave sleep duration ($r = 0.4933$, $p = 0.0056$) and the change of ALFF in left cerebellum 6 of the slow-5 frequency was positively correlated with the change of REM duration ($r = 0.4563$, $p = 0.0113$) before and after CPAP treatment. Moreover, the change of ALFF in left cerebellum 6 of the slow-4 frequency band was also positively correlated with the change of mean oxygen saturation during REM ($r = 0.459$, $p = 0.0107$) and NREM sleep ($r = 0.4492$, $p = 0.0128$).

Discussion

For the first time, we used the slow-4 and slow-5 frequency bands of ALFF to analyze the characteristics of resting-state frequency in OSA patients and explored the changes of ALFF values in OSA patients after one-night CPAP treatment. Our study found that there were differences in ALFF between the severe OSA group and the control group in many brain regions. In addition, ALFF changes in brain regions were also found after one-night CPAP treatment. Correlation analysis further revealed the relationship between the changes of ALFF in the brain region and the changes of polysomnography parameters. The above results are more obvious in the slow 4-band.

ALFF differences between the OSA and HC groups

Our study showed that in the slow-5 frequency band, OSA patients showed significantly reduced ALFF in the left inferior temporal gyrus. But in the slow-4 band, the signals of OSA patients were reduced in the bilateral inferior temporal gyrus brain region. The inferior temporal gyrus is related to processing memory and text information, as well as the processing of emotions (28, 29). Previous fMRI studies (8, 30) indicated that the regional cerebral blood flow of the temporal lobe was

TABLE 1 Demographic and polysomnographic data of participants.

	Pre-CPAP ($n = 30$)	CPAP night ($n = 30$)	Health control ($n = 19$)	P^a	P^b
Age (years)	42.50 ±5.82	42.50 ±5.82	40.32 ±2.89	0.136	ns
BMI (kg/m^2)	29.41 ±3.08	29.41 ±3.08	23.97 ±2.57	<0.001	ns
Education (years) §	13.63 ±2.36	13.63 ±2.36	14.37 ±4.23	0.566	ns
ESS	15.37 ±5.96	15.37 ±5.96	3.42 ±1.50	<0.001	ns
TST (min)	452.68 ±67.37	429.42 ±51.79	418.35 ±55.217	0.071	0.142
REM (min)	63.93 ±33.57	111.00 ±36.18	73.37 ±22.96	0.290	<0.001
NREM (min)	388.75 ±64.93	318.42 ±37.74	344.98 ±45.03	0.014	<0.001
SWS (min)§	6.10 ±13.70	32.22 ±42.15	16.24 ±16.90	0.004	<0.001
AHI (events/h)	71.01 ±21.08	13.56 ±8.65	3.50 ±1.633	<0.001	<0.001
REM SaO_2 (%)	80.43 ±10.31	94.70 ±1.43	94.42 ±2.48	<0.001	<0.001
NREM SaO_2 (%)	88.17 ±4.80	94.03 ±1.67	94.37 ±1.74	<0.001	<0.001
TOTAL SaO_2 (%)	87.53 ±4.97	94.33 ±1.45	94.47 ±1.65	<0.001	<0.001

§ Non-parametric test (Mann–Whitney U). P^a, test between pre-CPAP OSA patients and HC; P^b, test between CPAP night and pr-CPAP OSA patients. REM, the time of REM stage sleep; NREM, the time of NREM stage sleep; SWS, slow wave time; ESS, Epworth sleepiness scale; TST, total sleep time, ns, non-statistically significant.

TABLE 2 The differences of ALFF in each frequency band between OSA groups and HC groups.

Condition	Region	Brodmann area	Cluster size (voxels)	Cluster size (mm^3)	MNI coordinates			Peak intensity:
					X	Y	Z	
	(A) Slow-5 frequency band (0.01–0.027 Hz)							
OSA<HC	Temporal_Inf_L	BA20_L	31	837	−60	−42	0	−4.78389
	Temporal_Inf_L	BA20_L	26	702	−51	−12	−36	−4.70627
OSA>HC	Frontal_Inf_Tri_L	BA48_L	28	756	−39	30	15	6.46229
	Frontal_Mid_L	BA48_L	23	621	−27	33	27	5.80003
	Frontal_Sup_R	BA46_R	23	621	24	45	21	5.2604
	Temporal_Mid_R	BA39_R	24	648	39	−51	21	6.30294
	(B) Slow−4 frequency band (0.027–0.073 Hz)							
OSA<HC	Temporal_Inf_L	BA20_L	57	1,539	−51	−33	−27	−4.87198
	Temporal_Inf_L	BA20_L	31	837	−48	−6	−39	−4.93815
	Temporal_Inf_R	BA20_R	54	1,458	60	−42	−18	−4.80968
	Temporal_Inf_R	BA20_R	40	1,080	42	−6	−45	−4.74978
OSA>HC	Precuneus_L	BA29_L	29	783	−9	−48	15	5.06875
	Cingulum_Post_R	BA29_R	20	540	9	−39	15	4.73092
	Cingulum_Mid_R	BA23_R,	25	675	12	−45	33	5.27274
	Temporal_Mid_R	BA39_R	39	1,053	39	−51	21	7.13999
	Frontal_Inf_Oper_R	BA44_R	21	567	39	12	36	5.2112
	Frontal_Mid_L	BA46_L	40	1,080	−27	36	24	6.85861
	Frontal_Inf_Tri_L	BA48_L	20	540	−39	30	15	5.68692

All clusters were reported with a voxel-level threshold of $P < 0.001$, GRF correction, and cluster-level of $P < 0.05$, two tailed.

reduced in OSA patients, and the functional connectivity of the brain regions of the prefrontal, parietal and temporal lobes was reduced in the default mode network (DMN). The results of these studies are consistent with the results of the present study. Therefore, it can be speculated that cognitive dysfunction in severe OSA patients is related to temporal lobe dysfunction.

In addition, OSA patients were found to have signal increased in the right inferior frontal gyrus and left middle frontal gyrus region by analysis of slow-5 and slow-4 frequency bands compared with HC. Previous studies (31, 32) identified that the frontal lobe of OSA patients had a variety of brain function abnormalities. Paul et al. (31) reported that the gray matter volume of the anterior superior frontal gyrus in both hemispheres decreased in OSA patients. The other study (32) reported that children with OSA showed regional homogeneity (ReHo) decreased in the left medial superior frontal gyrus.

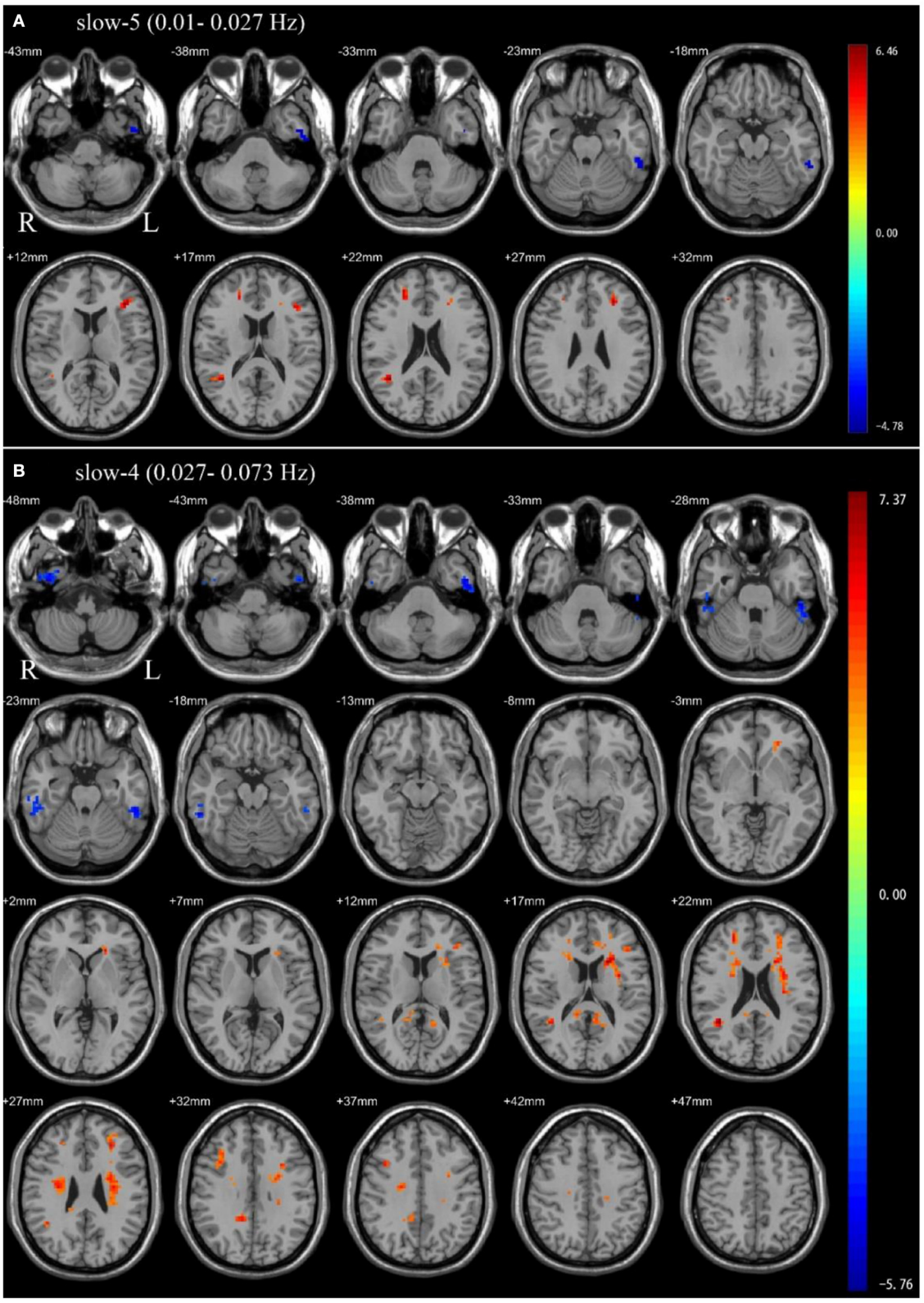

FIGURE 1
Independent sample *t*-test between health control groups and pre-CPAP OSA patients: **(A)** slow-5 frequency band (0.01–0.027 Hz). **(B)** slow-4 frequency band (0.027–0.073 Hz). Results were reported at voxel-level $p < 0.001$ and cluster-level $p < 0.05$, GRF corrected.

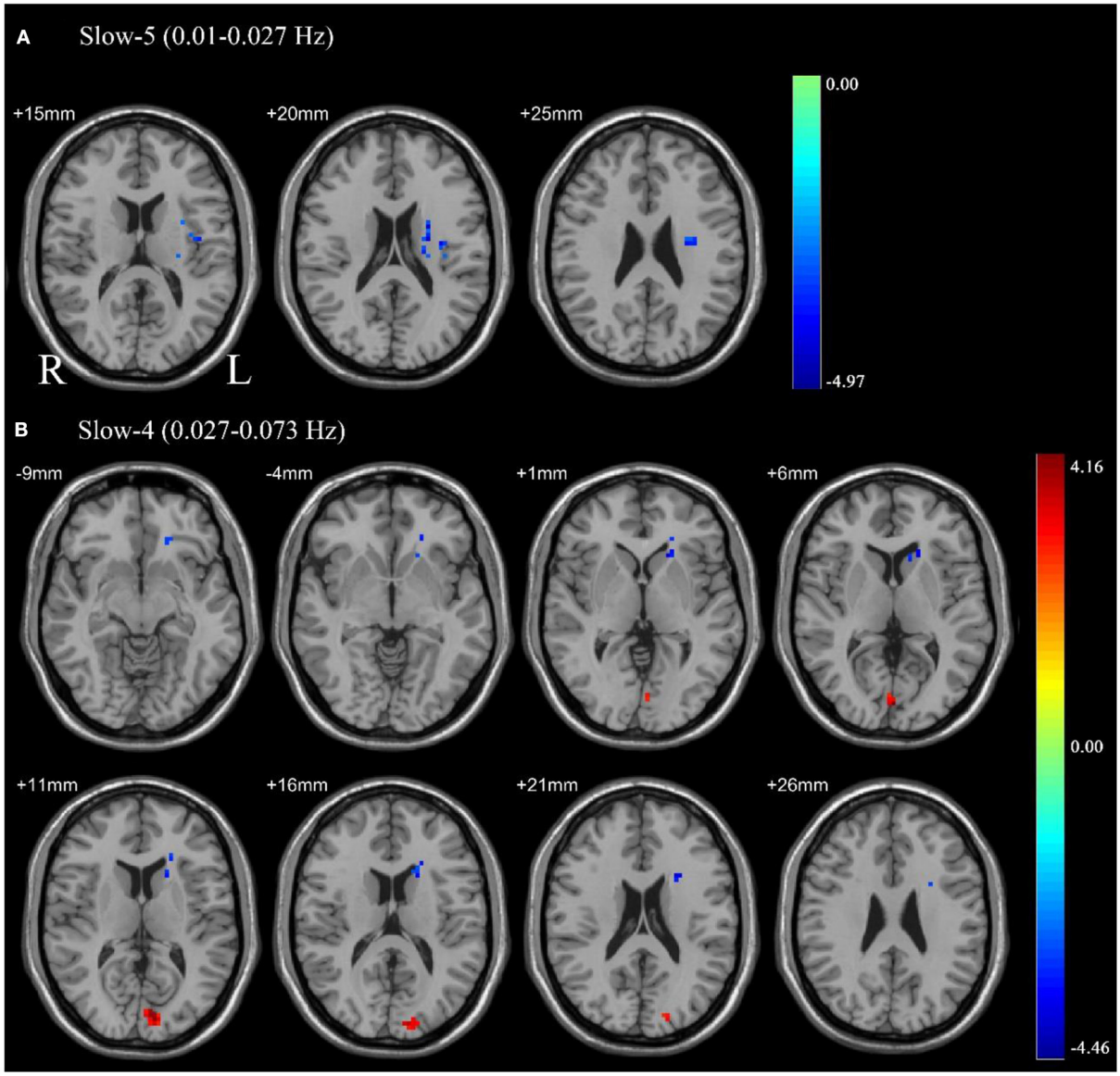

FIGURE 2
Pair sample *t*-test in the slow-5 frequency band (0.01–0.027 Hz) **(A)**, the slow-4 frequency band (0.027–0.073 Hz) **(B)**. All results were reported at voxel-level $p < 0.01$ and cluster-level $p < 0.05$, GRF corrected.

Sleep fragmentation and hypoxia in OSA affect nocturnal sleep-related recovery processes, causing chemical and structural damage to brain cells. It has recently been reported that sleep disturbances preferentially lead to the prefrontal cortex dysfunction, suggesting that the frontal lobe is a functionally and structurally vulnerable region in OSA patients (31). Although these studies failed to support the changes of ALFF in the frontal lobe, we believe that the increase of ALFF in the frontal lobe may be a compensatory response to hypoxia and sleep fragmentation in severe OSA patients. Previous study (19, 33) reported that the OSA patient group had higher ALFF values in the left medial superior frontal gyrus and right inferior frontal gyrus. These results are consistent with our study. Therefore, long-term chronic sleep deprivation caused by sleep fragments and intermittent hypoxemia in OSA patients may be important factors leading to the dysfunction of the inferior frontal gyrus.

Posterior cingulate gyrus and precuneus are important nodes of the default network. Our study also found that OSA patients showed increased signal in the right posterior cingulate gyrus, right middle cingulate, and left precuneus brain region in the slow-4 band compared with HC. DMN inactivation in OSA patients was found to be abnormally inactivated during working memory tasks and was significantly positively correlated with behavioral performance (34). In addition, the

TABLE 3 The differences of ALFF in each frequency band between the pre-CPAP and post-CPAP group.

Condition	Region	Brodmann area	Cluster Size (voxels)	Cluster Size (mm^3)	MNI coordinates			Peak intensity:
					X	Y	Z	
	(A) Slow-5 frequency band (0.01–0.027 Hz)							
Pre-CPAP<post-CPAP	Insula_L	BA48_L,	53	1,431	−24	−21	18	−4.60315
	(B) Slow-4 frequency band (0.027–0.073 Hz)							
Pre-CPAP<post-CPAP	Caudate_L,	BA11_L	52	1,404	−16	16	18	−4.45842
Pre-CPAP> post-CPAP	Calcarine_L	BA18_L	43	1,161	0	−87	6	4.15529

All clusters were reported with a voxel-level threshold of $P < 0.01$, GRF correction, and cluster-level of $P < 0.05$, two tailed.

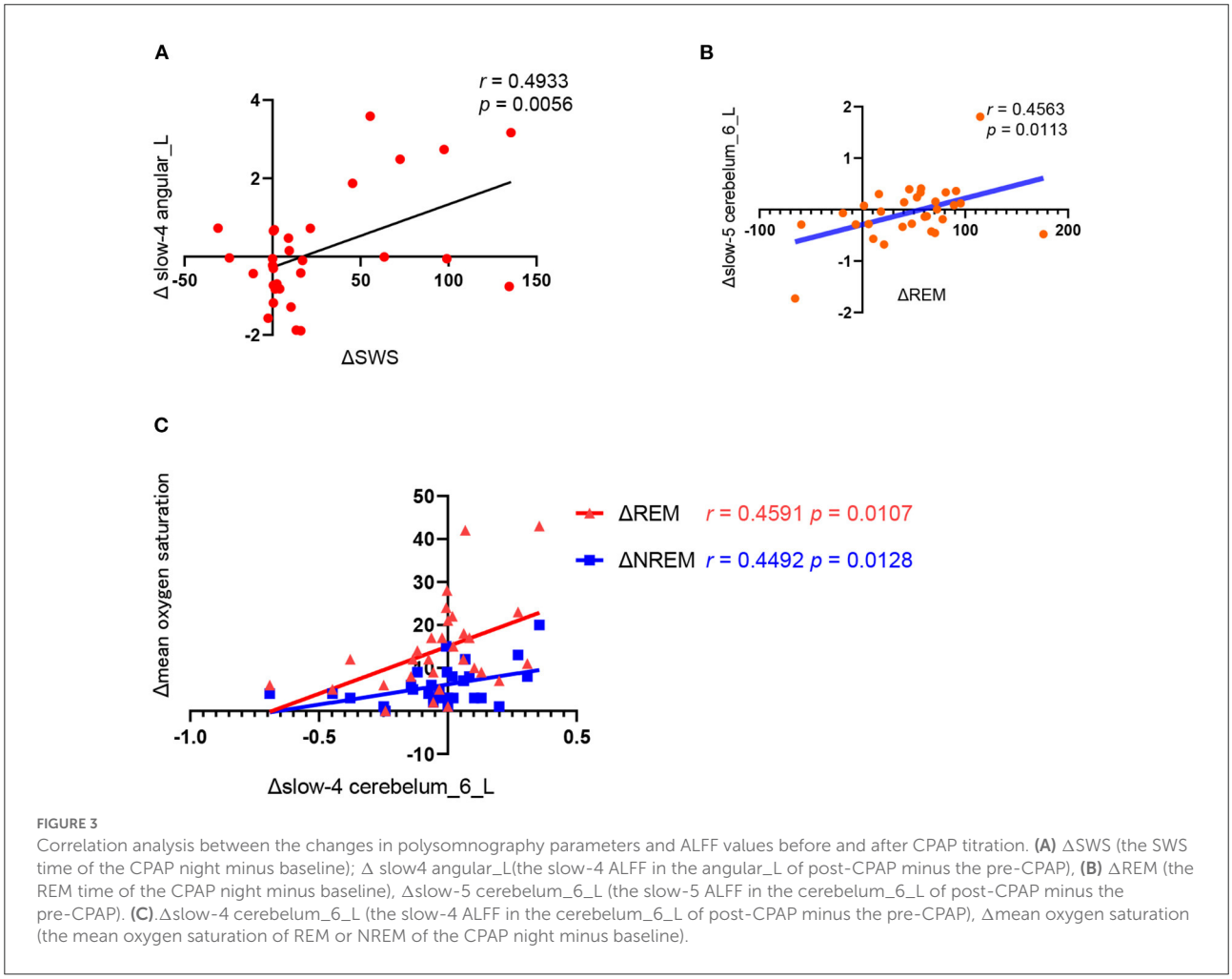

FIGURE 3
Correlation analysis between the changes in polysomnography parameters and ALFF values before and after CPAP titration. **(A)** ΔSWS (the SWS time of the CPAP night minus baseline); Δ slow4 angular_L(the slow-4 ALFF in the angular_L of post-CPAP minus the pre-CPAP), **(B)** ΔREM (the REM time of the CPAP night minus baseline), Δslow-5 cerebelum_6_L (the slow-5 ALFF in the cerebelum_6_L of post-CPAP minus the pre-CPAP). **(C)**.Δslow-4 cerebelum_6_L (the slow-4 ALFF in the cerebelum_6_L of post-CPAP minus the pre-CPAP), Δmean oxygen saturation (the mean oxygen saturation of REM or NREM of the CPAP night minus baseline).

posterior cingulate gyrus is closely related to respiratory control, emotional control and is involved in autonomic functions, including maintaining blood pressure, and salivation. Therefore, the increased cingulate signal in OSA patients may be related to functional compensation. Joo et al. (35) found that OSA reduced gray matter concentration in the cingulate cortex, which could explain clinical manifestations of respiratory, emotional, and cardiovascular disorders. Ayalon et al. (36) found that OSA patients suffered from decreased brain activation in the left precentral gyrus, left anterior cingulate gyrus, and posterior cingulate gyrus during attentional tasks compared with controls, which may also explain the cognitive impairment in OSA patients. Although this study suggested that cingulate gyrus activation was reduced, this study was a fMRI study in the task state, while our study was resting state, which may lead to inconsistent results. In addition, previous studies found that

ReHo (37) and ALFF (33) in the cingulate were increased in OSA patients. These signal changes in the cingulate gyrus of OSA patients compared are consistent with our findings. Sleep fragmentation and oxygen reduction may be the key factors in the posterior cingulate gyrus and precuneus dysfunction, which suggests cognitive dysfunction in OSA.

ALFF differences between the pre-CPAP and post-CPAP

We found that the signal in the left insula increased in the slow-5 frequency band after CPAP treatment. And in the slow-4, the signal increased in the left caudate area, while the signal reduced in the left calcarine area. The human insula is small but the insular cortex has extensive connections to the frontal, temporal, cerebellum, and limbic regions and is involved in a large number of different functions, cortical regulatory regions of emotion and sensorimotor function (38). Zhang's study (39) showed that the ALFF value of the insula was decreased under hypoxia, which may be related to the decreased ventilatory driving force. After one-night CPAP treatment, the blood oxygen saturation improved significantly, so the function of the insula was restored and the signal was enhanced. Therefore, the above study further supported our findings. Qin's study (19) in Tibetans found that the ALFF value of the right insula significantly increased in OSA patients. This study is inconsistent with our results, but the author explained in the article that Tibetans had strong adaptability, that is, they can improve the ventilation function to adapt to hypoxia. Neuroimaging studies suggest that insular dysfunction is thought to be a factor in airway collapse in OSA (40). There is reliable evidence showing that OSA is associated with structural and functional abnormalities of the central nervous system, especially damage in the insular cortex (40). In addition, the insular cortex receives pain and visceral sensory input and has a significant influence on the activity of the sympathetic and parasympathetic nervous systems, and is also involved in the control of certain autonomic functions, including respiration, blood pressure, and salivation (41). The insula regulates sympathetic nerve function, resulting in a decrease in the activity of sympathetic function, leading to hypertension and a high risk of cardiovascular disease in OSA patients. OSA can lead to an increase in blood pressure, but after CPAP treatment, the function of the insular cortex is restored. Therefore, the change of insular function caused by CPAP treatment may be an important mechanism of blood pressure decline in OSA patients after CPAP.

The function of the caudate nucleus is involved in the regulation of respiration. Binks's research (42) suggested that a compensatory increase in blood flow in the caudate nucleus can occur in a hypoxic environment, which is a self-protective response of cerebral blood vessels in a hypoxic environment. We believe that the signal changes of the caudate nucleus after CPAP treatment may be more related to hypoxia, and the improvement of blood oxygen saturation leads to the functional recovery of caudate nucleus. Therefore, after CPAP treatment, blood oxygen saturation increased, caudate nucleus function recovered and its hypoxia compensation was relieved, so the signal increased after CPAP treatment. The above research also supported our findings.

The calcarine cortex change was also found in this article. Only a few studies (43) had reported that OSA patients had significantly longer reaction times than controls in visual tasks, suggesting that these patients have impairments in the underlying mechanisms of visual processing. Future studies can pay more attention to the changes in the function of the calcarine cortex in OSA patients, and whether sleep fragmentation and hypoxia lead to the dysfunction of the calcarine cortex.

Although our study found that ALFF changes in brain regions after one-night CPAP treatment were not consistent with those in OSA patients vs. controls. The possible reason is that one-night CPAP treatment can quickly change the function of brain areas that can be improved after a short period of treatment, and these brain areas may be associated with daytime sleepiness and cognitive function, which can be improved after one-night CPAP treatment. However, the differences of OSA patients and controls are more likely to be related to brain dysfunction caused by long-term chronic effects.

Correlation analysis

A correlation analysis was performed to identify the relationship between changes in brain function and polysomnography parameters. Our study showed that there was a significant correlation between the left angular and the SWS of sleep. The proportion of SWS in OSA patients after CPAP treatment increased significantly, suggesting that the angular signal was also enhanced after CPAP treatment. The angular gyrus plays an important role in regulating emotion, consciousness, memory and introspection (44). There is also a significant difference between the left angular gyrus and the normal group in the children's OSA study (32). We believe that angular gyrus may be more related to sleep depth. Because children have significantly more deep sleep than adults, it is easier to find differences in children's studies compared to normal people. After CPAP treatment, SWS in OSA patients increased significantly, and there was a significant correlation between SWS and memory improvement. We speculate that the impairment of angular gyrus function in OSA patients may be more related to the reduction of slow wave sleep caused by sleep apnea.

In addition, we found that the cerebellum is associated with sleep architecture and blood oxygen saturation. The slow-5 frequency band was positively correlated with the difference in the REM phase, suggesting sleep rebound in the REM phase more affected the slow-5 frequency band signal in the cerebellum. However, the slow-4 frequency band was related to the mean blood oxygen saturation in the REM and NREM phases, and the correlation between blood oxygen saturation in the REM phase was greater. It suggests that the slow-4 frequency band in the cerebellum is more related to the correction of blood oxygen, especially the blood oxygen saturation in the REM phase. The above results suggested that the slow-5 band in the cerebellar region was related to sleep structure, while the slow-4 band was related to blood oxygen. Therefore, sleep fragmentation and intermittent hypoxia significantly affect the function of cerebellar regions. Studies on brain function in patients with heart failure have shown that cerebellar gray matter loss is associated with hypoxia, which further indicates that hypoxia may lead to cerebellar dysfunction. This research supported our findings (45). Recently, more and more scholars have begun to pay attention to changes in the cerebellum of OSA patients. For example, joo (35) reported that the gray matter concentrations of OSA patients were significantly decreased in biventer lobules in the cerebellum. Park et al. (46) found that OSA showed decreased network integration connectivity in the cerebellum, which was susceptible to hypoxia or ischemia. After long-term CPAP treatment, patients with OSA may have increased cerebellar volume (47, 48). In our study, even one-night CPAP treatment can reverse the brain function of the cerebellum. Therefore, we speculate that effective CPAP therapy can improve oxidative stress in patients with hypoxemia and disturbed sleep architecture, leading to a reversal of cerebellar network integration and cerebellar connectivity. Thus, we conclude that CPAP treatment can reverse cerebellar damage in OSA patients.

Therefore, we believe that one-night CPAP treatment can also find changes in the brain function of OSA, which is similar to changes in brain function after long-term CPAP treatment. We speculate that brain function changes after one-night CPAP treatment may predict the changes after long-term CPAP treatment, and we also can explore the main areas of acute and chronic brain function damage caused by OSA. These injury areas may be related to the complications of OSA patients, such as cognitive dysfunction and hypertension. These corresponding brain regions intervention studies can be carried out in the future to explore the main mechanisms of dysfunction in OSA patients.

There are several limitations in the current study. Only male patients with severe OSA were included in this study, and female and mild-to-moderate OSA patients were not included. The sample size of cases and controls in this study was relatively small.

Conclusion

We found that the use of the slow-4 frequency band may be more specific in OSA studies. These results suggest that the severe OSA patients have frequency-related abnormal spontaneous neural activity, which may contribute to a better understanding of the pathological basis of OSA-related diseases and may provide potential therapeutic targets for OSA patients.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Human Research Ethics Committee of West China Hospital, Sichuan University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YS: conceptualization, data curation, methodology, software, investigation, formal analysis, and writing—original draft. MX: methodology, software, and writing—original draft. SY: methodology and writing—review and editing. KZ: resources, supervision, and writing—review and editing. XT: supervision. 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.2022.985321/full#supplementary-material

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The nature, consequences, mechanisms, and management of sleep disturbances in individuals at-risk for psychosis

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There is strong evidence that sleep disturbances are commonly experienced by people with psychosis. Evidence has also shown that sleep disturbances are present since the very early stages of the disease, even during the pre-diagnostic phase. More recently, research involving young individuals at ultra-high risk (UHR) for psychosis documented frequent occurrence of sleep disturbances in this group. The very early onset of sleep disturbances in the course of psychosis has drawn attention to the possible links between sleep parameters and the risk of psychosis. To date, the nature of sleep disturbances characterizing the UHR stage remains unclear, with available studies having yielded mixed findings. In this regard, we performed this review to update the body of literature on the nature of sleep disturbances, their underlying mechanisms, their clinical and functional consequences, the prevention and intervention strategies in the at-risk for psychosis population. Our findings provided further support to the presence of disturbed sleep in UHR individuals as evidenced by subjective and objective sleep measures such as polysomnography, sleep electroencephalograms, and actigraphy. Reviewing the possible mechanisms underlying the relationship between sleep and psychosis emphasized its complex and multifactorial nature which is yet to be determined and understood. Further research is warranted to determine which facets of sleep disturbances are most detrimental to this specific population, and to what extent they can be causal factors or markers of psychosis.

KEYWORDS

sleep, UHR, at-risk mental state, psychosis, early intervention

Introduction

Sleep is an essential biological function that results from a complex interaction between neurobiological, hormonal, and homeostatic processes. Sleep disturbances are highly prevalent worldwide, affecting one out of five adult people in the community (1). In particular, there is strong evidence that sleep disturbances are experienced to a higher extent by people with psychosis than healthy individuals (2, 3). Substantial sleep problems are reported by up to 80% patients with psychosis in remission (2, 4), are linked to impaired cognitive and functional capacities (5), and contribute to a significant decrease in life expectancy (6). Evidence has also shown that sleep disturbances are present since the very early stages of the disease (7), even during the pre-diagnostic phase (8, 9). More recently, research involving young individuals at ultra-high risk (UHR) for psychosis documented frequent occurrence of sleep disturbances in this group (10, 11). The very early onset of sleep disturbances in the course of psychosis has drawn attention to the possible links between sleep parameters and the risk of psychosis; and has led some authors to suggest that sleep problems are not causally related to chronic symptoms or medication but rather appear to be promising biomarkers of the disease (7, 12). The UHR state refers to the presence of one of the following: attenuated psychotic symptoms, brief limited intermittent psychotic episode, and genetic risk and deterioration syndrome (i.e., trait vulnerability with marked decline in functioning) (13). Being able to intervene during the UHR stage through targeting modifiable factors, such as sleep, offers the opportunity to be more impactful on outcomes by resorting to simpler, more personalized and less harmful treatments (14–16). However, the nature of sleep disturbances characterizing the UHR stage remains unclear, with available studies having yielded mixed findings (10). In addition, potential mechanisms involved in the association between sleep and psychosis etiology are still largely unknown (17). We could find only one previous review that included data prior to February 2020 to examine sleep disturbances in the UHR state, with the specific goal of exploring the relationships between sleep and psychotic symptoms, functioning and quality of life (18). Some interesting new studies have emerged since then [e.g., (19–22)]. This, along with the identified knowledge gaps, have motivated the present review aiming at synthetizing the existing literature to update and extend our understanding of: (1) the nature of sleep disturbances, (2) their underlying mechanisms, (3) their clinical and functional consequences, as well as (4) the prevention and intervention strategies in the at-risk for psychosis population.

Methods

In the present mini-review, we performed a literature search using electronic databases (i.e., Pub Med, Web of Science, and Scopus). All studies have been selected according to the following criteria: (1) original peer-reviewed articles written in English, with no time period limits; (2) study samples comprising individuals (aged 12–35 years old) defined as meeting UHR criteria based on the presence of attenuated psychotic symptoms, genetic risk, and functional deterioration; as ascertained by structured clinical interviews [e.g., the Comprehensive Assessment of the At Risk Mental State (CAARMS) (23); the Structured Interview for Prodromal Symptoms (SIPS) (24), the Structured Clinical Interview for DSM Disorders (SCID) (25)]; and (3) studies providing data on sleep disturbances in UHR individuals as assessed using either subjective or objective measures. The articles were selected using cross-matched keywords combination: [At-Risk Mental State [OR] Clinical high risk state [OR] Ultra-high risk [OR] prodromal state [OR] prepsychotic phase [OR] psychosis risk [OR] emergent psychosis [OR] early psychosis) [AND] (sleep [OR] sleep disorders [OR] sleep problems [OR] sleep disturbances [OR] sleep quality [OR] insomnia [OR] sleepiness [OR] circadian rhythm [OR] chronotype [OR] polysomnography [OR] actigraphy]. In addition, a backward search and a Google search were conducted in order to detect any other possible missing relevant research studies or unpublished (gray) literature.

The nature of sleep disturbances in UHR individuals

There are two ways to measure sleep disturbances; one is subjective through self-reported [e.g., PSQI (26)] or interviewer-reported [e.g., Scale of Prodromal Symptoms (SOPS)/Structured Interview for Psychosis-Risk Syndromes (SIPS) sleep disturbance items (24)] sleep questionnaires, and the other is objective (e.g., sleep parameters/architecture according to actigraphy or polysomnography). As such, this section will be divided into two parts; the first part reports findings on subjective sleep disturbances, while the second one includes characteristics of objective sleep assessments for UHR individuals (see Table 1 for further details on key findings of the reviewed studies).

Subjective sleep disturbances in UHR individuals

Most of the existing studies found that sleep disturbances were highly prevalent in UHR individuals based on the structured interviews SIPS/SOPS sleep disturbance scores (27–30); and were reported to a greater extent by UHR groups compared to clinically lower risk patients (29) and healthy volunteers (30, 31). Beyond general sleep disturbances, some previous studies documented worse overall sleep quality (according to higher PSQI scores) in UHR individuals as

TABLE 1 Summary of the previous research findings on sleep disturbances in UHR individuals*.

First authors	Country	Study design	Study population	Sleep measures	Summary of key findings
Studies using subjective measures of sleep					
Goines (31)	Canada, USA	Longitudinal	$N = 740$ UHR (43% females; aged 18.5 ± 4.26 years) + 280 HC	SOPS sleep disturbance score	• UHR individuals reported higher levels of sleep disturbance than HC (mean sleep disturbance scores of 2.31 ± 1.568 vs. 0.48 ± 0.904, respectively). • In the UHR group: - Baseline sleep disturbances were significantly linked to greater positive symptoms (i.e., paranoia and hallucinations). - No significant differences were found in baseline sleep disturbance between participants who remitted, remained symptomatic, had prodromal progression, or converted to threshold psychosis during follow-up.
Grivel (27)	USA	Longitudinal	$N = 200$ UHR (28% females)	SIPS sleep disturbance score	• UHR individuals with any lifetime trauma ($n = 47$) had significantly higher sleep disturbance than those with no history of trauma ($N = 153$) (mean sleep disturbance scores of 3.17 ± 1.539 vs. 2.50 ± 1.727, respectively)
Lederman (34)	Australia	Cross-sectional	$N = 10$ UHR (20% females) + 10 FEP + 10 HC	PSQI	• UHR participants had significantly poorer overall sleep quality than FEP patients and HC (PSQI total scores of 8.0 ± 3.3, 5.5 ± 3.4 and 3.9 ± 1.5, respectively; $p = 0.01$). Specifically, daytime dysfunction and sleep medication use (psychotropics prescribed with the primary purpose to improve sleep) were significantly greater among UHR participants than both FEP patients and HC.
Lindgren (40)	Finland	Longitudinal	$N = 54$ UHR (81% females; aged 16.7 ± 0.85 years) + 107 non-UHR psychiatric patients	SIPS sleep disturbance score	• Sleep disturbance was significantly associated with current and lifetime suicidality. No association was found between sleep disturbance and intentional self-harm during follow-up (mean sleep disturbance scores of 2.5 ± 1.4 in "No self-harm" group as compared to 2.0 ± 1.2 in "Self-harm" group, $p = 0.43$).
Lunsford-Avery (12)	USA	Cross-sectional	$N = 33$ UHR (33% females; aged 18.73 ± 1.89 years) + 33 HC	PSQI	• UHR adolescents had significantly higher PSQI total scores, increased latency and greater disturbances compared to HC. • In the UHR group: - More sleep difficulties (increased latency, reduced quality and duration of sleep) were significantly associated with increased negative symptoms. - No association has been found between PSQI variables and positive symptoms. - Bilateral thalamus volume reductions were linked to increased latency, reduced efficiency, and decreased quality of sleep.

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TABLE 1 (Continued)

First authors	Country	Study design	Study population	Sleep measures	Summary of key findings
Lunsford-Avery (41)	USA	Cross-sectional	$N = 59$ UHR (42% females; aged 18.93 ± 1.67)	PSQI	• A total of 23 UHR participants (33.9%) had poor sleep quality (PSQI>8) • "Poorer sleepers" exhibited lower overall cognitive performance, increased negative symptom severity and similar functioning levels compared to "better sleepers." • Sleep disturbances (i.e., latency, efficiency and sleep quality) were significantly associated with procedural learning deficits.
Michels (36)	Germany	Cross-sectional	$N = 14$ UHR (36% females; aged 23.29 ± 3.91 years) + 17 patients with schizophrenia + 17 Healthy relatives of patients with schizophrenia + 29 HC	Self-developed Likert-type single items assessing self-reported frequency of dream recall and nightmare during the last 2 months	• UHR participants reported higher nightmare frequencies compared to patients with schizophrenia, first-degree relatives and HC (Means of nightmare frequency of 3.79 ± 1.93, 3.65 ± 2.50, 2.41 ± 2.00, and 1.90 ± 1.92, respectively). • UHR participants had higher dream recall frequencies compared to patients with schizophrenia (while relatives and HC reported lower and similar mean scores)
Miller (28)	Canada, USA	RCT	$N = 60$ UHR (35% females; aged 17.8 ± 4.8 years)	SOPS sleep disturbance score	• Sleep disturbance was reported by 37% of UHR participants (which represents the percent of patients scoring between 3 "moderate" and 6 "extreme" in the SOPS sleep item)
Nuzum (19)	UK	Retrospective	$N = 795$ UHR (44% females; aged 22.72 ± 4.89)	Sleep disturbances reported by clinicians (Any form of insomnia or disturbed sleep that happened more than once and was having an impact on the client's life)	• 59.5%, of UHR individuals experienced sleep problems (22.01% and 58.11% of individuals reported insomnia and disturbed sleep, respectively)
Poe (30)	USA	Longitudinal	$N = 194$ UHR (27% females; aged 20.0 ± 3.8 years) + 66 HC	SIPS sleep disturbance score	• UHR subjects displayed significantly higher sleep disturbance scores than HC. • In the UHR group, sleep disturbance was related to higher positive and negative symptoms and more impaired functioning.
Reeve (50)	UK	RCT	$N = 160$ UHR (39% females; aged 20.9 ± 4.2 years)	Economic Patient Questionnaire Interview	• At baseline, 85% of UHR individuals experienced 'Bad' night with a mean sleep duration of 4.14 h. • The baseline cross-sectional evaluation revealed that a shorter sleep duration was significantly associated with increased positive symptoms (delusional ideas and hallucinations) and distress.
Ruhrmann (39)	England Finland Germany Netherland	Longitudinal	$N = 245$ UHR (44% females; aged 23.0 ± 5.2 years)	SIPS sleep disturbance score	• Sleep disturbances score >2 on SIPS helped predict transition to psychosis at 18-month follow-up.

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TABLE 1 (Continued)

First authors	Country	Study design	Study population	Sleep measures	Summary of key findings
Tso (29)	USA	Cross-sectional	$N = 203$ UHR (43% females; aged 16.8 ± 3.3 years) + 87 individuals with clinically lower risk + 44 very early FEP (<30 days of positive symptoms)	SOPS sleep disturbance score	• UHR participants displayed higher sleep disturbance scores than individuals with clinically lower risk (Scores of sleep disturbance were the highest in FEP patients).
Waite (90)	UK	Qualitative	$N = 11$ UHR (54% females; aged 18.27 ± 1.95 years)	Interviews	• Participants reported delayed sleep phase, lack of routine, circadian rhythm disruption (i.e., day-night reversal). • They also described a complex and reciprocal relationship between sleep disturbance, mental health problems, and daily functioning.
Zaks (20)	USA	Longitudinal	$N = 478$ UHR participants: 67 converters to psychosis (46% females, aged 18.85 ± 4.02 years) and 411 non-converters (45% females; aged 18.30 ± 4.10 years) + 94 HC	PSQI RU-SATED questionnaire	• All PSQI subscores (i.e., duration, latency, disturbance, efficiency, daytime dysfunction, subjective quality, and medication use) and total score were significantly higher in UHR participants (at a similar extent between converters and non-converters) related to HC; indicating an overall poor sleep quality in UHR groups compared to good sleep quality in HC. • No significant differences were found between UHR and HC individuals in napping frequency or the RU-SATED items timing and regularity. • In UHR individuals, baseline disturbed sleep did not predict conversion to psychosis up to >2 years later. • Sleep disturbance was strongly associated with increased positive symptoms over time.
Studies using objective ± subjective measures of sleep					
Castro (33)	Brazil	Cross-sectional	$N = 20$ at-risk individuals: 13 UHR and 7 at bipolar risk (35% females; aged 18.3 ± 4.01 years) + 20 HC	Actigraphy PSQI ESS MEQ	• Participants of the at-risk group had worse sleep quality compared with HC (PSQI total scores of 7.70 ± 3.69 compared to 4.95 ± 2.16, respectively; $p = 0.010$); whereas no significant differences were noted between the groups regarding sleepiness and chronotype profiles. • The actigraphy data indicated that the at-risk group displayed longer nap duration during waking (44 vs. 23 min), lower autocorrelation functions, lower interdaily stability, higher intradaily variability, lower most active 10 h of the day (M10), and higher beginning of the M10.
Lunsford-Avery (35)	USA	Longitudinal	$N = 36$ UHR (47% females; aged 18.73 ± 1.89 years) + 31 HC	Actigraphy PSQI	• The actigraphy data revealed that UHR participants presented increased WASO, decreased efficiency, and increased movements during sleep relative to HC • In the UHR group: increased WASO, decreased efficiency, increased movements, and number of awakenings were longitudinally associated with symptoms over 12-month follow-up.

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TABLE 1 (Continued)

First authors	Country	Study design	Study population	Sleep measures	Summary of key findings
Lunsford-Avery (38)	USA	Longitudinal	$N = 34$ UHR (56% females; aged 18.79 ± 1.93 years) + 32 HC	Actigraphy	• UHR individuals displayed significantly more fragmented circadian rhythms and later onset of nocturnal rest compared to HC. • In the UHR group: Circadian disturbances were associated with greater psychotic symptoms at baseline, and predicted severity of symptoms and psychosocial dysfunction at 12-months follow-up.
Mayeli (21)	USA	Cross-sectional	$N = 22$ UHR (54% females; aged 20.3 ± 4.6 years) + 20 HC	• hd-EEG • Polysomnography	• UHR individuals had more WASO and higher NREM sleep gamma EEG power in a large fronto-parieto-occipital area compared to HC. • No significant difference between groups was found regarding arousal index during NREM sleep. • In the UHR group: higher NREM sleep gamma power in medial frontal-anterior frontal and posterior regions was related to worse negative symptoms.
Ristanovic (22)	USA	Cross-sectional	$N = 57$ CHR (aged 18.89 ± 1.82) including 38 participants who had actigraphy data collected + 61 HC	Actigraphy	• Automatic maladaptive responsivity to family stressors (i.e., greater involuntary engagement stress response) was associated with disrupted sleep (i.e., poorer sleep efficiency) in the CHR but not HC group. • Impaired stress tolerance was associated with all objectively assesses sleep parameters (i.e., sleep duration, continuity, and efficiency).
Zanini (2015) (32)	Brazil	Cross-sectional	$N = 20$ UHR (35% females: aged 18.3 ± 3.91) + 20 HC Females of the UHR group=35%	Polysomnography PSQI ESS MEQ	• UHR individuals reported significantly poorer sleep quality than HC (PSQI total scores of 7.70 (±3.68 vs. 4.95 ± 2.16, respectively; $p = 0.007$). • No differences found between groups regarding sleepiness and chronotype profiles. • Polysomography findings indicated that the UHR group presented significantly higher sleep latency onset and REMOL than HC.

*UHR state was evidenced using structured interviews (e.g., CAARMS, Comprehensive Assessment of the At Risk Mental State; SIPS, Structured Interview for Prodromal Symptoms; SOPS, Scale of Prodromal Symptoms).
FEP, First Episode Psychosis; HC, Healthy controls; RCT, Randomized Controlled Trial; PSQI, Pittsburgh 464 Sleep Quality Index; ESS, Epworth Sleepiness Scale; MEQ, Morningness and Eveningness Questionnaire; RU-SATED, Regularity, Satisfaction, Alertness, Timing, Efficiency, Duration; hd-EEG, High Density Electroencephalography; WASO, Wakefulness After Sleep Onset; NREM, Non-Rapid Eye Movement; REMOL, Rapid Eye Movement Sleep Onset Latency.

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compared to healthy controls (12, 20, 32–34), and even to first episode psychosis (FEP) patients (34). In particular, UHR individuals displayed longer sleep latency (i.e., the amount of time between reclining in bed and the onset of sleep) (12, 32, 35), shorter sleep duration in hours per night (20), greater daily sleep disturbances (e.g., night time and early morning awakenings) (12), greater daytime dysfunction due to sleepiness (20, 34), and increased sleep medication use (20, 34). Conversely, other studies did not find any differences in self-reported sleep latency (34) sleep duration (12, 34) and sleepiness scores (33) between UHR subjects and healthy controls. One prior research showed that UHR respondents exhibited significantly higher self-reported nightmare frequencies compared to healthy controls, and more dream recall frequencies compared to patients with schizophrenia (36). Finally, two studies using the Morningness and Eveningness Questionnaire (MEQ) (37) found no significant differences in self-reported chronotype profiles between UHR and healthy individuals (32, 33).

Objective sleep disturbances in UHR individuals

We could find only two polysomnography studies, which revealed that the UHR group presented significantly more Wake After Sleep Onset (WASO) (21) and increased sleep latency (i.e., more difficulty falling asleep) than HC (32). Zanini et al. (32) did not find significant differences in the polysomnographic sleep efficiency percentages, WASO scores, and total sleep time and of UHR participants relative to controls. The actigraphy data indicated that UHR individuals experienced increased WASO, decreased efficiency (22), increased night time movements (35), longer daytime nap duration (33), more fragmented circadian rhythms (33, 38) and later onset of nocturnal rest (38) compared to healthy controls. Based on sleep high density-Electroencephalography (hd-EEG) recordings, Mayeli et al. (21) found that UHR participants presented increased EEG gamma activity during non-rapid eye movement sleep in a large fronto-parieto-occipital area compared to controls.

Summary of past subjective and objective studies

In sum, previous studies highlighted a wide range of both subjectively and objectively assessed sleep disturbances in UHR individuals, including increased sleepiness, daytime naps, sleep latency, night time movements, nightmares, and a disrupted circadian rhythm. Overall, studies using subjective measures were more represented in the existing literature than those using objective measures, and mainly focused on general sleep disturbance [non-specific sleep disturbance severity scales of the SIPS/SOPS; $n = 7$ studies (27–31, 39, 40)], sleep quality [SPSQI; $n = 7$ studies (12, 20, 32–35, 41)], sleepiness [ESS; $n = 2$ (32, 33)], and chronotype [MEQ; $n = 2$ studies (32, 33)]. However, yet no studies assessed insomnia symptoms in UHR subjects using self-report measures [e.g., Insomnia Severity Index (42), Athens Insomnia Scale (43)]; despite having shown to be prevalent and severe in patients with psychosis (44, 45). We could identify only six previous studies using objective sleep measures; four of them used Actigraphy (33, 35, 38) and two used polysomnography (21, 32). All these studies involved small sample sizes (20–38 UHR individuals), and four of them had a cross-sectional design. These identified gaps may limit the conclusions drawn from the current review, and contribute to give an insight to future research in this field. Additional long-term cohort observation studies using objective sleep parameters and large sample sizes to better represent the UHR population are still very needed. It is also important that we draw attention to the fact that all studies in this topic have been performed in Western countries. Research from other parts of the world would be highly informative and should be encouraged.

Associations between sleep disturbances and clinical/functional outcomes in UHR individuals

Sleep disturbances have proven to be associated with various negative outcomes in patients with early and chronic psychosis, including heightened psychotic symptom severity, greater suicidality, increased cognitive deficits, as well as impaired functioning and quality of life (11, 46, 47). In this section, we propose to review the available research on the effects of sleep disturbances on various clinical and functioning outcomes in UHR individuals.

Associations between sleep disturbances and clinical outcomes

A limited amount of research has specifically addressed the contribution of sleep disturbances to psychotic symptoms in UHR individuals (11, 48–50). Some studies found that several disrupted sleep parameters at baseline (e.g., increased WASO, reduced efficiency, heightened night-time movements and more awakenings, lowered sleep time, fragmented circadian rhythm) were significant longitudinal predictors of the later severity of positive (35, 38, 50) and negative (38) psychotic symptoms. A recent longitudinal study (20) tracked sleep during 8 months in 478 UHR individuals, and showed that sleep disturbance was strongly and prospectively linked to increased psychotic symptoms (positive, negative, disorganized, and general) over time. Lunsford-Avery et al. (35) found that both baseline self-reported and actigraphic-measured sleep disturbance (i.e.,

decreased sleep efficiency, increased WASO, greater number of awakenings, and increased movements) helped predict the longitudinal course of positive symptoms specifically in UHR individuals; whereas no significant correlation has been found between actigraphic variables and negative symptoms over time. More particularly, findings from a large retrospective study from the UK demonstrated a specific association between sleep problems and greater perceptual abnormality frequency and severity in young UHR individuals (19). Similarly, Goines et al. (31) pointed to the specific effect of hallucinations on sleep over other attenuated psychotic symptoms. While these two studies (19, 31) suggested that perceptual abnormalities may lead to sleep disturbances in UHR individuals, other authors claimed a reversed pattern of association (51); highlighting the need for additional studies to elucidate the direction and nature of this relationship.

To summarize, the majority of the existing longitudinal studies cited above agreed that sleep disturbances are associated with subsequent psychotic symptoms exacerbation, which may in turn lead to poor mental health and functional outcomes even in individuals recovering from their at-risk state (52, 53). However, the observed impact of sleep disturbance on psychotic symptoms evolution over time is still unclear mainly due to a lack of longitudinal studies (20), which highlights the need for further investigations.

Associations between sleep disturbances and functional outcomes

Sleep problems have been consistently shown to impact cognitive processes and daytime functioning (54). Severe cognitive deficits and subsequent daily functional impairment are common outcomes in UHR youth, regardless of eventual conversion to threshold psychosis (53, 55, 56). Some cross-sectional evidence suggested that sleep disturbances are associated with more psychosocial dysfunctioning (30, 41). However, to date, little attention has been paid to the prospective relationship between sleep and functional outcomes in UHR individuals (10). One longitudinal research by Lunsford-Avery et al. found that objectively assessed circadian rhythm disruption at baseline predicted worse psychosocial functioning levels at 12-months follow up (38). More recently, Nuzum et al. (19) investigated 795 clinical records of UHR patients and found that sleep problems predicted worse follow-up levels of social functioning. Although sleep is a potentially modifiable factor (57, 58), that when treated could substantially and independently improve functional outcomes (59), its impact on functioning, quality of life and overall wellbeing in UHR states remain largely understudied (10). Therefore, further studies allowing a deeper understanding of the pathways linking sleep to developmental and long-term outcomes in UHR youth are required.

Sleep disturbance as a risk factor for transition to psychosis

It is well-established that a proportion of UHR individuals will convert later to a clinical psychosis (60, 61). Although evidence showing that sleep disturbances are present in UHR individuals before any psychosis onset (8, 31, 32, 39), there has been very limited interest so far on how abnormal sleep patterns may contribute to the transition risk (20). The first attempt to use sleep disturbances in the prediction of transition to psychosis was performed by Ruhrmann et al. (39) through a large prospective European study (39), and documented sleep as a strong predictive factor of transition from subthreshold to full-threshold psychosis over 18 months of follow-up (39). Inconsistent findings have emerged thereafter; with some studies showing that sleep problems represented a risk indicator for both the persistence and/or exacerbation of psychotic symptoms over time (35, 62); while others found no significant effect of sleep on psychosis transition (20, 30, 31). More recently, Nuzum et al. (19) found that, despite a lack of significant association between sleep parameters and transition to psychosis, sleep disturbances were significantly correlated with a shorter time to transition in UHR individuals converted to psychosis. Zaks et al. (20) suggested that disrupted sleep patterns may act as risk factors for transition only in aggregation with other potential factors. Overall, the pathways between sleep and psychosis are rather complex and have been hypothesized to be bidirectional (63). The eventual role that sleep would play in the development and progress of psychotic symptoms raises the question of its underlying mechanisms of the effects of sleep on the pathogenesis of psychosis (11, 49, 64). We propose to address this question in the next section.

Explaining mechanisms of the relation sleep disturbances–psychosis

The implication of sleep on the development and progress of psychosis has attracted a growing interest during the last years. A key hypothesis that has particularly received attention is the presence of structural brain abnormalities and neural development alterations which may likely lead to sleep alterations, and in turn psychotic symptoms, from the very early stages of psychosis (64). Structural brain alterations in the thalamic region are involved in both human sleep dysregulation (65), and the etiopathogeny of schizophrenia (66, 67). A thalamic volume reduction is noted early during the course of psychotic disorders,

and exacerbates as the disease progresses (68). In this regard, a study by Lunsford-Avery et al. revealed that UHR individuals had a reduced bilateral thalamic volume that significantly related to poorer sleep quality (12). A recent review suggested that aberrant thalamic function could result in sleep spindle deficits and altered EEG microstate dynamics (69). These alterations [e.g., increased non-rapid eye movement gamma EEG activity (21)] have been previously reported in UHR individuals, and could, in turn, represent "potent endophenotypes" and "vulnerability factors" for psychosis (69). This brings us back to the hypothesis stated earlier by Feinberg (70), that the great rearrangement of brain function and structure occurring during early adolescence, including maturational changes in EEG sleep patterns (i.e., decline in EEG amplitude), may have resulted from a decrease in cortical synaptic density, which may in turn underlie the emergence of schizophrenia. In this line of research, a relevant hypothesized biological mechanism underlying the effect of sleep on psychosis risk is a defective synaptic transmission. Acetylcholine has been shown to play a major role in both sleep and hallucinatory phenomena (71). As such, it has been suggested that sleep deprivation can be a direct cause of hallucinations and progression toward psychosis due to cholinergic depletion (51).

Other explaining mechanisms for the association between sleep and subsequent psychosis have been identified, such as negative affects (i.e., depression and anxiety) (72–74), endocrine dysfunction due to exposure to psychosocial and biological stress, and cognitive deficits (64). In this regard, some biological markers have been found to interfere with both psychosis proneness and sleep disturbances through a stress-induced activation of the hypothalamic–pituitary–adrenal (HPA) axis, including elevated cortisol levels (75, 76) and pro-inflammatory cytokines (77, 78). Interestingly, an increased reactivity to stress has recently been found to directly affect sleep in the UHR stage. For instance, Ristanovic et al. (22) found that maladaptive responsivity to family stressors and impaired stress tolerance were associated with disrupted sleep as assessed objectively in UHR subjects. Another previous study (41) suggested a pathway in which sleep problems amplify stress indirectly through a negative effect on cognition.

All the above-mentioned factors would interplay and together contribute to sleep disturbances and psychosis in vulnerable young people, highlighting "a possible role for sleep dysfunction within a neurodevelopmental diathesis–stress model for schizophrenia" (64). In sum, despite increased efforts to elucidate the complex relationship sleep-psychosis, a long way remains ahead before understanding what mechanisms are behind the observed patterns of relationships between these two constructs.

Prevention and intervention strategies targeting sleep for UHR individuals

Our review of the literature identified several altered subjective and objective sleep parameters in the at-risk stage of psychosis (10, 16), that have even been hypothesized as causal mechanisms of psychosis development and persistence (49, 79). Sleep is a malleable factor that has been shown to worsen psychotic symptoms when non-treated (20, 35, 62, 72), or reduce them and improve functional outcomes when treated (59, 80). As such, we suggest that although the directionality and the specific mechanisms underlying the relationship sleep-psychosis have not yet been elucidated, treatment of sleep problems has the potential to either reduce the risk of developing psychosis (as a causal factor) (49, 79), or prevent worsening of the disease outcomes (as an effect of prodromal symptoms) (59, 80).

When present, sleep disturbances are recommended to be screened for, monitored and treated according to the DSM-5 recommendations (81). Therefore, we suggest that screening for and addressing sleep disturbances should be a routine practice in early intervention services to help with reducing their clinical and functional impact on young UHR individuals (82). Promoting sleep in this vulnerable population may be a promising intervention target for symptom and functioning improvement (20), and possibly for delay or prevention of transition to psychosis (39, 83).

Sleep management in psychosis has been shown to be limited by several challenges. First, sleep disturbances are often not given the required focus (10) and are thus underestimated and undertreated. Second, clinicians tend to evaluate sleep informally and offer no or inadequate treatment (e.g., pharmacotherapy instead of the recommended first-line psychotherapy) (84, 85). Third, at the present time no consensual recommendations are available for the management of sleep problems in UHR patients. Basic sleep hygiene education has proven to be beneficial in people with psychosis (11, 46). In this regard, some authors demonstrated the benefits of a low cost and simple sleep intervention for early psychosis patients, consisting of sleep hygiene advice along with a provision of a wearable sleep tracker (86). Accumulated evidence has confirmed the effectiveness of the Cognitive Behavioral Therapy for insomnia (CBTi) in UHR states (80, 82, 87). The CBTi has also been proven to have wider benefits by improving depression, anxiety (44, 80, 88), and attenuated psychotic symptoms (44, 80). Other sleep interventions have been specifically designed and tested for use in young UHR people, such as the brief psychological intervention "SleepWell" that targets key sleep parameters (i.e., hyperarousal, sleep pressure, and circadian rhythm), and has yielded promising preliminary results (82). The SleepWell is now being tested

in a randomized trial in young patients at ultra-high-risk of psychosis [for further details, see the published protocol (89)].

Conclusion and perspectives

The current review extends our existing knowledge by further highlighting the presence of disturbed sleep in UHR individuals as evidenced by subjective and objective sleep measures such as polysomnography, sleep electroencephalograms, and actigraphy. Reviewing the possible mechanisms underlying the relationship between sleep and psychosis emphasizes its complex and multifactorial nature which is yet to be determined and understood. Our literature search revealed that this topic has attracted relatively scant research attention so far. Nevertheless, the early intervention field is a growing area of research and we expect that studies on sleep and UHR will continue to increase during the coming years. As such, we believe that our Mini review will shed light on the importance of further focusing on this promising avenue of research. Further high-quality longitudinal and experimental research on sleep involving large samples of UHR individuals and using a broad range of sleep parameters is warranted to determine which facets of sleep disturbances are most detrimental to this specific population, and to what extent they can be causal factors or markers of psychosis. This research can help deepen our understanding of the continuum of psychosis vulnerability; and inform psychosis-risk prediction models as well as prevention and early intervention programs.

Author contributions

FF-R wrote the first draft. SH, MC, and HJ provided intellectual contributions to strengthening the manuscript. All authors were involved in revising the manuscript and approved the final version.

Conflict of interest

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

Publisher's note

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Efficacy of auricular plaster therapy for sleep disorders in preschool children with autism spectrum disorders: Study protocol for a randomized controlled trial

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Background: Children with autism spectrum disorders (ASDs) suffer from sleep disorders to a considerable degree; however, there is no safe and effective treatment available in clinical practice. The objective of the trial is to assess the clinical effectiveness of auricular plaster therapy (APT) in treating sleep disorders in children with ASD.

Method: This is a single-center, patient-assessor blind, randomized controlled trial. A total of 44 preschool children with sleep disorders with ASD will be included in this study. Eligible participants will be randomly assigned to either the auricular plaster group or the sham auricular plaster group in a 1:1 ratio. Participants in the different groups will receive APT or sham APT, respectively, for a total of 30 sessions over 30 days. The primary outcome includes the Children's Sleep Habits Questionnaire (CSHQ), while secondary outcomes include the Autism Behavior Checklist (ABC) and polysomnography (PSG) for total sleep time, sleep latency, awakening duration, and sleep structures. The CSHQ and ABC will be assessed at baseline, 10, 20, 30, 60, 90, and 120 days after randomization, whereas PSG will be assessed at baseline and 30 days after randomization. The follow-up period will be scheduled to be 60, 90, and 120 days after randomization.

Discussion: The results of this study may provide evidence of the efficacy of APT, as well as offer new alternatives for the treatment of sleep disorders in children with ASD.

Trial registration: CHiCTR.org.cn (ChiCTR2100048257). Registered on July 5, 2021.

KEYWORDS

auricular plaster therapy, sleep disorders, autism, preschool children, study protocol

Introduction

Autism spectrum disorder (ASD) is a complex developmental condition characterized by difficulties in social interaction, communication, and common repetitive behavior patterns (1). Globally, the World Health Organization reported that 0.76% of children have ASD, accounting for 16% of the total number of children throughout the world (2). It is estimated that over 44% of children with ASD will develop sleep disorders, and these sleep disorders exist for a long period of time (3, 4). Sleep disorders commonly present as difficulty falling asleep, poor sleep quality, wakefulness, irregular sleep patterns, short sleep duration, and a tendency to wake up during the night (5).

As outlined by published guidelines (6–10) (Table 1), the primary treatment for autistic children with sleep disorders is to improve sleep habits. For parents of children with ASD, it will take a long time and a great deal of patience to teach children proper sleep habits, such as a comfortable sleep environment, regular bedtimes, encouraging the child to sleep alone, and avoiding naps (11). Moreover, it is unclear whether improving sleep habits could effectively treat sleep disorders in children with ASD (12).

After reviewing currently published randomized controlled trials (RCTs) for sleep disorders in children with ASD, we found that these studies had several limitations: relatively small sample sizes (<40 participants), a less rigorous study design (unblinding method), and adopted different diagnostic criteria for ASD (12–25) (Table 2). The only drug currently available in children with ASD is melatonin, which regulates circadian rhythms and improves sleep (26). The first RCT on melatonin, with 11 participants, showed benefits for sleep disorders in children with ASD (25). Another trial concluded that melatonin had efficacy for sleep disorders only for a short duration (22). In 2021, Hayashi et al. (13) conducted an RCT of melatonin in 196 children and reported that melatonin was effective in treating sleep disorders in children with ASD. Nevertheless, melatonin was also associated with some adverse events (AEs), including nervous system disorders, infections and infestations, and pharyngitis. According to the 2020 American Academy of Neurology guideline, melatonin has not been clinically evaluated for safety, and its potential role in decreasing sleep disorders in children with ASD is dubious (11, 18). Moreover, taking melatonin has some potential side effects, such as enuresis, headache, and dizziness (11, 27). Other complementary alternative medicines to treat sleep disorders in children with ASD, such as aquatic exercise (14), ferrous sulfate (16), carnosine (17), weighted blanket (20), lack evidence-based recommendations, and thus remain controversial (11).

As a part of traditional Chinese medicine (TCM), acupuncture is a vital component with a long history of treating diseases such as mental illness (28–30), cardiovascular disease and cerebrovascular disease (31), and tumor disease (32, 33). Auricular therapy is one treatment modality of acupuncture, which involves stimulating specific acupoints on the outer ear in an effort to promote health and wellbeing (34). As a form of auricular therapy, auricular plaster therapy (APT) is composed of a round and hard cowherb seed and a sticky adhesive tape with a size of 0.5 cm * 0.5 cm (35). Due to the non-invasive, safe, and convenient nature, once auricular plaster is affixed by the doctor, patients themselves can press and stimulate the points at the convenience of their own time. Although the mechanism by which APT treats insomnia is not fully understood, numerous studies have indicated that APT helps relieve insomnia by modulating neurotransmitter activity and affecting the nervous system (36). Several systematic reviews and meta-analyses of APT show that APT appears to be an effective and safe treatment for patients with primary insomnia (37–41). In the most recent study, a retrospective cohort study of APT treatment of 84 patients with coronavirus disease 2019 (COVID-19) with insomnia showed that APT was effective in alleviating insomnia and anxiety (42). Another RCT of 50 patients receiving methadone maintenance treatment (MTT) showed that APT combined with electroacupuncture could significantly improve sleep quality, sleep latency, and increase MMT adherence (43). In addition, the application of APT

TABLE 1 Summary of clinical guidelines for the treatment of sleep disorders in children with autism spectrum disorders.

Guidelines	Recommendations of treatment for sleep disorders
2021 NICE guideline	Not mentioned
2020 AAN guideline	Behavioral strategies are first-line treatment approach (Level B). Clinicians should offer melatonin to children and adolescents with ASD if behavioral strategies have not been helpful (Level B). No evidence to support the routine use of weighted blankets or specialized mattress technology for improving disrupted sleep (Level B).
2017 BAP guideline	Melatonin, if possible, in combination with a behavioral intervention (Strength of recommendation: A). Prolonged use of benzodiazepines and related GABA agonists is not recommended (Strength of recommendation: S).
2017 NICE guideline	Not mentioned
2013 NICE guideline	Not mentioned

NICE, National Institute for Health and Care Excellence; ASD, autism spectrum disorders; AAN, American Academy of Neurology; BAP, British Association for Psychopharmacology; GABA, gamma-aminobutyric acid.

TABLE 2 Randomized controlled trials of sleep disorders in children with autism spectrum disorders.

References	Country	Center	Intervention group	Control group	Sample size	Blinding	Primary outcomes	Conclusion
Hayashi et al. (13)	Japan	Multicenter	Melatonin	Placebo	196	Double blind	Sleep onset latency	Melatonin is effective for sleep disorders.
Ansari et al. (14)	Iran	Single	Aquatic exercise	None	40	Not mentioned	CSHQ	Aquatic exercise may improve sleep quality and reduce the serum IL-1β and TNF-α.
Papadopoulos et al. (15)	Australia	Single	Sleep behavioral intervention	Usual clinical care	61	Not mentioned	CSHQ	A brief behavioral sleep intervention can improve sleep problems.
Reynolds et al. (16)	USA	Single	Ferrous sulfate	Placebo	20	Double blind	Bedtime and wake time	No improvement in insomnia in treated with ferrous sulfate.
Mehrazad-Saber et al. (17)	Iran	Single	Carnosine	Placebo	43	Double blind	CSHQ	Carnosine could be effective in improving sleep disorders.
Gringras et al. (18)	USA	Single	PedPRM	Placebo	125	Double blind	SND and CSDI	PedPRM is effective and safe for treatment of insomnia.
Frazier et al. (19)	USA	Single	Pre-STS mattress	After-STS mattress	45	Double blind	Sleep diary	STS could improve sleep duration and sleep efficiency.
Gringras et al. (20)	USA	Single	Weighted blankets	Placebo	73	Not mentioned	TST	The use of a weighted blanket does not help children with ASD sleep.
Johnson et al. (21)	USA	Single	BPT program for parents	Not BPT	40	Not mentioned	Treatment fidelity checklist	BPT has a certain effect on sleep disorders.
Cortesi et al. (22)	Italy	Single	CBT and melatonin	Melatonin or Placebo	160	Double blind	Sleep variables*	In the short term, CBT and melatonin have efficacy for sleep disorders
Adkins et al. (12)	USA	Single	Sleep education to parents	No sleep education	36	Not mentioned	Changes in sleep latency	The sleep education pamphlet did not improve sleep latency.
Wright et al. (23)	UK	Single	Melatonin	Placebo	22	Double blind	Sleep variables†	Melatonin improved sleep latency and total sleep but not number of night awakenings.
Wirojanan et al. (24)	USA	Single	Melatonin	Placebo	12	Double blind	Sleep variables‡	The efficacy and tolerability of melatonin treatment for sleep problems can be affirmed.
Garstang and Wallis (25)	UK	Single	Melatonin	Placebo	11	Double blind	Sleep variables¶	Melatonin was beneficial for sleep disorders.

CSHQ, children's sleep habits questionnaire; TNF, tumor necrosis factor; PedPRM, prolonged-release melatonin minitablets; SND, sleep and nap diary; CSDI, composite sleep disturbance index; STS, sound-to-sleep; TST, total sleep time; BPT, behavioral parent training; CBT, cognitive behavioral therapy.
*Represents sleep latency, total sleep time, wake after sleep onset, and the number of awakenings in sleep variables.
† Represents sleep latency, total sleep, and night awakening in sleep variables.
‡ Represents sleep-onset time, total night sleep duration, sleep-onset latency time, and the number of night awakenings in sleep variables.
¶Represents sleep latency, number of awakenings, and total sleep duration in sleep variables.

has also been extended to the treatment of pain management (44, 45), postoperative rehabilitation (46), attention deficit (47), primary dysmenorrhea (48), and other conditions. Nevertheless, to our knowledge, there have been no RCTs evaluating the efficacy of APT for sleep disorders in children with ASD. Given that APT is effective in treating insomnia in adults, we aim to test the safety and efficacy of auricular plaster therapy for the treatment of sleep disorders in preschool children with ASD, which may provide a viable alternative treatment method.

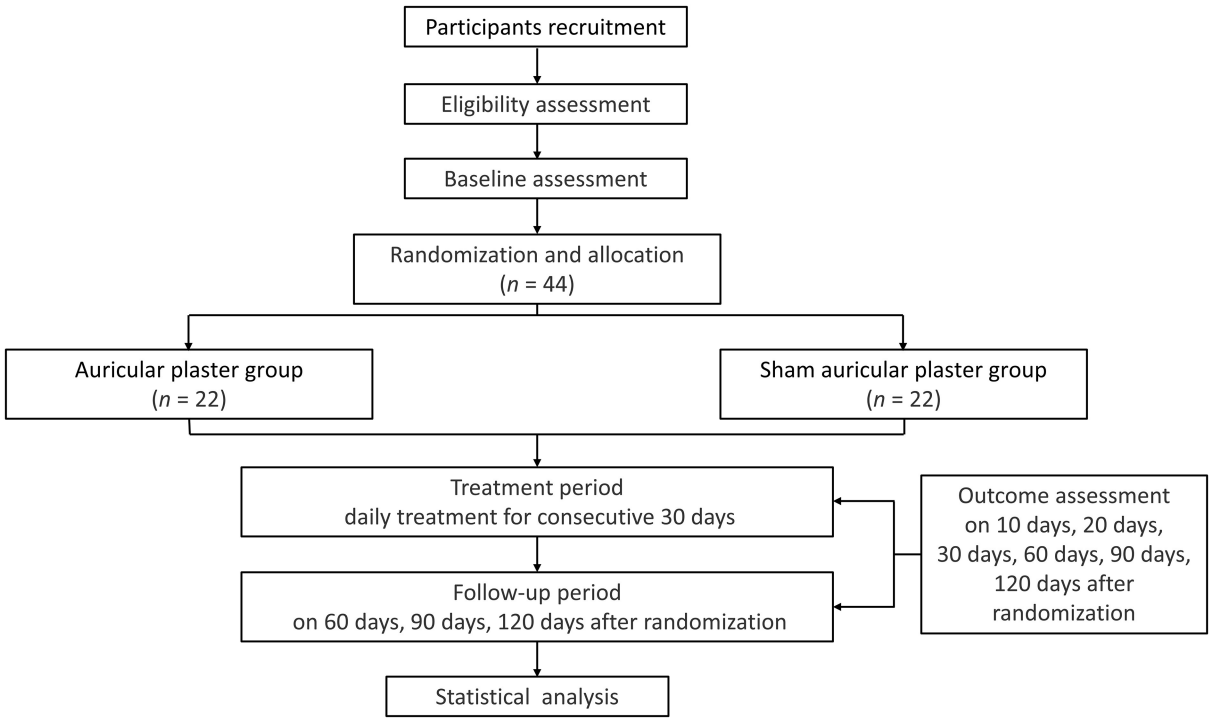

FIGURE 1
Study flowchart.

Methods and analysis

Study design

This study is a parallel-design, patient-assessor blind randomized controlled trial (RCT) comparing the use of APT with sham APT. The recruitment of participants will take place from 1 August 2021 to 31 December 2022. The program will enroll autistic preschoolers with sleep disorders who will be assessed at the Sichuan Beidouxing Rehabilitation Service Center as well as three other community hospitals (Fuqin Community Health Service Center, Tiaodenghe Community Health Service Center, and Xianqiao Community Health Service Center). The clinical trial was registered on CHiCTR.org.cn (ChiCTR2100048257) before we enrolled our first participant, and the study was approved by the Second Affiliated Hospital of Chengdu Medical College, China National Nuclear Corporation 416 Hospital Ethics Committee (KJ2021012).

Eligible participants will be randomly assigned to the APT group or the sham APT group on a 1:1 basis. An observation period of 120 days will be conducted, including a 30-day treatment period and a 90-day follow-up period. Children will receive APT continuously for 1 month. Assessments will be conducted at baseline as well as 10, 20, 30, 60, 90, and 120 days after randomization. The study flowchart is shown in Figure 1, and the schedule of the trial is shown in Table 3.

The protocol complies with the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines (49). The Consolidated Standards of Reporting Trials (50) as well as the Standards for Reporting Interventions in Clinical Trials of Acupuncture (51) provide a framework for designing this clinical trial.

Participants

We will include preschoolers who meet the diagnostic criteria for autism and sleep disorders. Upon meeting the inclusion criteria and not meeting any of the exclusion criteria, an ASD child will be considered eligible.

Inclusion criteria

Participants who meet all of the following inclusion criteria will be included: (1) meet the diagnostic criteria for sleep disorders (ICSD-3) (52) and autism (1); (2) aged 2–6 years old; (3) did not receive relevant treatment measures 1 week prior to enrollment; and (4) written informed consent obtained from parents.

TABLE 3 Study schedule of the trial.

	Study period								
	Enrollment	Allocation	Post-allocation				Follow-up period		
Timepoint (days)	-7	0	1	10	20	30	60	90	120
Enrollment									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
Interventions									
Auricular plaster				←	—	→			
Sham auricular plaster				←	—	→			
Assessments									
CSHQ			X	X	X	X	X	X	X
ABC			X	X	X	X	X	X	X
PSG			X			X			
AEs				X	X	X			

CSHQ, Children's Sleep Habits Questionnaire; ABC, Autism Behavior Checklist; PSG, polysomnography; AES, adverse events.

Exclusion criteria

Participants who meet any of the following criteria will be excluded: (1) known severe cardiovascular, cerebrovascular, liver, kidney, blood, and other systemic diseases; (2) known history of Asperger's syndrome, Heller syndrome, Rett syndrome, specific receptive language disorder, or childhood schizophrenia before (53–55); (3) known taking part in other clinical trials.

Drop-out criteria

Participants drop out for the following reasons: (1) they experience severe adverse events (SAEs) and are ineligible for further study; (2) they withdraw from the clinical study; and (3) they have manifestations of allergies to auricular plaster.

Randomization and blinding

Based on a random number generated by SAS (Version 9.3, SAS Institute Inc., Cary, NC, USA), participants will be randomized in a 1:1 ratio to either the auricular plaster group or the sham auricular plaster group. Random numbers are generated by a statistician who is not participating in the trial. The random grouping results are sent to the acupuncturists by message. However, the particular characteristics of auricular plaster therapy make it difficult for acupuncturists to be blinded. Participants do not know which group they belong to. APT will be administered to participants in separate rooms according to their assigned groups. Researchers and statisticians in the trial will be blinded to the grouping scenario.

TABLE 4 Locations of auricular points.

Auricular point	Location
Heart (CO15)	Located at the middle of the concha
Jiaogan (AH6a)	Located at the junction of the front end of the lower part of the antihelix and the inner edge of the helix
Shenmen (TF4)	Located at the upper of the posterior third of the triangular fossa
Subcortex (AT4)	Located at the medial side of the antitragus
Kidney (CO10)	Located at the rear of the lower part of the antihelix
Spleen (CO13)	Located at the posterior upper part of the concha

Basic treatment regimen

Participants will receive standard rehabilitation training for autism according to the published guidelines (6), including physical activities, rhythm classes, sensory integration classes, discrete unit teaching methods, and natural environment teaching. These rehabilitations will be guided by qualified professionals.

Interventions

Based upon clinical experience in APT for sleep disorders and characteristics of TCM treatment of sleep disorders in children with ASD, the acupoints of the heart (CO15), Jiaogan (AH6a), Shenmen (TF4), subcortex (AT4), kidney (CO10), and spleen (CO13) are chosen in this study (56). The locations of

the auricular points can be found in Table 4 and Figure 2. Both groups will be treated with APT for 30 consecutive days. Before participating in the trial, the acupuncturists qualified as Chinese medicine practitioners have at least 3 years of clinical experience, and successfully passed a relevant test, including auricular point positioning, auricular point duration, and participant attention. The auricular plaster (Heshi MedTech Co., Ltd., Hengshui, Hebei, China) consists of cowherb seeds wrapped in a tape of 0.5 cm * 0.5 cm. Participants in the sham APT group will only be treated with the same shape as auricular plaster without cowherb seeds. To increase compliance, we also manufacture special auricular plaster, which is covered with cartoon stickers. Acupuncturists will change the auricular plaster application for participants every day. Participants are not allowed to take any therapeutic drugs (e.g., melatonin) for sleep disorders during the study.

Auricular plaster group

Based on conventional rehabilitation training for children with ASD, children in the auricular plaster group will be provided with APT. Children themselves or their parents are told to press the auricular plaster three times a day (8 a.m., 2 p.m., half an hour before sleep at night), each point for 30–60 s, so that the auricular point produces an acidic and swollen sensation that can be tolerated by the children.

Sham auricular plaster group

Participants will receive a sham APT on the same auricular point location as the APT group. They will not be instructed to press the sham plasters.

Outcome measurements

Primary outcome

The primary outcome is the Children's Sleep Habits Questionnaire (CSHQ) (57), which contains seven items, including bedtime, sleep habits, sleep behavior, night wake, morning wake, daytime sleepiness, and total sleep time, with different items representing different sleep problems. Higher scores indicate a greater problem with sleep (58). The CSHQ will be evaluated at baseline and 10, 20, 30, 60, 90, and 120 days after

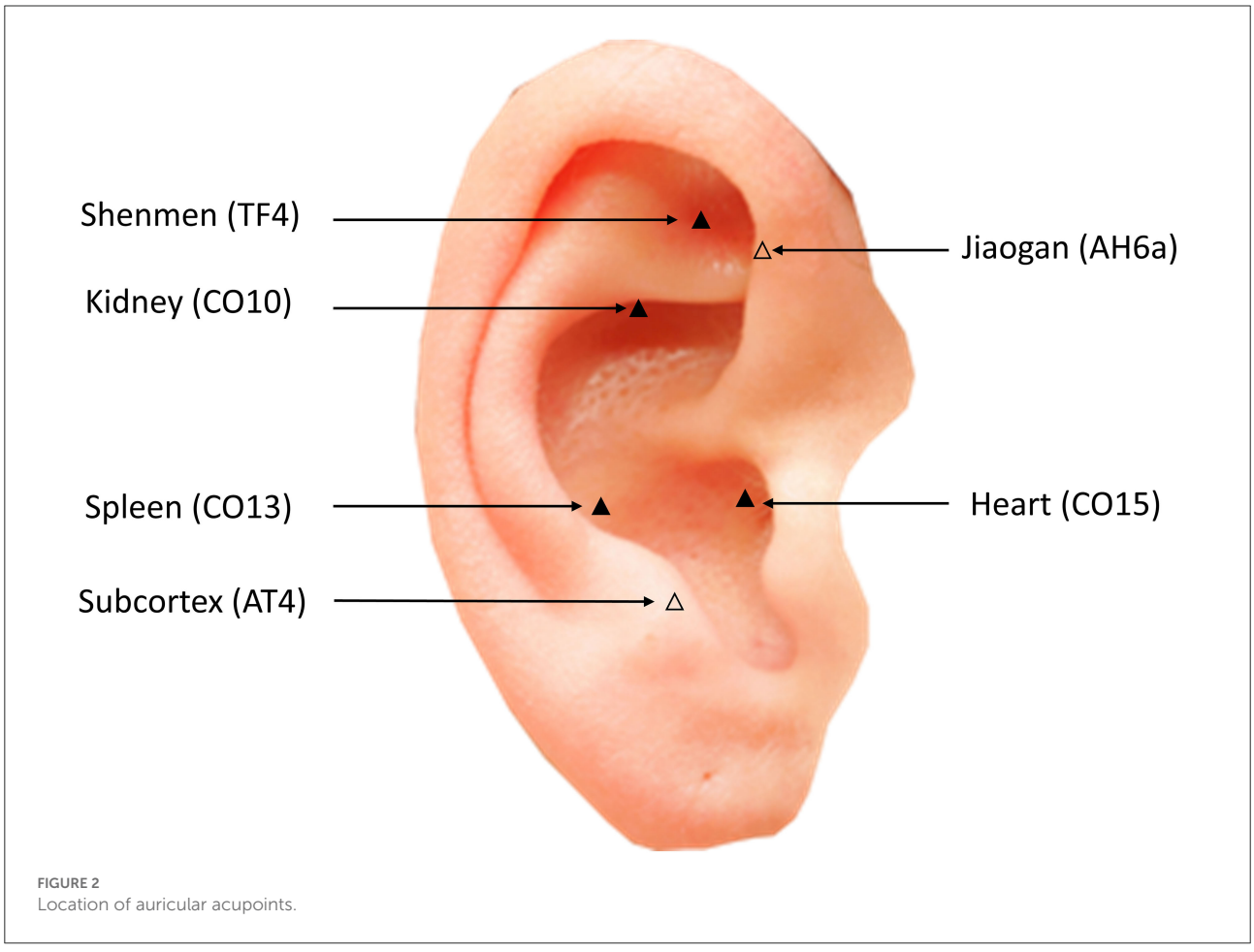

FIGURE 2
Location of auricular acupoints.

randomization. Sleep assessment ranges from 1 month prior to baseline, every 10 days in the treatment period, and every 30 days in the follow-up period.

Secondary outcomes

Secondary outcomes include the following:

1) The polysomnography (PSG) system (Natus Neurology Incorporated, Wisconsin, USA), a clinical measure for evaluating sleep conditions, is considered to be the "gold standard" for determining sleep-related disorders (59). The sleep variables of PSG include the following: total sleep time (TST), sleep latency (SL), awakening duration, and sleep stages (non-rapid eye movement sleep stage 1 (NREM1), NREM2, NREM3, rapid eye movement (REM) sleep latency and REM sleep) (60). Sleep stages are determined by analyzing the electroencephalogram (EEG), electrooculogram (EOG), and chin electromyogram (EMG) recording. EEG derivations F4-M1, C4-M1, and O2-M1 are obtained from the electrical activity in frontal, central, and occipital brain regions. The frequency filter for these derivations ranges from 0.3 to 35 Hz. The EOG derivations E1-M2 and E2-M2 are determined by electrodes placed in the left and right outer canthus, respectively, with frequency filters ranging from 0.35 to 35 Hz. Three electrodes placed at the chin provide the EMG derivations EMG1, EMG2, and EMG3, which have a frequency filter of 10–100 Hz. Children with ASD will receive 16-h PSG monitoring at baseline and the end of treatment. The PSG data will be analyzed by Natus ® SleepWorks™ PSG software. A certified neurosurgeon with 8 years of experience (Dr. Yan Ni) who has passed the Chinese PSG technical operation examination will audit the PSG data.
2) Autism Behavior Checklist (ABC), which is one of the five components of the Autism Screening Instrument for Educational Planning (61). There are 57 items divided into five parts in the ABC, which are categorized into five areas: sensory, relating, body and object use, language, and social and self-help skills. The ABC follows the same assessment schedule as the CSQH. The CSHQ and ABC questionnaires were assessed by one independent assessor who was blinded to group allocation.

Sample size

A multisite case-control study which including 552 sleep problem in two to five children with ASD showed that the mean score of the CSHQ for ASD children was 48.5, and the standard deviation (SD) of CSHQ was 9.7 (62). Another study utilizing scalp acupuncture to treat sleep disorders in children with ASD showed a significant improvement in total CSHQ scores of 38 after treatment (63). Based on these two studies, we assume that the mean CSHQ score of children with ASD after receiving APT treatment is 40, and the SD in the auricular plaster group and sham auricular plaster group was 9.7. Assuming a significance level of 0.05 and a study power of 0.8 with a 10% dropout rate, 44 participants were required for this study, with 22 participants in each group. The sample size was calculated using power analysis and sample size (Version 11.0.7, NCSS, Englewood, New Jersey, USA).

Data collection and management

Data of the participants will be stored in the case report forms (CRFs), and the data will be input into the electronic CRFs by a specialized data reader. Data are managed by the China National Nuclear Corporation Hospital Data Management Committee. Data will be checked by the manager once a month. Therapists will not have access to the data during the study.

Quality control

All the researchers will be trained with the trial methodology and APT technique before the first participant is included. During the trial process, the China National Nuclear Corporation Hospital Data Management Committee is in charge of quality control.

Adverse events and safety assessment

The AEs included allergies to auricular plaster, swelling, and severe pain. When SAEs occur that pose a threat to the participant's safety, the study will be stopped immediately and the blinding will be canceled to preserve the participant's life. A detailed record of all AEs/SAEs will be kept during the course of the study, including the date, duration, treatment measures, and results.

Statistical analysis

An analysis of the data will be conducted using SPSS (Version 24, IBM, Armonk, New York, USA). Data will be analyzed on the basis of intention-to-treat (ITT) and per-protocol (PP) analysis. The ITT analysis includes all the participants who received at least one acupuncture treatment and one assessment of the primary outcome. The PP analysis includes participants who complete the trial. Continuous data will be expressed as medians and interquartile ranges. Categorical data will be presented as numbers and percentages.

Continuous variables will be compared using the independent-sample *t*-test or the Mann–Whitney *U*-test. Categorical variables will be compared with the chi-squared test or Fisher's exact test. Missing values will be addressed by multiple imputations, having appropriately explored the missingness mechanism and in accordance with good practice. Two-sided $P < 0.05$ will be considered significant.

Discussion

In children with ASD, sleep disorders are significantly more common than in normal children, which could lead to a lifelong problem if not addressed early on (4, 64). Sleep disorders are typically associated with communication difficulties and restrictive and repetitive behaviors, which are major symptoms of ASD. Children with ASD often suffer from sleep disorders, which adversely affect their moods, emotional regulation, behavior, and cognitive function. The consequences of abnormal behavior during the day can negatively impact the quality of sleep, resulting in a vicious cycle. Additionally, sleep disorders have a greater impact on obesity, injuries, and attention deficit in children with ASD than in other children (11, 65, 66).

Autism management is a lengthy and challenging process, which is a huge mental and economic burden on families. Children with ASD are often young and in their development stage. Treatments involving prescription drugs and complicated, painful, and invasive nonpharmacological therapies are not well accepted by children with ASD. In contrast to the placebo effect, acupuncture is one of the most effective ways to treat sleep disorders (67). Auriculotherapy is an important part of acupuncture (38), which can contribute to the improvement of sleep disorders for a variety of reasons (68–71). In this study, APT will be used to treat sleep disorders in children with ASD. It is a non-invasive, painless, and inexpensive treatment for children and is highly acceptable to both children and their parents. Hence, this acceptance could serve as a promising starting point for the study. In our study, parents are encouraged to participate and are taught how to press auricular plaster, which is in accordance with the guideline (6).

In recent years, there have been controversies regarding the effectiveness of both real acupuncture and sham acupuncture in treating disease. Sham acupuncture involves superficial needling and non-acupoint needling. A review of acupuncture for sleep disorders compared the efficacy of acupuncture, electroacupuncture, acupressure, and sham acupuncture/placebo (72), which showed that acupressure was more effective than sham acupuncture/placebo in improving sleep disorders.

As part of the study design, different groups of participants receive treatment in separate rooms, resulting in less communication between the groups and guaranteed blindness. Moreover, both the auricular plaster and sham auricular plaster have the same shape, which also prevents participants from identifying which group they belong to.

In TCM theory, ASD is attributed to a deficiency of the spleen and kidney. The main physiological functions of the spleen are to regulate transportation and transformation and dominate muscles and limbs (73). The function of the kidney is to store essence and maintain growth, development, and reproduction (73). By stimulating these two auricular points, children with sleep disorders and ASD can benefit from the improvement of their clinical symptoms by promoting musculoskeletal growth and transportation of qi and blood. Thus, the ear kidney (CO10) and ear spleen (CO13) were selected. As the heart regulates the blood vessels and governs the mind, TCM also believes that sleep disorders are closely related to the heart. *Inner Canon of the Yellow Emperor* states that "the heart is the residence of the spirit," which means that good sleep is dependent on a sufficient supply of heart qi and enough blood. Shenmen (TF4) and heart (CO15) are most closely related to the heart and thus are selected. Moreover, the ear subcortex (AT4) can coordinate the excitatory and inhibitory functions of the cerebral cortex, and Jiaogan (AH6a) is able to regulate sympathetic nerve functions, which are closely related to the regulation of sleep. Thus, the acupoints of Jiaogan (AH6a) and subcortex (AT4) are selected in this study.

Outcome determination is of great importance for the trial. According to the pediatric International Classification of Sleep Disorders, the CSHQ is a classification scale designed specifically for diagnosing sleep disorders in school-aged children (57). As a scale for detecting sleep disorders in preschool children with abnormal sleep behaviors, the CSHQ has shown adequate reliability, validity, and internal consistency across long-term clinical studies (62, 74, 75), and in recent years, research has demonstrated that the CSHQ could be successfully applied to assessing sleep disorders in children with ASD (76–79). A study evaluating the psychometric properties of the CSHQ in 469 school-aged children (4–10 years old) with sleep disorders concluded that the CSHQ demonstrated internal consistency and test-retest reliability (57). Therefore, the CSHQ is used as the primary outcome to assess sleep disorders in children with ASD before and after treatment in this study. ABC is a well-established tool for screening and diagnosing autism (80, 81). Krug et al. (61) first investigated the psychometric properties of the ABC and found that the split-half reliability was 0.87. Subsequently, Yousefi et al. (82) assessed the psychometric features of ABC in 114 children (aged 6.82 ± 1.75) with ASD and found that the ABC can be used as an initial screening tool in the clinic. Thus, ABC is chosen as another outcome measurement. PSG can detect sleep problems that are often unnoticeable by other means, such as problems in sleep structure, sleep latency, and total sleep duration. In a cross-sectional study conducted by Aathira et al. (83) in 71 children with autism spectrum disorders, it was found that there was reduced sleep efficiency, decreased rapid eye movement, and reduced slow wave sleep duration in

PSG, which may then affect the behavioral phenotype. Moreover, several studies also confirmed that children with ASD suffered from disrupted sleep structure, which included decreased REM sleep, longer sleep latency, lower sleep efficiency, and increased NREM1 sleep (84, 85). According to an RCT conducted in 2017, acupuncture could improve NREM1 and increase TST in patients with peri-menopausal insomnia (86). Therefore, PSG is selected as a secondary outcome to assess the effectiveness of APT in improving sleep structure.

Autistic preschool children with sleep disorders are recruited primarily from the Sichuan Beidouxing Rehabilitation Service Center and three other community hospitals. There are currently more than 200 preschool children with ASD in the Sichuan Beidouxing Rehabilitation Service Center, and approximately 50 preschoolers with ASD have enrolled in school annually, ensuring the inclusion of participants.

Our study has several limitations. First, the sample size of the trial is still relatively small, which is not a huge improvement compared with published studies. Second, researchers could not be blinded to group allocation because of the particularity of APT. Third, PSG is a challenge for children with ASD, although a specially designed PSG room was decorated in a cartoon style to improve adherence among children with autism and their parents accompany them at all times. Furthermore, PSG was monitored for only one night, resulting in an inevitable first-night effect.

In conclusion, the results of this study not only confirm the clinical efficacy of APT in treating sleep disorders in children with ASD but also provide new alternatives in the treatment of sleep disorders in children with ASD.

Trial status

At the time of submission, recruitment of participants is currently underway.

Ethics statement

The studies involving human participants were reviewed and approved by the Second Affiliated Hospital of Chengdu Medical College, China National Nuclear Corporation Hospital Ethics Committee (KJ2021012). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

TL and DD contributed to the conception and design of this trial. DD, LH, and TL drafted the manuscript. HC planned randomization and statistical analysis. DD and YL participate in the recruitment and treatment of participants. WW is responsible for collecting the data. 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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Tiredness, depression, and sleep disorders in frontline healthcare workers during COVID-19 pandemic in Vietnam: A field hospital study

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Background: The COVID-19 outbreak witnessed in the autumn of 2021 led to unprecedented changes in healthcare systems in some emerging countries. Many field-hospitals, temporary sites of care for COVID-19 patients, were built around the country and followed by the healthcare workers who were mobilized. This study aimed to measure sleep disorders, depression, and fatigue in volunteers working at field hospitals during the COVID-19 outbreak.

Methods: This was a cross-sectional study. The self-report questionnaire was used for each study subject. Sleep characters, including STOP's elements were questioned. Healthcare workers' burnout was detected by using Pichot's questionnaire.

Results: One hundred front-line healthcare workers (FHWs), predominantly last year and graduated medical students, were included in the study (86% female subjects). The mean sleep-time of FHWs before, while working, and during the isolation period after working at COVID-19 field hospitals were: 7.78 ± 1.48, 5.71 ± 1.40, and 8.78 ± 2.31 h per day, respectively. Burnout was not a crucial issue for these volunteer subjects. The mean scores of Pichot's Fatigue Scale and Pichot's Depression Scale, measured after 4 weeks working at field hospitals, were 4.18 ± 5.42 and 2.54 ± 3.36, respectively. Thirteen participants were suspected of depression. The fatigue scores decreased significantly in the group who claimed short sleep latency. The factor that increased the depression score was "anxious feeling" ($p = 0.001$). Other significant factors were "short sleep latency," "observed sleep apnea," "tiredness, daily sleepiness" and "snoring."

Conclusion: Appropriate work schedule, better sleep conditions, and mental health support could be helpful for FHWs. The mandatory 2 weeks of isolation after working in field hospitals provided opportunity for FHWs' recovery.

KEYWORDS

COVID-19, sleep disorders, depression, burnout, frontline health workers

Introduction

The COVID-19 pandemic is the deadliest since the 1918 Spanish influenza and is still an ongoing challenge. From the beginning of the COVID-19 pandemic to June 8th, 2022, as stated by WHO, 530,896,347 confirmed cases and 6,301,020 cumulative deaths have been reported worldwide (1). In Vietnam, even after several months of implementation of the Zero-COVID strategy, the virus has spread rapidly since April 2021. Currently, more than 10,727,918 people have been infected and 43,081 people died (2). Despite being affected much later than other countries, the healthcare system in Vietnam was also boosted. Volunteer healthcare workers around the country were mobilized to help the most affected areas. In this context, healthcare providers and medical students from the provinces or cities with low rates of COVID-19 cases, voluntarily moved to those areas with high levels of COVID-19 to work at the COVID-19 field hospitals.

Physician fatigue, also known as burnout, is a highly prevalent but often underrecognized result of workplace stressors (3, 4). The consequences of burnout can include poor work-life integration, isolation, depression, and suicide. The study on the intern doctors in China showed that burnout may have serious implications not only for the quality of emotion and their professional efficacy but also for their health and wellbeing (5). Given the context COVID-19 front-line healthcare workers (FHWs: people working in all healthcare sectors such as physicians, assistant physicians, nurses, pharmacists, medical technicians, graduated, or last year medical students) had to face, under constant high risk of infection; it makes sense that they suffered from stress, work overload, and lack of sleep (6). Reciprocally, sleep disorders and burnout have been shown to be associated with risk of COVID-19 infection (7). Since the beginning of the pandemic, Kang and colleagues also reported that up to 34.4% of medical staff working in Wuhan suffered from mild mental health disorders and emphasized the need for mental health care for FHWs fighting the pandemic (8). Approximately 30% of the internists and primary care physicians who participated in a Japanese study had symptoms of burnout, anxiety, and insomnia, whereas 15% were depressed during the COVID-19 pandemic (9).

The present study aimed to demonstrate the psychological struggles of FHWs, which focused on tiredness, depression, and sleep disorders in those caring for COVID-19 patients. This study also analyzed the main factors related to the psychological struggles of the FHWs and the efficacy of a 14-day self-isolation period to help recover from any psychological stressors burdened during a FHW's time fighting COVID-19.

Methods

Study design and participants

This multi-center, prospective observational study looked at different groups of volunteer healthcare workers of Lam Dong province who came to Binh Duong province and Ho Chi Minh City–Vietnam. These volunteer healthcare workers were physicians, pharmacists, nurses, medical technicians, and graduated or last year medical students. They came from healthcare centers and Lam Dong Medical College to be mobilized to take care of patients with COVID-19 in the field hospitals of other cities (called FHWs).

Participants were free to fill the questionnaire on Google Form, developed by the Scientific Committee of Vietnamese Society of Sleep Medicine (VSSM), during their working and isolation periods. The isolation period was the obligated two-week time for all FHWs after they finished working in the field-hospitals and came back to Lam Dong province. This isolation period was reserved only for FHWs without COVID-19 infection after their mission. FHWs with COVID-19 infection during their mission in the field-hospitals were excluded from the present study.

The content of these questionnaires was also published on the local society website (https://forms.gle/oR9aaWLtE6oELVK67). The present study ensured confidentiality and provided an explanation without inducement for any unclear questionnaire items. Data collection closed at the end of the 2 weeks of isolation to describe sleep disorders and exhaustion during their frontline mission and recovery time. There were also no formal hypotheses being implemented to drive the sample size and calculation and all persons were included in the study. The study was approved by

Institutional Review Board (IRB) of Lam Dong Medical College (no. 07.2021/NCKH-LMC).

Questionnaire

Because the SARS-CoV-2 pandemic work in the field hospitals was unprecedented, the working period at the field hospitals was relatively short. Thus, an available simple questionnaire, which included 4 items of STOP score, was used in the present study instead of other complicated sleep scales previously used to diagnose the risk of sleep breathing disorders such as obstructive sleep apnea (OSA). It included four yes/no questions related to snoring, tiredness during the daytime, observed apnea during sleep, and hypertension.

FHW's tiredness was measured using the Pichot's Fatigue scale. This is a practical scale, consisting of 8 questions (items), scored progressively from "0" (not at all) to "4" (extremely). The score ranged from 0 to 32 and a total score above 22 revealed excessive fatigue. Additionally, the Pichot's Depression scale, measuring depression, consists of 13 binary questions and yields a score of 0 to 13. A total score above 7 indicated a depressive mood. The Pichot scale allows us to determine the possible role played by depression on possible cognitive impairment (10).

The questionnaire also includes socio-demographic data, medical problems such as cardiovascular problems or pulmonary disorders, depression, sleep habits, television and smartphone use, and night shift work.

Data analysis

All the questionnaires received were checked by double blind verification to assure the data's validity and reliability. The present study expressed descriptive data as mean (SD) or median (IQR) for continuous variables and number/percentage (%) for categorical variables. This study assessed differences between "before the frontline working period," "during the frontline working period," and "during the post-working isolation period" using the two-sample *t*-test for continuous variables and Chi square for categorical variables. Tests were two-sided with significance set at <0.05. The Stata 13.0 software was applied for all analyses.

Results

General characteristics of study participants

One hundred FHWs from Lam Dong province were included in the present study. Most of these FHWs in COVID-19 field hospitals were female medical students and still young (Table 1). More than half of the participants ($n = 58$) claimed to be physically active. The mean active time was 2.30 h/day for the total study sample. There was only one participant with hypertension and three others with depressive states.

TABLE 1 General characteristics of study participant ($n = 100$).

Characteristics		%
Gender	Female	86.0
	Male	11.0
	Others	3.0
Education level	College	79.0
	University	13.0
	Post-graduated	8.0
Career	Physicians and nurses	6.0
	Graduated students*	28.0
	Last year students**	66.0
Marital situation	Single	90.0
	Married	10.0
Age class	From 18 to 25 years old	88.0
	From 26 to 45 years old	11.0
	Over 46 years old	1.0
Medical history	No	96.0
	Hypertension	1.0
	Depressive status	3.0

*graduated students: student who finished their studies and were waiting to work. **last year student: students who were in the last year of their education for being assistant physicians or nurses. These study subjects (FHWs) had to stop online study (last year student) and work under supervision as nurses or assistant doctors in the field-hospital similar with local official nurses or assistant physicians.

Self-declared sleep disorders and sleep characteristics of study participants

Most participants claimed insufficient sleep during the working period at COVID-19 field hospitals (64 vs. 26% before). Only 19% of them claimed insufficient sleep during the isolation period. Similarly, there were significant differences between the sleep-time within the 3 periods. The mean sleep-time of FHW before frontline work, during frontline work, and during the isolation period after working at COVID-19 field hospitals was 7.78 ± 1.48, 5.71 ± 1.40, and 8.78 ± 2.31 h per day, respectively.

The difference between before and during the working period was statistically significant with $p < 0.001$. The daily sleep-time during the isolation period was not only longer than during the working period but also the period before frontline work began ($p < 0.01$). Similarly, the severity of sleep disorders was also ameliorated during the isolation (Figure 1). To possibly explain sleep difficulty, FHW revealed some environmental factors and working conditions (Table 2). The night shift was the primary factor influencing the FHW's sleep. The quality of their

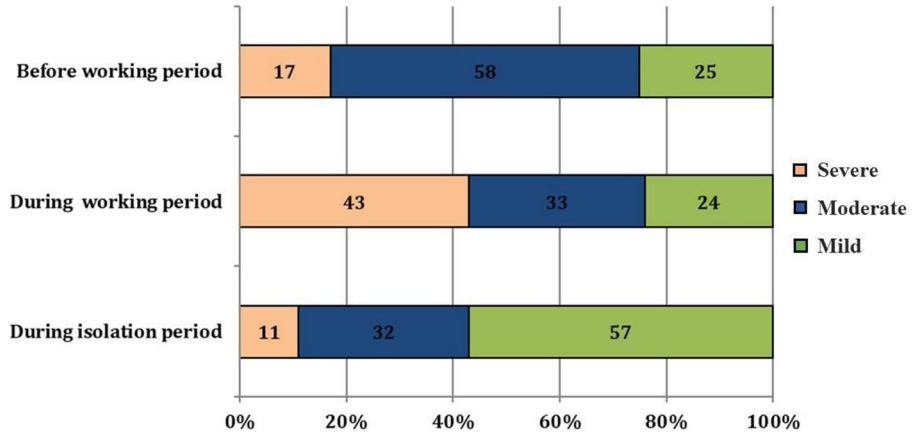

FIGURE 1
Self-declared sleep disorder severity of study participants.

TABLE 2 Factors influencing sleep quality of study participants ($n = 100$).

Factors	Before working period (a) (%)	During working period (b) (%)	During isolation period (c) (%)	p(a)*vs.*(c)	p(a)*vs.*(b)	p(b)*vs.*(c)
Light and noise	14	7	0	-	0.053	-
Bed quality	3	15	3	0.001	0.002	0.002
Climate	2	8	3	0.149	0.026	0.21
Mosquito	1	6	5	0.166	0.027	1.00
Night shifts	0	21	0	-	-	-
Nothing	80	43	89	<0.001	<0.001	<0.001

bed took second place. Reportedly, 43% of participants did not have any influencing factors to their sleep quality (Table 2).

FHWs fatigue and depression in study participants

The mean score of Pichot's Fatigue Scale was 4.18 (SD = 5.42). The maximum point was 19 and no one was considered as burned out according to this scale (>22 points). The mean value of each element scored varied from 0.33 to 0.65. The Pichot's Depression mean score was 2.54 (SD = 3.36). The highest point was 13 and only 13 subjects scored above 7 for fatigue, which indicated depression. The mean value of each element scored varied from 0.08 to 0.35. The two elements with the lowest mean scores were "feeling oneself at an impasse" and "making every effort" (mean scores: 0.08 and 0.09, respectively. The element with the highest score was "feeling sad" (mean score: 0.35).

Pichot's Fatigue mean score was lower in those who declared they slept enough (3.90, SD = 5.05) vs. those that did not (4.96, SD = 5.55), although it was not statistically significant ($p = 0.39$). Similarly, the Pichot's Depression mean scores in these two groups were also not statistically significant with a mean score of 2.31, SD = 3.04 and 3.19, SD = 4.14 ($p = 0.25$), respectively. The mean values for 3 participants with depression history were 10.67 (SD: 4.62; $p = 0.03$) for fatigue and 4.0 (SD: 5.29; $p = 0.45$) for depression scores.

FHWs fatigue and depression in the relation with sleep disorders

We compared the differences in the Pichot's scores within the sub-groups in the two following tables (Tables 3, 4). The fatigue scores decreased significantly in the group claiming short sleep latency. Most of the remaining score factors increased slightly, except for "snoring" and "observed sleep apnea." The factor that increased the depression score was anxious feeling ($p = 0.001$). Other significant factors were "short sleep latency," "observed sleep apnea," "tiredness, daily sleepiness" and "snoring".

TABLE 3 Sleep characteristics and Pichot's Fatigue score of study participants ($n = 100$).

Factors			*n*	Mean	SD	t	*p*
STOP items	Snoring	Yes	11	5.36	4.67	−0.77	0.02
		No	89	4.03	5.51		
	Tired / Daily sleepiness	Yes	44	3.73	5.39	0.74	0.46
		No	56	4.53	5.47		
	Observed (Sleep apnea)	Yes	19	6.74	6.05	−2.33	0.02
		No	81	3.58	5.12		
	Pressure (Hypertension)	Yes	1	8.00	-	-	-
STOP score (+)		Yes	6	5.67	5.24	−0.69	0.49
		No	94	4.08	5.44		
Other sleep characteristics	Fast to sleep	Yes	47	3.00	4.33	2.08	0.02
		No	53	5.23	6.08		
	Fragmented sleep	Yes	31	4.71	5.77	−0.65	0.51
		No	69	3.94	5.28		
	Morning headache	Yes	28	4.82	5.93	−0.74	0.46
		No	72	3.93	5.23		
	Cognitive impairment	Yes	39	4.28	4.79	−0.15	0.88
		No	61	4.11	5.82		
	Anxiety	Yes	30	4.53	5.30	−0.42	0.67
		No	70	4.03	5.50		
	Overweight	Yes	4	3.25	6.50	0.35	0.73
		No	96	4.22	5.40		

Discussion

The COVID-19 pandemic has put enormous pressure on the healthcare system globally, resulting in the establishment of many field hospitals and isolation camps throughout the world. This temporary solution, with no doubt, has led to the suspension of adequate environmental conditions for patients and for healthcare workers (11), subsequently increasing their risk for infection. Hence, in many articles, FHWs suffered from sleep disorders and mental health disabilities. In a study with renal healthcare practitioners during the COVID-19 social lockdown in Belfast, UK, 35.9 % participants developed severe levels of emotional exhaustion, 16.7% had severe levels of depersonalization, and 21.1% experienced low levels of personal accomplishment (12). A Mexican cross-sectional study reported that of the 507 interviewed healthcare workers, 70.02% were at risk of burnout (13). Furthermore, 57.31, 7.91, and 2.77% had a mild, moderate, and severe risk of post-traumatic stress disorder, respectively. Of the predominantly female population examined in this study, the most commonly affected individuals were female healthcare workers and those diagnosed with COVID-19 or exposed to a person infected with COVID-19 (13).

Surprisingly, no one in our study was classified as exhausted prior to the working period, during the working period, or during the isolation period according to the Pichot's Fatigue score. Our mean score was far lower than the cut-point of the scale (4.18, SD = 5.42 vs. 22). The majority of participants included in this study were identified as female students who were relatively young and in good health. Previous studies demonstrated that the prevalence of sleep problems increased among adolescents and among university students when compared with the general population (14). Furthermore, a study among FHWs in Saudi Arabia showed those with fewer years of experience had higher burnout symptoms (15). Based on this information, young age may not be concluded as the sole protective factor for healthcare workers and work conditions may serve as a more likely explanation. The COVID-19 outbreak happened in Vietnam later than most countries around the world, thus giving the country more time and experience to organize the field work in preparation for the virus. These findings serve as our hypotheses, but the lack of preparation and infrastructure to protect the public and healthcare practitioners might exert pressure on people and the healthcare system (16).

Within the items of Pichot's Depression scores, few participants admitted to "feeling oneself at an impasse" or "feeling drained." The most common complaint from participants was "sadness." Indeed, 13 cases were suspected of depression, including those from 3 participants that had previously been diagnosed with depression. In a cross-sectional, self-administered registry enrollment survey performed on US healthcare workers, 41% responded that they were experiencing burnout. In a study from 2021, participants were instructed

TABLE 4 Sleep characteristics and Pichot's Depression score of study participants ($n = 100$).

Factors			n	Mean	SD	t	*p*
STOP items	Snoring	Yes	11	4.27	4.43	−1.8	0.07
		No	89	2.32	3.17		
	Tired / Daily sleepiness	Yes	44	3.29	3.62	−2.02	0.04
		No	56	1.95	3.04		
	Observed (Sleep apnea)	Yes	19	4.16	4.40	−2.39	0.02
		No	81	2.16	2.97		
	Pressure (Hypertension)	Yes	1	0.00	-	-	-
STOP SCORE (+)		Yes	6	3.33	4.08	−0.59	0.55
		No	94	2.49	3.33		
Other sleep characteristics	Fast to sleep	Yes	47	1.59	2.13	2.73	0.01
		No	53	3.38	3.99		
	Fragmented sleep	Yes	31	2.74	3.29	−0.40	0.69
		No	69	2.45	3.41		
	Morning headache	Yes	28	3.43	3.83	−1.66	0.10
		No	72	2.19	3.12		
	Cognitive impairment	Yes	39	3.41	3.51	−2.10	0.04
		No	61	1.98	3.16		
	Anxiety	Yes	30	4.20	4.15	−3.40	0.001
		No	70	1.83	2.69		
	Overweight	Yes	4	3.25	5.25	−0.43	0.67
		No	96	2.51	3.29		

to respond to the questions on the survey based on the day before they were currently completing it. The results from the survey identified that 53% of participants reported feeling tired over most of the day, 51% felt feelings of stress, 41% had trouble sleeping, 38% experienced worry, 21% experienced sadness, 19% reported physical pain, and 15% felt feelings of anger (17). Another study on pharmacists revealed that 40% experienced more anxiety and 25% experienced more sadness and/or depression during the COVID-19 pandemic (18).

There was no significant difference between the mean scores of clinical suspected cases of obstructive sleep apnea (OSA) and the rest of the cases. However, while analyzing each STOP item, the Pichot's fatigue score was significantly significant for two symptoms of obstructive sleep apnea — "snoring" and "observed sleep apnea." These two symptoms also slightly increased the depression score. The STOP questionnaire that we used to classify the patients as high or low risk of having OSA was demonstrated to have a high combination of both sensitivity and specificity. Using the apnea-hypopnea index (AHI) with a score >5 as a cutoff value to evaluate it, the sensitivity was 65.6%, the specificity was 60.0%, the PPV (positive predictive value) was 78.4%, and the NPV (negative predictive value) was 44.0% (19). Hence, we suspect that the relationship between Pichot's scores and the STOP items were more so related to the participant's personal state rather than work conditions.

Another related factor to Pichot's scores was "fast to sleep." Short sleep-onset latency could be a symptom of tiredness, depression, or other sleep disorders. But falling asleep quickly at night is also necessary for health recovery (20). That is why "fast to sleep" appeared as a protective factor against tiredness and depression in our study. Feelings of anxiety and difficulty to recall memories were two of depression's symptoms. These two were also significantly related to Pichot's Depression score in our study, which confirmed our finding. The 13% supposed cases were relatively lower than other studies. Surveys on frontline health workers in China showed that depression symptoms accounted for 34.4% to 50.4 % participants (8, 21, 22). Another study of Rossi et al. (23) in Italy reported a lower rate with 24.7% (23). The result of another survey on 173 healthcare workers at 2 hospitals in Hanoi, Vietnam was also lower than overseas with the rate of depression symptoms being 20.2% (24).

There was also an increase in sleep difficulty and its severity during the working period at COVID-19 field hospitals. About two-thirds of subjects claimed insufficient sleep. The mean sleep-time decreases more than 2 h in comparison with their habitude. As a result, 44% of our participants suffered from tiredness or daily sleepiness due to the FHWs' work demand, especially those with shift work or night shifts. As already established, shift work and night shifts are very common in healthcare organizations worldwide. Here, healthcare professionals doing shift work and night shifts are

exposed to several stressors with psychological, social, physical, and sleeping consequences (25). Fortunately, these intensive work conditions didn't relate to our health workers' fatigue as our participants worked only in the field hospital for a short determinate period, however, we understand the importance of recognizing the burden shift work and night shifts place on the permanent practitioners in the hospitals.

The sleep conditions at field-hospitals are also important. Appropriate preparations to help FHWs feel safe at work whilst sleeping are not enough. Instead, basic sleeping conditions required for a good sleep such as the quality of the bed, light, and noise must be improved. It was proved that the evening light environment in hospitals can be designed to produce less disruptive effects on the circadian system and improve sleep (26). Fatigue and daily somnolence are frequently viewed because of non-restorative sleep (27). To prevent burnout, it is imperative to decrease the charge, ameliorate stress levels and to find strategies to promote personal recharge, especially restorative sleep. In our study, the two isolation weeks after working at field-hospitals take place during the restorative period. Our participants slept more and with a higher quality of sleep, than during and even before their work period. Even extending sleep duration does not always clearly correspond to reductions in daytime fatigue or improvements in mood (28). Nevertheless, providing healthcare workers with better control over their work schedules and opportunities for improved sleep may improve their job attitudes (29).

Finally, the present study has several limitations such as the absence of the control group and the skewness in the data due to the sample consisting of almost 90% female subjects and 94% of study subjects were last year students and graduated students from medical college. Therefore, the results of this study did not represent the spectrum of healthcare workers in Vietnam during COVID-19 pandemic. In addition, the mobilization of medical students, who did not have enough experience to participate in the care of patients contracting COVID-19, during the epidemic as assistants or working under supervision may not be as common elsewhere. The small sample size was also an additional limitation of the present study because it limits the analysis of the characteristic differences between sub-groups. Hence, similar studies with large and representative samples are necessary in the future to demonstrate the mental and sleep disorders of FHWs during a pandemic.

Conclusion

The majority of young volunteer healthcare workers have passed through the working period at COVID-19 field-hospitals with exhaustion and/or depressive mood. This problem might be due to poor quality sleep, sleep disorders' influence, or fatigue. Pre-established conditions such as appropriate work schedule, better sleep conditions, and mental health support for FHWs during the COVID-19 pandemic are crucial. Thus, the mandatory 2 weeks of isolation after working in field hospitals may provide the opportunity for FHWs' recovery.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB) of Vietnam Society of Sleep Medicine (VSSM-03.2021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SD-Q, ST-D, KB-D, DH-C-B, QV-T-T, and VN-N: conceptualization, validation, and writing—original draft preparation. SD-Q, ST-D, and VN-N: methodology and writing—review and editing. SD-Q, ST-D, and QV-T-T: Software. SD-Q, ST-D, KB-D, and DH-C-B: formal analysis. 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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A scoping review of mobile apps for sleep management: User needs and design considerations

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Sleep disorders are prevalent nowadays, leading to anxiety, depression, high blood pressure, and other health problems. Due to the proliferation of mobile devices and the development of communication technologies, mobile apps have become a popular way to deliver sleep disorder therapy or manage sleep. This scoping review aims to conduct a systematic investigation of mobile apps and technologies supporting sleep, including the essential functions of sleep apps, how they are used to improve sleep and the facilitators of and barriers to using apps among patients and other stakeholders. We searched articles (2010 to 2022) from Scopus, Web of Science, Science Direct, PubMed, and IEEE Xplore using the keyword sleep apps. In total, 1,650 peer-reviewed articles were screened, and 51 were selected for inclusion. The most frequently provided functions by the apps are sleep monitoring, measuring sleep, providing alarms, and recording sleep using a sleep diary. Several wearable devices have been used with mobile apps to record sleep duration and sleep problems. Facilitators and barriers to using apps were identified, along with the evidence-based design guidelines. Existing studies have proved the initial validation and efficiency of delivering sleep treatment by mobile apps; however, more research is needed to improve the performance of sleep apps and devise a way to utilize them as a therapy tool.

KEYWORDS

mobile apps, human computer interaction, sleep disorder, sleep management, sleep apnea

Introduction

Sleep is an essential biological need for human beings that will support us in getting resting, healing, and being ready for the next day. It is widely accepted that disturbed sleep is an influential factor leading to many mental health disorders. According to the Sleep Health Survey of Australian Adults (1), inadequate sleep has affected 33–45% of adults in Australia. Sleep disorders include short sleep duration, insomnia, snoring, sleep apnea, parasomnias, and restless leg syndrome. The treatment of sleep disorders varies, and some can be delivered online, such as Cognitive Behavioral Therapy for insomnia. With the development of technology, there are fewer barriers to accessing mobile phones, and we can establish mobile apps with many useful functions. Thus, mobile apps have become a popular tool for delivering sleep treatments. For example, with the microphone and sound sensor of the mobile phone, we can monitor people's breath while sleeping. It

is crucial to analyse the utilization of mobile apps to support sleep and further improve the quality of daily life.

Previous studies have already analyzed the validation and efficiency of sleep apps. For example, Baron et al. (2) conducted a scoping review of the use of consumer-targeted wearable and mobile technology. They found that most of the articles they reviewed focused on validation of sleep application, and there was a gap in interventions in more target populations such as patient populations (2). Shin et al. (3) stated that mobile phone interventions could attenuate sleep disorders and improve sleep quality. With a three-piece test set up by Stippig et al. (4), the result shows that most apps cannot distinguish and record snoring noises from various disturbing noises in real-life situations. Cajita et al. (5) also stated in their scoping review that the utility of wearable activity monitors in improving sleep needs more evidence to support it. An app review completed by Choi et al. (6) found that most sleep apps in the market cannot meet the quality, content, and functionality requirements to manage sleep by users. Therefore, guidelines are needed to improve the performance of sleep apps, and this paper aims to review the current apps to understand the research gaps and provide guidelines to design better sleep apps. We have conducted a scoping review of the articles published in 2010–2022 to understand the features of the sleep apps, user requirements and the design guidelines to improve those apps.

Methodology

We applied the scoping review methodology proposed by Arksey and O'Malley (7), which had been further improved by the methodology developed by the Joanna Briggs Institute (8).

Stage 1: Identifying the research questions

In this step, we reviewed previous research works and determined the gaps. The research questions are as follows:

1. What are the key functions of the current sleep apps?
2. What are the limitations of sleep apps?
3. What are the user requirements and design guidelines of sleep apps?

Stage 2: Identifying relevant studies

We used keywords such as sleep apps and sleep monitoring. To find relevant articles, we searched Scopus, Web of Science, Science Direct, PubMed, and IEEE Xplore. Only peer-reviewed articles written in English and published from 2010 to 2022 were considered.

Stage 3: Study selection: Inclusion and exclusion criteria

After exporting research results into Endnote and deleting the duplication, we screened the titles and abstracts of all these articles and removed those unrelated to our topic. The following inclusion criteria were followed: (1) Does the article involve a sleep app? (2) Does the article report the testing of a sleep app? and (3) Is the article written in English?

A full-text review was carried out for these references, and those only 51 articles were selected to extract data for analysis. More detailed information can be found in Figure 1.

Step 4: Charting the data

All included studies were reviewed and charted using a data extraction sheet. The details about the articles such as the country of publication, research method, year of publication, target group, target sleep issue, and the information about the functions provided by the sleep apps, the limitation and outstanding of sleep apps, the user requirement of the app and the design guidelines were extracted for analysis.

Stage 5: Collating, summarizing, and reporting the results

The filtered studies were analyzed, and the details were presented using tables and graphs.

Results and discussion

Overview of the studies

In total, 51 articles were included in the final review. Thirty-three percentage (17/51) of these publications come from the United States, 20% (10/51) from the UK, 12% (6/51) from China, 10% (5/51) from Canada, 8% (4/51) from Korea, 6% (3/51) from Ireland and 6% (3/51) from Austria. Thirty-one percentage (16/51) of the articles did not focus on one particular issue of sleep disorders or changing sleep habits. Only 20% (10/51) of them are related to apnoea issues, 12% (6/51) of them aimed to help people to develop healthy sleep habits, 22% (11/51) tried to treat insomnia and 12% (6/51) focused on recording sleep and wake detection. Two articles focused on sleep onset and utilized external stimuli to help people fall asleep faster.

Functions of the current sleep apps

Sixty-six percentage (34/51) articles have mentioned the monitoring functions of mobile sleep applications, indicating

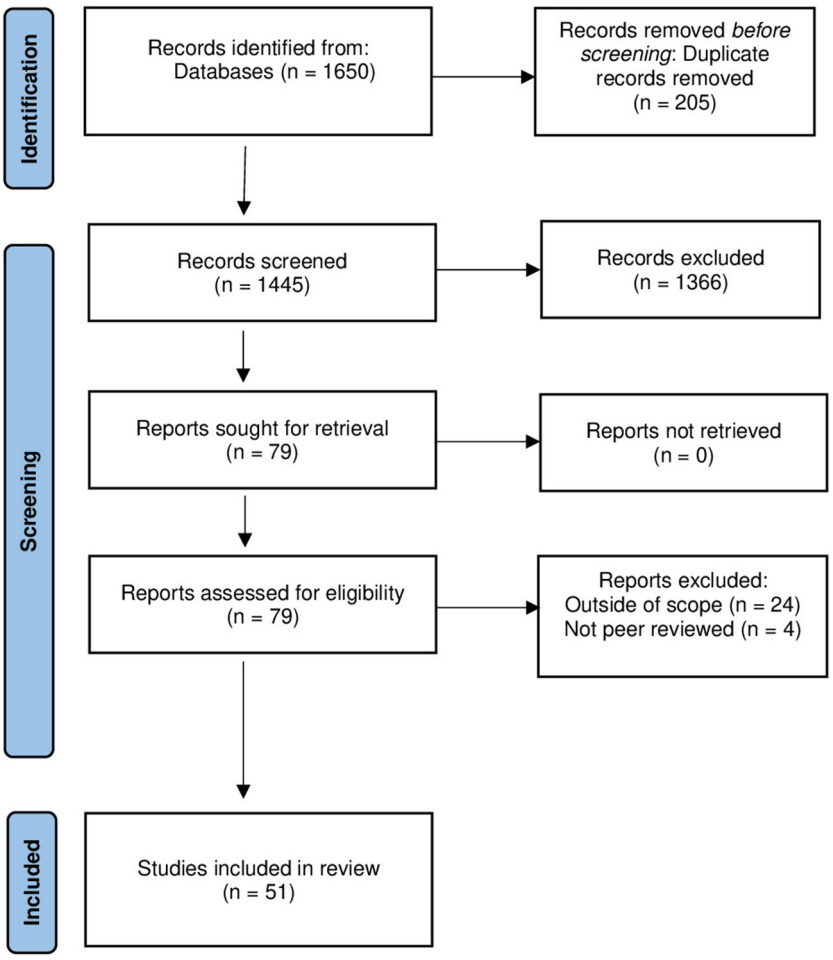

FIGURE 1
PRISMA diagram showing the article selection process.

that monitoring sleep is the most common function among the existing applications (9–11). Rönkkö (12) has connected mobile apps with an activity tracker; thus, the data collected by the external tracker can be transferred to the mobile app. The mobile app has several functions such as monitoring, reminding, alarm and goal setting. Validated smartphone apps can help detect sleep times and related sleep issues to support clinical treatment. Such a treatment can be provided by a smartphone app called UP! that is capable of accurately measuring sleep durations for individuals with bipolar disorder (13). Non-invasive sleep monitoring using Ballistocardiography (BCG) can help people wake up smoothly compared to Polysomnography (PSG) (14). In addition, a smartphone meditation app can help the prehypertensive population to measure sleep quality (15).

According to the data extracted from these 51 articles, an alarm is the second most frequent function. The concept of alarm in different apps can sometimes have different meanings. Firstly, it is the regular clock that users need to set a time in the app in advance, and then the app will start an alarm at that time. In this case, users determine the time when to awake. Some apps monitor users' sleep and measure light and deep sleep so that the app will awaken users in light sleep (16). In this case, the app will determine the time to awake users.

CBT-I Coach is a mobile application that delivers cognitive behavioral therapy for insomnia (17–19). These apps offer sleep diaries, education, alarm and relaxation exercise functions. The app enables insomnia patients to update their sleep prescription from CBT-I providers to the app, and then the app will help manage and remind users of their own needs, such as recommended bedtime and wake time. Users can also export their sleep diary for further usages, such as translation, to health professionals for treatment.

Several other apps have been developed to support people with insomnia. For instance, researchers developed a mobile app to deliver Sleep restriction therapy (SRT) for people with insomnia (20). Another mobile app called "MIND MORE" can help with the self-management of insomnia (21). Similar to

"MIND MORE," "Insomnia Coach" app helps people to self-manage insomnia (22). KANOPEE app provides behavioral intervention for individuals with insomnia symptoms through an interaction with a virtual agent (23). This app provides more benefit than an electronic sleep diary to support people with insomnia.

Sleep quality and quantity are two factors for measuring sleep. Most mobile apps are implemented by consumer sleep tracking devices to collect and utilize data to measure users' sleep quality and quantity (24). The measurement accuracy of these tracking devices and mobile apps is always low compared to traditional polysomnography, the gold standard for sleep assessment. The current technology cannot support mobile apps as accurate as polysomnography; however, it can be a suitable replacement because of its high cost and low convenience (25). Researchers have developed an EarlySense contact-free sensor and smartphone app to collect vital signs and analyse sleep patterns (26). Validation of the EarlySense sensor showed accuracy in detecting sleep and wake states relative to the gold standard polysomnography.

Sleep disorder detection is one crucial function provided by mobile apps (27). Disorders in the early stage are much easier to be treated than later. Tseng et al. (28) and Behar et al. (29) developed an intelligent mobile app to screen users and detect obstructive sleep apnoea patients. The SleepAp (29) uses signal processing and machine learning algorithm to screen for obstructive sleep apnoea at a negligible cost. Researchers also developed a smartphone app called "Firefly" to measure obstructive sleep apnoea (30). The app is reliable and accurate in detecting obstructive sleep apnoea compared to polysomnography.

With the internet, mobile apps can enable users in the same community and share information and data. Being in the community can be achieved within users and also external identities. Users can share their sleep goals and get competed in the app presented by Rönkkö (12), and they can also export the data from mobile apps and transfer it by a network to other individuals such as health care providers (18).

Limitations of sleep apps

The most significant limitation of sleep apps is the accuracy to monitor sleep ($n = 5$). Mansukhani and Kolla (31) evaluated the major shortcoming and limited utility of sleep apps in the clinical population. They concluded that sleep data gathered from tracking devices are less reliable in patients with insomnia and fragmented sleep problems. The tracking devices accommodated with sleep apps could not distinguish various sleep stages in different users (31). Several smartphone applications were developed for sleep–wake detection through sound and movement sensors (32). While comparing the performance of the apps, the sleep wake detection was found not sufficiently reliable compared with polysomnography. Wearable devices have been used with a mobile app to record sleep; however, they have shortcomings in measuring sleep problems (33). For instance, ActiGraph wGT3X-BT accelerometers have been used with the SleepBot app for people with schizophrenia to measure sedentary behavior and sleep. It was observed that the app's measure of sleep was inaccurate. Smartphone applications and associated wearable sleep tracking devices have limitations in detecting sleep durations, efficiency, and sleep cycle detection sleep compared to polysomnography (PSG) (34). Therefore, to improve the accuracy of sleep predictions, researchers suggest combining actigraphy-based sleep detection by using the data from movement sensors with the use of technology detected by smartphones (35).

The issue of poor sleep cycle detection by smart phone app has been reported in Bhat et al. (36) and the results suggest that current sleep apps need to have improved accuracy to be used as potential clinical utility tool.

While mobile apps collect and manage users' sleep data, the privacy of the data becomes a common concern. Leigh et al. (37) assessed the quality of apps designed for chronic insomnia disorders from the Android Google Play Store and evaluated their risk along with the privacy policy. Fino et al. (32) compared the performance of four existing sleep apps with polysomnography. The result showed that none of these four apps could detect rapid eye movement sleep, and the overall performance of sleep apps was worse than polysomnography. Short battery life is also a limitation of sleep apps, especially for those accommodated with small sensor devices (38).

User requirements and design approaches to improve the performance of sleep apps

Different user populations will have different characteristics regarding sleep, and each individual will further require unique demands from sleep apps. User-centered design is an efficient approach to developing clinical applications proved by Luna et al. (39) and McCurdie et al. (40). Aji et al. (41) applied a mixed-method study to explore and determine the end users' requirements and preferences for sleep applications. Users prefer the free app so that they can make a long-term commitment. Personalisation is an essential requirement for users to sleep apps. Nguyen (42) presented an approach to personalizing smart apps by personality traits and chorotype. Users are more likely to choose an app that provides a privacy policy with a high-security level (28).

Mobile apps can be used to support healthy sleep habits. Grigsby-Toussaint et al. (43) examined 35 apps and found that only a few apps included features to change behavior.

TABLE 1 Some key features of sleep apps and design considerations.

Sleep app features	Frequency	App design considerations	Frequency
Sharing information: being part of a social community	4	Personalisation	4
Instant feedback	4	Simple device	2
Education	3	Evidence-based	10
Monitor	34	Theory-based	6
Alarm	5	Low cost	1
Relaxation exercises	3	Accessible format	1
Measure sleep	6	Easy to use	2
Diary	5	Engagement	5
Sleep disorder screen	5	User control	1
Recommend ideal sleep time	2	User centered	3
Sleep–wake detection	2	Social connectedness	4

Theory-based, evidence-based and user-based are the three approaches to develop sleep apps as observed in those articles. Antezana et al. (44) evaluated thirty existing apps for physical activity, diet and sleep and determined whether they had followed theory-based behavior change techniques. All the 30 apps included at least one behavior change technique (BCT) in their design, and the most frequently used ones were goal setting and feedback.

User-centered is one of the basic design method for developing sleep apps (41). The preferences and social and cultural contextual factors of target populations should be considered when designing sleep apps (45). Evidence-based principles are also frequently included in app designs (46). Users preferred the apps that provide sleep tips based on empirical evidence (47). Personalized feedback (48), connection to other apps and multifunctional (49), and engaging content and easy-to-follow format (46) are some other design guidelines included in the articles. To engage the users, the app's content can be more interactive, such as a virtual pet (50).

The apps that automatically track sleep should enable users to edit the records manually, let the users take control of their data, and enable them to export the data (6). Hosszu et al. (51) stated that sleep apps should connect users with medical professionals and consider ethical issues when designing. Shin et al. (3) and Fino and Mazzetti (52) also suggested developing apps following design guidelines that are evidence-based and include behavior change techniques. Table 1 summarizes the key features of sleep apps and design considerations found in our included studies.

Conclusion

Mobile apps have become a popular way to support sleep, and many such apps exist in the market. The most frequently provided functions by the apps are sleep monitoring, measuring sleep, providing alarms, and recording sleep using a sleep diary. There is a lack of apps that support active medical therapy. Therefore, the role of sleep apps in supporting sleep disorder treatments still needs further investigation. Easy-to-use, low-cost, simple device, mobility and flexibility features make the sleep apps an excellent choice to support sleep. However, current sleep apps have some limitations, such as accuracy, privacy and security issues, short battery life and information quality. Frequently reported design guidelines for developing sleep apps are user-centered, evidence-based, theory-based, engagement, feedback, accessible format and social connectedness. We did not find much information about the user requirements of sleep apps for different populations. Future research is needed to determine the user requirements for diverse populations.

Author contributions

AA and OM conceived and designed the review. JW collected data and conducted the initial analysis with the help of AA. JW and AA wrote the manuscript, which was reviewed, and revised by OM. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

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The mobile sleep medicine model in neurologic practice: Rationale and application

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Background: Undiagnosed obstructive sleep apnea (OSA) is prevalent in neurological practice and significantly contributes to morbidity and mortality. OSA is prevalent in US adults and causes poor quality sleep and significant neurocognitive, cardiovascular, and cerebrovascular impairments. Timely treatment of OSA reduces cardio-cerebrovascular risks and improves quality of life. However, most of the US population has limited systematic access to sleep medicine care despite its clinical significance.

Focus: We discuss the importance of systematic screening, testing, and best-practice management of OSA and hypoventilation/hypoxemia syndromes (HHS) in patients with stroke, neurocognitive impairment, and neuromuscular conditions. This review aims to introduce and describe a novel integrated Mobile Sleep Medicine (iMSM) care model and provide the rationale for using an iMSM in general neurological practice to assist with systematic screening, testing and best-practice management of OSA, HHS, and potentially other sleep conditions.

Key points: The iMSM is an innovative, patient-centered, clinical outcome-based program that uses a Mobile Sleep Medicine Unit—a "sleep lab on wheels"—designed to improve access to OSA management and sleep care at all levels of health care system. The protocol for the iMSM care model includes three levels of operations to provide effective and efficient OSA screening, timely testing/treatment plans, and coordination of further sleep medicine care follow-up. The iMSM care model prioritizes effective, efficient, and patient-centered sleep medicine care; therefore, all parties and segments of care that receive and provide clinical sleep medicine services may benefit from adopting this innovative approach.

KEYWORDS

stroke, neuromuscular conditions, ambulatory sleep testing, home sleep apnea test (HSAT), screening, mobile sleep medicine, sleep-disordered breathing, cognitive impairment

Introduction

Undiagnosed and untreated sleep-related breathing disorders (SDB) are prevalent in neurological practice and contribute significantly to the development of morbidity and mortality (1–10). In the US, 70% of adults report obtaining insufficient/"unprotected" sleep at least one night a month, and 11% report obtaining insufficient sleep every night. Sleep-related problems are estimated to affect 50–70 million Americans of all ages and socioeconomic classes (11, 12).

Approximately 25 million US adults suffer from obstructive sleep apnea (OSA)—a leading sleep-disruptive force that breaks down sleep protection and causes insufficient sleep, significant neurocognitive, cardiovascular, and cerebrovascular (CCV) impairments in humans (13). The timely treatment of OSA with positive airway pressure (PAP) therapy protects human sleep, reduces cardio-cerebrovascular risks and improves the quality of human life (4–10, 14).

Currently, 80% of the general US population and about 36 million annually hospitalized patients have limited systematic access to sleep medicine care despite alarming statistics affirming the significant prevalence of OSA in vulnerable populations.

While the prevalence of OSA in an unselected adult population is generally estimated at ∼5% (4, 15, 16), the prevalence of OSA in some medical and neurological populations is significantly elevated, ranging from 10 to 82% in patients with epilepsy (1–3), from 50 to 94% in patients with stroke and transient ischemic attack (TIA) (4–10), from 11 to 82% in patients with arterial hypertension (HTN) (17, 18), from 30 to 40% in patients with the acute coronary syndrome (ACS) and myocardial infarction (MI) (4, 14), from 3 to 49% in patients with atrial fibrillation (19–22), from 10 to 43% in patients with congestive heart failure (CHF) (4, 23–25), 23% in patients with traumatic brain injury (TBI) (26), from 21 to 38% in patients with multiple sclerosis (MS) (27, 28), from 20 to 56% in patients with Parkinson's disease (PD) (29–34), 40% in patients with Alzheimer's dementia (35), from 11 to 36% in patients with neuromuscular conditions (36), and 17 to 76% in patients with amyotrophic lateral sclerosis (ALS) (37, 38).

Timely delivered PAP therapy appears to have beneficial effects on patients with OSA in the general population (39, 40), ischemic stroke and TIA (41–43), epilepsy (44–46), HTN ACS/MI (47–50), atrial fibrillation (51–53), CHF (54–56), TBI (26), multiple sclerosis (27), PD (57), Alzheimer's dementia (35, 58–60) and neuromuscular conditions (61, 62), and ALS (16, 62–65).

Timely delivered non-invasive airway pressure therapy (NIPAP) appears to produce beneficial effects on patients with sleep-related hypoventilation/hypoxemia syndromes (HHS) in neuromuscular disorders (61, 62), obesity hypoventilation (66), and ALS (16, 62–65).

The goals of this review are to (1) introduce and describe a novel, integrated Mobile Sleep Medicine care model (iMSM); (2) provide the rationale for the implementation of iMSM in general neurological practice to assist with systematic screening, testing, and the best-practice management of the most common SDB (OSA and HHS) in patients with stroke, neurocognitive impairment, and neuromuscular conditions (67).

The rationale for implementation of iMSM in general neurological practice

Here, we discuss the importance of systematic screening, testing, and best-practice management for OSA and HHS in patients with (1) stroke, (2) neurocognitive impairment, and (3) neuromuscular conditions.

Sleep-disordered breathing in patients with stroke

OSA causes intermittent pauses in breathing (apneas) during sleep, exposing the cardiovascular system to recurrent physiological stressors that activate the sympathetic nervous system, raise blood pressure, and impair vascular endothelial function (68). Such physiological alterations closely link OSA with vascular disease, and OSA is an independent risk factor for HTN (69), atrial fibrillation (70), MI (71), stroke (72), and mortality (73).

OSA is prevalent after stroke/TIA

OSA occurs in more than 70% of stroke/TIA survivors (6), and even 3 years after stroke, the prevalence of OSA remains just as high (74), suggesting that screening for OSA at any point after a cerebrovascular event may provide clinical benefit. Rates of OSA do not vary according to the method of detection used (e.g., polysomnography vs. portable sleep equipment) (6).

OSA negatively impacts outcomes post-stroke

Left untreated, moderate-to-severe post-stroke OSA garners a three-fold increase in mortality (41) and a five-fold increase in recurrent vascular events (75). Moreover, a diagnosis of OSA is an independent predictor of worse functional outcomes at hospital discharge (76, 77) and is associated with longer hospitalization in the rehabilitation setting (78).

Post-stroke treatment of OSA improves outcomes

Treatment of post-stroke OSA using continuous positive airway pressure (CPAP) in randomized trials has been shown to improve functional, and motor outcomes (79–84), increase

quality of life (85), reduce daytime sleepiness (81, 85), improve mood (86), and enhance cognition (59, 87). In observational studies, compliance with CPAP has been shown to reduce incident vascular events (75) and mortality (41). Outside the stroke/TIA setting, RCTs have demonstrated beneficial effects of CPAP for blood pressure (88) and lipid control (89).

Clinicians do not routinely screen for OSA after stroke or TIA

Despite its high prevalence and detrimental effect on health, OSA remains underdiagnosed and undertreated after stroke/TIA (90). Detection of OSA after stroke/TIA is challenging because OSA presents atypically in patients with cerebrovascular disease (e.g., the absence of excessive daytime sleepiness or obesity) (91, 92), not surprisingly, stroke clinicians infrequently refer patients for sleep-related investigations (90). Since commonly used screening questionnaires show poor correlations with polysomnography findings in stroke patients (93), objective measures are best suited to accurately diagnose OSA.

In traditional sleep medicine testing model the lack of availability of in-laboratory polysomnography ("Gold Standard") is a major barrier to efficiency screening for OSA in hospital settings

Technologist-monitored, in-laboratory sleep studies (polysomnography or PSG) are the "Gold Standard" for diagnosing OSA, but limited availability of polysomnography and lengthy wait times frequently prohibit timely evaluations (90, 94). In addition, some patients are unwilling to spend a night in a sleep laboratory. Finally, polysomnography involves costly equipment, an on-site technologist, and high healthcare expenditures.

OSA can be accurately detected using a simple, portable sleep monitoring ("Silver Standard")

These devices are much less expensive, more accessible, and more convenient and demonstrate good diagnostic performance compared with in-laboratory polysomnography in adult patients with a high pretest probability of moderate to severe obstructive sleep apnea (e.g., the post-stroke/TIA population) (95, 96).

Home/hospital sleep apnea testing (HSAT; "Silver Standard") has been shown to improve outcomes after stroke/TIA

In a randomized controlled trial involving 250 consecutively recruited stroke/TIA patients, patients were randomized to undergo home/hospital sleep apnea testing (HSAT) vs. in-laboratory polysomnography. Those randomized to HSAT had higher rates of OSA diagnosis and treatment, reduced daytime sleepiness, and improved functional outcomes. Moreover, a cost-effectiveness analysis, including the cost of initial diagnostic tests, broken/lost equipment, etc., revealed that HSAT was economically attractive for detecting OSA compared with in-laboratory sleep testing (97). Overall, this study suggested that ambulatory "Silver Standard" approach to sleep testing may improve clinical outcomes in stroke/TIA patients. The cost-effectiveness of an ambulatory "Silver Standard" approach to sleep testing *via* the mobile sleep unit would likely extend to other clinical populations at high risk for OSA.

Sleep disorder breathing in Alzheimer's disease/dementia

Cognitive impairment has a devastating impact on society

Approximately 747,000 Canadians live with Alzheimer's disease or another form of dementia (98), and the associated care costs ~$33 billion annually (98). **Alzheimer's disease (AD)** is the leading cause of dementia worldwide (99). **Vascular cognitive impairment (VCI)** is the clinical syndrome in which cognitive impairment, encompassing mild cognitive impairment and dementia, can be attributed to vascular disease such as clinically overt stroke and/or silent brain infarction (100, 101). Vascular brain injury accounts for up to 33% of dementia risk according to autopsy studies (102) and frequently co-exists with AD (103), making VCI a significant public health issue (101). **Mild cognitive impairment (MCI)** causes cognitive problems that do not interfere with everyday life. However, amnestic MCI increases the risk of developing AD (98).

OSA is closely linked with AD and VCI

OSA gives rise to physiological alterations that contribute to the cognitive impairment seen in both AD and VCI, such as transient sympathetic activation, systemic inflammation, endothelial dysfunction in the vasculature of the brain (104), and impaired sleep-dependent memory consolidation through sleep fragmentation (105). Sleep fragmentation from OSA can also lead to impaired glymphatic and vascular drainage of amyloid (106, 107), which is postulated to contribute to the development of AD (108). Furthermore, OSA is strongly associated with cerebrovascular disease and is an independent risk factor for high blood pressure (69), overt (73), and covert stroke (109).

OSA is an independent risk factor for AD, VCI, and MCI

In elderly patients without dementia at baseline, the presence of OSA is an independent risk factor for the development of MCI or dementia (110), and a meta-analysis suggested that OSA is an important modifiable risk factor for dementia

and other cognitive impairment (111). Furthermore, given the close association of neurodegeneration with vascular disease, treatment of OSA—a well-established vascular risk factor (68)—may also have important implications for brain health even beyond the potentially beneficial effects on cognition and daily function.

Obstructive sleep apnea is prevalent in AD/VCI

More than 70% of patients with VCI endorse symptoms consistent with OSA (112). Moreover, prior work has demonstrated that nearly 90% of patients with Alzheimer's disease have obstructive sleep apnea when objectively tested (113). Again, rates of OSA do not vary with the method of detection (i.e. "Gold Standard" vs. "Silver Standard") (6).

Treatment of OSA using CPAP improves cognition

OSA is treated with CPAP, which provides mild air pressure to maintain airway patency during sleep. A review of five systematic reviews and meta-analyses concluded that treatment with CPAP improved attention/vigilance, executive dysfunction, memory, and global cognitive functioning in non-demented individuals (114). A more recent systematic review demonstrated a protective effect that treatment with CPAP has on MCI and AD incidence (115). Several studies have suggested that treating OSA using CPAP in AD patients may slow the rate of cognitive decline (58, 59, 116). In the only randomized controlled trial examining subjects with VCI and OSA, CPAP-treated patients showed improved attention and executive functioning compared to controls who did not receive CPAP (87).

Clinicians do not routinely screen for OSA in patients with AD/VCI

Despite its high prevalence and negative impact on cognition, OSA remains underdiagnosed and undertreated.

Use of polysomnography within traditional sleep medicine testing model is associated with many barriers

Technologist-monitored, overnight, level 1 PSG ("**Gold Standard**") is the current standard tool for diagnosing sleep disorders, but high costs, lengthy wait times, and patient unwillingness to spend a night in a sleep laboratory frequently prohibit timely assessments (117). Moreover, the traditional sleep medicine testing model is particularly inconvenient for patients with cognitive impairment, who may depend on others for care and may require a familiar environment to sleep and avoid delirium.

HSAT ("Silver Standard"), has been extensively validated against in-laboratory PSG for detecting obstructive sleep apnea (95, 96, 118). In addition, an unattended sleep study ("**Silver Standard**") may be potentially less expensive and more accessible.

HSAT is feasible for use in patients with AD/MCI

Our prior work has demonstrated that the use of unattended sleep study ("**Silver Standard**") is feasible in patients with AD/MCI/VCI; >85% of patients who attempted to use unattended sleep study ("**Silver Standard**") were able to obtain analyzable data (119).

Sleep-disordered breathing in neuromuscular disorders

In patients with progressive neuromuscular disease (NMD), respiratory failure caused by respiratory muscle weakness is the most common cause of death. Respiratory muscle weakness, changes in chest wall mechanics, and difficulty with airway secretion clearance leads to ineffective alveolar ventilation and both acute and chronic respiratory failure (120).

Physiological change in sleep

During sleep, minute ventilation decreases, muscle activity alters, respiratory workload increases (121), ventilatory response to hypoxemia and hypercapnia declines (122), and upper airway resistance increases (123). In REM sleep, skeletal muscle tone is abolished, while the diaphragm is relatively spared (121). Patients with NMD cannot compensate for physiological changes in sleep, and inadequate alveolar ventilation may first occur during REM sleep. As the disease progresses, hypoventilation may extend to non-REM sleep, and eventually, daytime hypercapnia may occur.

Prevalence of SDB

The prevalence of SDB is high in most NMDs, and chronic respiratory failure occurs with disease progression. A prior study using a home PSG sleep study without CO_2 monitoring showed a high prevalence of SDB in a group of chronic neuromuscular disorders. The prevalence of SDB with respiratory disturbance index (RDI) >15/h was 42%, higher than the general population. Respiratory events were primarily hypopneas, and 23% of patients had nocturnal hypoxemia (124). Patients with NMD usually have a normal ventilatory drive (125). Using EMG to monitor the activity of respiratory muscles during PSG in patients with NMD revealed that hypopneas that happened in REM sleep were mostly "central" in nature due to reduced muscle activity, and that nocturnal hypoxemia was

inversely correlated with diaphragm strength (126). Studies have confirmed that nocturnal hypoxemia and hypercapnia in REM sleep are common in patients with NMD (127, 128).

Non-invasive ventilation (NIV) significantly benefits the quality of life, survival, and respiratory status in different NMD types

Studies have provided evidence that NIV significantly prolonged survival in patients with ALS (129–132). Early initiation of NIV slowed the rate of forced vital capacity (FVC) decline (131) and improved survival (131, 133). Berlowitz et al. found survival benefits of 11–15.5 months in both bulbar and non-bulbar ALS patients (129). Using NIV $\geq$4 h were associated with longer survival for patients with ALS (134). NIV was well-tolerated and may improve quality of life and survival in patients with Duchenne muscular dystrophy (DMD) (135, 136) and SMA (137).

Polysomnography (PSG) with capnometry ("Gold Standard") plays a role in determining the nature and severity of SDB in NMD

SDB in NMD patients includes pseudo-central or diaphragmatic SDB, central sleep apnea, obstructive sleep apnea, nocturnal hypoxemia, and hypoventilation in sleep. Non-invasive ventilation is indicated at the first sign of hypoventilation. A sleep study should be considered with at least one symptom and/or sign related to respiratory muscle weakness such as dyspnea, tachypnea, orthopnea, disturbed sleep, morning headaches, accessory muscle use at rest, paradoxical breathing, daytime fatigue, or daytime sleepiness (ESS > 9) (138). A PSG ("**Gold Standard**") can evaluate respiratory muscle weakness during sleep and confirm the need for NIV. The absence of nocturnal hypoxemia does not exclude nocturnal hypercapnia. Nocturnal hypercapnia predicts impending daytime hypercapnia and is an indicator for nocturnal NIV before daytime hypercapnia occurs (139).

Scoring respiratory events during sleep in patients with NMD requires specific expertise. Patients with NMD usually present a decrease in airflow and respiratory effort with or without a reduction in pulse oximetry (SpO_2). These events may be associated with increased transcutaneous carbon dioxide ($TcCO_2$). Paradoxical breathing may result from respiratory muscle weakness and should not be interpreted as "obstructive events" (126). Periods of "reduced ventilation" or paradoxical breathing, especially during REM sleep, justify the initiation of NIV in patients with NMD (139).

According to the 2017 AASM guidelines, an unattended sleep study ("**Silver Standard**") is not recommended in adults with NMD or known or suspected hypoventilation (140). However, as technology advances, "Silver Standard" sleep study devices that can accurately determine sleep stages plus capnography may be used to evaluate SDB in patients with NMD. The integrated Mobile Sleep Medicine Unit is designed to overcome the shortcomings of the traditional sleep medicine testing model and can deliver the entire spectrum of sleep testing to individuals with NMD. The iMSM includes sleep testing and PAP titration technology, which can be delivered to all levels of patient care from hospital to home, under the supervision of a board-certified sleep medicine physician. It means that we can deliver the Mobile Sleep Unit with portable PSG, capnography, and PAP titration directly to a patient's home and provide virtual monitoring for ventilators if necessary.

In-lab titration of NIV by PSG is not required but recommended by AASM before initiating NIV to identify optimal settings, reduce patient-ventilator asynchrony and improve treatment tolerance

Guidelines to initiate ventilation in NMD defined in 1999 include the presence of symptomatic daytime hypercapnia ($PaCO_2 \geq 45$ mmHg), nocturnal desaturation ($SpO_2 \leq 88\%$ for 5 consecutive minutes), MIP < -60 cmH_2O, or FVC $< 50\%$ predicted (141). Commonly used NIV modes include Bilevel PAP with a backup rate (BPAP ST), or volume assured pressure support (VAPS) (66). Titration of non-invasive ventilation by attended polysomnography is the gold standard to identify effective parameters to correct SDB, including hypoventilation as well as central, pseudo-central, and obstructive sleep apnea. Patient-ventilator desynchrony may include ineffective effort, triggering asynchrony, cycling asynchrony, etc (142, 143). An in-lab titration of NIV by polysomnography study may improve patients' NIV treatment tolerance by observing and reducing patient-ventilator asynchrony (142).

The AASM consensus in 2010 non-invasive positive pressure ventilation (NPPV) titration with PSG to determine an effective level of nocturnal ventilatory support in patients with chronic alveolar hypoventilation. If the patient is started on NPPV empirically, a PSG would be considered necessary to confirm that the final settings are effective and to identify desynchronization or arousals from leaks (144).

However, logistic issues prevent attended sleep studies from being utilized in patients with NMD. These issues include long wait times, mobility, transportation, lift use, insurance coverage, etc.

Telemonitoring is one of the most revolutionary changes in home-assisted ventilation

Evidence is emerging that telehealth provides timely and cost-effective support for an individual with motor neuron disease (MND). Respiratory assist devices (RAD) and portable home ventilators transmit patient usage and home ventilation machines' efficacy data to a cloud-based platform *via* wireless networks. These enable physicians to access efficacy data updated daily *via* a cloud-based platform

to provide personalized ventilation machine management at home and individualized care. Physicians may view breath-by-breath waveforms, trends in clinical data, and precise therapy values over periods of days, weeks, and months within 1 to 24-h windows.

Through telemonitoring, physicians can monitor disease progression, titrate modes and settings in a monitored environment and in a stepwise fashion, depending on the patient's symptoms and tolerance. In addition to optimizing device function, clinicians can quickly identify and troubleshoot ventilation issues.

Studies have shown that patients with ALS can be well-managed at home *via* telemonitoring. Benefits of telemonitoring include reduced ED visits and hospital admissions, increased survival, and improved functional status in patients with ALS (145, 146).

The integrated mobile sleep medicine care model

The integrated **Mobile Sleep Medicine Care Model (iMSM)** is an innovative, progressive, patient-centered, integrative, complete cycle, clinical-outcome-based program that uses a Mobile Sleep Medicine Unit as a methodological tool—a "sleep lab on wheels"—designed to improve systematic access to OSA management and sleep care for approximately 80% of Americans at all healthcare levels, from hospital to home (67).

The protocol for the iMSM delivery model includes three levels of operations (see Figure 1):

1) Screening.
2) Testing/Treatment.
3) Follow-up.

Components of the mobile sleep medicine unit

- *Module 1.* "Gold Standard": Mobile Polysomnography (mPSG).
- *Module 2.* "Silver Standard": Portable Out-of-Center Sleep Testing (OCST) (Nox-T3, Embletta, Stardust, ApneaLink Air, MediByte Jr, Alice, Cerebra Sleep System, BresoDx, etc.).
  - Synonyms:
    - Cardiopulmonary studies (CP).
    - hospital/home sleep ambulatory testing (HSAT).
    - (OCST) = (CP) = HSAT.
- *Module 3.* PAP titration unit: CPAP/BiPAP/AVAPS/ASV.

Mobile Sleep Unit—"sleep lab on wheels"—is a technological, methodological tool designed to deliver sleep medicine evaluation directly to the patient's bedside. The mobile sleep unit assembles with three functional technological modules representing modern sleep technology, which is the standard of care in the sleep medicine (67).

Mobile sleep medicine unit

Module 1: "Gold Standard": Mobile PSG-attended type 1 sleep testing device.

- Mobility and portability: Full sleep lab service delivered directly to the patient's bedside, either inside the hospital or at the patient's place of residence.

Module 2: "Silver Standard": Unattended type 3 sleep testing device named in sleep literature (detailed above).

- Mobility and portability: Type 3 (four channels) sleep lab service is delivered directly to the patient's bedside, either inside the hospital or at the patient's place of residence, with an average set-up time of 5–10 mins.

Module 3: PAP titration unit: CPAP/BiPAP/AVAPS/ASV: Provides titration sleep study "on the spot."

- Used for PAP titration in combination with Module 1/mobile PSG ("Gold Standard") to perform mobile-attended PSG/Split or/PAP titration studies.

Cost: Vertical integration payment system (VIPS) model

Designed to obtain collections from sleep-related operations performed at each level of care from hospital to sleep lab/home:

1) Technical charges and professional charges will be collected based on appropriate CTP codes for the type of study performed.
2) Sleep studies (unattended and attended).
3) Clinical in-patient sleep consults and outpatient sleep clinical visits.
   a. Collections from each level will be combined to 100% and directed to support mobile sleep unit operations from hospital to home.
   b. The sources of reimbursement obtained from each level of care.

a) *Acute hospital level of care*

   i. Screening/evaluation for SDB will bring up diagnosis-related group reimbursement based on the following.

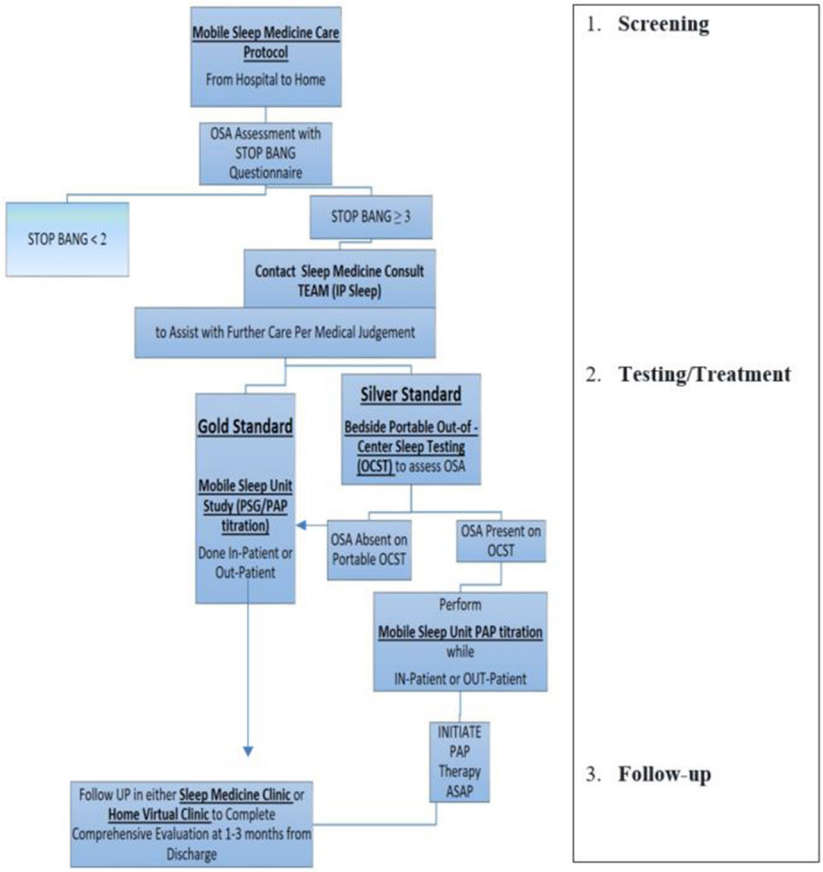

FIGURE 1
Example of mobile sleep medicine care protocol. (1) *Screening:* Designed to provide effective and efficient SDB screening for patients admitted to hospital (or any other health care facility, e.g., rehab, specialty/subspecialty clinic, etc.), including patients with a high risk of CCV (stroke, MI, CHF, atrial fibrillation, hypertension, preeclampsia, etc.). After completing SDB screening either in-person, *via* EMR, or *via* Tele-Virtual/My Chart system, the Primary Team communicates with the Mobile Sleep Medicine Team/ in-patient Sleep Medicine Consulting Team (IP Sleep) to request sleep consultation for further management. (2) *Testing/Treatment:* The board-certified sleep medicine physician from the integrated mobile sleep medicine Team will discuss the sleep study results with patients and coordinate further management. Designed to deliver timely sleep medicine expertise to patients who screen positive for OSA. The IP sleep/mobile sleep medicine team evaluates patients and develops the diagnostic and treatment plan using mobile sleep unit technology. (3) *Follow-up:* IP sleep/mobile sleep medicine team coordinates further sleep medicine care in a sleep clinic, sleep lab, home health, and virtual telemedicine health. https://d11tooehygcg9z.cloudfront.net/My.AASM/AgentsOfChange/587417.pdf; https://aasm.org/winners-of-inaugural-change-agents-competition-propose-new-approaches-for-sleep-apnea-care.

ii. Elevated complexity of comorbidities rule and increased case mix index.
iii. Improvement of hospital performance statistics due to a significant reduction in readmission rates in sensitive CCV population (CHF, chronic respiratory failure, obesity, hypoventilation, stroke, atrial fibrillation, MI, hypertension, seizure disorders, myasthenia gravis, ALS, etc.). All admitted patients in the CCV population are at high risk for SDB and should be evaluated by the inpatient mobile sleep medicine team (IP Sleep Team). The IP sleep team would decide the appropriate delivery (i.e., Gold vs. Silver Standard) for a given patient based on local standards of care and the availability of devices in the community. The mobile sleep medicine model provides flexibility in diagnosing and delivering necessary sleep care without delay.
iv. 1–33% of collections from each level will be directed to support mobile sleep unit operations from hospital to home. These are approximate, proposed figures, which can be modified based on local administrative protocols for utilization of services. Each given IP sleep team would choose its own proportion of collections to fit its needs for sustained clinical operations and to make the service self-sufficient based on local finances, insurance coverage, administrative support, grants, etc.

b) *Sleep lab/sleep center:* Sleep medicine referrals from inpatient sleep medicine consulting service (IP sleep):

- Will boost the sleep referral base to the internal sleep lab/center by about 1,300 patients per year (5 consults per day × 5 days per week × 52 weeks).
- Will prevent "referral leaks" to external systems and maintain the integrity of collections.
- 1–33% of collections from each level will be directed to support Mobile Sleep Unit Operations from hospital to home.

c) *Home health integration:* Patient-centered, unattended, or/and attended sleep studies will be conducted at the patient's residence (house, rehab, nursing home, etc.) and achieve the following:

- Integrate mobile sleep medicine care into the home health care model.
- Reduce the operational costs by 50% with a flexible technician: patient ratio (from 1:3 to 1:10) for unattended studies with strong reimbursement for each study performed.
- 1–33% of collections from each level will be directed to support mobile sleep unit operations from hospital to home.

The *mobile sleep medicine care model* prioritizes effective, efficient, and patient-centered sleep medicine care; therefore, all parties and segments of care that receive and provide clinical sleep medicine services will benefit in various measurable ways (67).

A. *Benefits for patients*

1) Patient-centered sleep care is delivered directly and conveniently to a patient at any setting/level of care: hospital, home, virtual telemedicine clinic, or in-person clinic.
2) The *iMSM* improves the overall patient experience by bringing sleep medicine expertise and testing directly to the patient's bedside without the unnecessary delays in care currently observed in the traditional sleep medicine model (e.g., self-scheduling for sleep clinic and sleep lab with long waiting times, and/or multiple missed/canceled appointments, etc.).
3) Improved sleep quality, sleep-related quality of life, participation in recovery and rehab activities due to controlled OSA-related issues: daytime sleepiness, fatigue, concentration and/or memory, altered mental status, delirium, and dyspnea.

B. *Benefits for Hospital/Healthcare System*

1) Screening/evaluation for SDB will upgrade the case-mix index and bring up diagnosis-related group reimbursement based on:

a) Elevated complexity of comorbidities rule and increased case mix index.

b) Improvement of hospital performance statistics due to:

i. Significant reduction in in-hospital mortality and readmission rates in CCV-sensitive populations (CHF, chronic respiratory failure, obesity hypoventilation, Stroke, atrial fibrillation, MI, hypertension, seizure disorders, neuromuscular disease, myasthenia gravis, ALS, etc.).
ii. Shortened the length of the following:
a. The intensive care unit stays.
b. Hospital stays (i.e., patients with OSA, OHS, post-operative respiratory failure, COPD, CHF, etc.).
iii. Prevention of escalation in the level of care, intubation, transfer to the intensive care unit, a rapid response team.
iv. Prevention of hypoxemia and/or hypoventilation.
v. Control of referral base and prevention of referral leaks (increase referral base to sleep center by 1300 patients per year).

C. *Benefits for payors*

1) Low cost for improved access to Neuro-Sleep Medicine care for pediatric and adult patients.
2) Reduced costs and more effective management of CCV, AD, and NMD.

D. *Benefits for the Academic Neuro-Sleep Medicine Field:*

1) Expansion of neurosomnology into all medical settings and levels of care with opportunities to monitor relevant SDB-related clinical outcomes and measure responses to targeted clinical interventions in real time while a patient is moving *via* levels of care;
2) Establishing the methodological basis for the development of digital evidence-based precision neuro-sleep medicine:

a) To effectively control and manage pertinent comorbidities in CCV, AD, and NMD.
b) Improve recovery and rehabilitation.

3) Removal of the "stigma" of being an "Outpatient Only" specialty with minimal impact on patient's clinical outcomes.

E. *National health benefits*

1) Overall reduction of SDB-related morbidity and mortality.
2) Data from iMSM would contribute to the development of evidence-based precision sleep medicine.

The **integrated iMSM, if implemented in the** general neurological practice, would provide the systematic screening, testing, and best-practice management of the most common

sleep-related breathing disorders: OSA, HHS and potentially other sleep disorders.

We anticipate that **iMSM** with **mobile sleep unit methodology** has the potential for a positive, measurable impact on all parties involved in neurological care, including the neurological patient, the hospital/healthcare system, and the fields of neurology and sleep medicine.

Author's note

The mobile sleep medicine model was presented during the 2021 AASM Sleep Disruptors competition and won the People's Choice Award. Information can be found at the following links: https://d11tooehygcg9z.cloudfront.net/My.AASM/AgentsOfChange/587417.pdf; https://aasm.org/winners-of-inaugural-change-agents-competition-propose-new-approaches-for-sleep-apnea-care.

Author contributions

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Conflict of interest

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

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Association of sleep characteristics with renal function in menopausal women without recognized chronic kidney disease

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Objective: To delineate the association between sleep characteristics and renal function in peri-post menopause free of Chronic kidney disease (CKD) as well as cardiometabolic and hormone indicators.

Methods: Cross-sectional data from a total of 823 Han-Chinese women aged 40–67 years who visited the Menopause Clinic in the Shanghai Sixth People's Hospital from November 2011 to November 2020 were analyzed through the Pittsburgh Sleep Quality Index (PSQI) and serum cystatin C (Cys-C). Logistic regression models were used to assess the association between cumulative/each sleep parameter and renal function after adjusting for cardiometabolic variables.

Results: After confounding factors, we identified that poor perceived sleep quality, shorter sleep duration (<6 h), low sleep efficiency (<75%), delayed sleep latency and worse sleep disturbance elevated more than doubled the odds ratio for declining renal function (≥0.91 mg/dL, the highest Cys-C) in postmenopause in a graded fashion. Meanwhile, multiple logistic regression analysis revealed that sleep disorder (PSQI ≥ 8), late postmenopause, highest quartile independently increased the odds ratio for declining renal function (OR 2.007, 95% CI: 1.408–2.861, OR = 3.287, 95%CI: 3.425–8.889, OR = 2.345, 95% CI: 1.310–4.199, respectively), while participants with menopausal hormone replacement (MHT) lower the odds of declining renal function (OR = 0.486, 95% CI: 0.324–0.728).

Conclusion: The findings proposed that maintaining good sleep quality should be attached great importance to postmenopausal women, which provides clinical evidence for the feasible early detection and effective prevention such as MHT of renal disease progression in postmenopausal women.

KEYWORDS

sleep characteristics, cystatin C, renal function, menopause, menopausal hormone therapy (HT)

Introduction

Chronic kidney disease (CKD) is determined as ongoing deterioration of renal function manifested by decreased glomerular filtration rate (GFR), leading to an increasing risk of hospitalization and mortality (1), and thus results in substantial health economic burden globally (2). As an endocrine organ, the kidney serves as the main target for hormone action (3). Many studies have revealed that menopause was supported to be associated with a higher risk of developing CKD due to diminished ovarian hormones (3–5). Therefore, identification of potential patients in menopause is paramount for the initiation of effective therapies to slow or delay disease progression.

Although estimated GFR (eGFR), based on the measurement of serum creatinine, is the most commonly used method to evaluate renal function, the change of creatinine is not significant in the early stages of renal impairment and influenced by muscle mass and body weight (6), which could result in less sensitivity of eGFR measurements (7). While Serum cystatin C (Cys-C), constantly secreted from all nucleated cells, has been purported as a more sensitive and specific biomarker than serum creatinine (8, 9). Therefore, Cys-C may be highly applicable as an early marker of preclinical renal disease. In addition, it serves as a much better-diagnostic tool for kidney function independent of age, sex, inflammation, liver disease, diet, and individual constitution and muscle mass (10, 11).

Menopause is a critical physiological stage of women's life with various complaints. Besides vasomotor symptoms, sleep disorder is another marker of menopause (12). Women who experience poor sleep are more vulnerable to diseases, which is of great concern for women's life quality and long-term health. In addition, a review proposed that OSAHS (obstructive sleep apnea-hypopnea syndrome) may contribute to CKD development either indirectly through its influences on diabetes, obesity and hypertension, or directly through the sympathetic nervous system and renin-angiotensin-aldosterone system (13). However, literature on the relationship between sleep disorder and clinically latent renal disease in menopause is scant.

As the burden of CKD in women after menopause is increasing, there is an emerging need for menopausal women-based research designed to disentangle the interactions between sleep disorder and renal function. In this study, we aim to investigate the association between sleep characteristics evaluated by the Pittsburgh Sleep Quality Index (PSQI) and serum Cys-C in terms of menopause, to identify the potential predicting value of sleep disorder for preclinical kidney disease among Chinese women without CKD in different menopausal status.

Materials and methods

Study design and participants

This cross-sectional study enrolled participants who visited the Menopause Clinic in the Shanghai Sixth People's Hospital from November 2011 to November 2020. Han-Chinese woman aged 40–67 years were recruited. The study protocol was approved by the Ethics Committee of Shanghai Sixth People's Hospital, and the study was performed in accordance with the approved guidelines. All the participants provided written informed consents after full explanation of the study. All study protocols were performed in accordance with the principles of the Declaration of Helsinki. Participants were excluded as follows: (1) suspected renal insufficiency, with an eGFR less than 60 mL/min/1.73 m^2; (2) history of chronic nephritis, nephrotic syndrome, nephrectomy, polycystic kidney disease, organ or bone marrow transplant, immunosuppressive drugs for kidney disease in the past 6 months; (3) night work shifts and irregular sleep schedule; (4) menopausal hormone replacement (MHT)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; eGFR, estimated GFR; Cys-C, cystatin C; OSHS, obstructive sleep apnea-hypopnea syndrome; PSQI, Pittsburgh Sleep Quality Index; MHT, menopausal hormone replacement; STRAW, Stages of Reproductive Aging Workshop; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FSH, follicle-stimulating hormone; FBG, Fasting plasma glucose; MetS, metabolic syndrome; OSA, obstructive sleep apnea; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

past users (women who reported past not current use for over previous 6 months); (5) current smoking (at least once per week for the previous 6 months); (6) progressive malignancy currently undergoing radiotherapy or chemotherapy; (7) with missing data. Ultimately, 823 participants were recruited in this study.

General questionnaire

A general questionnaire (14–16) was used by well-trained investigators through face-to-face interview to collect sociodemographic information, including age, last menstrual period, education, marital status, employment status, income per month, years since menopause, MHT use (including estradiol + dydrogesterone, estradiol only, tibolone), history of chronic disease (hypertension, diabetes mellitus, CKD, metabolic syndrome, dyslipidemia, obesity, as well as medication use), lifestyle (i.e., smoking, alcohol consumption). Women who reported current use $\geq$ 6 months were classified as current MHT users, while women who had never taken were classified as never users. On the basis of the Stages of Reproductive Aging Workshop (STRAW + 10) (17), participants were categorized into peri-menopausal group (consecutive irregularities over 7 days of menstrual cycle), early postmenopausal group (absence of menstrual periods for 1–5 years) and late postmenopausal group (absence of menstrual periods for 5 years or more) (14).

Anthropometric and lab parameters

Height (cm) and weight (kg) were recorded and used to computed Body mass index BMI (kg/m^2). Blood pressure was measured with the average of the 3 readings after 5-min sitting 0.19 Hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mm Hg, diastolic blood pressure (DBP) $\geq$ 90 mm Hg or use of antihypertensive medications (16).

After an overnight fast for at least 10 h, venous blood samples were collected for all study participants for biochemical measurements analysis. Serum Cys-C, creatine, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and creatinine were measured using an automated AU-5800 analyzer (Beckman Coulter, Brea, CA, USA). Fasting plasma glucose (FPG) was measured with the glucose oxidase method using an automated AU-5800 analyzer (Beckman Coulter, Brea, CA, USA). Female sex hormone levels were evaluated by chemiluminescence (Cobas E601; Roche, Basel, Switzerland). The sensitivity for follicle-stimulating hormone (FSH) detection was 0.100 mIU/mL, and the range of measurement was 0.100–200.0 mIU/mL; for estradiol (E2), the sensitivity and range of measurement was 5 pg/mL and 5–3,000 pg/mL, respectively. Intra- and inter-assay coefficients of variation were always <5% for FSH and E2.

Definitions of study outcomes

Dyslipidemia was defined as previous diagnosis or meeting any of the following criteria: (1) TC $\geq$ 6.22 mmol/L; (2) TG $\geq$ 2.26 mmol/L; (3) LDL $\geq$ 4.14 mmol/L; (4) HDL<1.05 mmol/L (18). Hypertension and diabetes were diagnosed based on self-reported previous diagnosis, or by criteria $\geq$ 140/90 mmHg and FPG $\geq$ 7 mmol/L (18, 19). BMI $\geq$ 28 kg/m^2 was regarded as obesity. Definition of metabolic syndrome (MetS) was defined as the presence of two or more of the following components (20): (1) obesity (waist-hip-ratio > 0.85 and/or BMI $\geq$ 28 kg/m^2); (2) TG $\geq$ 1.7 mmol/L; (3) HDL-c < 1.05 mmol/L; (4) blood pressure $\geq$ 140/90 mmHg or current use of antihypertensive medications; (5) FBG $\geq$ 7.0 mmol/L. CKD was defined as eGFR < 60 (mL/min/1.73 m^2), which was calculated by recently revised CKD Epidemiology Collaboration (CKD-EPI) equation for the Chinese population (21).

Assessment of sleep quality

The validated Chinese version Pittsburgh Sleep Quality Index (PSQI) (22) was used to evaluate sleep quality over the past month for the participants. In brief, 18 items, including in the PSQI, were used to weigh scores based on the following 7 subscales: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. Each parameter ranges from 0 to 3 scale. Subjective sleep quality was categorized into 0 to 3 scores, corresponding to very good, good, poor, very poor, sleep duration into >7 h, 6–7 h, 5–6 h, <5 h, sleep efficiency into>85%, 75–85%, 65–75%, <65%, sleep use of medication into none, <1 time/week, 1–2 times/week, $\geq$ 3 times/week. The total PSQI ranged from 0 to 21, with a higher score indicating worse sleep quality. A PSQI score of 8 or higher was indicative of sleep disorder (14, 23), which has been recommended in Chinese clinical practice and research.

Statistical analysis

All the variables were tested for normal distribution by Kolmogorov-Smirnov test. Levene's test of homogeneity of variance were further performed. They were depicted as means $\pm$ standard deviation (SD) or number (%). One-way ANOVA (normal distributions), the Kruskal Wallis H-test (skewed continuous variables) and $\chi 2$ test (categorical variables) were carried out to compare the differences among the four groups on the quartiles of serum Cys-C levels (Q1:<0.70 mg/dL, Q2:0.71–0.72 mg/dL, Q3:0.73–0.90 mg/dL, Q4: $\geq$ 0.91 mg/dL). We defined Cys-C with 0.91 mg/dL (Q4, the highest quartile group) as declining renal function. The multivariate logistic

regression analyses were performed to examine independent determinants for Q4. In addition, the association between each sleep parameter and Q4 was computed by logistic regression analysis. A two-sided $p < 0.05$ was considered to be a significant difference. Logistic regression model was assessed by the Hosmer-Lemeshow test. All statistical analyses were performed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA).

Results

Characteristics of the study participants based on cystatin-C quartiles

In a total of 823 eligible subjects, the baseline characteristics among quartile groups divided by the serum Cys-C: (Q1: <0.70 mg/dL, Q2: 0.71–0.72 mg/dL, Q3: 0.73–0.90 mg/dL, Q4: ≥ 0.91 mg/dL) were presented in Table 1. The prevalence of sleep disorder (PSQI ≥ 8) was 38.6% in our study.

Interestingly, the prevalence of sleep disorder (PSQI ≥ 8) increased in a dose-dependent manner according to the serum of Cys-C: 39.13% (Q1) vs.41.46% (Q2) vs.48.53% (Q3) vs.65.22% (Q4) ($p < 0.001$). We also observed the growing value of FSH, years since menopause, age, BMI, DBP, creatine, while decreasing level of eGFR from Q1 to Q4 quartiles ($p < 0.001$). Moreover, there showed a decreasing incidence of MHT use, while an ascending incidence of early, late postmenopause (compared with perimenopause), as well as hypertension, diabetes mellitus with the increasing of Cys-C quartiles ($p < 0.05$). On the other hand, lipid profiles (including TC, TG, LDL-C, HDL-C), FBG, E2, SBP did not show significant trends across Cys-C quartiles. Furthermore, Table 2 showed score for sub-scales of PSQI based on Cys-C quartiles. There were significant differences in six sub-scales of PSQI (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance and daytime dysfunction) (All $p < 0.05$).

Independent determinant factors for declining renal function

To investigate the independent determinant factors for declining renal function, we conducted a multivariate logistic stepwise regression analysis. As shown in Figure 1, after adjusting for confounding covariates, including age, BMI, menopausal status, years since menopause, FBG, lipid profiles (TC, TG, LDL-C, HDL-C), SBP, hypertension, diabetes, obesity, MetS, we identified the independent risk factors for declining renal function as PSQI ≥ 8 [odds ratio (OR) 2.007, 95% confidential interval (CI): 1.408–2.861], hypertension (OR 2.659, 95% CI: 1.624–4.353), diabetes (OR 2.008, 95% CI: 1.008–3.706), early postmenopause (OR 1.624, 95% CI: 1.050–2.511), BMI (OR 1.089, 95% CI: 1.018–1.165), age (OR 1.047, 95% CI: 1.002–1.094), while MHT served as a protective role in renal function (OR = 0.486, 95% CI: 0.324–0.728). In addition, the regression analysis revealed that the ORs of declining renal function were twofold higher (OR = 2.345, 95% CI: 1.310–4.199, $p < 0.001$) in the highest FSH quartile compared to the lowest.

Odds ratio of sleep disorder for declining renal function stratified by menopause status

We further investigated the role of menopause in sleep disorder-renal function relation in unadjusted or multi-covariates adjusted model (Figure 2). Then the total subjects were divided into three groups: peri-, early post- and late post-menopause. However, in peri-menopause, the risk indicator of PSQI ≥ 8 for declining renal function vanished (OR = 1.178, 95% CI: 0.917–1.661, $p = 0.089$), while the ORs of declining renal function were twofold (OR = 1.968, 95% CI: 1.772–3.845) and threefold (OR = 3.287, 95% CI: 3.425–8.889) higher in early and late postmenopausal status, respectively. Thus, we put forward that in postmenopausal not perimenopause women, sleep disorder served as an independent determinant for declining renal function, while the odds ratio was higher in late postmenopause than in early one.

Odds ratio of each sleep parameter of Pittsburgh Sleep Quality Index for declining renal function

Next, we investigated the association between each sleep parameter and declining renal function. As shown in Figure 3, after multivariable adjustment of confounding factors, compared with >7 h (score 0), 5–6 h [score 2 OR 95% CI: 3.073 (1.824–5.178)] and <5 h [score 3 OR 95% CI: 3.295 (1.837–5.91), $p<0.001$] were associated with threefold higher odds ratio for declining renal function. Compared with sleep efficiency 85% (score 0), 65–75% [score 2 OR 95% CI: 2.145 (1.351–3.403)] and<65% [score 3 OR 95% CI: 2.338 (1.522–3.591), $p<0.001$] were associated with twofold higher odds for declining renal function.

The other significant sleep parameters were sleep quality [score 2 OR 95% CI: 2.179 (1.139–4.169), score 3 OR 95% CI: 3.165 (1.543–6.491), $p < 0.05$], sleep latency [score 3 OR 95% CI: 1.719 (1.117–2.647), $p < 0.05$], sleep disturbance [score 2 OR 95% CI: 4.047 (2.084–7.858), score 3 OR 95% CI: 4.233 (3.215–6.798), $p < 0.05$], sleep efficiency [score 2 OR 95% CI: 2.145 (1.351–3.403), score 3 OR 95% CI: 2.338 (1.522–3.591), $p < 0.001$]. In a summary, our fully adjusted model revealed that subjective poor sleep quality, shorter sleep duration (<6 h), low sleep efficiency (<75%) and longer sleep latency and higher sleep

TABLE 1 Characteristics of the study participants distributed by quartile of cystatin C.

Variables	Q1 <0.70 mg/dL	Q2 0.71–0.72 mg/dL	Q3 0.73–0.90 mg/dL	Q4 ≥0.91 mg/dL	Total	*p*-value
Age (years)	50.15 ± 5.04	51.18 ± 5.09	51.56 ± 4.67	52.58 ± 4.56	51.37 ± 4.91	<0.001
Height (cm)	159.7 ± 4.99	160.43 ± 4.5	160.59 ± 4.97	160.8 ± 5.18	160.38 ± 4.93	0.116
Weight (Kg)	55.51 ± 7.33	57.68 ± 7.9	57.94 ± 7.01	58.76 ± 7.99	57.47 ± 7.65	<0.001
BMI (Kg/m^2)	55.51 ± 7.33	57.68 ± 7.9	57.94 ± 7.01	58.76 ± 7.99	57.47 ± 7.65	0.004
SBP (mmHg)	119.13 ± 14.99	118.15 ± 13.83	120.52 ± 15.62	120.75 ± 17.98	119.64 ± 15.69	0.289
DBP (mmHg)	72.75 ± 10.44	72.9 ± 9.62	74.32 ± 9.30	75.17 ± 10.16	73.79 ± 9.93	0.036
FPG (mmol/L)	5.3 ± 0.72	5.44 ± 1.06	5.37 ± 0.76	5.42 ± 0.86	5.38 ± 0.86	0.376
Tg (mmol/L)	1.27 ± 0.94	1.22 ± 0.72	1.23 ± 0.77	1.29 ± 0.95	1.25 ± 0.85	0.812
TC (mmol/L)	5.32 ± 0.99	5.16 ± 1.01	5.2 ± 1.07	5.1 ± 1.02	5.2 ± 1.02	0.154
HDL-C (mmol/L)	1.62 ± 0.5	1.52 ± 0.59	1.44 ± 0.4	1.5 ± 0.55	1.52 ± 0.52	0.005
LDL-C (mmol/L)	3.1 ± 0.82	3.1 ± 0.96	3.13 ± 0.89	3.06 ± 0.81	3.1 ± 0.87	0.873
E2 (pg/mL)	68.99 ± 98.61	60.59 ± 79.23	51.04 ± 71.6	63.44 ± 131.86	61.05 ± 98.29	0.309
FSH (mIU/mL)	59.89 ± 31.89	63.62 ± 31.27	67.43 ± 28.95	70.69 ± 30.27	65.41 ± 30.83	0.002
Cystatin C (mg/L)	0.58 ± 0.07	0.72 ± 0.01	0.83 ± 0.04	1.05 ± 0.15	0.79 ± 0.19	<0.001
Creatine	53.74 ± 8.85	56.75 ± 7.03	58.28 ± 8.06	61.32 ± 11.18	57.52 ± 9.32	<0.001
eGFR (mL/min/1.73 m^2)	129.61 ± 24.81	119.86 ± 17.73	116.89 ± 21.09	111.69 ± 26.56	119.52 ± 23.70	<0.001
PSQI total score	7.29 ± 4.72	7.15 ± 4.39	8.25 ± 4.97	10.02 ± 4.87	8.18 ± 4.87	<0.001
PSQI ≥ 8	81 (39.13%)	85 (41.46%)	99 (48.53%)	135 (65.22%)	400 (38.60%)	<0.001
Years since menopause	1.95 ± 2.89	3.02 ± 4.68	3.03 ± 4.25	3.53 ± 4.86	2.89 ± 4.28	0.002
Menopausal status, *n* (%)						<0.001
Perimenopause	104 (50.24%)	78 (38.05%)	62 (30.39%)	52 (25.12%)	296 (35.97%)	
Early postmenopause	73 (35.27%)	77 (37.56%)	88 (43.14%)	104 (50.24%)	342 (41.56%)	
Late postmenopause	30 (14.49%)	50 (24.39%)	54 (26.47%)	51 (24.64%)	185 (22.48%)	
Marital status						0.261
Married	199 (96.14%)	200 (97.56%)	200 (98.04%)	205 (99.03%)	804 (97.69%)	
Single/widowed	8 (3.86%)	5 (2.44%)	4 (1.96%)	2 (0.97%)	19 (2.31%)	
Education, *n* (%)						0.305
Junior or below	30 (14.49%)	38 (18.54%)	45 (22.06%)	38.48 (26.14%)	153 (18.59%)	
Senior high	74 (35.75%)	83 (40.49%)	80 (39.22%)	79.48 (25%)	316 (38.4%)	
College or above	103 (49.76%)	84 (40.98%)	79 (38.73%)	89.04 (24.86%)	354 (43.01%)	
Employment status, *n* (%)						0.051
Work	119 (57.49%)	116 (56.59%)	93 (45.59%)	94 (45.41%)	422 (51.28%)	
Departure	74 (35.75%)	78 (38.05%)	90 (44.12%)	106 (51.21%)	348 (42.28%)	
Retirement	14 (6.76%)	11 (5.37%)	21 (10.29%)	7 (3.38%)	53 (6.44%)	
Income (RMB/month), *n* (%)						0.052
<1,000	16 (7.73%)	20 (9.76%)	19 (9.31%)	6 (2.9%)	61 (7.41%)	
1,000–3,000	48 (23.19%)	58 (28.29%)	66 (32.35%)	82 (39.61%)	254 (30.86%)	
3,000–5,000	54 (26.09%)	68 (33.17%)	69 (33.82%)	68 (32.85%)	259 (31.47%)	
5,000–10,000	58 (28.02%)	34 (16.59%)	37 (18.14%)	37 (17.87%)	166 (20.17%)	
>10,000	31 (14.98%)	25 (12.2%)	13 (6.37%)	14 (6.76%)	83 (10.09%)	
Overweight/obesity, *n* (%)	23 (11.11%)	32 (15.61%)	31 (15.20%)	48 (23.19%)	136 (16.52%)	0.018
Hypertension	26 (12.08%)	26 (12.68%)	41 (20.10%)	65 (31.40%)	158 (19.20%)	<0.001
Diabetes	9 (4.35%)	15 (7.32%)	15 (7.35%)	26 (12.56%)	65 (7.90%)	0.019
Dyslipidemia, *n* (%)	69 (33.33%)	85 (41.46%)	78 (38.24%)	77 (37.2%)	309 (37.55%)	0.398
MetS, *n* (%)	10 (4.83%)	13 (6.34%)	23 (11.27%)	23 (11.11%)	69 (8.38%)	0.033
MHT use, *n* (%)	75 (36.23%)	99 (48.29%)	70 (34.31%)	51 (24.64%)	295 (35.84%)	<0.001

Two-sided $P < 0.05$ was considered significant.

eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; FBG, fast blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; E2, estriol; FSH, follicle-stimulating hormone; MetS, metabolic syndrome; MHT, menopausal hormone replacement.

TABLE 2 Separate sleep parameter of PSQI by quartile of cystatin C.

PSQI items	Q1 <0.70 mg/dL	Q2 0.71–0.72 mg/dL	Q3 0.73–0.90 mg/dL	Q4 ≥0.91 mg/dL	Total	*p*-value
Subjective sleep quality						<0.001
Very good	28 (13.53%)	31 (15.12%)	27 (13.24%)	16 (7.73%)	102 (12.39%)	
Good	123 (59.42%)	108 (52.68%)	109 (53.43%)	87 (42.03%)	427 (51.88%)	
Bad	38 (18.36%)	50 (24.39%)	46 (22.55%)	65 (31.40%)	199 (24.18%)	
Very bad	18 (8.70%)	16 (7.80%)	22 (10.78%)	39 (18.84%)	95 (11.54%)	
Sleep latency (minutes)						<0.001
≤15	85 (41.06%)	93 (45.37%)	83 (40.69%)	70 (33.82%)	331 (40.22%)	
16–30	74 (35.75%)	73 (35.61%)	63 (30.88%)	49 (23.67%)	259 (31.47%)	
31–60	29 (14.01%)	20 (9.76%)	31 (15.20%)	32 (15.46%)	112 (13.61%)	
>60	19 (9.18%)	19 (9.27%)	27 (13.24%)	56 (27.05%)	121 (14.70%)	
Sleep duration (hours)						<0.001
>7	60 (28.99%)	53 (25.85%)	47 (23.04%)	24 (11.59%)	184 (22.36%)	
6–7	63 (30.43%)	59 (28.78%)	53 (25.98%)	39 (18.84%)	214 (26%)	
5–6	57 (27.54%)	65 (31.71%)	71 (34.8%)	92 (44.44%)	285 (34.63%)	
<5	27 (13.04%)	28 (13.66%)	33 (16.18%)	52 (25.12%)	140 (17.01%)	
Sleep efficiency(%)						<0.001
>85	111 (54.68%)	107 (52.45%)	83 (41.09%)	63 (30.58%)	364 (44.66%)	
75–84	26 (12.81%)	32 (15.69%)	34 (16.83%)	25 (12.14%)	117 (14.36%)	
65–74	25 (12.32%)	34 (16.67%)	38 (18.81%)	48 (23.30%)	145 (17.79%)	
<65	41 (20.2%)	31 (15.2%)	47 (23.27%)	70 (33.98%)	189 (23.19%)	
Sleep disturbance						<0.001
None	47 (22.71%)	46 (22.44%)	29 (14.22%)	14 (6.76%)	136 (16.52%)	
<1/week	132 (63.77%)	128 (62.44%)	118 (57.84%)	117 (56.52%)	495 (60.15%)	
1–2/week	27 (13.04%)	31 (15.12%)	55 (26.96%)	75 (36.23%)	188 (22.84%)	
≥3/week	1 (0.48%)	0 (0.00%)	2 (0.98%)	1 (0.48%)	4 (0.49%)	
Use of sleep medication						0.171
None	173 (83.57%)	179 (87.32%)	169 (82.84%)	165 (79.71%)	686 (83.35%)	
<1/week	11 (5.31%)	10 (4.88%)	9 (4.41%)	9 (4.35%)	39 (4.74%)	
1–2/week	7 (3.38%)	2 (0.98%)	3 (1.47%)	11 (5.31%)	23 (2.79%)	
≥3/week	16 (7.73%)	14 (6.83%)	23 (11.27%)	22 (10.63%)	75 (9.11%)	
Daytime dysfunction						0.024
None	48 (23.19%)	58 (28.29%)	41 (20.1%)	38 (18.36%)	185 (22.48%)	
<1/week	69 (33.33%)	63 (30.73%)	71 (34.8%)	51 (24.64%)	254 (30.86%)	
1–2/week	53 (25.6%)	44 (21.46%)	42 (20.59%)	59 (28.5%)	198 (24.06%)	
≥3/week	37 (17.87%)	40 (19.51%)	50 (24.51%)	59 (28.5%)	186 (22.60%)	

disturbance were independently associated with declining renal function in a graded fashion.

Sleep disorder and menopausal hormone replacement on the prevalence of declining renal function

To investigate the role of MHT in sleep disorder-renal function relation, we then distinguished the participants by using MHT and sleep disorder to analyze the prevalence of declining kidney function (Cys-C ≥ 0.91 mg/dL, Q4) with different combinations of two-score based PSQI and MHT.

Compared with MHT non-users, the prevalence of sleep disorder for declining kidney function was significantly lower than in MHT user group (34.89 vs. 22.22%) ($p < 0.05$). On the whole, we found that the prevalence of declining renal function in sleep disorder was higher than without sleep disorder group, while MHT may lower the prevalence (Figure 4).

Discussion

To our knowledge, this is the first study to document the relationship between sleep characteristics (total PSQI score as well as each sleep parameter) and latent renal function

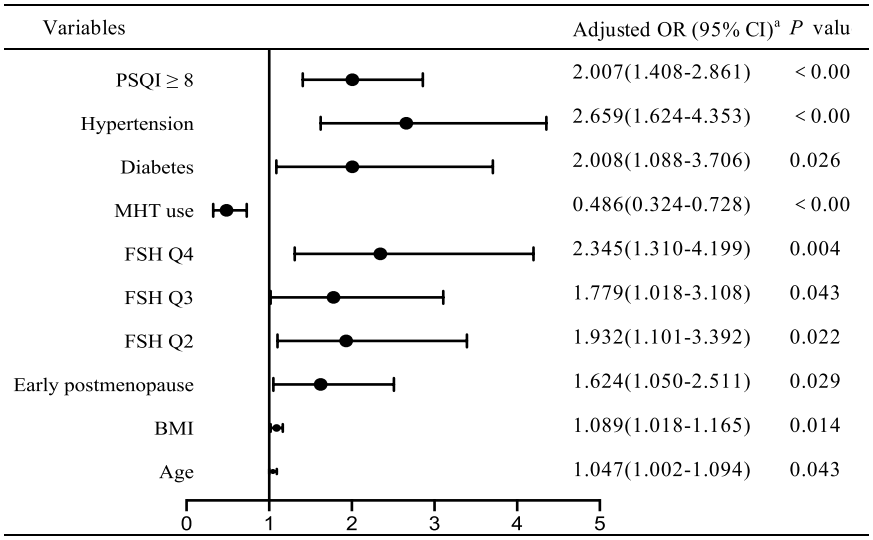

FIGURE 1
Adjusted odds ratio for declining renal function by logistic regression [a]adjusted for age, BMI, menopausal status, years since menopause, SBP, FBG, lipid profiles, hypertension, diabetes, obesity, MetS. OR, odds ratio; CI, confidential interval.

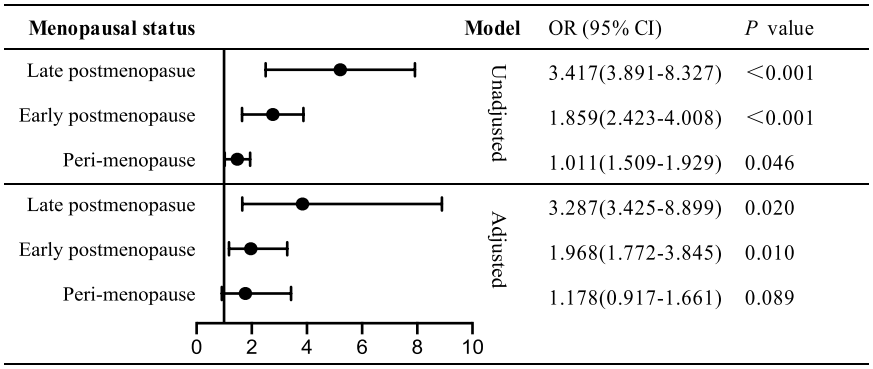

FIGURE 2
Odds ratio of PSQI ≥ 8 for declining renal function stratified by menopause status.

(estimated by serum Cys-C) in peri-post menopausal women without CKD in addition to cardiometabolic and hormone indicators. In our study, we found that sleep disorder (PSQI ≥ 8) served as a determinant risk factor for declining renal function (Cys-C ≥ 0.91 mg/dL, Q4) independent of cardiovascular variables, while the risk was higher in late postmenopause than in early postmenopause. In addition, we observed that poor subjective sleep quality, shorter sleep duration (<6 h), low sleep efficiency (<75%) and delayed sleep latency and higher sleep disturbance showed increasing odds ratio for declining renal function in a dose-manner fashion.

Previous studies have supported that short sleep duration (<5 or 6 h), poor sleep quality and obstructive sleep apnea (OSA) are associated with a higher prevalence of CKD progression estimated by eGFR in patients with diabetic kidney disease, type 2 diabetes (16, 24–26). In addition, a 16.8 years of follow-up study demonstrated that both short and long sleep durations were associated with a higher risk of end-stage renal disease in Chinese population (27). However, little attention was paid to the menopausal women. The strength of our study was that we focused on the interaction of sleep characteristics and clinically latent renal disease in terms of menopause. Accordingly, we suggested that sleep disorder (both total PSQI score and sleep parameter) adversely impacted renal function independent of cardiovascular risk factors. Additionally, we indicated that longer years since menopause served as an incremental role of sleep disorder for declining renal function.

In addition, our multiple logistic regression analysis identified that a higher level of FSH was independently associated with declining renal function. In particular,

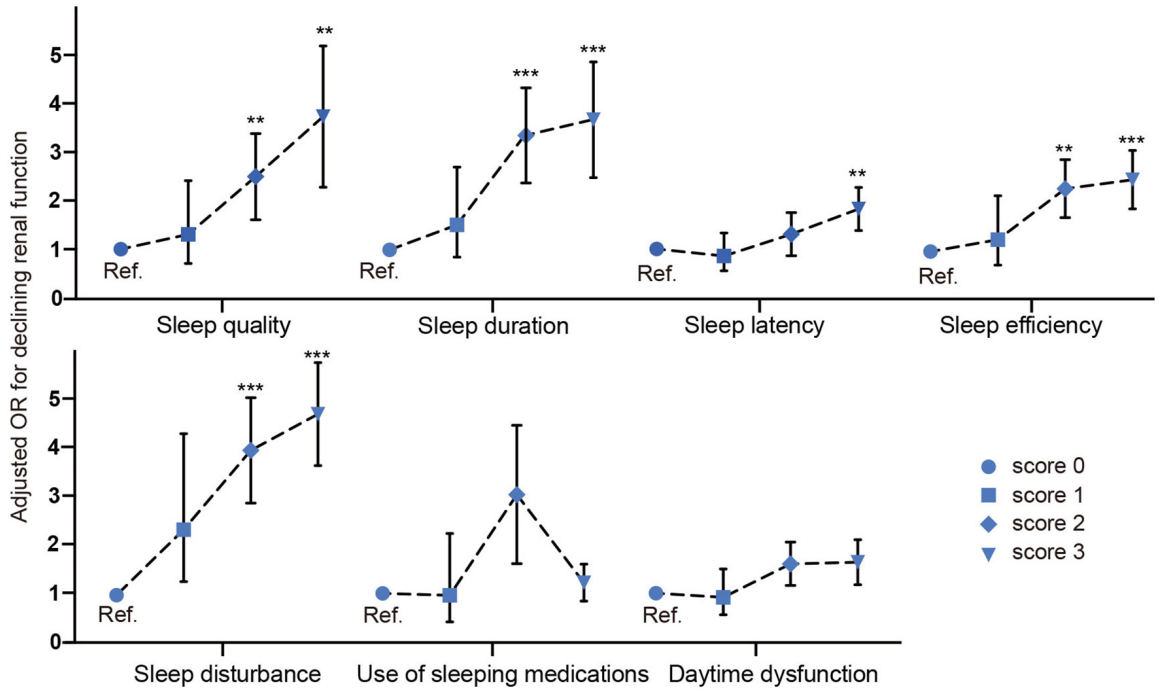

FIGURE 3
Odds ratio of each sleep parameter of PSQI for declining renal function. $^{**}p < 0.05$, $^{***}p < 0.001$.

participants in the fourth FSH were more likely to have renal dysfunction, which was in agreement with the results of the previous study that higher FSH was an independent risk factor declined eGFR and CKD in postmenopausal women (5). Of interest, we also found that MHT was an independent protective indicator associated with declining renal function. Our finding was consistent with the previous study that MHT can delay CKD progression and improved eGFR (28). Menopause is known to be a vital physiological stage of women's lives characterized by increased FSH concentrations as a result of ovarian failure. Thus, our above results confirmed that the higher FSH level caused by menopause contributed to the worsening of renal function in women, whereas MHT may reversely attenuate the kidney injury. While the possible mechanism was that FSH promoted renal fibrosis in aging women *via* bonding to FSH receptor, which was expressed in kidney tissue (29, 30).

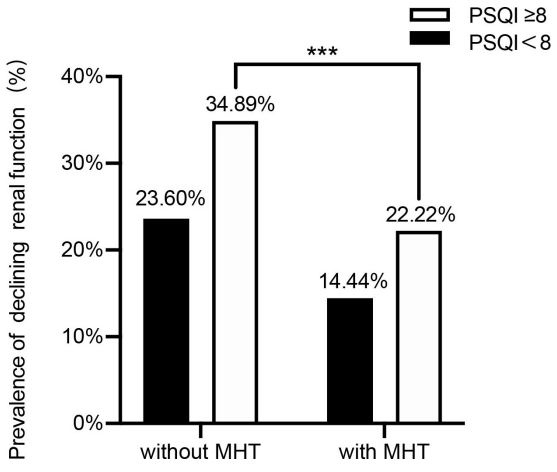

FIGURE 4
Sleep disorder and MHT on the prevalence of declining renal function. $^{***}p < 0.001$.

Other classical independent factors such as hypertension, diabetes, older age, BMI, postmenopause for declining renal function were compatible with previous studies (5, 29–31).

Although the underlying mechanisms by which sleep disorder induced declining renal function in menopause are not fully understood, the admissible mechanisms can be boiled into direct and indirect ways. Sleep disorder can lead to inflammation, oxidative stress, endothelial dysfunction, increased sympathetic tone, activation of the renin-angiotensin system, circadian timing dysfunction and subsequent systemic and intraglomerular pressure, which hereby adversely affects kidney function (24–26, 31, 32). Another possible explanation is the impact of sleep disorder on hypertension (33, 34), diabetes (35, 36), obesity (37), and metabolic syndrome (38), which were known to accelerate deterioration of kidney function.

Several limitations deserve mention in this research. First, our study is a cross-sectional analysis, the inherent drawback

of an observational survey may weaken the causal relationship. Secondly, sleep quality ascertained by questionnaire would produce memory bias. Therefore, further longitudinal study is needed to confirm these relationships. Our team is now working on the following-up investigation.

Conclusion

Taken together, our study demonstrated that both cumulative (PSQI total score) and separate sleep dimension (subjective sleep quality, shorter sleep duration, low sleep efficiency delayed sleep latency and higher sleep disturbance) were independently associated with declining renal function (the highest Cys-C, Q4) in postmenopausal women. Thus preclinical prevention such as MHT should be taken for postmenopausal women with sleep problems.

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 study protocol was approved by the Ethics Committee of Shanghai Sixth People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MT conceived and designed the study. YZ analyzed the data. JT wrote the manuscript. CL and JH took part in the investigation and data collection. YT revised the manuscript. All authors read and approved the final manuscript and 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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Current medical education improves OSA-related knowledge but not confidence in residents: An underappreciated public health risk

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Background: Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder and induces a growing health care burden. However, a large proportion of patients with OSA do not receive appropriate treatment and are underdiagnosed or misdiagnosed in primary care. A contributing factor to the phenomenon is the lack of education, which reflects the current inadequacies in medical education. Therefore, assessing the level of knowledge and attitudes toward OSA and associated factors among resident physicians is highly warranted.

Methods: A validated questionnaire, the OSA Knowledge and Attitudes (OSAKA) questionnaire was distributed to residents who had already completed undergraduate education and were attending an internal medicine residency training program. The questionnaire consists of 2 parts: including an assessment of (1) OSA-related knowledge involving epidemiology, pathophysiology, clinical manifestations, diagnosis, and treatment; (2) the importance of OSA and confidence in diagnosing and treating OSA patients. Other information including demographics, training experience, and questions exploring the future form of the sleep breathing disorder course was collected together.

Results: Of the 160 residents who participated in the survey, 153 (95.6%) completed the survey and the mean total knowledge score was 12.6/18 (70% correct). Although all respondents believed that OSA was an important clinical disorder, only a minority of the residents felt confident in identifying patients at risk for OSA (38%), managing OSA patients (27.5%), or continuous positive airway pressure therapy (CPAP) (26.2%). We found that OSA training experience significantly increased knowledge scores ($p = 0.002$) but not confidence scores ($p = 0.248$). As for the specific form of medical education, "Small classes during residency training" was the most popular form of sleep-breathing disorder educational training in the future of the resident training program.

Conclusion: Despite adequate knowledge of OSA, there was still a generalized lack of confidence in the management of OSA patients among residents.

Current medical education can not build enough confidence for physicians, which may in turn affect patients' trust and reduce long-term compliance. Untreated OSA places a significant health threat and economic burden on not only the patients but also their families and society, causing an underappreciated public health risk. In the future, merely increasing OSA courses is not sufficient, a more specific focus on the course format and training effect is required.

KEYWORDS

medical education, survey and questionnaires, residency training, obstructive sleep apnea, training effect

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder characterized by repetitive obstruction of the pharyngeal airway during sleep, causing nocturnal hypoxemia and fragmented sleep (1). It has been estimated that 936 million adults worldwide aged 30–69 years suffer from OSA (2). However, most OSA patients remain underdiagnosed, untreated, or undertreated in primary care mainly because of the cumbersome and time-consuming diagnostic and treatment process (3). With the ongoing obesity epidemic, the estimated prevalence of OSA represents substantial increases over decades (4). Untreated OSA can negatively affect multiple systems in the long term, leading to hypertension, coronary heart disease, stroke, diabetes, and neurocognitive abnormalities (5–7). Therefore, OSA is a very significant public health issue and has been included in chronic disease management programs, which requires clinical attention, especially from general practitioners and other primary care physicians (8, 9).

Despite the increased risk for sleep disorders among minority or medically indigent individuals, in some community settings, the diagnosis rates of OSA were <1% (10). A contributing factor to the phenomenon that sleep disorders are commonly underdiagnosed among health care providers is the lack of education (11, 12). It is believed that improving physicians' knowledge about OSA is critical for improving OSA-related screening and treatment practices (13, 14). More time needs to be devoted to education on sleep disorders in medical school curricula. However, instruction on sleep and sleep disorders during medical education and training remains limited over the years (15, 16). A survey across 12 countries found that the average time spent on sleep education is just under 2.5 h, with nearly one-third of medical school do not provide sleep education (11). Although corresponding guidelines for the management of OSA among physicians have been issued around the world, their effect on clinical work is insufficient as more physicians need related practice (17, 18). At present, unified curriculums or requirements for sleep education medical residency training programs do not exist. A recent survey revealed that absent sleep medicine training in most residency training is limited in the US (12). To date, no such study has been conducted or reported in China.

As the first step of clinical training for medical students, residency training is a unique opportunity for resident physicians to improve basic clinical skills and has been promoted nationally over the last decade (19, 20). Serve as a unique window, residency training programs provide opportunities for the residents to formally expose to sleep medicine. Since exposure is associated with subspecialty choice, increasing resident exposure may help to improve the current workforce shortage in sleep medicine (21), which is associated with many health risks. The medical fields of internal medicine, family medicine otolaryngology, psychiatry, and neurology are deemed to be the most important for knowledge regarding sleep disorders (12). Among them, internal medicine physicians frequently come into contact with OSA patients and their chronic complications (22). Thus, it makes more sense to investigate residents in the internal medicine residency training program, who are more likely to be responsible for the OSA diagnosis and treatment upon completion of their training.

Peking Union Medical College Hospital (PUMCH, an experienced residential training base) is the top hospital in China and has the oldest history and abundant experience in residency training programs throughout the country (23). Investigating the knowledge and attitudes of residents in PUMCH could help improve the national resident training program. Therefore, the purposes of this study were to understand the current status of OSA education among residents and their ability to identify and manage OSA patients, which may be helpful for future education improvement.

Materials and methods

Study design and ethics approval

This was a cross-sectional survey conducted among resident physicians during residency training programs in PUMCH

between December 2019 and June 2020. The study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital (Approval No. S-K 954). Informed consent was obtained from all individual participants included in the study.

Study participants and data collection

We recruited residents who were attending an internal medicine residency training program in PUMCH at the time of the survey. By querying the registration information of the hospital education office, we obtained the contact details of all resident physicians. Eligible physicians ($n = 160$) were contacted by phone to obtain permission to send them the study questionnaire. An informed consent form and questionnaire links were sent to participants' phones *via* WeChat. Data was collected *via* Wenjuanxing software. Residents were excluded from the study if they declined to participate ($n = 7$). Finally, 153 questionnaires were collected. Participation was voluntary.

A self-administered questionnaire which included the Chinese version of the Obstructive Sleep Apnea Knowledge and Attitude (OSAKA) questionnaire was used to collect data. OSAKA has been translated from English into Chinese version by two researchers with repeated revisions independently to ensure translation accuracy. All doctors attending the internal medicine residency training programs were invited to participate in the study, including internal medicine residents, general medicine residents, and others. According to their residency training years, the residency was classified into postgraduate years (PGY) 1, 2, and 3. And age was categorized into 3 groups (<25 years, 25–30 years, and >30 years).

Survey structure

The validated OSAKA questionnaire was used to evaluate the knowledge, attitudes, and confidence of PUMCH residents about OSA (13). The questionnaire was divided into three parts.

1. The first part evaluated basic OSA knowledge involving epidemiology (Q3, Q13, Q15), pathophysiology (Q9–10, Q12), symptoms (Q1, Q4–5, Q18), and diagnosis (Q6, Q11, Q14, Q17), and treatments (Q7–8, Q2, Q16). There were 18 questions with "True," "False," and "Unsure/Do Not Know" options, and the generated total scores ranged from 0 to 18. Correct responses scored 1 point, while incorrect and "Unsure/Do Not Know" answers received 0 points.

2. The second part assessed the attitudes of two sections: the importance of OSA and confidence in diagnosing and treating OSA patients. The questionnaire used the five-point Likert scale. Sections on importance ranged from 1 (not important) to 5 (extremely important), and those on confidence ranged from 1 (strongly disagree) to 5 (strongly agree). Additionally, demographic data, including participants' age, gender, and level of training, were also collected.

3. The last part included two additional questions investigating the willingness and the future form of the sleep breathing disorder course. Multiple-choice questions were used to show residents' preferences.

Statistical analyses

Statistical calculations were performed using SPSS software (version 25). GraphPad Prism9 were used for chart production. Descriptive analyses were calculated for demographic characteristics. We summarized all categorical variables as proportions (%) and numbers (n) and described continuous variables as means and standard deviation (M ± SD). The association between demographic characteristics and OSA knowledge and attitude scores was examined using two-sample t-test and oneway-ANOVA for continuous variables. ANOVA was followed by *post hoc* LSD (Least Significant Difference) test to determine whether there is a significant difference between groups, as appropriate. Pearson's correlation was used to determine the relationship between the knowledge scores and the attitude scores. To identify independent determinants of the total knowledge scores and attitude scores, we used multivariable linear regression models. A p-value of < 0.05 was considered statistically significant.

Results

Participants characteristics

A total of 153 questionnaires were received from 160 residents with a response rate of 95.63%. The basic information is shown in Table 1. Approximately two-thirds of the respondents (64.1%) were aged 25–30 years, and the majority (71.9%) were females. Most of the respondents had the highest education level of a doctoral degree (54.9%), followed by a master's (32.7%) and a bachelor's degree (12.4%). Residents who specialized in internal medicine represented about 82.4%, constituting the majority. More than half of the residents (57.5%) had not participated in OSA training before. There were 38.6% of the residents denied the experience of treating OSA patients.

Knowledge of OSA

The average knowledge score for all respondents was 12.6 ±2.7 (70% correct, Figure 1A and Table 2). We calculated separately the correct percentage of respondents for each part of OSA knowledge. In general, the correct rate of treatment

TABLE 1 Demographic characteristics of the participants ($N = 153$).

Variables	Characteristic	N	(%)
Age (years)	<25	46	(30.1)
	25-30	98	(64.1)
	>30	9	(5.9)
Gender	Male	43	(28.1)
	Female	110	(71.9)
Highest level of education	Bachelor	19	(12.4)
	Master	50	(32.7)
	Ph.D. or MD	84	(54.9)
Specialty	Internal medicine	126	(82.4)
	General medicine	7	(4.6)
	Other	20	(13.1)
Level of training	PGY 1	53	(34.6)
	PGY 2	49	(32.0)
	PGY 3	51	(33.3)
Had OSA training	Yes	65	(42.5)
	No	88	(57.5)
Treated OSA patients	Yes	53	(34.6)
	No	59	(38.6)
	Unsure	41	(26.8)

Ph.D., Philosophy Doctor; MD, Medical Doctor; PGY, Post Grad Year.

part (35.5%) is lower than 50%, while pathophysiology (83.2%), symptoms (88.7%), diagnosis (76.6%), and epidemiology (70.4%) are higher than 50%. Compared with residents without OSA training, residents with previous OSA training have higher knowledge scores related to the pathophysiology ($p = 0.015$), symptoms ($p = 0.001$), and treatments ($p = 0.022$) in Figure 1B and Supplementary Table S1.

Attitude toward OSA

Overall, the average OSAKA attitude score for all respondents was 3.6 ± 0.2 and detailed results are shown in Supplementary Table S2. Residents with different seniorities all considered OSA as an important clinical disorder and regarded it as important to identify suspected OSA patients. Regarding the confidence in identifying patients at risk for OSA, ability to manage OSA patients, and manage patients on continuous positive airway pressure (CPAP) therapy, favorable confidence scores (agree/strongly agree) were reported only in 38.0%, 27.5%, and 26.2% of all respondents, respectively (Figure 1C).

Analysis of differences between groups

Younger residents (<25 years old) had a lower average knowledge score (11.6 ±3.3) when compared with the older residents (25–30 years old, 13.0 ± 2.3; > 30 years old, 13.1 ± 3.0). There were no statistically significant differences between specialty or education level (Table 3). As expected, junior residents' average knowledge scores (PGY1, 11.7 ± 3.2) were significantly lower compared to senior residents' (PGY2, 13.1 ± 1.8; PGY3, 13.1 ± 2.7). Residents who had attended OSA training or treated OSA patients before had higher knowledge scores ($p < 0.05$). Aside from age, there were no significant differences observed in gender, the highest level of education, level of training, and OSA training experience in attitude scores.

Factors influencing knowledge and attitude scores

We found several variables had a statistically significant correlation with knowledge scores and attitude scores (Table 4). Further validation was performed using multivariate linear regression analysis to explore the independent determinants. The result indicates that knowledge scores are only significantly positively correlated with OSA training experience ($p = 0.002$). While attitude scores are only significantly positively correlated with age ($p < 0.001$) (Figure 2).

Training for OSA

To enhance physicians' recognition of OSA's role in clinical practice, we performed an exploratory survey to investigate the form of the sleep breathing disorder course received in the past and future in detail (Figure 3). The main source of previous OSA training is compulsory theory courses (49.0%). As for the future course format, small classes during residency training were the most popular and accounted for 29.1% of the participants. Compulsory theory courses (24.0%) ranked second in the list, followed by lectures (15.5%).

Discussion

The results of this study show that knowledge of OSA among residents was relatively acceptable. Specifically, the accuracy percentage of knowledge on the OSA treatment still needs to be improved. Unexpectedly, despite positive attitudes, the majority of residents in this study reported a generalized lack of confidence in identifying and managing OSA. Further investigation finds that OSA training experience increases knowledge, but not confidence, and the current form of sleep medicine course is not ideal. This finding is worrisome since physicians don't have confidence, let alone patients, resulting in low treatment adherence. Different from previous studies, our results emphasize the core deficiencies in medical education and remind substantial public health risks.

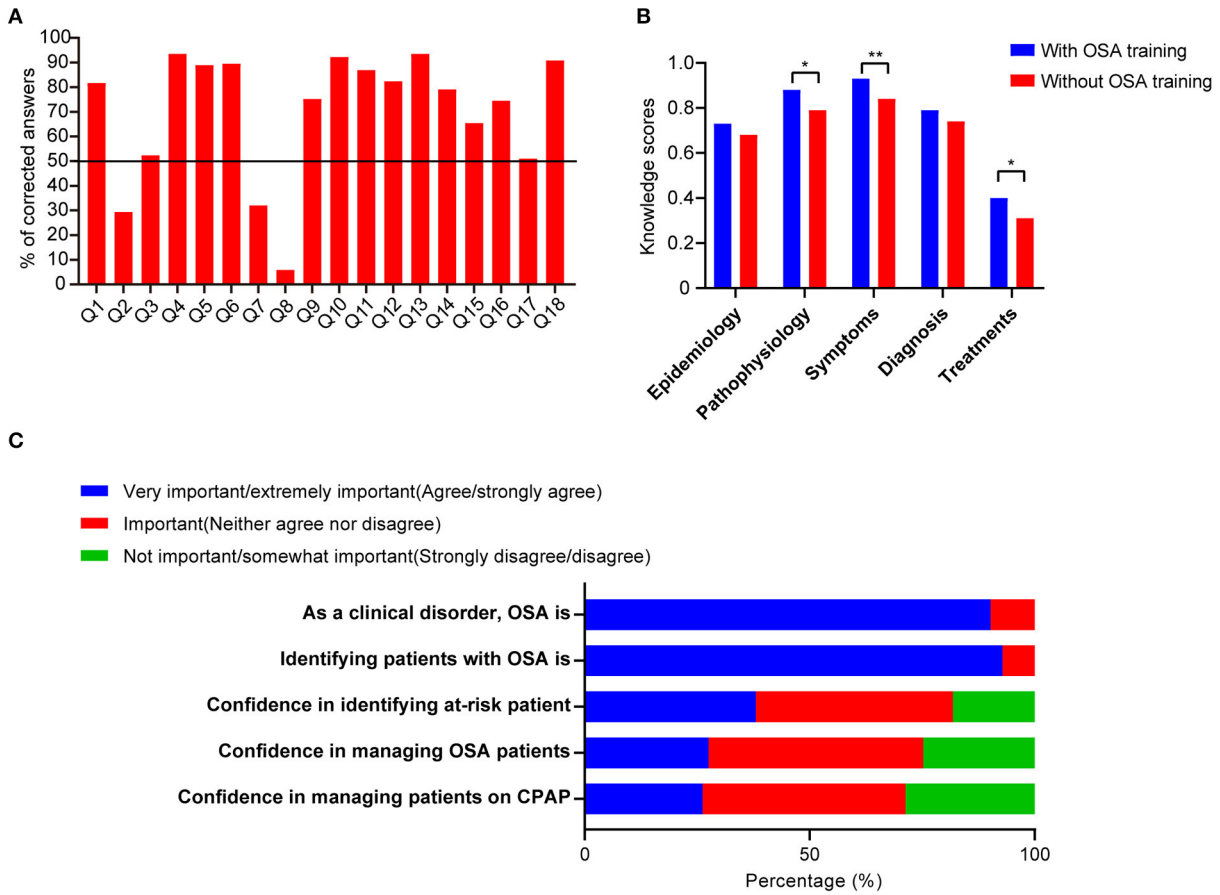


FIGURE 1
Results of knowledge and attitude scores. **(A)** Percentage of corrected answers among the knowledge items. **(B)** The bar graph demonstrated a comparison of knowledge scores related to different characteristics among residents who had OSA training education or not. **(C)** Comparison of the composition of the responses in the attitude scores. *$p < 0.05$, **$p < 0.01$.

In this study, we found that the mean knowledge score was 12.6 (±2.7), with a mean correct rate of 70%. To better assess our results, a comparison to previous studies is also shown as follows. In Nigeria, the mean knowledge score of resident doctors in Internal Medicine was 10.7 (59.4%) (24), and internists from the United States (Washington University Physicians Network) was 13.3 (72.2%) (13). The results of the present study lie midway between the two literature results. For primary care physicians, the mean rate of correct varied from Latin American (25) (60%) to the Middle East and North Africa regions (70%) (26). These study results reveal the highly heterogeneous geographical heterogeneity which may be explained due to differences in sleep medicine education and training. There are also differences in the knowledge scores in different medical specialties. The mean rate of correction is around 55% among speech-language pathologists and dentists (27, 28). Also, Years of medical training appeared to be associated with an increase in correct responses rate, from recent graduates (53.5%) to practicing physicians (60.4%) (29). Nigerian graduating medical students reported the lowest score (42 %) (30). Putting our results in a global context, knowledge of OSA among residents was relatively acceptable since the correct rate is close to the highest score (US 72.2%) and higher than the lowest score reported so far (13).

When compared with other domestic studies, the mean knowledge score of the residents in the resident training program is higher than that of general practitioners in community medical institutions but still lower than that of specialist physicians, such as otolaryngologists and pulmonary physicians (31, 32). Regretfully, none of the residents answered all the questions correctly. When it comes to each problem, the lowest correct answer in this study was regarding laser-assisted uvuloplasty as an appropriate treatment for severe OSA (5.9%). Only 29.4% of the residents correctly answered the

TABLE 2 Specific items of knowledge questions and the proportion of correct answers ($N = 153$).

Knowledge questions	Correct answer	Number of correct responses	
		N	(%)
Q1. Women with OSA may present with fatigue alone	True	125	(81.7)
Q2. Uvulopalatopharyngoplasty is curative for a majority of people with OSA	False	45	(29.4)
Q3. The estimated prevalence of OSA among adults is between 2 and 10%	True	80	(52.3)
Q4. The majority of patients with OSA snore	True	143	(93.5)
Q5. OSA is associated with hypertension	True	136	(88.9)
Q6. An overnight sleep study is the gold standard for diagnosing OSA	True	137	(89.5)
Q7. CPAP (continuous positive airway pressure) therapy may cause nasal congestion	True	49	(32.0)
Q8. Laser-assisted uvuloplasty is an appropriate treatment for severe OSA	False	9	(5.9)
Q9. The loss of upper airway muscle tone during sleep contributes to OSA	True	115	(75.2)
Q10. The most common cause of OSA in children is the presence of large tonsils and adenoids	True	141	(92.2)
Q11. A craniofacial and oropharyngeal examination is useful in the assessment of patients with suspected OSA	True	133	(86.9)
Q12. Alcohol at bedtime improves OSA	False	126	(82.4)
Q13. Untreated OSA is associated with a higher incidence of automobile crashes	True	143	(93.5)
Q14. In men, a collar size 17 inches or greater is associated with OS.	True	121	(79.1)
Q15. OSA is more common in women than in men	False	100	(65.4)
Q16. CPAP is the first line of therapy for severe OSA	True	114	(74.5)
Q17. Less than 5 apneas or hypopneas per hour is normal in adults	True	78	(51.0)
Q18. Cardiac arrhythmias may be associated with untreated OSA	True	139	(90.8)
Total OSA Knowledge score [mean (SD)]		12.6	(2.7)

OSA, obstructive sleep apnea, CPAP, continuous positive airway pressure.

question "uvulopalatopharyngoplasty is an effective therapy for most OSA patients." Comparing the results of other studies, the correct rate for the same question is 64% in North Africa and 81.8% in the United States (13, 26). Less than half of the residents correctly answered the question "CPAP therapy may lead to nasal congestion" (32.0%). These results suggested that there was a lack of knowledge among residents regarding OSA treatment in the present study. Consistent with previous studies, most physicians ranked surgical treatment as more important than CPAP therapy (25). As the first-line therapy for OSA, CPAP adherence in China has been relatively much lower than that in Western countries (33). Insufficient and incorrect knowledge of OSA treatment may influence the patient's choice of therapy. Despite the highly educated majority (Master's degree or higher), nearly two-thirds of the residents had not been exposed to any courses about OSA. Indeed, we have observed significant differences between participants with and without OSA training in mean knowledge scores. Similar statistical differences were also observed in age and level of training, which further confirms the role of clinical experience in improving OSA knowledge.

The mean attitude score was 3.6 ($\pm$0.6). We found that over 90% of the residents considered both OSA as a clinical disorder and identifying possible OSA patients very/extremely important. None considered these two aspects unimportant. However, only a minority of the residents either strongly agreed or agreed that they had confidence in identifying patients at risk for OSA (38%). Even with higher knowledge scores, the confidence is generally lower than primary care physicians in Latin America (73.5%), internal medicine residents in Nigeria (72%), and even graduating medical students (41%) (24, 25, 30). When it comes to confidence in managing OSA patients or CPAP therapy, the favorable proportion (strongly agreed or agreed) was even lower than 30%. In contrast to previous studies conducted in other countries, our results showed lower confidence despite the leading knowledge and attitude score. Lack of confidence in identifying potential OSA patients can further aggravate the underdiagnosis and misdiagnosis, and these patients cannot be referred promptly, leading to delays in treatment. Also, the ability of OSA diagnosis and treatment is of equal importance. Although traditionally suspected OSA patients were referred to a sleep specialist, the current diagnosis and treatment journey is cumbersome, time-consuming, and often frustrating, clearly affecting treatment adherence (3). In contrast to the increasing trend of OSA prevalence, workforce shortages in sleep medicine are expected to become more severe in the coming years (34). Since it is assumed that the influx of new sleep physicians is far from sufficient to replace those who are retiring. As OSA is a common chronic condition in need of a comprehensive

TABLE 3 Association between demographic characteristics and means of OSA knowledge and attitude score.

Variables	Knowledge score		Attitude score	
	Mean (SD)	*p*-value	Mean (SD)	*p*-value
Age (years)		**0.009**		**0.001**
<25	11.6(3.3)	**0.003***	3.3(0.6)	**<0.001***
25–30	13.0(2.3)	0.940†	3.7(0.6)	0.530†
>30	13.1(3.0)	0.120‡	3.8(0.7)	**0.020**‡
Gender		**0.017**		0.430
Male	11.8(3.4)		3.5(0.8)	
Female	12.9(2.4)		3.6(0.6)	
Highest level of education		0.196		0.282
Bachelor	13.3(2.2)		3.5(0.7)	
Master	12.9(2.5)		3.7(0.6)	
Ph.D. or MD	12.3(2.9)		3.6(0.7)	
Specialty		0.050		0.511
Internal medicine	12.8(2.7)		3.6(0.6)	
General medicine	10.3(3.1)		3.3(0.6)	
Other	12.3(2.9)		3.6(0.8)	
Level of training		**0.013**		0.065
Post grad year 1	11.7(3.2)	**0.012**§	3.5(0.7)	
Post grad year 2	13.1(1.8)	0.945 ‖	3.7(0.6)	
Post grad year 3	13.1(2.7)	**0.009** ¶	3.7(0.6)	
Had OSA training		**0.002**		0.591
Yes	13.4(2.4)		3.7(0.6)	
No	12.0(2.8)		3.6(0.7)	
Treated OSA patients		**0.003**		0.445
Yes	13.3(2.5)	**0.002** **	3.6(0.5)	
No	11.7(3.0)	**0.011** ††	3.5(0.8)	
Unsure	13.1(2.2)	0.704 ‡‡	3.7(0.6)	

*p-value:<25 vs. 25–30; †p-value: 25–30 vs.>30; ‡p value:<25 vs. >30; §p value:PGY1 vs. PGY2; ‖ p-value:PGY2 vs. PGY3; ¶p value:PGY1 vs. PGY3; **p-value: Yes vs. No; ††p value: no vs. unsure; ‡‡p value: yes vs. unsure. Significant differences are in bold.

TABLE 4 Correlation analysis of the knowledge score and the attitude score.

Variables	Knowledge score		Attitude score	
	r	*p*-value	r	*p*-value
Age	0.217	**0.007**	0.337	**<0.001**
Gender	0.113	0.117	0.064	0.430
Highest level of education	−0.140	0.085	−0.079	0.334
Specialty	−0.122	0.133	−0.025	0.755
Level of training	0.210	**0.009**	0.171	**0.035**
Had OSA training	0.250	**0.002**	0.044	0.591
Treated OSA patients	0.254	**0.002**	0.059	0.472

Significant differences are in bold.

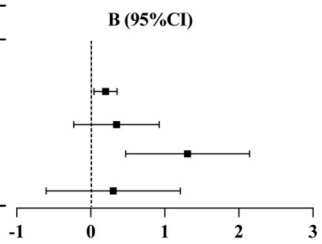
chronic condition management approach, the current disease management pattern is not enough and more doctors are needed to participate in the management of OSA (9). It is necessary to strengthen the training and education of residents and help them increase confidence in treating OSA patients. On the one hand, increasing resident exposure may affect subspecialty choice and help to improve the current workforce shortage in sleep medicine. On the other hand, residents' complete knowledge and confident attitudes can help provide adequate patient education and increase patients' confidence and long-term compliance (35).

Junior residents had a significantly lower average knowledge score than senior residents. Residents who attended OSA training or treated OSA patients in the past had higher knowledge scores. Only 38.6% of the residents denied previous exposure to any OSA patients. Likewise, their mean knowledge scores were significantly reduced compared with those who had experience in managing OSA patients. Although the clinical management of OSA patients seemed effective in improving OSA knowledge, our analysis showed that a certain number of physicians (26.8%) answered "unsure" on the identification of patients, indicating a not optimistic situation and the possibility of missed diagnosis. No significant differences were detected between the above factors and attitude scores except for age. Further, we explored the independent determinants of the knowledge and confidence scores. Unexpectedly, OSA training is an important factor positively correlated with knowledge scores but not confidence scores. This reflects that current education can improve knowledge, but not confidence in OSA among residents.

The ability of physicians regarding OSA is a critical factor that influences the clinical suspicion of OSA and the likelihood of making appropriate referrals (36). Lack of physician knowledge about OSA leads to a misdiagnosis, missed diagnosis, and a delay in treatment. Untreated OSA is associated with the development of certain comorbid conditions and mortality, increased incidence of vehicular accidents, and reduced longevity (14, 37). With the high prevalence of sleep-disordered breathing recorded, OSA has increasingly become a public health concern (38). In the present, most surveys on current sleep medicine education reported are not satisfactory. In particular, for residency training programs, there are no unified curriculums or requirements so far. Strengthening residency education in OSA would help reduce the disease burden and prevent long-term complications. From a clinical perspective, increasing resident exposure to residents with board certifications in sleep medicine or sleep fellowship training would significantly improve the breadth of resident experience in the evaluation and treatment of sleep-related disorders. From didactic perspective, as exposure is associated with subspecialty choice, increasing resident exposure may help to improve the current shortage of sleep specialists/clinics.

A

Variables	B	95% CI	*p*-value
All			**0.004**
Age	0.147	-0.049 to 0.343	0.140
Level of trainning	0.369	-0.210 to 0.949	0.210
Had OSA training	1.341	0.496 to 2.186	**0.002**
Treated OSA patients	0.970	-0.054 to 1.995	0.063



B

Variables	B	95% CI	*p*-value
All			**0.001**
Age	0.470	0.235 to 0.705	**<0.001**
Level of trainning	-0.015	-0.708 to 0.679	0.967
Had OSA training	0.594	-0.418 to 1.606	0.248
Treated OSA trainning	-0.521	-1.748 to 0.706	0.403

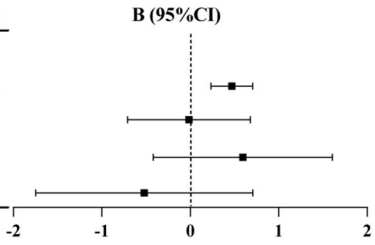


FIGURE 2
Multiple linear regression analysis revealed factors influencing knowledge **(A)** and attitude scores **(B)**. Significant differences are in bold.

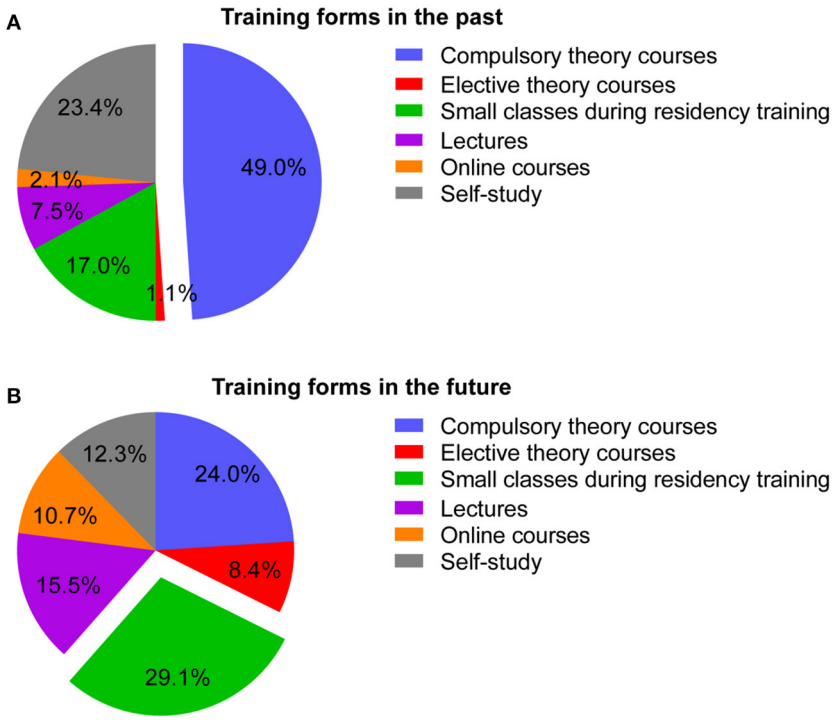


FIGURE 3
Composition of the form of the sleep breathing disorder course received in the past **(A)** and chosen in the future **(B)**.

Given the current condition of low confidence and lack of relevant OSA training in resident physicians, we further explored the effective training forms to improve future medical education. In the additional component of this survey, the willingness to participate in sleep breathing disorders-related courses and their specific forms were investigated. Almost all

residents enthusiastically agreed that sleep breathing disorders should be included in medical education. As to specific course forms, small classes during residency training were chosen as the first choice instead of compulsory theory courses. Small classes during clinical rotation can provide case-based learning and help to apply the theory to clinical practice. Besides, this course form may be more interactive and thereby provide a better understanding of CPAP treatment (39). Compared with traditional courses, small classes have the advantages of flexible time, short duration, and high participation, especially during clinical rotations. Since Chinese resident physicians have a heavy clinical workload, this kind of active learning is more effective and was most favored by Chinese resident physicians in the present study. Thus, in order not to increase the additional burden on resident physicians, we recommend the provision of a course format change in the future. Moreover, open access to residency programs to sleep centers where infrastructure exists to deliver a clinical experience in sleep disorders should be encouraged. On-site teaching regarding OSA knowledge can make it vivid and easier to comprehend. Additionally, more creative mechanisms to enhance OSA training are needed. For instance, remote education can be used as an effective strategy to provide sleep medicine courses. This allows residents to learn during the fragmented time.

There are strengths and limitations to the present study. This was the first study to evaluate the knowledge and attitudes of OSA among residents in residency training programs in China. Conducted in the top-ranked residential training hospitals, the results are representative, residents here lack confidence, let alone in the country. Another strength of this study was the exploration of specific forms of the sleep-breathing disorder course, providing important references for future residency training. The limitations of this study included its relatively smaller sample size. Additionally, the confidence of residents in the OSAKA sleep questionnaire may not necessarily match competence in clinical work. Thus, practice questions need to be evaluated in future studies.

Conclusion

This study revealed that despite adequate OSA knowledge among residents, they still have low confidence in OSA management. OSA training can only positively affect knowledge scores but not confidence scores. This reflects that current education does not increase physicians' confidence in the management of patients with OSA, which may affect subsequent treatment compliance and pose an underappreciated public health risk. More attention should be paid to strengthening residency education on OSA management, helping reduce the disease burden, and preventing long-term complications. In the future, simply adding courses is far from enough, improvements in content and form focusing on enhancing the physicians' confidence are strongly warranted.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Peking Union Medical College Hospital (Approval No. S-K 954). The patients/participants provided their written informed consent to participate in this study.

Author contributions

RC and JL conceived and designed the study. RC and LS acquired the data. LS analyzed the data and drafted the manuscript. YX and JL critically revised 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

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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.2022.973884/full#supplementary-material

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Promoting children's sleep health: Intervention Mapping meets Health in All Policies

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Background: To design a comprehensive approach to promote children's sleep health in Amsterdam, the Netherlands, we combined Intervention Mapping (IM) with the Health in All Policies (HiAP) perspective. We aimed to create an approach that fits local infrastructures and policy domains across sectors.

Methods: First, a needs assessment was conducted, including a systematic review, two concept mapping studies, and one cross-sectional sleep diary study (IM step 1). Subsequently, semi-structured interviews with stakeholders from policy, practice and science provided information on potential assets from all relevant social policy sectors to take into account in the program design (HiAP and IM step 1). Next, program outcomes and objectives were specified (IM step 2), with specific objectives for policy stakeholders (HiAP). This was followed by the program design (IM step 3), where potential program actions were adapted to local policy sectors and stakeholders (HiAP). Lastly, program production (IM step 4) focused on creating a multi-sector program (HiAP). An advisory panel guided the research team by providing tailored advice during all steps throughout the project.

Results: A blueprint was created for program development to promote children's sleep health, including a logic model of the problem, a logic model of change, an overview of the existing organizational structure of local policy and practice assets, and an overview of policy sectors, and related objectives and opportunities for promoting children's sleep health across these policy sectors. Furthermore, the program production resulted in a policy brief for the local government.

Conclusions: Combining IM and HiAP proved valuable for designing a blueprint for the development of an integrated multi-sector program to

promote children's sleep health. Health promotion professionals focusing on other (health) behaviors can use the blueprint to develop health promotion programs that fit the local public service infrastructures, culture, and incorporate relevant policy sectors outside the public health domain.

KEYWORDS

sleep, Intervention Mapping, program development, Health in All Policies (HiAP), policy, children, childhood, intervention development

Introduction

Healthy sleep is vital for children's psychosocial and physical health (1), and preventing non-communicable diseases such as diabetes (2) and cardiovascular disease in later in life (3). Sleep health is a five-domain concept, consisting of, sleep duration [i.e., 9 h of sleep or more for children aged 6–13 years old (4)], regular sleep timing, good sleep efficiency (i.e., ease of falling and staying asleep), sleep quality, and daytime wakefulness (5). Currently, many children experience poor sleep health, with declining sleep duration in the past decades (6) and poor sleep efficiency and sleep quality being widely prevalent (7–9). Promoting children's healthy sleep is therefore an important public health challenge (10).

Thus far, programs that aimed to promote children's healthy sleep have shown only minor effects, if any (11). A reason for this may be the lack of a systematic, evidence-based program development process (11, 12), which is crucial for a program to target relevant determinants *via* appropriate behavior- or environmental change techniques. Another reason may be that previous programs were insufficiently adapted to fit targeted policy infrastructures. Sustainable implementation requires in-depth knowledge of the existing local context. Without an in-depth development process, the program may neglect the complexity of the health problem and interrelated factors, which reduces the chances of sustainable success (12). An additional reason for programs' limited success thus far may be the lack of community stakeholder participation during program development and implementation, which is key in achieving program acceptability and appropriateness (12, 13). Lastly, the lack of rigid epidemiological evaluations has thus far made it impossible to distill (in)effective elements from existing programs (11, 12, 14).

Intervention Mapping (IM) provides a framework for systematically developing health promotion programs (12). IM is specifically designed to achieve sustainable success within complex systems. It also provides support to program developers to create programs that are grounded in theory and evidence. It further encourages taking into account the system related to the health problem and considers potential interrelationships between factors, activities, stakeholders, and settings. Overall, IM provides guidance to include the most important determinants of the health problem in the relevant social-ecological context and to target these determinants *via* appropriate methods, as one coordinated whole. A noteworthy strength of this approach is that it emphasizes the importance of community stakeholder participation throughout the research, development, and implementation process of the program. Although IM will create a rich overview of the complexity of the health problem and promotes community participation in the creation of intervention actions, it does not necessarily promote sustainable impact.

To create sustainable and positive impact on children's sleep health within the complex system children live in, higher socio ecological levels (e.g., policy/society) need to be taken into account. One way to do this is by taking a Health in All Policies (HiAP) perspective (15), which may bring additional determinants, stakeholders, and assets across public policies to light. HiAP promotes active and systematic incorporation of health across important policy sectors (16). Public policy is the foundation for most health promotion work (17) and some previous health promoting programs that include policy action(s), to positively stimulate the underlying determinants, have shown to be effective (18). Furthermore, many of the determinants that influence health are not solely influenced by the public health and health care policy sectors. Therefore, instead of a program implemented in or by solely one policy sector, coordinated efforts on all relevant public policies (e.g., education, social security, and living environment) are needed to create impact on the system as one integrated multi-sector approach to optimally promote children's sleep health.

This paper describes a blueprint for the development of an integrated multi-sector program to promote children's sleep health in Amsterdam, the Netherlands, using a novel approach combining IM with HiAP.

Materials and methods

The Amsterdam Healthy Sleep Project

The Amsterdam Healthy Sleep Project started in 2016 as a collaboration between the Amsterdam University Medical

Abbreviations: HiAP, Health in All Policies; IM, Intervention Mapping.

Centers (Amsterdam UMC, location VU University Medical Center), the Public Health Service of Amsterdam, and the Vrije Universiteit Amsterdam. One researcher (LB) was appointed at two organizations (Amsterdam UMC and Public Health Service of Amsterdam) and closely involved with two other organizations. One organization was "The Amsterdam Healthy Weight Approach" of the City of Amsterdam, which is a long-term municipal health-promoting program that reaches into every domain of a child's life (19). The second organization was "Sarphati Amsterdam" research institute, which is a collaboration between the City of Amsterdam and the five knowledge institutes in Amsterdam. These organizations are part of the public health sector, and initiated this project since no programs to promote children's sleep existed in Amsterdam yet. The managers of the two latter organizations were closely involved, regularly updated by the research team, and their feedback was taken into account throughout the project. The overall project aim was to systematically develop a program for promoting healthy sleep among primary school children in Amsterdam using IM. The public health sector chose a focus on primary school aged children (4–12 years in the Netherlands) since many policy- and practice organizational structures, as well as local city council orders (i.e., local governmental decisions and agreements), are organized around the schools systems and the local political priority at the time was focused on primary school children. All studies that were part of this project were approved by the Medical Ethics Committee of the VU University Medical Center (protocol no. 2017.013 and 2018.170).

IM is a six-step protocol including (1) logic model of the problem; (2) program outcomes and objectives, logic model of change; (3) program design; (4) program production; (5) program implementation plan; and (6) evaluation plan. This paper describes our approach to the first four steps of the IM protocol. Below we explain step-by-step how the combination of IM and HiAP was applied for these four steps of IM. Figure 1 describes this development process.

Step 1. Logic model of the problem

Creating a logic model of the problem produces a schematic overview of the factors related to a specific health problem, in this case, children's inadequate sleep health within the local context of the City of Amsterdam, which includes a population with various cultural backgrounds. This model is used to define the health problem, and to identify the ecological levels (e.g., interpersonal, community level) and related stakeholders connected to the problem. Creating a logic model of the problem consists of four tasks: (1) creating planning groups; (2) conducting a needs assessment, (3) describing the local context for the program, and (4) stating program goals. Regarding the first tasks, one of the planning groups as part of this project was an *advisory panel*, which included academic researchers with expertise in applying IM and developing preventative public health programs, sleep researchers, a somnologist, youth policy- and youth health advisors, a communication professional from the City of Amsterdam, and a policy manager. An advisory panel meeting was held two times on location, followed by individual consultation sessions with advisors separately. In addition to this advisory panel, we consulted a *parent advisory panel* within the community ($n = 4$–7) two times during this project. In addition, we consulted a group of parents working at the Public Health Service ($n = 7$) two times to test materials that were used in the parent advisory panel (e.g., a timeline exercise where parents mapped behaviors before bedtime) and to assist with creating performance- and change objectives.

The *needs assessment* (IM) included a combination of acquiring qualitative, quantitative, and mixed-methods data (see Figure 1). We conducted a systematic review to summarize the longitudinal evidence for factors related to children's sleep health (i.e., sleep duration, sleep quality, and sleep timing) (20). Next, two concept mapping studies were performed with different stakeholder groups (i.e., children aged 9-12 years, parents of children aged 4-12 years, and professionals) from various cultural backgrounds to explore the perceived determinants of children's inadequate sleep health (21, 22). These mixed-method studies were supplemented with a cross-sectional study among a culturally diverse group of children and their parents in Amsterdam ($n = 382$) to explore potential factors related to children's sleep (i.e., sleep duration, sleep quality, and sleep timing). A detailed description of the results of these studies are placed outside the scope of this paper and can be found elsewhere (20–23).

To get insight into the local context (i.e., local resources, capacities, and policy infrastructures) where the program will be implemented, and potentially existing local programs or program elements, an *asset assessment* was conducted (IM and HiAP) (12, 24). For this assessment, we used the framework created by Springer and Evans (24). This framework starts with identifying the settings where children and parents can be reached (e.g., neighborhoods, schools). When the settings had been mapped, we explored the environmental assets within those settings as part of four domains: (1) social environment; (2) information environment; (3) policy/practice environment (including the HiAP perspective); and (4) physical environment. To retrieve information on potential assets, we held 64 semi-structured interviews, between January 2019 and September 2020, with stakeholders and professionals in the field of policy, practice, and science. Local policy sectors were considered relevant when they were related to one or more behavioral- or environmental factors underlying children's inadequate sleep health. Additionally, HiAP created a focus on public administration and organization during these interviews. This directed the focus toward roles, assignments, and responsibilities of the different stakeholders. When the logic model of the problem was completed with the information from the needs

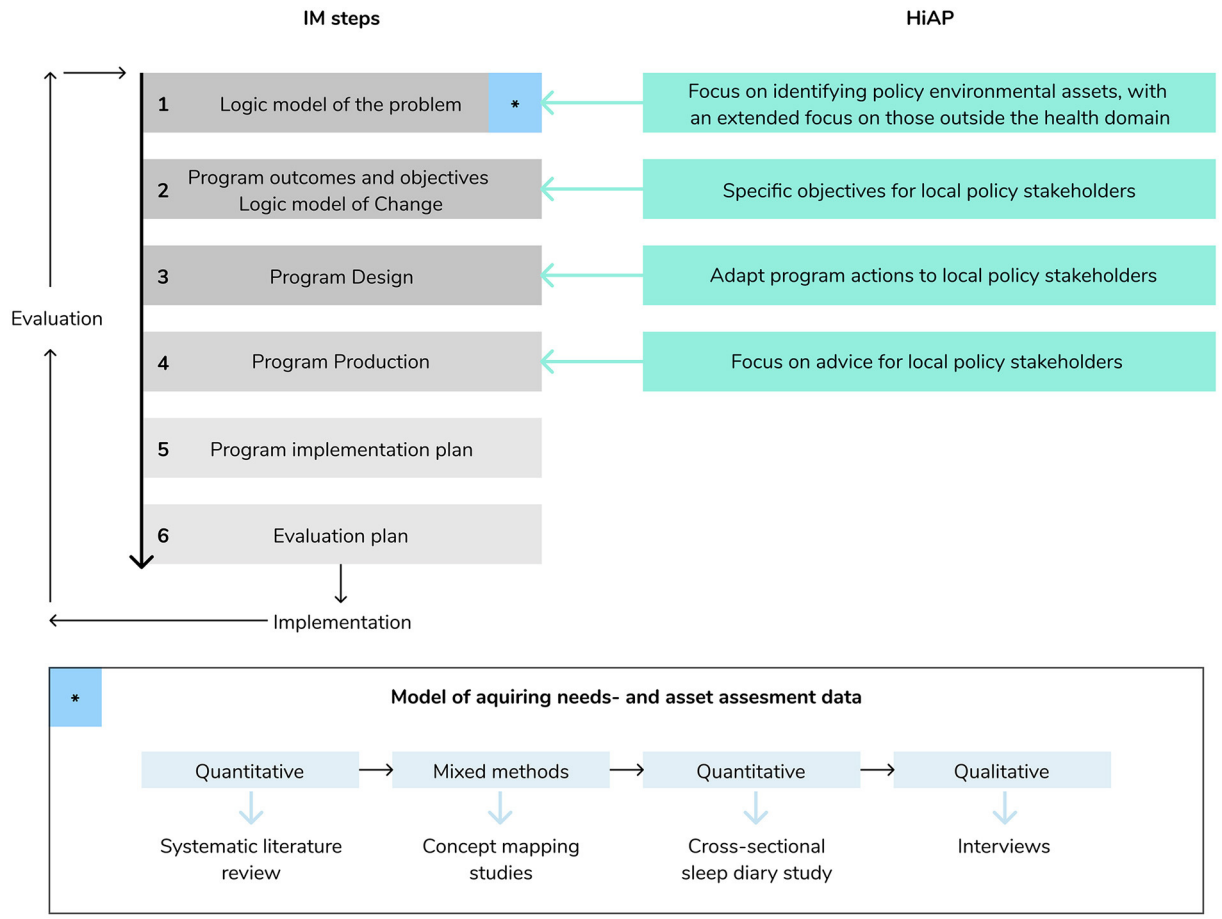

FIGURE 1
Development process combining IM with HiAP.

assessment and the asset assessment, the program goals were specified.

Step 2. Logic model of change

Creating a logic model of change produces a schematic overview of expected program effects and what is required to promote children's sleep health. Creating a logic model of change (IM) consists of five tasks: (1) stating expected behavioral- and environmental outcomes, (2) specifying performance objectives, (3) selecting personal determinants, (4) specifying change objectives, and (5) combining this in one structured schematic overview. The factors related to children's sleep health were used to determine the behavioral and environmental outcomes. Behavioral outcomes are behaviors that need to change as a result of the program at the level of the children; e.g., "children engage in a relaxing bedtime routine". Environmental outcomes are environmental conditions that need to change in stakeholders at the interpersonal (e.g., parents), organizational (e.g., community and welfare organizations, parent- and child teams social services), community (e.g., community leaders, religious leaders, community center staff members), and society/policy levels (i.e., policy officers working for the relevant policy sectors). These outcomes were then further specified into performance objectives to provide a clear and exact description of the desired actions of stakeholders at the individual (i.e., children) and higher social-ecological levels (e.g., parents, child healthcare professionals, teachers, policy makers) to reach the outcomes; e.g., "children create a relaxing bedtime routine together with their parents". To create change objectives (i.e., what needs to change related to the determinant to reach the performance objective), the performance objectives were combined with selected personal determinants. Personal determinants are factors that exist within individuals (children and other stakeholders) and can be changed or influenced by public health programs, such as knowledge of sleep promoting practices, attitude toward these practices, and the confidence in one's own ability to obtain such practices (i.e., self-efficacy). Examples of change

objectives linked to this performance objective are "parents list the reasons for creating a relaxing bedtime routine" (knowledge) and "parents express positive feelings toward a relaxing bedtime routine" (attitude). Supplementary Table S1 presents an explanation for the selection of personal determinants of parents, which was based on our previous studies (20–23), other relevant literature (25–33), and theoretical models for health behavior (34–37). To select the personal determinants of children, the research team used the list of parental personal determinants and checked these on their relevance for children. The personal determinants were only excluded for children when this determinant was perceived as inappropriate for that performance objective. Matrices of change objectives were created. For this study, we focused on specifying the behavioral outcomes for children (aged 4–12 years) and environmental outcomes for parents (based on the interpersonal level) and the related performance and change objectives. See Table 1 for more examples. For each of these objectives, theoretical methods need to be selected and incorporated in practical applications, i.e., the actual program elements. These program elements need to be carefully tailored to the local context and culture, and developed together with different stakeholder groups. The objectives for stakeholders outside the intrapersonal and interpersonal level were not included in the logic models, because the higher-level environmental stakeholders differ per setting, while objectives for children and parents are relatively stable compared to other stakeholders. However, some examples are presented for different multi-sector policy stakeholders in Table 2. These objectives are linked to HiAP maturity stages; (0) unrecognized (i.e. no specific attention for the problem), (1) recognized (i.e. recognition of the problem and HiAP solution), (2) considered (i.e. preparatory HiAP actions on part of the problem), (3) implemented (i.e. HiAP investments in multiple problem areas), (4) integrated (i.e. quality HiAP processes integrated as part of policy), and (5) institutionalized (i.e. systematic improvement of quality HiAP) (38).

Step 3. Program design

Designing the program includes selecting suitable change methods for behavioral- and environmental outcomes, and potential practical program elements. From the IM point of view, our aim was to design a coherent, deliverable program. The HiAP perspective contributes to the creation of a program that can be structurally embedded in existing organizational structures of public policy and practice. Consequently, we first mapped the existing organizational structure of the local policy environment. Next, we followed an iterative process wherein we selected potential practical applications *via* a context-driven HiAP approach. This was followed by an exploration of potential practical applications, mechanisms, and communication channels based on (1) feasibility, (2) usefulness, and (3) extent of implementation in existing policy and practice structures. For this, we used semi-structured interviews with different stakeholders, such as policy professionals, child healthcare professionals, and community management professionals. The exploration of potential practical applications was an iterative process, where every interview could lead to new potential applications and new stakeholders for an interview. This resulted in a set of program elements that fits this structure and therefore promotes successful implementation. Furthermore, to build upon what already exists in Amsterdam, we created an overview of existing practical applications and services for the behavioral-, environmental-, and personal factors of children's sleep health. Based on what already existed and the interviews with stakeholders, we created a set of potential practical applications that fit the local environmental structure and therefore promote successful implementation. This final set of program elements can be constituted as one multi-sector approach to promote children's sleep health within the local context of Amsterdam.

Step 4. Program production

Based on the program design, together with professionals from policy and practice, we created an extensive policy brief for the City of Amsterdam's aldermen and policy officers working for the policy sectors related to children's sleep and its underlying factors. During the design of this policy brief, continuous interaction between the research team, the teams of "The Amsterdam Healthy Weight Approach", "Sarphati Amsterdam" research institute, and policy makers, resulted in opportunities per relevant policy sector on how they can increase their impact on the behavioral- and environmental factors related to children's sleep health. For each policy sector, at least one policy officer was asked to collaborate in creating the policy brief. This policy brief aimed to promote the HiAP process from stage 0 "unrecognized", to stage 1 "recognized". The policy brief will help the aldermen and policy officers to recognize the problem and the solution of HiAP and offer a perspective on how to organize an effective approach to alleviate the problem (38).

Results

This section presents a stepwise description of the findings of the first four steps of IM.

Step 1. Logic model of the problem

We created a logic model of the problem (Figure 2). This model gives an overview of the identified quality of

TABLE 1 Examples of performance and change objectives for children and parents.

Performance objective	Personal determinants						
	Knowledge	**Awareness**	**Attitude**	**Self-efficacy**	**Skills**	**Perceived barriers**	**Subjective norm**
Behavioral/environmental outcome: Children obtain a relaxing bedtime routine/parents hold a relaxing bedtime routine for their child							
Children create a relaxing bedtime routine together with their parents	• List reasons for creating a relaxing bedtime routine • List relaxing activities	• Review current bedtime situation • Recognize the need to create a relaxing bedtime routine	Express positive feelings toward a relaxing bedtime routine	Express confidence in ability to create a relaxing bedtime routine with their parents			Experience that most children have a relaxing bedtime routine
Children adhere to the relaxing bedtime routine they created with their parents			Express positive feelings toward adhering to the relaxing bedtime routine	Express confidence in ability to adhere to the relaxing bedtime routine			
Parents talk to the other parent/caregiver about creating a relaxing bedtime routine for their child	Define a relaxing bedtime routine	Recognize the need to discuss their current bedtime situation	Express positive feelings about discussing a bedtime routine for their child, together with the other parent/caregiver	Express confidence in ability to talk to the other parent/caregiver about creating a relaxing bedtime routine for their child	Demonstrate ability to discuss with the other parent/caregiver about creating a relaxing bedtime routine for their child	Anticipate negative responses of other parent/caregiver toward creating a relaxing bedtime routine for their child	Explain that most parents/caregivers discuss creating a relaxing bedtime routine for their child
Parents create a relaxing bedtime routine together with their child	List reasons for creating a relaxing bedtime routine	Recognize the importance to create the bedtime routine together with their child	Express positive feelings toward a relaxing bedtime routine	Express confidence in ability to create a relaxing bedtime routine	Demonstrate ability to create a relaxing bedtime routine	Anticipate negative responses of their child about creating a relaxing bedtime routine	Experience that most parents/caregivers have incorporated a relaxing bedtime routine
Parents discuss the logic behind a relaxing bedtime routine with their child	Recall reasons for discussing the logic behind a new bedtime routine with their child	Recognize the need to discuss the logic behind a relaxing bedtime routine with their child		Express confidence in ability to discuss the logic behind a relaxing bedtime routine with their child	Demonstrate ability to discuss the logic behind a relaxing bedtime routine with their child		Explain that most parents/caregivers discuss the logic behind a relaxing bedtime routine with their child
Parents consistently adhere to the relaxing bedtime routine before taking him/her to bed	Recall their child's relaxing bedtime routine	Recognize the need to adhere to the relaxing bedtime routine of their child	Express positive feelings about consistently adhering to the relaxing bedtime routine before taking their child to bed	Express confidence in ability to carry out the relaxing bedtime routine with their child every day, regardless of the circumstances	Demonstrate ability to adhere to the created relaxing bedtime routine before taking their child to bed		

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TABLE 2 Examples of performance and change objectives for policy stakeholders.

Performance objective	Personal determinants						
	Knowledge	**Awareness**	**Attitude**	**Self-efficacy**	**Skills**	**Perceived barriers**	**Subjective norm**
Environmental outcome: Policy makers from various sectors incorporate children's sleep health and/or its underlying factors in their work							
Child health care and youth policy makers incorporate a broadly shared vision on HiAP (political and strategic) for children's sleep health and its underlying factors	Recall the relevance of incorporating a broadly shared vision on HiAP for children's sleep health	Recognize the importance of incorporating a broadly shared vision on HiAP for children's sleep health	Express positive feelings toward incorporating a broadly shared vision on HiAP for children's sleep health and underlying factors	Express confidence in ability to incorporate a broadly shared vision on HiAP for children's sleep health		Anticipate negative responses of council members toward incorporate a broadly shared vision on HiAP for children's sleep health	Experience that most municipalities incorporate a broadly shared vision on HiAP for children's sleep health
Public health policy makers collaborate with other sectors to prioritize children's sleep health (i.e., stakeholder engagement)	Recall the relevance of collaborating with other sectors to prioritize children's sleep health	Recognize the importance of collaborating with other sectors to prioritize children's sleep health	Express positive feelings toward collaborating with other sectors to prioritize children's sleep health	Express confidence in ability to collaborate with other sectors to prioritize children's sleep health	Demonstrate ability to advocate the importance of collaborating with other sectors to prioritize children's sleep health	Anticipate negative responses of policy stakeholders outside the public health domain toward collaborating to prioritize children's sleep health	Experience that within most municipalities policy sectors collaborate to prioritize children's sleep health
Education policy makers politically and administratively anchor the HiAP approach for children's sleep health and its underlying factors (i.e., sustainable implementation)	Recall the relevance of politically and administratively anchoring the HiAP approach for children's sleep health	Recognize the importance of politically and administratively anchoring the HiAP approach for children's sleep health	Express positive feelings toward politically and administratively anchoring the HiAP approach for children's sleep health	Express confidence in ability to politically and administratively anchor the HiAP approach for children's sleep health			Experience that most municipalities politically and administratively anchor the HiAP approach for children's sleep health
Social security and welfare policy makers incorporate HiAP in their policy documents to promote children's sleep health and its underlying factors	Recall the relevance of incorporating HiAP in their policy documents to promote children's sleep health	Recognize the importance of incorporating HiAP in their policy documents to promote children's sleep health	Express positive feelings toward incorporating HiAP in their policy documents to promote children's sleep health	Express confidence in ability to incorporate HiAP in their policy documents to promote children's sleep health			Experience that most municipalities incorporate HiAP in their policy documents to promote children's sleep health

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life outcomes, health outcomes, sleep outcomes, behavioral factors (on the interpersonal level; children), environmental factors (on the intrapersonal level; parents), and the personal determinants related to these factors. Most behavioral factors were related to sleep promoting practices, which can be defined as "a set of recommended behavioral- and environmental practices intended to promote healthy sleep" (39). Selected sleep promoting practices for this context included irregular sleep timing (i.e. bedtime variability), inadequate bedtime, inadequate amount of daytime physical activity, an unhealthy sleep environment (i.e. inadequate temperature, light or noise, uncomfortable bed), inability to let go of fear and worries and to relax, no bedtime routine, active activities close to bedtime (e.g. screen use, active games), emotional needs were not met, eating large amounts of food or products with a high amount of sugar or caffeine close to bedtime, inadequate exposure to daytime light, and the inability to fall asleep independently. The environmental factors on the level of parents included parental stress, poor sleep practices, inability to provide emotional support, and inadequate parenting practices (e.g., inability to set rules, monitor child's behavior, and create daily family routines). Both behavioral- and environmental factors relate to personal determinants. We identified eight personal determinants in total.

The logic model of the problem was complemented with an asset assessment (12, 24). Figure 3 illustrates some of the environmental assets for each of the four domains: social environment, information environment, policy/practice environment, and physical environment. The social environment included for example all personal assets of the important stakeholders and their network. The information environment included several types of information structures that could be used to reach the target population with a message *via* an existing communication channel. The policy/practice environment included the policies and practices, and existing local programs or program elements that can be exploited or improved to positively stimulate the underlying factors of children's inadequate sleep health. For example, social services and welfare support by the municipality already support families that are not yet financially independent, and this structure could be used to explore ways of providing further support, as financial instability creates a stressful family situation. The physical environment includes features of the built environment that could support children's adequate sleep health, such as housing and building. To select the program context, we integrated the HiAP perspective by including all relevant policy and practice assets for potential inclusion within the multi-sector program.

Based on the needs- and asset assessment, three program outcomes were set: (1) Children have healthy sleep practices; (2) Parents have healthy family sleep practices; (3) Multi-sectoral environmental assets support children and parents in healthy sleep practices, e.g., policy makers from various sectors incorporate children's sleep health and/or its underlying factors in their work.

Step 2. Logic model of change

We created a *logic model of change* to specify what performance objectives needed to be addressed to succeed in realizing the behavioral- environmental-, and program outcomes. This logic model of change was created for children (see Figure 4) and parents (see Figure 5). These logic models imply how a potential change in the personal determinants (e.g., knowledge, attitude, skills) is expected to impact the specified behavioral outcomes (e.g., healthy sleep practices) in children and parents. These change models also show how, in turn, more distal outcomes (i.e., sleep health and quality of life) are consequently impacted. These models of change are illustrative, not exhaustive, meaning that other changes besides parents' and children's personal determinants should be addressed eventually, such as higher-level environmental factors (e.g., characteristics of the built environment) and personal determinants of other stakeholders, e.g., policy makers, child healthcare professionals, and teachers. These logic models of change provide an overview of what factors need to be addressed *via* a health promoting approach within this local context. In a different context, these factors might be different according to the local context and culture. However, it is still unclear how these changes are to be realized. To clarify this, we applied IM to map what outcomes need to change, to create a whole of required changes and actions that together will make up the program. Tables 1, 2 present several illustrations of such created performance and change objectives. These objectives are not the program's messages and are only used by the program developers to match with appropriate evidence-based theoretical methods, and translate these methods into program elements including culturally sensitive messages.

Step 3. Program design

Creating the program goals, performance- and change objectives mapped the changes required to effectively impact children's sleep health. The next step in IM was to match these change objectives to appropriate theoretical methods for behavioral- or environmental change. However, to create a program that can be implemented in a durable and feasible way, these methods do not only need to be effective tools to change certain determinants, but also fit one's specific context of use. To ensure this match, we first carefully mapped Amsterdam's policy and professional practice infrastructures related to influencing (underlying factors of) children's sleep health (Figure 6). We displayed the organizational policy structure, the organizational practice structure, relevant local city council orders, and national

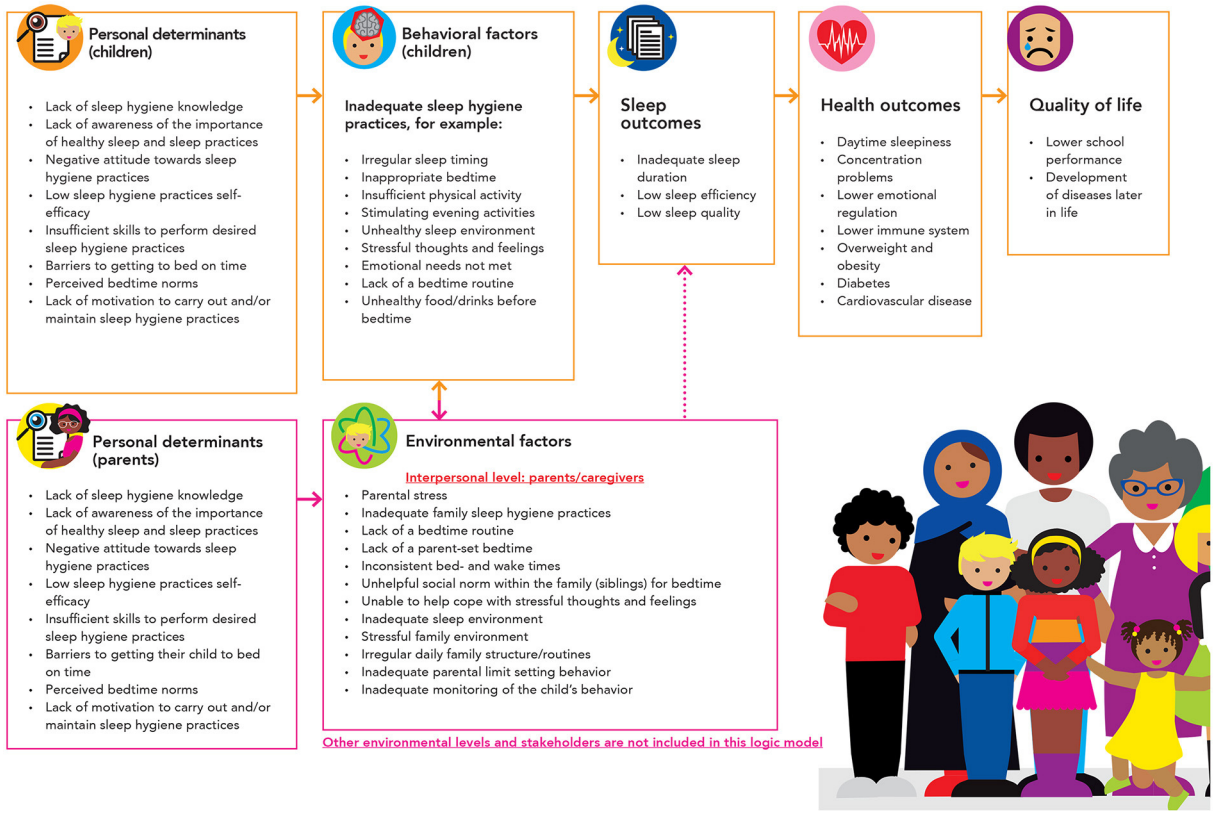

FIGURE 2
Logic model of the problem.

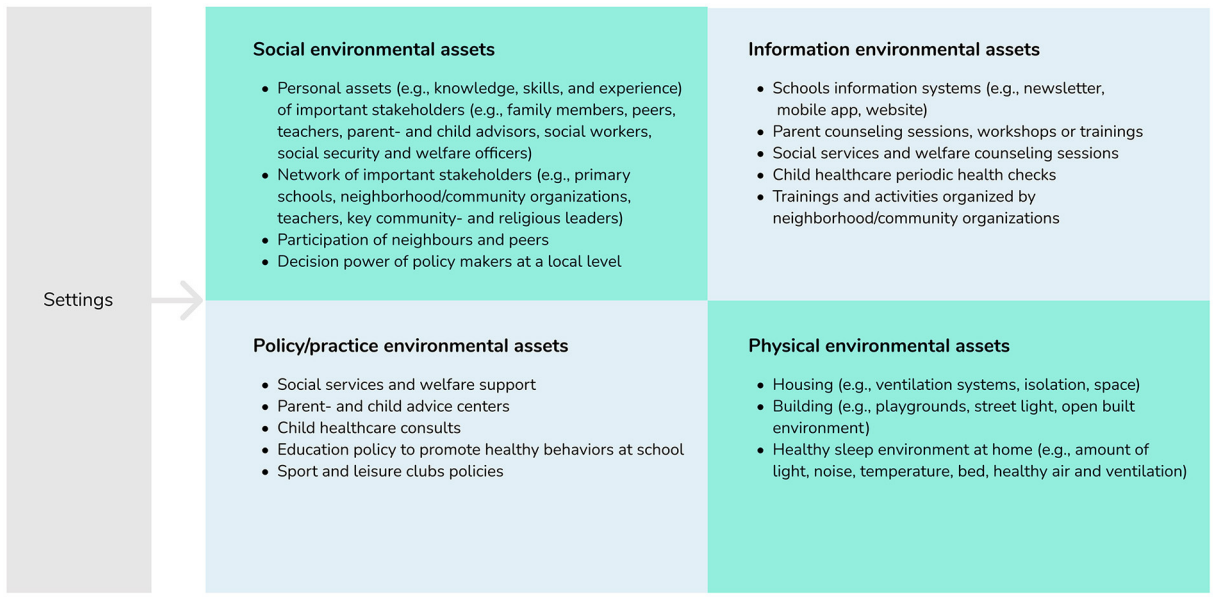

FIGURE 3
Environmental asset assessment, examples per domain.

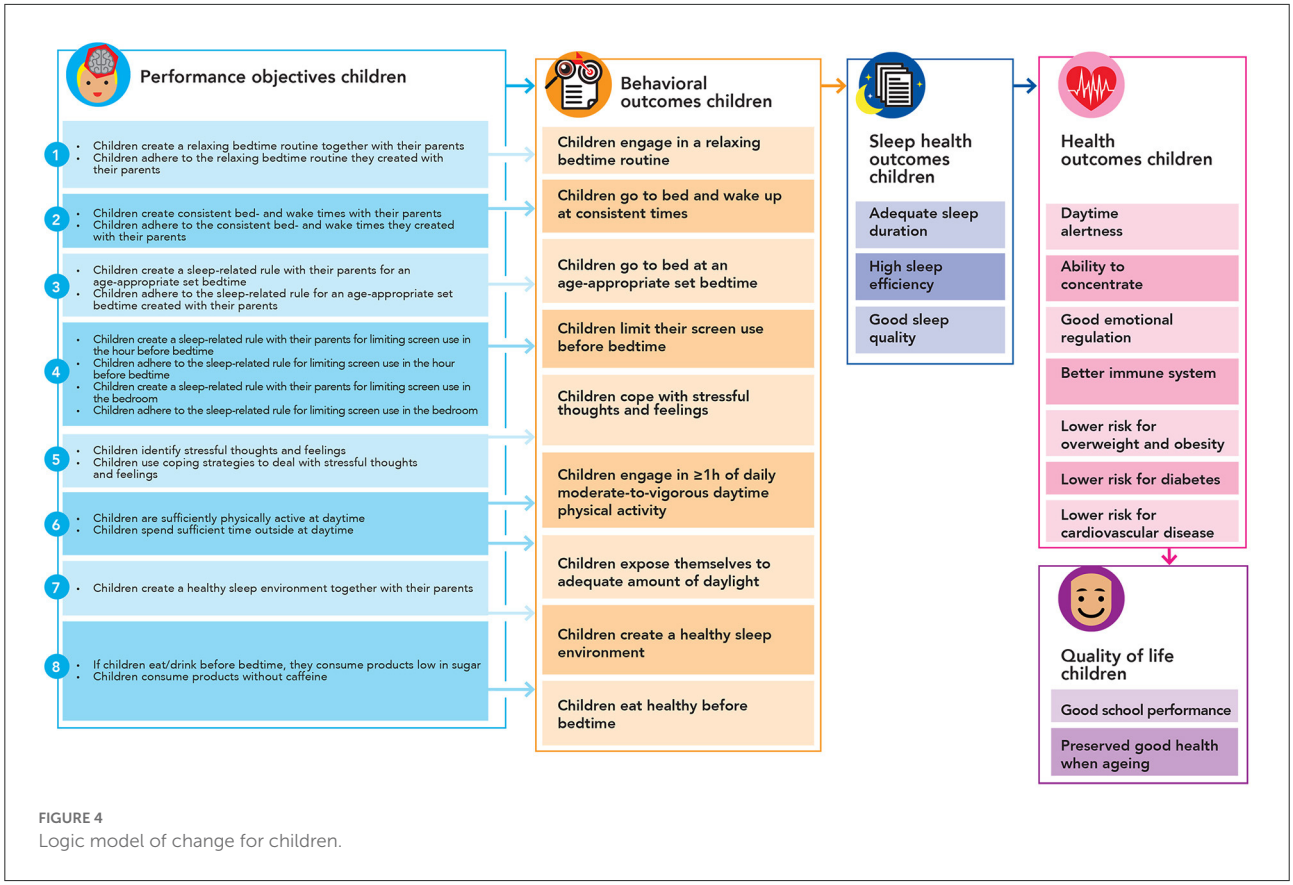

FIGURE 4
Logic model of change for children.

policies and organizations that are related to one or more organizational structures for policy and practice at the local level. We note that this overview is not exhaustive.

Table 3 presents the opportunities for sleep health in all policies for each identified public policy sector. We included all policy sectors within the social domain and an exploration of policy sectors outside the social domain. One example of an opportunity is that the education policy sector could incorporate sleep health and its underlying factors in education programs focused on promoting children's health. By promoting children's sleep health, they also promote education equality as well-sleeping children are better able to concentrate and perform within the education system.

Based on the results of the needs- and asset assessment, opportunities for program actions were created in close collaboration with policy- and practice stakeholders. Supplementary Table S2 presents these program actions linked to the policies presented in Figure 6. The program design was put into a physical end-product: a local policy brief. This document describes the opportunities and program actions for each policy sector. The target audience for this policy document are the aldermen and all policy officers at the City of Amsterdam, working in one of the included policy sectors.

Step 4. Program production

The product we created was the local policy brief. This policy brief creates awareness of the problem, the opportunities of HiAP as a solution to this problem, and clarity on potential program actions for each policy sector. *Via* the alderman and policy officers, the policy brief promotes the incorporation of children's sleep health and its underlying factors in multiple policy sectors in the city. The brief states the importance of children's sleep health related to each specific policy sector, sets out potential program actions for each sector, and describes how these sectors can effectively operationalize sleep health in their policy. The policy brief includes several infographics to increase comprehensibility. The full policy brief is in Dutch, not publicly available and therefore not included in this paper. The owner of this policy brief is the public health sector within the City of Amsterdam, and they are the responsible organization for advocating this policy brief and its implications within their organization. The policy brief was finalized and shared with the City of Amsterdam in February 2021. The policy makers responded positively to the proposed approach and potential health promoting actions. In the Amsterdam Health Policy brief (period 2021–2025) (40), that received unanimous support of the Amsterdam City Council in December 2021,

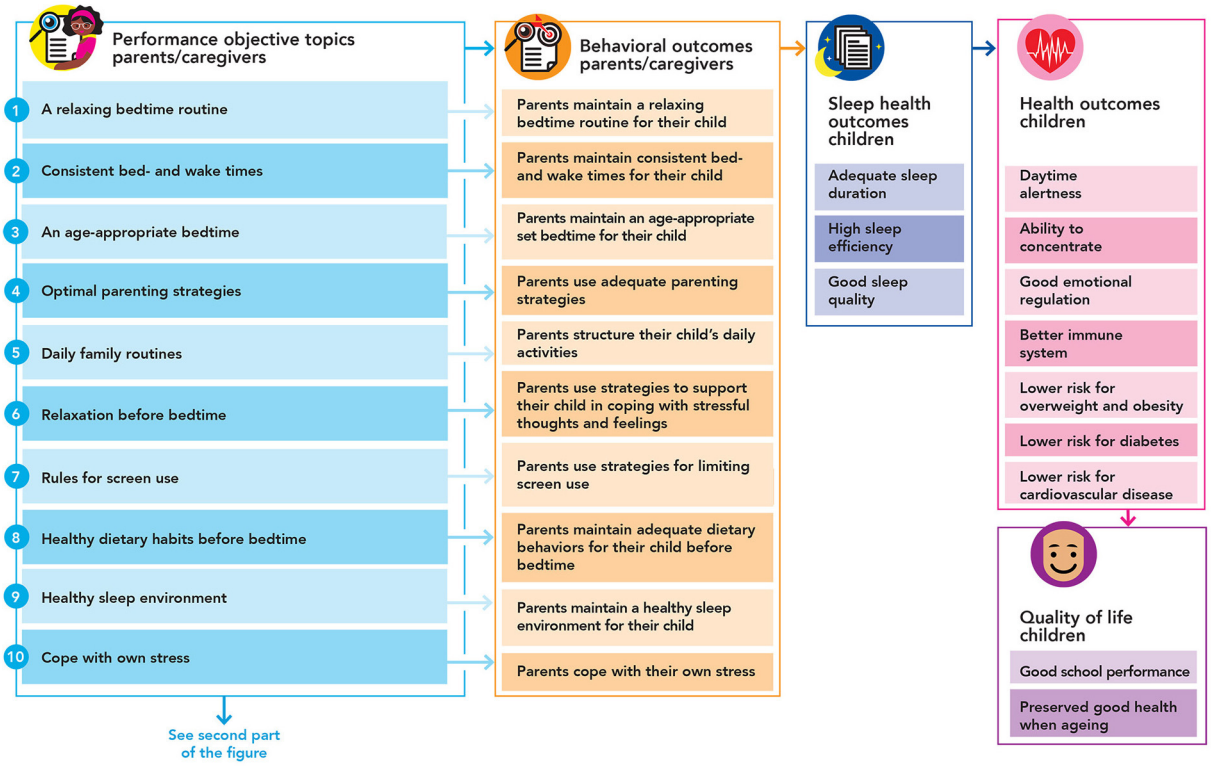

FIGURE 5
Logic model of change for parents.

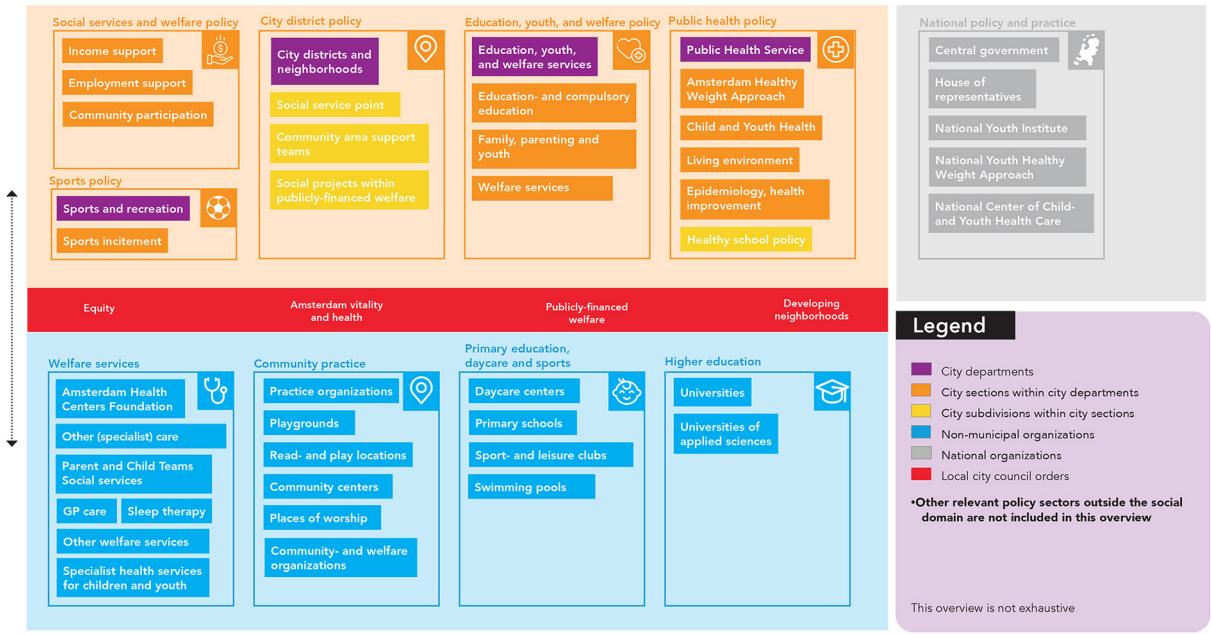

FIGURE 6
Overview of the local organizational system.

the topic of sleep health was adopted. The Amsterdam Health Policy is a joined policy brief that affects all parts of the local administration, which offers opportunities to realize the recommendations of the policy brief focused on children's sleep health.

Discussion

This paper describes a blueprint for the development of a program to promote children's sleep health by combining Intervention Mapping (IM) with Health in All Policies (HiAP). This resulted in a systematically developed outline to produce and structurally implement an integrated approach to promote children's sleep health across multiple policy domains, and a local policy brief.

As children's sleep health is influenced by a broad scope of various interconnected individual, social, and environmental factors (20), there is a need for a multi-level approach. IM provides a methodology to design such an approach in an evidence-based way (12). Combining IM with HiAP adds a focus on identifying the appropriate and relevant public policy sectors, and policy assets (i.e. existing local policy-related resources and capacities) to create an integrated, city-wide approach (15, 41). Many public policy sectors, (e.g. social security, education) influence (underlying factors of) children's sleep health (16, 41). By additionally including relevant non-public health policy sectors *via* HiAP, program outreach can be increased significantly (42). This combination of program development methodologies (i.e., IM with HiAP) could also benefit other health-behavior programs. Our approach takes the local (policy) context and culture into account and provides the most important stakeholders with tools to start changing factors related to (sleep) health behavior. The blueprint for program development that we created in this study is not restricted to the Amsterdam context but can be adapted to fit any local (policy) context, culture, and set of stakeholders.

One of the lessons learned while applying HiAP in our sleep health context was the importance of finding a joint interest within each policy sector that is related to the problem and use this common ground to build partnerships. Often, policy sectors other than the health sector are indirectly related to children's sleep *via* underlying factors, such as a stressful family situation or housing. However, in general, they did not view children's sleep health as a shared responsibility. As previous research showed, working from such a win-win starting point created stronger partnerships and more valuable results (43). To provide an example, many underlying factors of children's sleep health disproportionately affect families with a low socioeconomic position (44, 45). Since many of Amsterdam's municipal policy sectors are (partly) responsible for tackling the complex problem of (health) inequity, there could be a great deal of common ground. This can serve as a broad basis of support to engage policy makers from several policy sectors to create shared ownership in tackling

TABLE 3 Opportunities for sleep health in all policies for local policy in Amsterdam.

Policy sector	Description of policy sector	Opportunities for promoting children's sleep health
Health care and youth policy	Health care and youth policy strives to provide quality care for vulnerable households.	Health care and youth policy could influence the underlying factors of children's inadequate sleep, e.g., stressful family situation, parenting skills, children's fear and worries, parental stress.
Education policy	Education policy strives to provide children with quality education and minimize school absenteeism.	Health education programs could address sleep health and its underlying factors. Children's healthy sleep also promotes equity in education, as they are better able to concentrate and perform at school.
Sport policy	Sport policy strives to create a diverse range of sports- and exercise activities, stimulating sports and exercise and creating an active-friendly environment.	By promoting physical activity, sport policy indirectly already contributes to healthy sleep practices, as one of the sleep promoting practices is adequate physical activity. Children's healthy sleep is also important for children's health and energy level and could promote sports performance.
Public health policy	Public health policy supports the promotion of citizen health and reducing health disparities.	Positively stimulating sleep health and its underlying factors fits well within this policy, as this sector impacts factors that influence children's sleep, such as helping parents deal with stress or with developing parenting skills.
Social services-, welfare and poverty policy	Social services and welfare policy supports the guidance of welfare recipients toward work or participation. Poverty policy combats poverty with active and optimal income support.	These policies could indirectly impact the underlying factors of children's inadequate sleep health (e.g., stressful family situation, unhealthy sleep environment). Children's healthy sleep could also reduce parental stress.
Community participation policy	Community participation policy strives to enlarge participation of citizens through community activities.	Community activities could include sleep health and its underlying factors and are part of the organizational structure for transmission of (sleep) health information.

Other policies outside the social domain that can be explored are: spatial development policy, community services policy, mobility and public space policy, and national policies. In addition, partnerships with human services organizations or partly-financed governmental organizations can be explored.

the issue of children's inadequate sleep health. This shared ownership can further be stimulated by involving policy stakeholders early on in the research- and development process and creating co-ownership of program actions (46). The HiAP Maturity Model (38) incorporates several characteristics that underpin the importance of shared ownership, including the broadly shared vision on HiAP (political active engagement of governmental counselors and strategic inclusion of HiAP themes by the City Council), collaboration between sectors within the project (i.e. stakeholder engagement) and the political and administrative anchoring of the HiAP approach (i.e. sustainable implementation) within the governmental organization. Furthermore, this model enables the governmental organization to manage and control the HiAP processes (i.e., the key HiAP characteristics the organization tends to achieve), track their progress, and identify opportunities for improvement. In addition, the HiAP perspective created a specific focus during the interviews; on roles and responsibilities of stakeholders within the local organizational structure of policy and practice. This led to in-depth information on potential assets, which promotes a program design that fits the local context.

The blueprint for multi-sector program development created in the current study requires long-term involvement and commitment from both academia and partners from municipal policy organizations. This means commitment and involvement *via* e.g., stable funding mechanisms, establishing a supportive governmental structure with a shared HiAP vision across sectors, *via* creating ownership and shared responsibility for the HiAP implementation on the local level, and *via* engaging all sectors early on in the policy development (47, 48). To establish such commitment across sectors and allow policy stakeholders to give priority to HiAP actions, HiAP needs to be embedded in the local city council order. The HiAP progress can be monitored using the HiAP Maturity Model, which describes five levels of HiAP maturity and the characteristics for each level (38, 49). The development process toward an integrated approach to promote children's sleep health helped the city of Amsterdam to recognize both the problem and the importance of integral policy action; i.e., during the study period, Amsterdam moved from "Stage 0, unrecognized" to "Stage 1, recognized" within the HiAP Maturity Model in context of children's sleep health. Thereafter, it progressed to "Stage 2, considered", since the public health sector made a policy statement that a HiAP

approach is desirable when tackling the problem of children's sleep health. A future step toward further progress could be to create cross-sector collaboration and infrastructures. This could happen *via* a "HiAP Unit", which Baum et al. defined as "A dedicated pool of skilled staff that could provide assistance across government, and was largely responsible for creating and maintaining a networked, horizontal governance for HiAP across". Such a unit has shown to be helpful in gaining support from other sectors (38, 41, 50, 51). Another way might be to appoint one key policy sector (e.g., public health sector) as owner and main responsible sector for integrating HiAP within the local government, given sufficiently broad support among the other sectors. This owner can guide existing policy departments and their teams toward incorporating the HiAP perspective into their work and implement sustainable health-promoting policies. The decision on how to proceed depends on the local policy culture and context. Aiming to apply HiAP to create such structural impact within the governmental organization may also promote structural impact at different levels within the system of factors that influence children's sleep health. In case of sleep health specifically, it would also spill over to other social- and health related benefits, since sleep health is so strongly interwoven with other socially relevant outcomes and healthy child development (52).

Another lesson learned from applying HiAP was that valuable information about policy assets can be discovered by finding and involving stakeholders at all different hierarchical levels within the governmental civil service organization. Ideally, when developing public health programs, the direct implementers of the program are involved. These implementers are part of organizational sub-systems within the local government, which all work to realize their specific political goals and all have their standard ways of working. In our study it proved vital to first become thoroughly acquainted with the context of policy and practice, before being able to identify what specific stakeholders needed to be involved, which parts of their work practices required change, and where the power to realize those changes could be found. Furthermore, stakeholders at different hierarchical organizational levels can provide valuable information on policy assets. For example, they can help to understand how policies are operationalized in practice, how political agendas are shaped in local policies, and to provide knowledge on existing policies and governmental structures. Within our project, different policy stakeholders showed interest in cross-sector collaboration to promote the health of citizens. Collaborations created with and between such stakeholders are vital to sufficiently understand the system they aim to change together.

Although IM has long been a golden standard in behavior change intervention design, certain aspects appeared particularly important when designing a program blueprint for such a complex, multi-sector issue as children's sleep health. Firstly, incorporating a thorough needs- and asset assessment enabled us to ensure the developed actions would fit both community needs and existing environmental assets (12). In addition, the asset assessment helped to match existing resources and capacities in the communities to the actions that could be developed. This seems crucial for facilitating optimal program adoption, implementation and maintenance, which in turn is needed to create effective, sustainable programs (12). Secondly, we used a non-linear and iterative process of applying IM (12), as we went back and forth through the different steps in the IM process when new information appeared. This helped us to capture all necessary aspects of the system in which we aimed to create changes in order to stimulate children's sleep health.

Children's sleep health is shaped by the cultural context children live in, i.e. when, where, how, how much, and with whom children and families sleep (53). The program development approach that we described in this paper is suitable for developing programs in cross-cultural contexts, as the development approach (IM combined with HiAP) can be applied across various contexts and cultures (12). Additionally, HiAP specifically aims to create health equity, i.e. disproportionately promote the health of those who are most in need to close the gap between advantaged and disadvantaged groups through combined efforts of the relevant policy sectors (41). As in every health promoting program, specific attention needs to be directed to creating a culturally sensitive program that fits with the lived realities of the people that are at the center of the health topic at hand (54). In our project, we included stakeholders from different cultural backgrounds living in Amsterdam within the needs assessment (IM step 1). As a result, the program objectives are based on the local perspective of healthy sleep practices such as limiting the amount of noise, and sleeping alone. Instead of implementing such a locally informed program to another context, we propose to apply the blueprint for program development in another cultural context to promote cultural sensitivity of health promotion programs, and contributing to health equity (55, 56). Involving local cultural advisors throughout the project would be another way to improve cultural sensitivity of health promotion programs.

Strengths and limitations

A strength of our study is the combination of IM and HiAP, which resulted in a blueprint for developing an integrated multi-sector program to promote children's sleep health. Furthermore, using participatory research methods with children, parents and other stakeholders ensured the program was optimally geared toward the priority stakeholders. Another strength was that this research was performed through close, structural collaboration between academia, public policy, and public health practice. However, there are also some limitations to our approach. The needs assessment could have been extended by identifying the most relevant personal determinants quantitatively e.g., on basis of the confidence interval based estimation of relevance (CIBER)

approach instead of theoretical models and supporting research (57, 58). However, this was not possible because the personal determinants in our study were not specified per behavioral factor (57, 58). Furthermore, we did not include performance- and change objectives for *all* environmental stakeholders, which would have created an even broader socio-ecological approach to influence children's sleep health. However, since relevant environmental and policy structures differ per region, we want to encourage policy makers to identify performance and change objectives for their own sector when implementing the blueprint for program development that we offer *via* this paper.

Conclusion

Combining IM with HiAP for health promotion resulted in a comprehensive, evidence-based blueprint for the development of an integrated multi-sector program to promote children's sleep health. This blueprint can also serve to support the design of local (sleep) health promotion programs in other places with different local governmental structures within different cultures while taking into account the policy context.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request, meaning that they may be shared with researchers who provide a methodologically sound proposal and whose proposed use of the data has been approved by the study's authors and partners.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of the VU University Medical Center (Protocol No. 2017.013 and 2018.170). Written informed consent to participate in this study was provided by the participants and/or one of the participants' parent or caregiver where appropriate.

Author contributions

LB, MVS, IH, KDH, RR, MC, and VB conceptualized and designed the research project. LB, MVS, KDH, RR, MC, and VB interpreted the data. LB collected the data and wrote the initial manuscript and all other authors contributed to writing and editing the manuscript. 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.

Publisher's note

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Regional brain dysfunction in insomnia after ischemic stroke: A resting-state fMRI study

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Objective: This study aimed to explore the abnormality of local brain function in patients with post-stroke insomnia (PSI) based on fMRI and explore the possible neuropathological mechanisms of insomnia in patients with PSI in combination with the Pittsburgh sleep quality index (PSQI) score and provide an objective evaluation index for the follow-up study of acupuncture treatment of PSI.

Methods: A total of 27 patients with insomnia after stroke were enrolled, and the PSQI was used to evaluate their sleep status. Twenty-seven healthy participants who underwent physical examinations during the same period were selected as controls. Resting-state brain function images and structural images of the two groups of participants were collected, and the abnormal changes in the regional brain function in patients with PSI were analyzed using three methods: regional homogeneity (ReHo), the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF), and a correlation analysis with the PSQI scale score.

Results: Compared with the HCs, the ReHo values of the PSI group in the bilateral lingual gyrus, right cuneus, right precentral and postcentral gyri were significantly lower, and the ReHo values of the left supramarginal gyrus were significantly higher. In the PSI group, the ALFF values in the bilateral lingual gyrus were significantly decreased, whereas those in the bilateral middle temporal gyrus, right inferior temporal gyrus, right inferior frontal gyrus, right limbic lobe, right precuneus, left posterior cingulate gyrus, and left middle occipital gyrus were significantly increased. Compared with HCs, the fALFF values of the bilateral lingual gyrus, bilateral inferior occipital gyrus, and bilateral cuneus in the PSI group were significantly higher. The ReHo value of the left supramarginal gyrus in the PSI group was significantly negatively correlated with the total PSQI score.

Conclusion: Patients with PSI have abnormal local activities in multiple brain regions, including the visual processing-related cortex, sensorimotor cortex, and some default-mode network (DMN) regions. Over-arousal of the DMN and over-sensitivity of the audiovisual stimuli in patients with PSI may be the main

mechanisms of insomnia and can lead to a decline in cognitive function and abnormalities in emotion regulation simultaneously.

KEYWORDS

post-stroke insomnia, functional magnetic resonance imaging, regional homogeneity, amplitude of low-frequency fluctuations, fractional amplitude of low-frequency fluctuation

Introduction

Post-stroke insomnia (PSI) refers to insomnia symptoms that occur after a stroke, and the rate of sleep disturbance in post-stroke patients is approximately 30–48% (1). As many as 70% of acute stroke patients have associated sleep disorders, mainly manifested as difficulty in falling asleep at night, difficulty in maintaining sleep or awakening early, difficulty in falling asleep after awakening, and daytime sleepiness and fatigue (2). Sleep disturbance in patients with PSI is highly detrimental to stroke recovery and contributes to the deterioration of existing diseases, such as hypertension and diabetes, reducing patients' quality of life (3). Current studies suggest that the mechanisms of insomnia in patients with PSI are as follows: the stroke lesions in patients with PSI involve important brain regions, such as the thalamus and the basal ganglia, and the damage to these regional brain tissues leads to the blockage of transmission pathways of neurotransmitters such as 5-hydroxytryptamine and norepinephrine in the brain (4); or the reduction of gamma-aminobutyric acid content in the serum of patients with stroke leads to the reduction of neuronal activity that promotes sleep (5, 6); or the interaction between negative emotions, such as anxiety, after stroke and 5-hydroxytryptamine eventually leads to insomnia (7, 8). All these alterations lead to abnormalities in brain function, resulting in insomnia symptoms; however, the specific mechanism of PSI is still unclear.

Resting-state functional magnetic resonance (rs-fMRI) measures spontaneous low-frequency fluctuations in brain activity through blood oxygen level-dependent (BOLD) signals (9, 10), which can not only reveal the intrinsic function of the brain in healthy participants but also identify disease-state changes in the intrinsic functional connectivity (FC) of the brain (11–13) and reveal the brain mechanism of neuromodulation in the treatment of clinical diseases (14–16). Regional homogeneity (ReHo) (17) and amplitude of low-frequency fluctuations (ALFF) are two important indicators of rs-fMRI to measure regional brain functional activity. Their post-processing techniques are mature, and the results are stable and reliable (18, 19). Multiple studies (20–22) using ReHo analysis in patients with primary chronic insomnia have consistently found that ReHo values of the left cuneus and left parahippocampal gyrus are significantly increased, while activity abnormalities in other brain regions show variable findings in different studies, some studies even presented conflicting results. Most studies (20, 22) have shown that ReHo values change in brain regions related to emotion and cognition, negative emotions, and abnormal emotional regulation in patients with primary chronic insomnia lead to insomnia symptoms, but the mechanism remains unclear. However, studies (23, 24) using ALFF analysis in patients with primary chronic insomnia have found that the ALFF values are elevated in the temporal and occipital lobes and decreased in the prefrontal lobe and cerebellar hemispheres, which may be associated with cognitive impairment and hyperactive audiovisual responses, but further research is needed for confirmation.

We hypothesized that patients with PSI have similar arousal mechanisms with patients with primary chronic insomnia, and their abnormal brain functional activities may be related to their cognition and emotion regulation. We used rs-fMRI to explore abnormal changes in local brain function in patients with PSI to provide a basis for further research on the neuropathological mechanism of insomnia in patients with PSI.

Materials and methods

Participants

A total of 27 patients with insomnia after stroke were included in the PSI group, and 27 healthy controls (HCs) matched for age, sex, and years of education were enrolled in this study. The quality of sleep for all participants with PSI was assessed using the Pittsburgh Sleep Quality Index (PSQI) (25), which was not evaluated in the HCs.

The inclusion criteria for the PSI group were as follows: (1) All patients with stroke had ischemic stroke and the stroke lesion was diagnosed using brain MRI in the acute phase; the history of stroke was $\geq$ 6 months; the infarct location was confined to the deep white matter or basal ganglia, thalamus, brainstem. The lesion length in the luminal infarct was $\leq$ 10 mm, and the number of lesions in every patient was not limited. (2) Insomnia symptoms were secondary to stroke and fulfilled the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (26) diagnostic criteria for sleep disorders. (3) PSQI score $\geq$ 8 [referring to the criteria proposed by Nofzinger et al. (27) in

the American Journal of Psychiatry]. (4) The National Institutes of Health Stroke Scale (28) was used to evaluate the severity of stroke, and patients with a score ≤ 15 points with mild disease were selected. (5) Participants were aged 18–75 years, right-handed [assessed by the Edinburgh Handedness Scale (29)], and Han Chinese.

The exclusion criteria for the PSI group were as follows: (1) History of insomnia before the stroke occurrence. (2) Cerebral infarcts involving the cerebral cortex or cerebellar hemispheres; large cerebral infarcts across cerebral lobes; and the presence of moderate or severe stenosis of the cervical or intracranial large vessels. (3) Hearing impairment or communication problems or claustrophobia and unable to complete the MRI examination. (4) Presence of contraindications to MR scannings, such as metallic foreign bodies that cannot be removed from the body, magnetic stents, and cardiac pacemakers. (5) History of psychiatric diseases that severely affect brain cognitive function; or the presence of overt dementia symptoms. (6) History of brain tumor, intracranial infection or trauma (contusions, intracerebral hemorrhage, encephalomalacia, subdural hematochezia, etc.), and congenital cranial dysplasia. (7) History of alcohol dependence or other dependence on psychotropic drugs.

The inclusion criteria for the HCs were as follows: (1) participants were aged 18–75 years, right-handed; (2) no insomnia symptoms or history of insomnia, and (3) no history of intake of sedative drugs in the past 6 months. The exclusion criteria were the same as that of the PSI group, from exclusion criteria (3–7).

All included participants were informed regarding the purpose, methods, and precautions of the trial before it commenced, and they signed an informed consent form prior to participation.

fMRI data acquisition

All participants underwent the acquisition of functional and structural images of the brain in the resting state with a Siemens Magnetom Prisma 3T MRI scanner (Siemens, Erlangen, Germany), using a 64-channel head coil. The participants were instructed to close their eyes but remain awake during the functional scans. The three-dimensional (3D)-T1-weighted (T1W) structural image parameters were as follows: TR/TE = 2,530/2.98 ms, flip angle = 8°, slice thickness = 1 mm, no gap, matrix = 512 × 512, and field of view = 256 × 256 mm. A whole brain scan was performed parallel to the midsagittal plane with 192 scanned slices. Resting-state BOLD fMRI data were acquired using a gradient echo planar pulse sequence with Simultaneous Multi-slice parallel acquisition from Siemens Prisma to achieve high temporal resolution with TR = 500 ms, TE = 30 ms, slice thickness = 3.5 mm, no gap, field of view = 224 × 224 mm, matrix = 64 × 64, flip angle = 60°, 35 axial slices, acquisition time points of 960, and acquisition time of 8 min and 45 s.

Data pre-processing

Pre-processing of the resting-state fMRI data was performed using the Data Processing and Analysis for (Resting-State) Brain Imaging software package (version 5.0, DPABI, http://rfmri.org/DPABI) based on the MATLAB platform. The pre-processing steps included: data conversion from the DICOM format to the NifTi format and removal of image data of the first 10 time points; head motion correction (excluding participants with a displacement exceeding 3 mm in 3D space and rotation angle exceeding 3°); spatial normalization (resampling parameter 3 × 3 × 3 mm), smoothing [ReHo was first analyzed and smoothed, and ALFF and fractional ALFF (fALFF) were first smoothed and then analyzed with a 6-mm half-height bandwidth]; and removal of linear drift and low-frequency filtering (0.01–0.1 Hz bandwidth). Multiple linear regression analysis was used to reduce the effects of the white matter, cerebrospinal fluid signal, and head motion (six head motion parameters in head motion correction as covariates) on data.

Elimination of data

During the data pre-processing, three patients with PSI were excluded because of excessive head motion (exceeding 3 mm or 3° of angular motion relative to the first volume). One patient with PSI had artifacts localized to the parietal lobe on structural T1W images which was eliminated to avoid compromising the registration of functional images with structural images. Ultimately, 23 patients with PSI were analyzed.

Data analysis

Data analysis of ReHo, ALFF, and fALFF was performed using DPARSF (V5.2) in the DPABI software, and the analysis steps were referenced from the method proposed by Zang (30, 31). ReHo analysis was used to compute Kendall's coefficient of concordance (KCC) between a given voxel in a time series and its nearest 26 neighboring voxels. To reduce the influence of individual differences on the KCC values, we normalized the ReHo maps by dividing the KCC between each voxel by the average KCC of the whole brain. The resulting data were finally subjected to Gaussian space smoothing using a half-height bandwidth of 6 mm to reduce the effect of noise and anatomical differences in the results. Each voxel-filtered time series of the participant's brain was converted into a spectrum using a fast Fourier transform, and the power spectra were obtained; the square root of the power spectrum between 0.01

and 0.08 Hz was calculated and taken as ALFF, and ALFF at each voxel was divided by the global mean ALFF value to obtain a standardized ALFF for subsequent statistical analysis. fALFF is the ratio obtained by dividing the power at low frequencies by the power at full-frequency.

Statistical analysis

We used the Resting-State fMRI Data Analysis Toolkit (REST, Song Xiaowei, http://www.restfmri.net/forum/) to perform two-sample *t*-tests on two groups of ReHo, ALFF, and fALFF images after individual normalization. Age, sex, years of education, and head motion parameters of the two groups were included as covariates, setting a threshold of $p < 0.001$ for the individual voxel level and $p < 0.05$ for multiple comparisons (corrected using GRF, https://afni.nimh.nih.gov/). To explore the correlation between alterations in each of the above parameters and PSQI scores of sleep quality scales in patients with PSI, we extracted the mean ReHo, ALFF, and fALFF values of all voxels in significantly different regions separately using REST, and then performed correlation analysis between the mean values of significantly different regions and PSQI scale scores in SPSS Statistics for Windows (version 25.0, IBM Corp.). Data were evaluated for normality of distribution and homogeneity of variance, and partial correlation analysis was performed if the normal distribution and homogeneity of variance were followed; age and sex were used as covariates to determine the correlation between the two groups of data. If the normal distribution or homogeneity of variance was not satisfied, the values were obtained using the general linear model regression analysis based on age and sex for all data to be analyzed, followed by Spearman correlation analysis. Statistical significance was set at $p < 0.05$.

SPSS Statistics for Windows (version 25.0, IBM Corp.) was used to analyze the clinical data. We used the Chi-square test for sex differences between the two groups, and an independent *t*-test was used to compare the age and education level between the two groups. Statistical significance was set at $p < 0.05$.

Results

Demographic and clinical data

The distribution of the ischemic stroke lesions in the 23 patients with PSI after data screening was as follows: corona radiata area (7 cases), center of semiovale (seven cases), basal ganglia area (18 cases), thalamus (five cases), bridge brain (eight cases), and frontal and parietal white matter (5 cases). We delineated the regions of interest (ROIs) on the T1W structural image of all infarcts of the participants and used them as templates. All the templates of the participants were fused and superimposed. As shown in Figure 1, none of the infarct lesions involved the brain functional areas that needed to be analyzed.

A comparison of the demographics of PSI group and HCs is presented in Table 1. There were no significant differences in age ($p = 0.732$), sex ($p = 0.555$), and years of education ($p = 0.460$) between the two groups. The duration of insomnia in the patients with PSI was 3 to 36 months, with an average of 11.37 ± 6.58 months.

Results of the ReHo analysis

Comparing the ReHo values of PSI patients and HCs, we found that the ReHo values in multiple brain regions of patients with PSI including the bilateral lingual gyrus, right cuneus, right precentral gyrus, and postcentral gyrus were significantly decreased. Furthermore, the ReHo value of PSI significantly increased in the left supramarginal gyrus (Table 2 and Figure 2).

Results of the ALFF and fALFF analyses

Compared with HCs, patients with PSI had significantly decreased ALFF values in the bilateral lingual gyrus and significantly increased ALFF values in the bilateral middle temporal gyrus, right inferior temporal gyrus, right inferior frontal gyrus (orbital and triangular parts), right limbic lobe, right precuneus, left posterior cingulate gyrus, and left middle occipital gyrus (Table 3 and Figure 3).

Compared with HCs, patients with PSI had significantly decreased fALFF values in the bilateral lingual gyrus, bilateral inferior occipital gyrus, and bilateral cuneus, but no significant increase in fALFF values in any brain region (Table 4 and Figure 4).

Correlation analysis between regional brain dysfunction and PSQI scale

Among the mean values of ReHo extracted from brain regions with significant differences, the ReHo values in the left supramarginal gyrus were significantly negatively correlated with the PSQI total score ($r = -0.492$, $p = 0.023$; Figure 5). The ReHo value of the right cuneus was correlated with PSQI but not statistically different ($r = -0.408$, $p = 0.067$). However, the ReHo values of the other different brain regions and those with differences in ALFF and fALFF were not significantly correlated with the PSQI score.

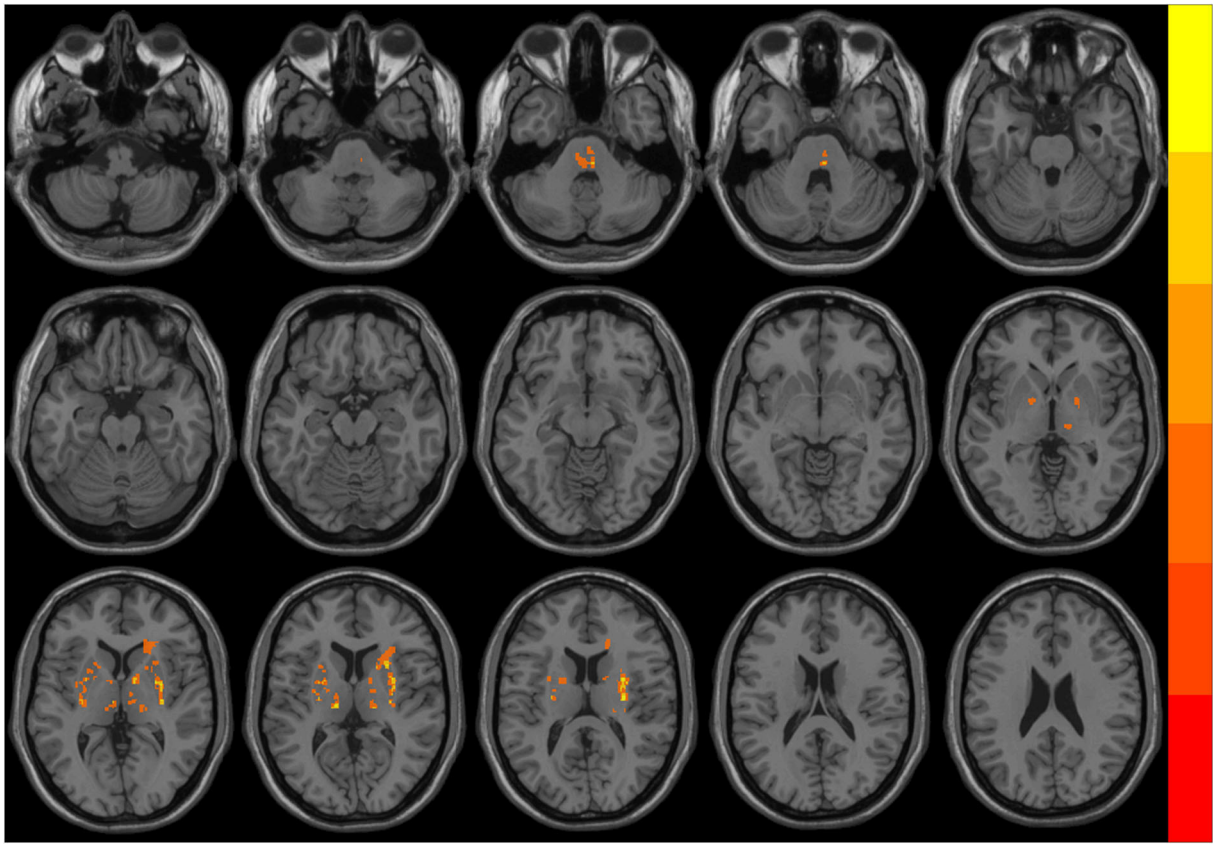

FIGURE 1
The overlapping distribution map of ischemic stroke lesions in patients with post-stroke insomnia (PSI). Different colors indicate the number of overlapping lesions at different brain regions. The infarct lesions mostly located in the pons, bilateral basal ganglia, and thalamus.

TABLE 1 Demographic and clinical traits of all participants.

Characteristics	PSI ($n = 23$)	HC ($n = 23$)	$t/Z/\chi^2$	P
Age (years)	62.48 ± 8.74	61.74 ± 5.44	−0.344	0.732
Sex (M/F)	12/11	10/13	0.348	0.555
Education (years)	11.83 ± 3.57	11.04 ± 3.66	−0.738	0.460
PSQI	14.17 ± 3.63	–		

PSQI, Pittsburgh Sleep Quality Index; PSI, post-stroke insomnia; HC, healthy controls. – means that there is no data of PSQI scale in the control group.

TABLE 2 Brain regions with abnormal ReHo in patients with PSI.

Brain regions	Voxels	Peak MNI coordinates			T-value
		X	Y	Z	
Cluster 1	195	−9	−87	24	−6.28
Lingual gyrus (L)	73				
Cluster 2	86	15	−63	−9	−4.55
Lingual gyrus (R)	73				
Cluster 3	120	12	−87	27	−5.11
Cuneus (R)	51				
Cluster 4	93	−63	−51	36	5.62
Supramarginal gyrus (L)	29				
Cluster 5	95	48	−15	48	−5.11
Precentral gyrus (R)	57				
Postcentral gyrus (R)	36				

ReHo, regional homogeneity; MNI, Montreal Neuroscience Institute; L, left; R, right. A positive T value indicates that the ReHo value of the PSI group was higher than that of the HCs. AAL templates were used to localize the brain regions.

Discussion

This study showed that compared with HCs, patients with PSI had regional brain dysfunction in multiple brain regions, and comprehensive ReHo, ALFF, and fALFF results revealed that the significantly different brain regions mainly included the bilateral lingual gyrus, bilateral cuneus/precuneus, left posterior cingulate gyrus, left supramarginal gyrus, right precentral and postcentral gyrus, right frontal and temporal lobes (including inferior frontal gyrus, middle temporal gyrus, and inferior temporal gyrus), and right occipital lobe (including the superior and inferior occipital gyri). From the functional divisions, these brain regions were mainly distributed in the

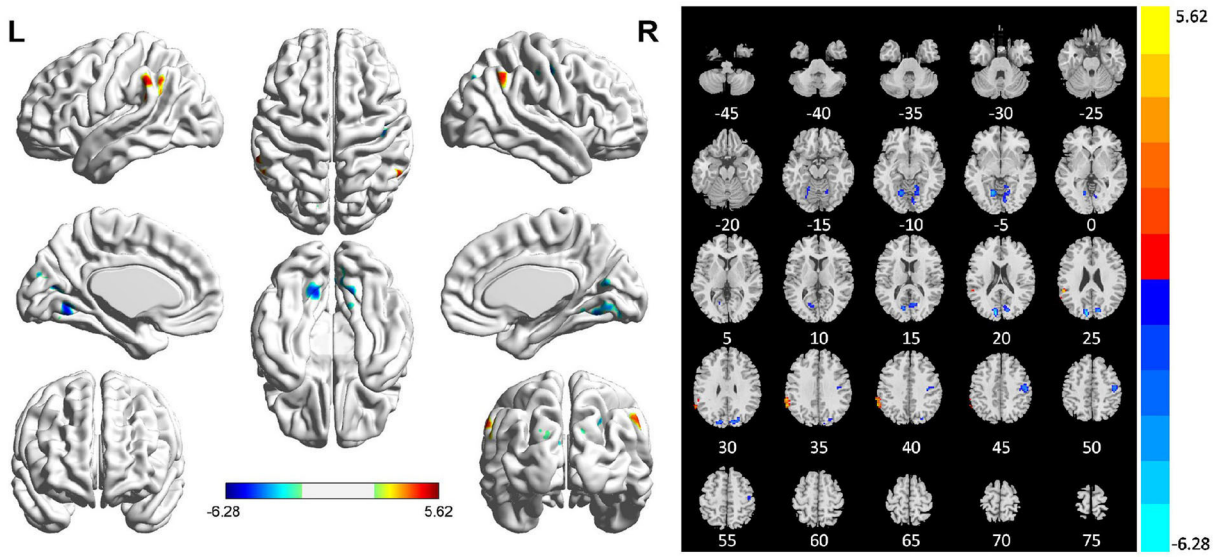

FIGURE 2
Statistically significant differences between patients with post-stroke insomnia (PSI) and healthy controls are shown in a regional homogeneity (ReHo) map of the whole-brain with magnetic resonance imaging (MRI). Patients with PSI showed a significant ReHo increase in the left supramarginal gyrus (warm colors), as well as a decrease in the bilateral lingual gyrus, right cuneus, right precentral gyrus, and posterior central gyrus with decreased ReHo values (cold colors). A T-score bar is shown below and right. Red and blue denote increases and decreases in ReHo, respectively.

TABLE 3 Brain regions with abnormal ALFF in patients with PSI.

Brain regions	Voxels	Peak MNI coordinates			*T*-value
		X	*Y*	*Z*	
Cluster 1	61	66	−12	−27	6.42
Middle temporal gyrus (R)	36				
Inferior temporal gyrus (R)	23				
Cluster 2	64	48	36	−12	6.17
Inferior frontal gyrus (orbital) (R)	36				
Inferior frontal gyrus (triangular) (R)	27				
Cluster 3	72	15	−51	−9	−5.28
Lingual gyrus(R)	57				
Cluster 4	59	−18	−60	−6	−5.51
Lingual gyrus (L)	55				
Cluster 5	74	3	−57	18	5.03
Limbic lobe (R)	52				
Precuneus (R)	31				
Posterior cingulate gyrus (L)	15				
Cluster 6	103	−60	54	27	6.66
Middle temporal gyrus (L)	35				
Middle occipital gyrus (L)	17				

ALFF, amplitude of low-frequency fluctuations; MNI, Montreal Neuroscience Institute; L, left; R, right. A positive T value indicates that the ALFF value of the PSI group is higher than that of the HCs. AAL templates were used to localize the brain regions.

visual processing-related cortex (e.g., lingual gyrus, middle temporal gyrus, and superior and inferior occipital gyrus), sensorimotor cortex (e.g., right precentral and postcentral gyrus), and some default mode network (DMN) (32) brain regions (e.g., cuneus/precuneus and posterior cingulate gyrus), suggesting that the mechanism of insomnia in patients with PSI might be associated with abnormalities in brain functions, such as visual processing, sensorimotor, and DMN.

Visual cortex dysfunction in patients with PSI

In this study, we found that the bilateral lingual gyrus showed a significant decrease in the ReHo, ALFF, and fALFF values, and the right inferior occipital gyrus also showed a significant decrease in the fALFF values. Previous studies (33–37) have shown that both the occipital lobes and lingual gyrus belong to the visual center, and the lingual gyrus has an important role in visual judgment and processing, which is mainly involved in visual information processing, and in preserving visual working memory information and working consolidation. Recent studies (38, 39) have argued that the dysfunction of the visual cortical neurons may also be an important factor in primary insomnia. Several studies (40–43) have shown some degree of brain dysfunction in

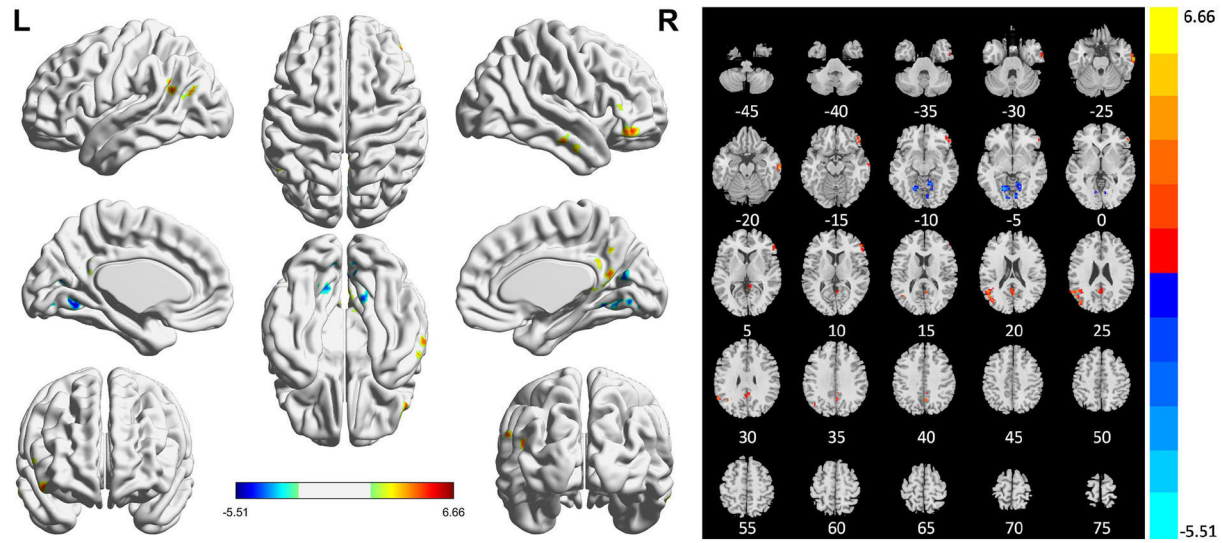

FIGURE 3
Statistically significant differences between post-stroke insomnia (PSI) patients and healthy controls are shown in the amplitude of low-frequency fluctuation (ALFF) map of the whole brain with magnetic resonance imaging (MRI). Patients with PSI showed a significant ALFF increase in the bilateral middle temporal gyrus, right inferior temporal gyrus, right inferior frontal gyrus, right limbic lobe, right precuneus, left posterior cingulate gyrus, and left middle occipital gyrus (warm colors), as well as a decrease in the bilateral lingual gyrus with decreased ALFF values (cold colors). A T-score bar is shown below and right. Red and blue denote increases and decreases in ALFF, respectively.

TABLE 4 Brain regions with abnormal fALFF in patients with PSI.

Brain regions	Voxels	Coordinate (Peak MNI, *X Y Z*)			*T*-value
Cluster 1	63	−36	−90	−18	−5.66
Inferior occipital gyrus (L)	33				
Cluster 2	118	18	−51	−12	−5.85
Lingual gyrus (R)	75				
Cluster 3	82	39	−69	0	−6.36
Inferior occipital gyrus (R)	43				
Cluster 4	263	−9	−81	21	−5.70
Lingual gyrus (L)	102				
Cuneus (R)	37				

fALFF, fractional amplitude of low-frequency fluctuation; MNI, Montreal Neuroscience Institute; L, left; R, right. A negative T value indicates that the fALFF value of the PSI group is lower than that of the HCs. AAL templates were used to localize the brain regions.

the visual central brain regions such as the lingual gyrus or occipital lobe, including migraines, anxiety symptoms, apnea syndrome, and cognitive impairment in patients with Parkinson's disease and hepatic encephalopathy, also indicating that the visual cortex is associated with cognitive and anxiety states. In a study of children with obstructive sleep apnea (44), the patient group showed significantly decreased ReHo values in the right lingual gyrus and left precuneus. The ReHo values in the right lingual gyrus were negatively correlated with verbal intelligence quotient (IQ) and full-scale IQ on the Wechsler Adult Intelligence Scale, indicating that the lingual gyrus also has some correlation with cognitive performance. In a study that employed visual picture stimuli for arousal (45), the precentral cortex and cingulate cortex of patients with psychophysiological insomnia exhibited higher BOLD activation to the stimuli, which was an overreaction; the overreaction of these brain regions tended to normalize after treatment by cognitive-behavioral therapy, indicating that the stimulation of the visual cortex in patients with insomnia is important for its return to normalcy.

Our results showing reduced brain activity in the bilateral lingual gyrus and right inferior occipital gyrus are consistent with previous studies on brain function in patients with primary insomnia, which may be explained by visual cortex-related cognitive decline and abnormal emotion regulation in patients with PSI. Based on the present and previous studies, we suggest that insomnia in patients with PSI causes a persistent reduction in visual cortical activity and, consequently, impaired cognition and anxiety.

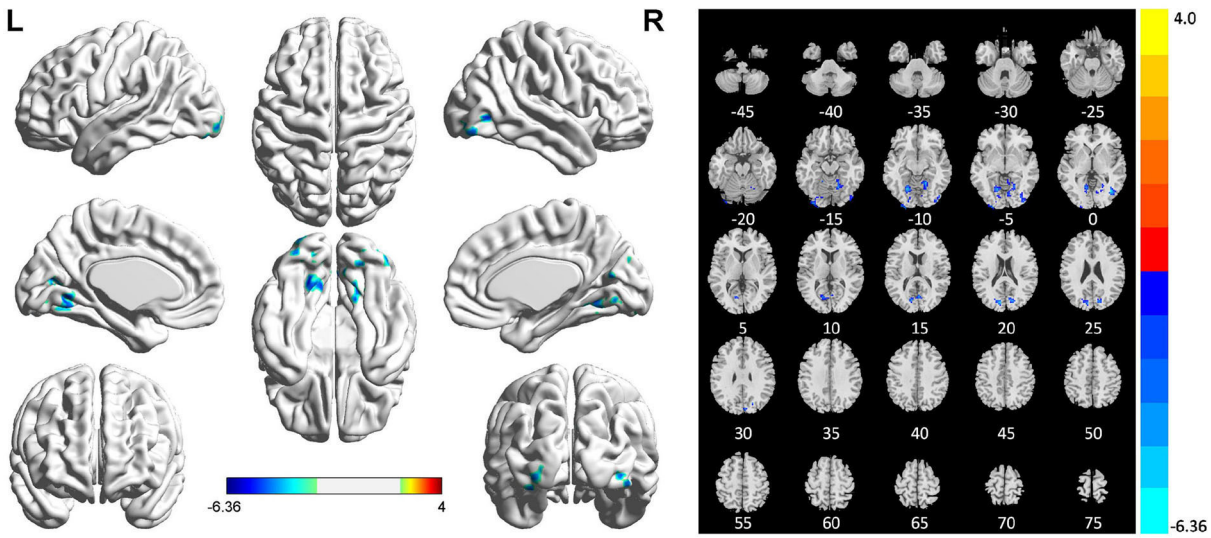

FIGURE 4
Statistically significant differences between post-stroke insomnia (PSI) patients and healthy controls are shown in the fractional amplitude of low-frequency fluctuation (fALFF) map of the whole brain with magnetic resonance imaging (MRI). Patients with PSI showed a significant decrease in fALFF in the bilateral lingual gyrus, bilateral inferior occipital gyrus, and bilateral cuneus (cold colors); no regions with increased fALFF were found. A T-score bar is shown below and right. Red and blue denote increases and decreases in fALFF, respectively.

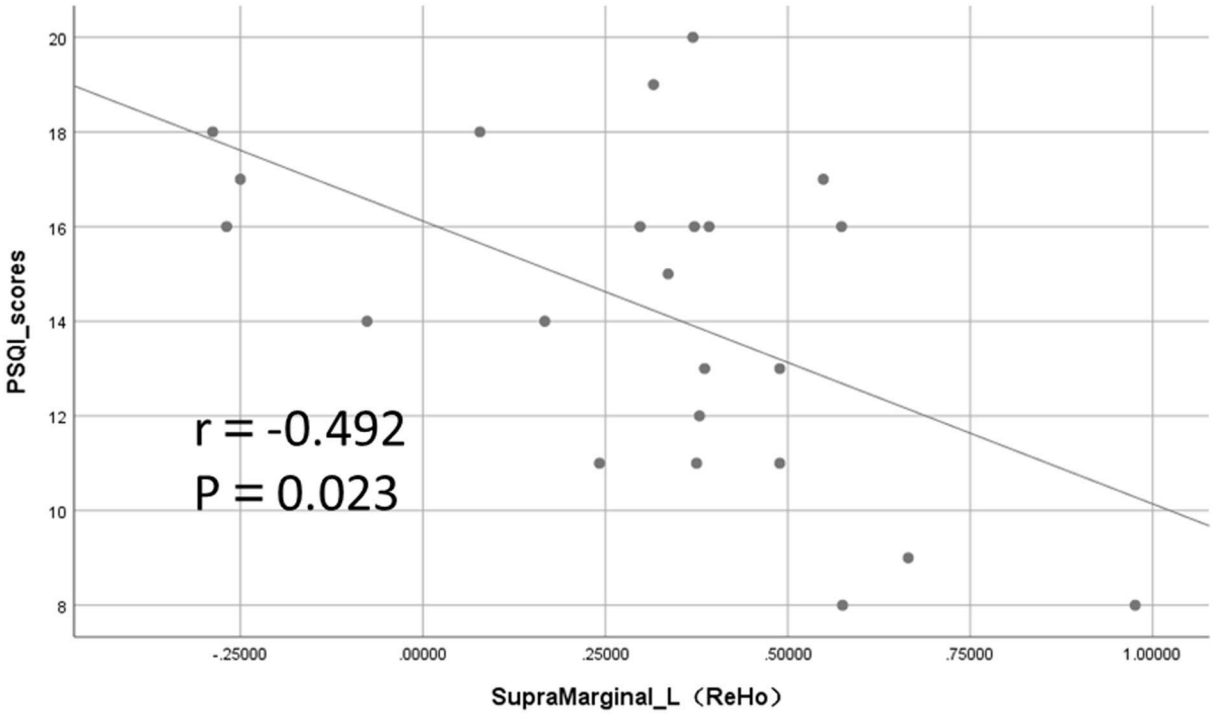

FIGURE 5
Significant negative correlation between regional homogeneity (ReHo) values and Pittsburgh Sleep Quality Index (PSQI) total score in the left supramarginal gyrus.

DMN dysfunction in patients with PSI

In this study, we found that the ALFF values increased in the right precuneus, right limbic lobe, and left posterior cingulate gyrus in patients with PSI. According to previous studies (46), both the precuneus and the posterior cingulate gyrus are important to brain regions in the DMN, and their connections to structures such as the hippocampus are important and sensitive to arousal mechanisms. The DMN is associated with excessive arousal of brain regions, and under normal physiological conditions, the neural activity of the DMN is more active during the awake resting state than during the task state but is shifted from the awake resting state to sleep, particularly during deep sleep, where functional activity in multiple brain regions is significantly diminished. Previous studies (47, 48) have also shown that the DMN of patients with primary insomnia disorder remains active during sleep. The DMN of patients with psychophysiological insomnia shows an exaggerated arousal response to sleep-related stimuli, and this overreaction can be reduced by effective behavioral treatments (45).

Previous studies (49) have argued that the precuneus is critically involved in episodic memory, emotion regulation, and self-thinking. The precuneus has been shown to play a central role in several highly integrated tasks, including visuospatial image processing, episodic memory retrieval, and self-regulation processing (50). Zhao et al. (51) analyzed the ALFF between patients with primary insomnia and normal controls and found a significant increase in the ALFF values in the right precuneus, which in turn showed a significant decrease after auricular vagal stimulation of patients with insomnia, which is believed to regulate the spontaneous activity of precuneus neurons. Inhibiting introspection and improving excessive arousal in the cerebral cortex of patients may be a key mechanism for stimulating the vagus nerve to treat primary insomnia. In this study, we also found that the ALFF value in the right precuneus was significantly higher in patients with PSI. Thus, we believe that excessive arousal of the DMN is one of the reasons for insomnia in patients with PSI.

Sensorimotor cortex dysfunction in patients with PSI

In this study, we found that ReHo values in the right precentral and postcentral gyri were significantly lower in patients with PSI than in HCs. The precentral and postcentral gyri belong to the sensorimotor cortex, which sends out nerve fibers to control the voluntary movement of skeletal muscles and to receive various sensations from the soma, including temperature and pain. Abnormalities in the sensorimotor cortex have also been mentioned in previous functional neuroimaging studies of patients with primary insomnia. Huang et al. (52) found increased FC between the sensorimotor cortex, premotor cortex, and amygdala in patients with primary insomnia compared with healthy controls, and the authors suggested that this increase in FC indicates a compensatory mechanism to overcome the negative effects of insufficient sleep. Killgore et al. (38) found enhanced FC between the primary sensory areas and the supplementary motor cortex in patients with insomnia who had difficulty falling asleep, whereas this result was not observed in those with insomnia who had difficulty maintaining their sleep state. These studies considered an increased functional activity in the sensorimotor cortex as a compensatory mechanism, which is less consistent with our findings; this may be due to different study participants leading to different results since stroke patients have multiple sites of infarct lesions. First, although we selected patients with lacunar infarcts to avoid the effects of corticospinal tract damage on the functional activity of the corresponding cortex, this may not be completely avoidable. Second, the compensatory mechanisms mentioned in these studies on primary insomnia may be insufficient to compensate for the decline in the sensorimotor cortex function caused by brain damage at the infarct lesion. Third, most fMRI studies of patients with insomnia disorder do not consider the duration of insomnia symptoms, and it is possible that, among patients with a longer duration, compensatory mechanisms in the sensorimotor cortex slowly weaken, eventually entering the decompensation phase, which leads to reduced functional activity in the precentral and postcentral gyri cortices.

The left supramarginal gyrus dysfunction in patients with PSI

Our study showed that the ReHo value of the left supramarginal gyrus was significantly increased and negatively correlated with the PSQI score. As a part of the somatosensory associative cortex in the brain, the supramarginal gyrus is an important functional node that plays an important role in touch, spatial and limb position perception, vision, reading, and language (53–55). One study (56) also suggested that the supramarginal gyrus is involved in emotional control, egocentricity, and episodic memory. Another study (57) in patients with chronic insomnia has shown that the FC between the left supramarginal gyrus and the left middle frontal gyrus increases, suggesting that patients with chronic insomnia have an overreaction to tactile, visual, and auditory stimuli; and this suggests that the hyperarousal state of the posterior sensory cortex in the locus coeruleus noradrenergic system is crucial for chronic insomnia disorder patients in the modulation of emotions and the sleep/wake cycle. Our results showed that the ReHo value in the left supramarginal gyrus was significantly increased, which may also be related to the hyperarousal state

caused by the hypersensitivity of auditory and visual perception in patients with PSI.

Limitations

Our study correlates with several limitations. First, a relatively small sample size in this study may reduce the statistical power and the reproducibility of a study, we will continue to recruit more patients in further work. Second, the patients with PSI have high heterogeneity because of their different duration and severity of stroke. Some patients may also complain of hypertension or type 2 diabetes, which exist a potential influence on the quality of sleep, therefore, affected the assessment of insomnia. Third, the cognitive and emotional scales were not assessed in patients and the PSQI scales were not assessed in the HCs, we plan to include the screening of cognitive behaviors, anxiety, and depression in the enrolled patients with PSI in further study. More replicated research with a larger sample size is needed to confirm our study results.

Conclusion

In general, by analyzing the regional brain functions of patients with PSI using rs-fMRI, we found that they have abnormal local activities in multiple brain regions, including the visual processing-related cortex, sensorimotor cortex, and some DMN regions. Over-arousal of the DMN and over-sensitivity of audiovisual stimuli in patients with PSI may be the main mechanisms of insomnia and can lead to a decline in cognitive function and abnormalities in emotion regulation simultaneously. The significant reduction in regional functional activity in the sensorimotor cortex in patients with PSI may be associated with brain damage in stroke, and this needs to be confirmed by further studies.

Data availability statement

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

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

HW, YH, and SQ: study concepts and study design. HY and DX: data acquisition. ML, JA, and SQ: quality control of data. ML, HW, and YH: data analysis and interpretation and manuscript preparation. JA and DX: statistical analysis. HW, YH, ML, HY, JA, XL, DX, and SQ: manuscript editing and reviewing. All authors read and approved the final 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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Efficacy of portable sleep monitoring device in diagnosing central sleep apnea in patients with congestive heart failure

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Introduction: Central sleep apnea (CSA) is a common and serious comorbidity mainly occurring in patients with heart failure (HF), which tends to be underdiagnosed and has not been widely studied. Overnight polysomnography (PSG) is the gold standard for diagnosing CSA; however, the time and expense of the procedure limit its applicability. Portable monitoring (PM) devices are convenient and easy to use; however, they have not been widely studied as to their effectiveness in detecting CSA in patients with HF. In the current study, we examined the diagnostic value of PM as a screening tool to identify instances of CSA among patients with HF.

Methods: A total of 22 patients under stable heart failure conditions with an ejection fraction of <50% were enrolled. All patients underwent PM and overnight PSG within a narrow time frame. The measurements of the apnea–hypopnea index (AHI), hypopnea index (HI), central apnea index (CAI), and obstructive apnea index (OAI) obtained from PSG, automatic scoring, and manual scoring of PM were recorded. The results obtained from PSG and those from PM (automatic and manual scoring) were compared to assess the accuracy of PM.

Results: Among the patients, CSA in 11 patients was found by PSG. The AHI measurements performed using manual scoring of PM showed a significant correlation with those performed using PSG ($r = 0.69$; $P = 0.01$). Nonetheless, mean AHI measurements showed statistically significant differences between PSG and automatic scoring of PM (40.0 vs. 23.7 events/hour, respectively; $P < 0.001$), as well as between automatic and manual scoring of PM (23.7 vs. 29.5 events/hour; $P < 0.001$). Central sleep apnea was detected by PM; however, the results were easily misread as obstructive apnea, particularly in automatic scoring.

Conclusion: PM devices could be used to identify instances of central sleep apnea among patients with HF. The results from PM were well-correlated with standard PSG results, and manual scoring was preferable to automated scoring.

KEYWORDS

sleep apnea, central sleep apnea, heart failure, portable monitor device, polysomnography

Introduction

Congestive heart failure (CHF) is a major disorder ubiquitous in the general population (1). CHF affects more than 64 million people worldwide, and the total cost of care for HF in the United States was estimated at 43.6 billion in 2020 (2). Central sleep apnea (CSA) is indicative of a poor prognosis in patients with CHF (3); however, it tends to be underdiagnosed (4). The ability to identify instances of CSA is crucial to formulating interventions for patients with CHF.

Polysomnography (PSG) is considered the gold standard for diagnosing sleep apnea in both obstructive and central types (1, 5); however, time and labor constraints make the large-scale screening of central apnea highly impractical (6). Portable sleep monitoring (PM) is a convenient approach for screening sleep apnea, and the results for obstructive sleep apnea have been verified (7–9); however, the results for central-type sleep apnea have yet to be verified.

In this study, we assessed the efficacy of portable monitoring devices as a screening tool for central sleep apnea in patients with CHF. Also, we compared the results obtained using automated PM and manual PM scoring with those obtained using PSG.

Materials and methods

Patients and study protocol

This study included patients who visited the cardiology clinic of the Chang Gung Memorial Hospital between June 2018 and June 2019. The inclusion criteria were adult patients (at least 20 years old), those with a left ventricular ejection fraction of <50%, and those with stable heart failure (a stable heart condition under medication control for at least 3 months prior to the study). A total of 41 patients who fit the criteria were included in the study. All patients underwent portable sleep monitoring, PSG, echocardiography, and blood tests following enrollment. PSG was performed within 1 month of testing using a portable monitoring device. A flowchart illustrating the study protocol is presented in Figure 1. Informed consent was obtained from all patients before examinations. The study complied with the guidelines of the Center for Medicare and Medicaid Service (CMS) (10). The study protocol was approved by the Institutional Review Board of the Chang Gung Memorial Hospital (IRB No. 201701305A3).

Portable respiratory monitor

The study analysis was performed using a type 3 portable monitoring (PM) device (Medibyte, Braebon Medical Corporation, Canada), which comprised two respiratory effort bands (the chest and the abdomen), a nasal cannula pressure transducer to detect airflow, and a finger pulse oximetry sensor (oxygen saturation and heart rate) (11). Both automated scoring and manual scoring were performed, and the results were recorded. The readings obtained using the PM were manually checked by well-trained pulmonologists specializing in sleep disorders to ensure accuracy in the detection of sleep apnea.

The criteria dictating the use of the PM to score apnea and hypopneas were based on guidelines published by the American Academy of Sleep Medicine (AASM), version 2.5 (12). It should be noted that PM recordings do not allow the documentation of arousals; therefore, arousals were excluded from the definitions of central apnea and hypopnea. Apnea was defined as the cessation of inspiratory airflow for >10 s. Hypopnea was defined as a decrease in the oronasal airflow of >30% of baseline for >10 s combined with 3% oxygen desaturation. CSA was defined as the absence of a rib cage and/or abdominal excursions in the absence of airflow. OSA was defined as the absence of airflow in the presence of a rib cage and/or abdominal excursions.

Full overnight polysomnography

Full overnight PSG was performed by a technician attendant in a sleep laboratory, and the data were analyzed in accordance with recommendations outlined in the 2014 AASM Guidelines, version 2.5 (12). PSG sensors obtained continuous recordings throughout the night to detect the body position, eye and leg movements, electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), electrocardiography (ECG), and oronasal airflow by pressure monitors and thermistors, chest and abdominal effort, and pulse oximetry for confirmation. The AHI for sleep apnea was the number of apnea and hypopnea

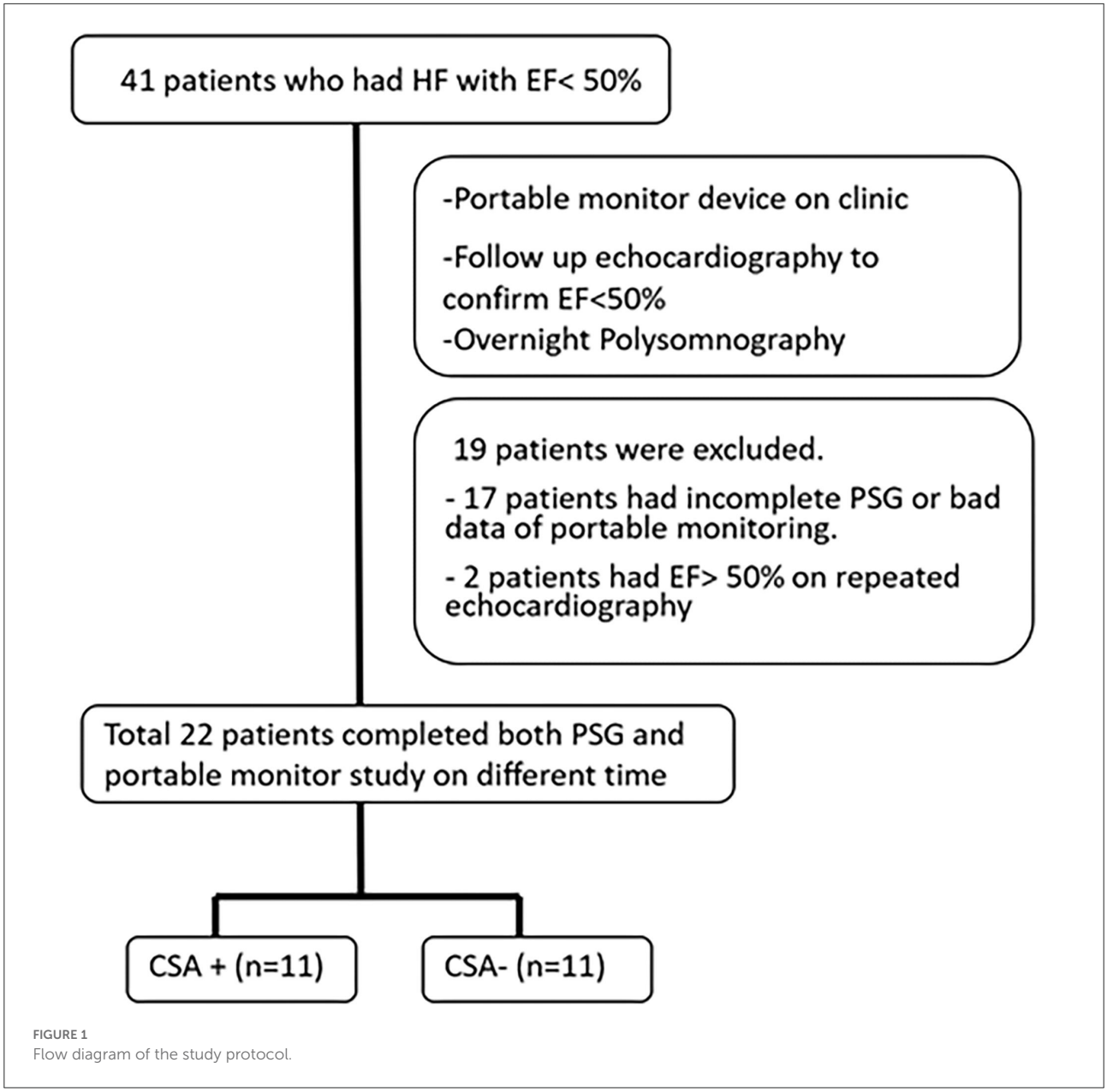

FIGURE 1
Flow diagram of the study protocol.

events per hour of total sleep time for polysomnography, and per hour of total recording time for portable monitoring. As mentioned earlier, the definitions of apnea, hypopnea, CSA, and OSA were the same as PM according to the 2014 AASM Guidelines.

Echocardiography

An echocardiographic study was performed by a cardiologist using a GE Vivid Q machine (GE Healthcare, United Kingdom) to confirm ejection fractions of <50%. M-mode echocardiography and two-dimensional echocardiography were performed in standard (i.e., long-axis, short-axis, apical two-chamber, four-chamber, and subcostal) views with the patient in the supine or the left lateral position. The parameters of left ventricle (LV) dimensions and functions were measured using standard procedures, and the ejection fraction (EF) was determined using Simpson's method. In total, two patients were excluded because the EF was higher than 50%.

Statistical analysis

Descriptive statistical analysis was performed. The data were presented as mean and standard deviation (SD), including all

TABLE 1 Baseline demographic characteristics of heart failure patients with or without central sleep apnea.

Characteristics	All patients ($N = 22$)	With CSA ($N = 11$)	Without CSA ($N = 11$)	*P*-value
Age, yr	64.13 ± 10.84	64.6 ± 7.5	63.64 ± 13.8	0.83
BMI, kg/m^2	26.46 ± 3.94	25.97 ± 4.68	26.95 ± 3.17	0.57
BNP (pg/ml)	493 ± 827.12	836 ± 1,078	150.1 ± 128.1	0.04*
EF, %	35.8 ± 0.89	36.0 ± 1.02	35.6 ± 0.7	0.92
Comorbidities				
Atrial fibrillation, *n* (%)	9 (40.9%)	5 (45.4%)	4 (36.4%)	0.66
Chronic kidney disease (eGFR), *n* (%)	84.1 ± 29.4	79.9 ± 21.55	88.2 ± 36.2	0.45
Diabetes mellitus, *n* (%)	6 (27.3%)	2 (18.2%)	4 (36.4%)	0.34
Hypertension, *n* (%)	11 (50%)	6 (54.5%)	5 (45.5%)	0.67
NYHA Functional class, *n*%				0.31
I	1 (4.5%)	1 (9%)	0	
II	19 (86.3%)	10 (90.9%)	9 (81.8%)	
III	2 (9%)	1 (9.1%)	1 (9.1%)	
IV	0	0	0	
Ischemic heart disease, *n*%	10 (45.5%)	6 (54.5%)	4 (36.4%)	0.41

Data are presented as means ± SD or as a number (percentage). *$P < 0.05$ was considered significant. BMI, body mass index; EF, ejection fraction; BNP, B-type natriuretic peptide; CSA, central sleep apnea; eGFR, estimated glomerular filtration rate; N, number.

performance metrics. Statistical analysis was performed using Prism version 5 (GraphPad Software Inc., La Jolla, CA, USA) and SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA). The two groups were compared using unpaired Student's *t*-test for normal distributions, and unpaired Wilcoxon's test for non-normal distributions. A $p < 0.05$ was considered statistically significant. Bland–Altman analysis was used to study the absolute differences of AHI measurements using PM and PSG. The correlation analysis was performed using Spearman's correlation coefficients.

Results

A total of 41 patients underwent portable monitoring, PSG, and echocardiography. Of the 41 patients, 19 patients failed to complete the study due to an inability to enter overnight PSG within 1 month, a refusal to continue due to inconvenience, an ejection fraction (EF) of >50% in follow-up echocardiographic analysis, or mortality (Figure 1). Comparisons were conducted only on the 22 patients (19 male patients; mean age = 64.1 ± 10.8 years) who completed all examinations and presented an EF of <50% (mean EF = 35.8 ± 0.9). Patient demographics are presented in Table 1.

Half of the patients ($n = 11$) experienced CSA during the overnight PSG session. The presence of CSA in patients with heart failure was associated with BNP levels exceeding those of patients without CSA (mean: 836+/−1,078 pg/ml vs. 150.1+/−128.1 pg/ml) ($P = 0.04$). No significant between-group differences were observed in terms of age, EF, etiology of heart failure, severity of heart failure (NYHA functional class), or underlying comorbidities (Table 1).

In our study, the mean sleep time recorded for all PSG tests was 242.9 ± 77.5 min, and the recorded total time for the PM tests was 378.2 ± 85.5 min. The AHI measurements obtained using the manually scored PM and PSG showed a moderately significant correlation (r = 0.69; $P = 0.014$). No correlation was observed between the automatically scored PM and PSG (r = 0.68; $P = 0.05$) (Figure 2). The Bland–Altman diagram (Figures 3, 4) illustrates absolute differences between automated PM scores and manual PM and manual PSG scores for the AHI and central sleep apnea index (CAI). The mean difference in AHI measurement obtained by automatic scoring of PM and PSG was 16.3/h, and that obtained by manual scoring of PM and PSG was 10.5/h. The mean difference in CAI measurement obtained by automatic scoring of PM and PSG was −5.1/h, and that obtained by manual scoring of PM and PSG was −5.1/h. It should be noted that 95% of the differences in the AHI ranged between −52.5 and 19.8 events per hour (automated scoring of PM and PSG) and −46.2 and 25.2 events per hour (manual scoring of PM and PSG). It should also be noted that 95% of the differences in the CAI ranged between −28.7 and 18.4 events per hour (automated scoring of PM and PSG) and −30.3 and 19.9 events per hour (manual scoring of PM and PSG).

The comparison of mean scores of the AHI, hypopnea index (HI), OAI, CAI, and mixed sleep apnea index (MAI) obtained by PSG with those obtained by PM scoring (automatic and manual scoring) is shown in Table 2. In the mean AHI measurement,

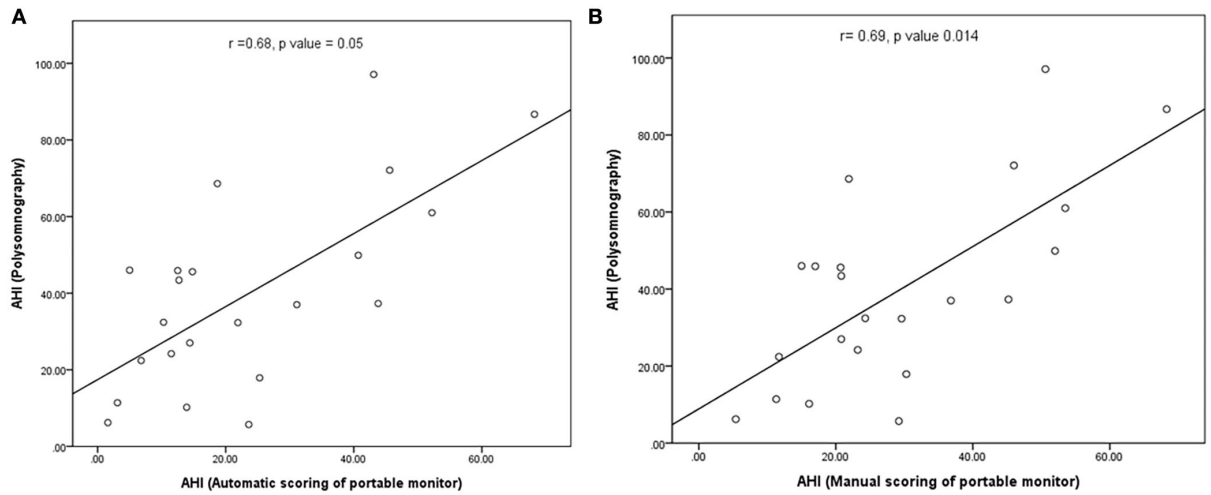

FIGURE 2
(A) Correlation between the number of apnea and hypopnea events in automated PM scoring and polysomnography; **(B)** correlation between the number of apnea and hypopnea in manual PM scoring and polysomnography.

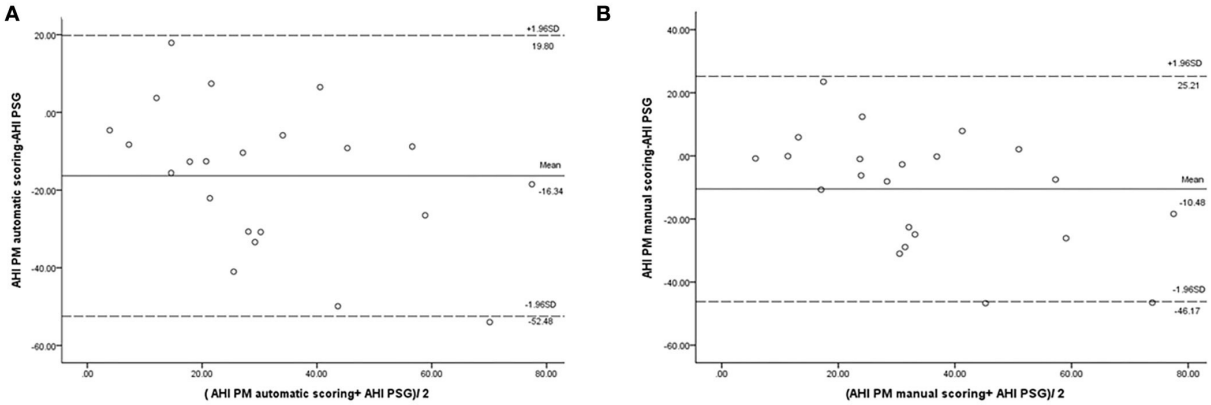

FIGURE 3
Bland–Altman plot comparing the apnea–hypopnea index: **(A)** derived from automated PM scoring and PSG; **(B)** derived from manual PM scoring and PSG.

we observed statistically significant differences between PSG and automatic scoring of PM (40.0 vs. 23.7 events/hour; $P < 0.001$), as well as between automatic and manual scoring of PM (23.7 vs. 29.5 events/hour; $P < 0.001$). In the mean scores of HI measurement, we also observed statistically significant differences between manual PSG and automated PM scores (26.6 vs. 22.1 events/hour; $P = 0.013$). The PM device reliably detected obstructive and central sleep apnea events; however, the incidence of central sleep apnea events detected by PM was lower than that detected by PSG. No statistically significant differences were observed between PSG and PM scores for the CAI or between PSG and automatic PM scores for the OAI (Figure 5).

Discussion

In this study, manual scoring of PM is strongly correlated with PSG in terms of the AHI, CAI, and OAI; however, the severity of PM estimate tends to be underestimated compared with PSG. The PM device was found to be effective in detecting central apnea events, but CSA events are easily misread as OSA events when measured by automatic scoring compared with when measured by manual scoring. Overall, the PM device underestimated the AHI and hypopnea events, and manual scoring was shown to be more accurate in estimating the AHI and hypopnea events than automatic scoring.

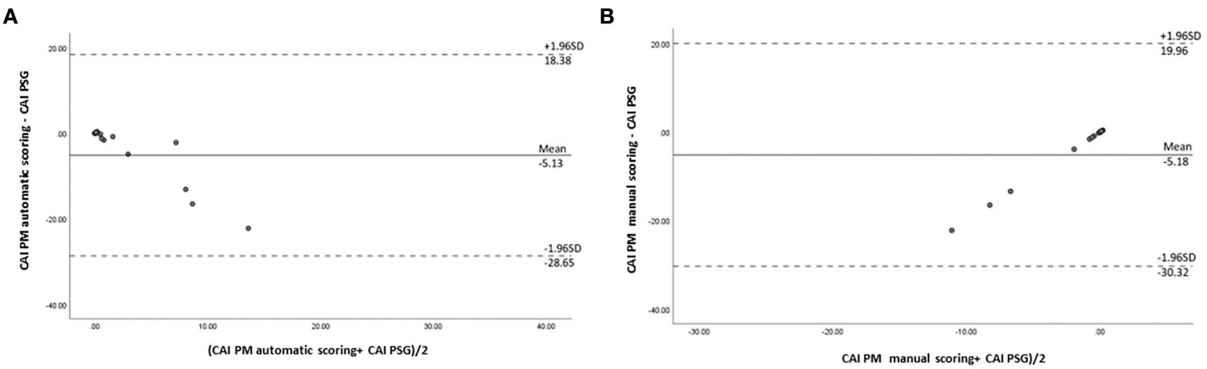

FIGURE 4
Bland–Altman plot comparing central sleep apnea indexes: **(A)** derived from automated PM scoring and PSG; **(B)** derived from manual PM scoring and PSG.

TABLE 2 Scoring of the apnea–hypopnea index, hypopnea index, obstructive apnea index, and central sleep apnea index during full overnight session involving polysomnography or a portable monitor device using automated scoring or manual scoring.

	Polysomnography	Portable monitor (automatic-scoring)	Portable monitor (manual-scoring)	*P*-value
Apnea-hypopnea index	40.01 ± 25.18	23.67 ± 18.01	29.53 ± 16.52	0.001*
Hypopnea index	26.58 ± 18.92	16.60 ± 14.74	22.06 ± 13.43	0.02*
Obstructive sleep apnea index	4.45 ± 5.69	6.0 ± 7.48	6.61 ± 7.66	0.29
Central sleep apnea index	5.98 ± 13.04	0.85 ± 1.62	0.8 ± 1.36	0.06
Mixed sleep apnea index	2.87 ± 4.07	NA	NA	NA

Data are presented as means ± SD. *$P < 0.05$ was considered significant.

CSA is highly prevalent in patients with HF; however, most cases are undiagnosed due to a lack of typical symptoms and a lack of resources for PSG testing (6, 13). There is a pressing need for screening devices for sleep apnea that are inexpensive, easy to use, and effective. A portable monitoring device has been reported as highly reliable in detecting obstructive sleep apnea (14–16) and is widely used as a diagnostic tool in clinical practice currently. However, the diagnostic efficacy of the PM device in patients with heart failure has been questioned, and there is a lack of information on the concurrence between PM and PSG results in the detection of CSA.

The reliability of portable monitoring devices was uncertain, and researchers have yet to establish the reliability of PM devices in identifying CSA (13, 17). Aurora et al. reported that sleep apnea can be accurately identified in patients with HF using PM in an inpatient setting (13), and that a strong agreement exists between PM and PSG results for obstructive sleep apnea (77.4%) and central sleep apnea (94.3%). However, their study was conducted under well-controlled conditions with PM and PSG testing performed at the same time (at admission), which is inapplicable to real-world clinical practice. It should also be noted that the patients were surveyed at the time of admission, which means that they were suffering from acute CHF, which could be construed as selection bias. Weinreich et al. also reported that there was a high diagnostic accuracy rate for detecting central respiratory events using PM in an in-laboratory setting (17).

In the current study, PM was performed in a sleep laboratory, and each PM reading was manually checked to ensure accuracy in the detection of CSA. Our study demonstrated that PM could be used to identify central sleep apnea events; however, PM often misread central apnea events as obstructive apnea due to poor airflow signals. Thus, it appears that automated PM results should be checked manually. We observed that the scoring of PM (either automatic or manual) underestimated sleep apnea events, and that standard PSG and manual scoring were superior to automatic scoring of PM. This study demonstrates the efficacy of PM in identifying central sleep apnea. Our findings challenge previous recommendations, discouraging the use of portable sleep monitors for patients with HF or for the detection of CSA (18).

There are a few limitations to this study. First, the sample size was small due in part to a large percentage of the patients dropping out of the study. Second, PSG and PM readings

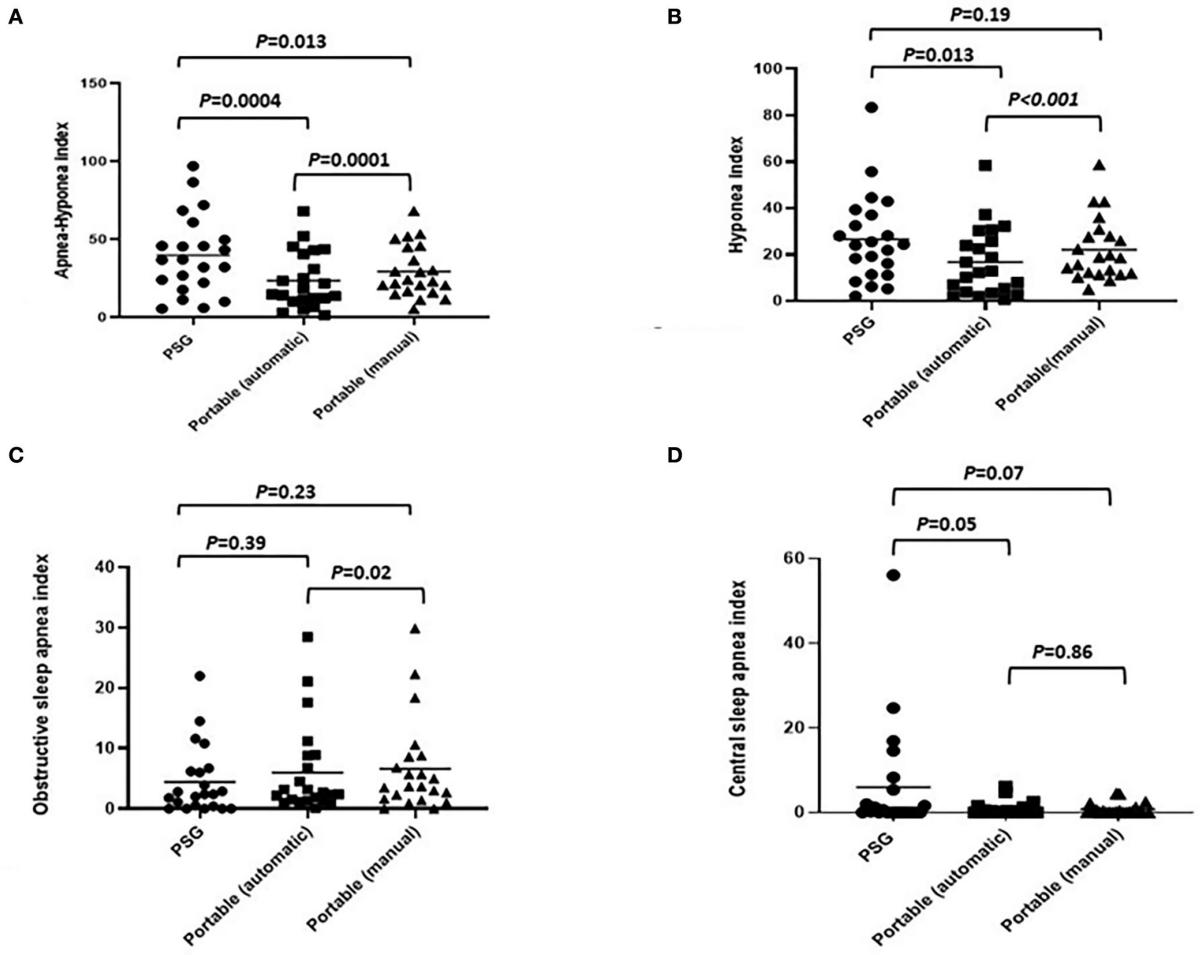

FIGURE 5
Comparison of various indexes (automated PM scoring vs. manual PM scoring vs. full overnight PSG: **(A)** apnea–hypopnea index; **(B)** hypopnea index; **(C)** obstructive apnea index; **(D)** central sleep apnea index.

could not be compared in our study since they were conducted at different time periods, unlike in previous studies in which both devices were measured at the same time. Third, we were well-aware of the fact that the Medibyte is a type 3 PM device and that there is a lack of detailed information on the efficiency of the device in detecting CSA in previous studies. Moreover, a limitation of PM is its inability to distinguish between sleep and wake periods. So, it is likely that PM underestimates the number of apnea and hypopnea incidences due to the use of total recording time, instead of total sleep time. Although PM devices are increasingly used, instead of PSG testing, in clinical practice for detecting OSA, prospective studies and large population samples are needed to verify the diagnostic accuracy of the PM device in identifying CSA.

Conclusion

A portable monitoring device is a viable tool for the identification of central sleep apnea in patients with heart failure. The incidence of central sleep apnea in the current study was underestimated; however, PM devices provided valuable data, particularly in light of the enormous number of patients with heart failure and the difficulty in enrolling patients for PSG.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 201701305A3). Written informed consent to participate in this study was provided by the patients/participants.

Author contributions

L-PC, S-WL, N-HC, and M-SW contributed to the study conception and design. Material preparation and data collection were performed by N-HC, K-CH, M-SW, and C-HL. Data analysis was performed by P-HT, H-CH, and L-PC. The first draft of the manuscript was written by P-HT, L-PC, and N-HC. M-JH, S-WL, K-CH, C-HL, W-CL, H-CH, and M-SW commented on the previous versions of the manuscript. All authors read and approved the final 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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Impairment of GABA inhibition in insomnia disorders: Evidence from the peripheral blood system

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Aim: To explore the change characteristics and related factors of various indexes of GABAergic system in peripheral blood of patients with insomnia disorder.

Methods: In this study, a total of 30 patients who met the DSM-5 diagnostic criteria for insomnia disorder and 30 normal controls were included. All subjects had a structured clinical interview with the Brief International Neuropsychiatric Disorder Interview, and PSQI was used to evaluate the sleep status of the subjects. Enzyme-linked immunosorbent assay (ELISA) was used to detect serum γ-aminobutyric acid (GABA), and RT-PCR was used to detect $GABA_A$ receptor α1 and α2 subunit mRNA. All data were statistically analyzed using SPSS 23.0.

Results: Compared with the normal control group, the mRNA levels of $GABA_A$ receptor α1 and α2 subunits in the insomnia disorder group were significantly lower, but there was no significant difference in the serum GABA levels between the two groups. And in the insomnia disorder group, there was no significant correlation between the GABA levels and the mRNA expression levels of α1 and α2 subunits of $GABA_A$ receptors. Although no significant correlation was found between PSQI and serum levels of these two subunit mRNAs, its component factors sleep quality and sleep time were negatively correlated with $GABA_A$ receptor α1 subunit mRNA levels, and daytime function was inversely correlated with $GABA_A$ receptor α2 subunit mRNA levels.

Conclusion: The inhibitory function of serum GABA in patients with insomnia may be impaired, and the decreased expression levels of $GABA_A$ receptor α1 and α2 subunit mRNA may become a reliable indicator of insomnia disorder.

KEYWORDS

insomnia, GABA, serum, $GABA_A$ receptor, subunits

Introduction

Insomnia disorder (ID) is a common sleep disorder, which means that patients are dissatisfied with the quality and/or amount of sleep and their daytime function is affected, although they have appropriate sleep environment and opportunities. The prevalence of insomnia disorder in European and American countries ranges from 6.9 to 27.3% (1–5), the prevalence of insomnia disorder among Chinese adults is about 15% in China (6). During the COVID-19 pandemic, the global prevalence of insomnia disorder reached 23.87% (7), and 29.2% in China (8). Insomnia disorder not only affects the social and cognitive functions of patients (9), but also increases the risk of mental diseases such as anxiety and depression, and physical diseases such as cardiovascular and cerebrovascular diseases,

metabolic syndrome, and immune diseases (10). Additionally, sick leave, accidental injuries, and accidents caused by insomnia have brought heavy economic and medical burdens to patients, their families and society (11, 12).

γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the mammalian central nervous system, and no less than 20% of neurons are GABAergic neurons (13, 14). Under the action of glutamic acid dehydrogenase (GAD), glutamate (Glu) is decarboxylated to GABA. The maintenance of human normal sleep and wakefulness depends on the dynamic balance of the ascending activation system and descending inhibition system of the brainstem reticular structure, and GABA is the main material basis for maintaining this dynamic balance (15). GABA in the preoptic hypothalamus, especially in the ventrolateral preoptic area, can promote sleep, and GABA can also directly or indirectly inhibit arousal to maintain sleep (16, 17). In addition, agonists (benzodiazepines, non-benzodiazepines, etc.) that act on the α1, α2, α3, or α5 subunits of $GABA_A$ receptors are commonly used clinically as drugs for the treatment of insomnia (15), which means GABAergic system may be involved in the development of insomnia. At present, studies on the correlation between GABAergic system and insomnia disorder mainly focus on the central nervous system, and few studies have explored the relationship between GABAergic system in peripheral blood system and insomnia disorder. Through Magnetic Resonance Spectroscopy (MRS) research, it was found that the overall level of GABA in the brain regions of patients with insomnia was lower than that of normal controls (18–20). Moreover, the research of Winkelman JW et al. showed that GABA levels were negatively correlated with Wake-time After Sleep Onset (WASO) (19). Although the study by Morgan et al. found that occipital GABA increased in insomnia disorder patients compared with normal controls, GABA remained negatively correlated with WASO. Therefore, they believed that the elevated occipital GABA levels in insomnia disorder patients may reflect an allogeneic response to chronic hyperarousal (21). Furthermore, some researchers improved the sleep quality of patients with insomnia disorder by increasing the content of peripheral blood GABA (22–25). However, we know little about the changes of peripheral blood GABAergic system in patients with untreated insomnia disorder. Therefore, in this study, we explored the peripheral blood serum GABA levels and the mRNA expression levels of $GABA_A$ receptor α1 and α2 subunits in patients with insomnia disorders.

Materials and methods

Subjects

The patients with insomnia disorder came from outpatients and inpatients who visited the Department of Psychiatry of the First Affiliated Hospital of Jinan University from May 2018 to March 2019. Inclusion criteria: (1) Meet the diagnostic criteria of DSM-5 for insomnia disorder; (2) Age 18–65. (3) Pittsburgh Sleep Quality Index (PSQI) ≥ 8 points. (4) Junior high school and above. Exclusion criteria: (1) Patients combined with other sleep–wake disorders. (2) Patients with other mental disorders in the past and present. (3) Patients with brain organic diseases and other physical diseases. (4) Using antidepressants, antipsychotic drugs, and sleep-promoting drugs. (6) Users of long-acting antipsychotic drugs in the past 1 month. (7) Pregnant and lactating women.

The controls were healthy volunteers recruited from the community during the same period. Inclusion criteria: (1) The Mini-International Neuropsychiatric Interview Chinese version 5.0.0 (M.I.N.I.) structured interview did not meet the diagnostic criteria of DSM-5 for insomnia disorder. (2) Age between 18 and 65 years old. (3) PSQI≤7 points. (4) Junior high school and above. Exclusion criteria: (1) Those who combined with other sleep–wake disorders. (2) Those who with any mental disorders in the past and present. (3) Those who with brain organic diseases and other physical diseases. (4) Using antidepressants, antipsychotic drugs, and sleep-promoting drugs. (6) Users of long-acting antipsychotic drugs in the past 1 month. (7) Pregnant and lactating women. (8) Those who have blood relationship with the case group.

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Jinan University, and all participants gave informed consent to this study and signed an informed consent form.

Demographic information

The demographic data of all subjects were collected, and the occurrence and development of diseases in insomnia subjects were collected. The former includes gender, age, marital status, work status, family history of mental illness, etc. The latter includes the age of first onset, total disease duration, and current disease duration.

Scale evaluation and diagnosis

All subjects were diagnosed consistent with the M.I.N.I. structured interview by two psychiatrists with intermediate professional titles, and then blood routine, liver function, kidney function, thyroid function, myocardial enzymes, electrocardiogram, abdominal B-ultrasound, head MR, and other related examinations were included in the study after excluding organic brain diseases and other physical diseases.

Pittsburgh sleep quality index

It is used to evaluate the subjective sleep quality of the subjects in the last 1 month. Consists of 19 self-assessment items and five other-evaluation items, of which the 19th self-evaluation item and five other-evaluation items do not participate in scoring, 18 items form seven factors, and each factor is scored on a scale of 0–3, the cumulative score of each component is the total score of PSQI, the total score ranges from 0 to 21, and the higher the score, the worse the sleep quality. Seven factors were sleep quality, sleep latency, sleep time, sleep efficiency, sleep disturbance factors, use of hypnotic drugs, and daytime dysfunction (4).

Sample collection and testing

All subjects collected 2 ml of fasting venous blood from the left elbow in dry tubes and EDTA anticoagulant tubes before receiving medication and physical therapy at 8–9 am on the next day after enrollment. The blood samples in the drying tube were left standing at 4°C for 30 min, centrifuged at 3,000 r/min at low temperature (4°C) for 10 min, and the supernatant was transferred to a sterile cryopreservation tube and stored in a −80°C refrigerator. The concentration of GABA was

detected by enzyme-linked immunosorbent assay (ELISA), and the ELISA kit was provided by Guangzhou Blue Dolphin Biotechnology Co., Ltd. The concentration of the standard substance of the GABA kit was as follows: 8, 4, 2, 1, 0.5, and 0 μmol/L. Detection range 0.25–8 μmol/L Sensitivity: The lowest detection concentration was less than 0.1 μmol/L, the intra-assay coefficient of variation is 6%, and the inter-assay coefficient of variation is 11%.

Blood samples in EDTA anticoagulant tubes were used to detect the expression levels of $GABA_A$ receptor α1 and α2 subunit mRNAs, and total RNA was extracted using the blood sample RNA extraction kit produced by OMEGA Company. At the same time, (1) purity test was completed: 1 μl RNA sample was diluted 50 times, and the OD value was measured on the BioPhotometer plus Eppendorf Nucleic Acid Protein Analyzer. The ratio of OD260/OD280 was greater than 1.8, indicating that the prepared RNA was relatively pure and free of protein contamination. (2) Integrity detection of total RNA: take 1 μl of RNA sample, electrophoresis on 1% agarose gel at 80 V × 20 min, observe the 5, 18, and 28 s rRNA bands of the total RNA with a gel imaging system, if the three bands are complete, it can be proved that the extraction of total RNA is relatively complete. cDNA was reverse-transcribed using a reverse transcription kit (provided by Guangzhou Blue Dolphin Biotechnology Co., Ltd.). According to the NCBI database sequence, the primers were synthesized by Shanghai Biochemical, and the primer sequences of the α1 and α2 subunits of the $GABA_A$ receptor were designed as follows: α1 forward primer: 5′-GTCAAGCCCGAAA CAAAACC, α1 reverse primer: GATTCCAAATAGCAGCGGGA-3′, α2 forward primer: 5′-TCGACATAGTCGTTGAAGCA, α2 reverse primer: GCAGGCACCCAAGATTAACA-3′. ABIPRISM®7500 sequence detection system was used to perform Reverse Transcription-PCR (RT-PCR) to measure mRNA levels. The RT-PCR reaction system included 5.0 μl of cDNA (1:20), 0.5 μl of upstream primers, 0.5 μl of downstream primers, 2xSYBR Green qPCRSuperMix (Invitrogen) 10 μl, dH2O 4.0 μl, 95°C for 5 min; 95°C for 15 s, 60°C for 32 s, and 40 cycles; melting curve analysis was performed after the cycle, and each sample was repeated three times. mRNA levels were calculated using the ($2^{-\Delta\Delta Ct}$) method.

Analysis

SPSS 23.0 was used for statistical analysis, and the statistics of measurement data were described as mean ± standard deviation and median (Lower quartile, Upper quartile). Count data were analyzed using chi-square test. Normally distributed measurement data, two groups were compared using *t*-test, non-normally distributed measurement data using *t*' test. Correlation analysis between two variables was performed by Pearson correlation analysis or Spearman correlation analysis. All tests were two-sided, with a test level of $\alpha = 0.05$.

Results

Demographic and clinical information

The results were shown in Table 1. This study included 30 patients in the insomnia disorder (ID) group, including 13 males. The age of ID group ranged from 18 to 65 years, with an average age of 39.13 ± 11.97. The total course of disease was 3 ~ 245 months, with a median of 25.00 (12.75, 79.50) months. The average age of first onset was 35.10 ± 9.69 years old. The duration of this onset was 2–93 months, with a median of 12.50 (4.00, 25.25) months. There were 30 subjects in the normal control (NC) group, 13 subjects were male. The age of NC group ranged from 20 to 64 years, with an average age of 34.67 ± 13.68 years. There was no significant difference in gender (χ^2=0.000, $p = 1.000$) and age ($F = 1.951$, $p = 0.183$) between the two groups. There was a significant difference in marital status between the two groups ($F = 8.864$, $p = 0.003$).

TABLE 1 Demographic characteristics of subjects.

Characteristics	ID	NC	*p* values
Number of subjects	30	30	-
Age (years) Mean ± SD	39.13 ± 11.97	34.67 ± 13.68	0.183
Age range (years)	18–65	20–64	-
Gender (male/female)	13/17	13/17	1.000
Married (yes/no)	25/5	14/16	0.003
Family history (yes/no)	3/27	0/30	0.236
First-episode (yes/no)	21/9	-	-
Total duration of illness (month)	25.00 (12.75–79.50)	-	-
Age of first onset	35.10 ± 9.69	-	-
Time of this course (month)	12.50 (4.00–25.25)	-	-

ID, insomnia disorder group; NC, normal control group; SD, standard deviation.

Comparison of GABA levels and the mRNA levels of $GABA_A$ receptor α1 and α2 subunits between insomnia disorder group and normal control group

There was no significant difference in serum GABA levels between ID group and NC group ($F = 0.458$, $p = 0.733$). However, compared with the NC group, the peripheral blood $GABA_A$ receptor α1 ($F = 1.573$, $p < 0.001$) and α2 subunits ($F = 8.757$, $p = 0.001$) levels in the ID group were significantly decreased (Figure 1).

Analysis of related factors of serum the serum mRNA levels of $GABA_A$ receptor α1 and α2 subunits in the insomnia disorder group

As shown in Table 2, we found that the mRNA expression levels of $GABA_A$ receptor α1 and α2 subunits were positively correlated with the age ($r = 0.462$, $p < 0.05$; $r = 0.483$, $p < 0.01$) and the age of first onset ($r = 0.498$, $p < 0.01$; $r = 0.454$, $p < 0.05$) of insomnia disorder patients, but no significant correlation was found between these two indicators and gender, total disease duration, and PSQI total score. We also analyzed the relationship between the expression levels of $GABA_A$ receptor α1 and α2 subunits mRNA and PSQI factors, and found that the expression level of $GABA_A$ receptor α1 subunits mRNA was negatively correlated with sleep quality ($r = -0.383$, $p < 0.05$) and sleep time ($r = -0.381$, $p < 0.05$), while there was a negative correlation between the expression of $GABA_A$ receptor α2 subunits mRNA and daytime function ($r = -0.491$, $p < 0.01$).

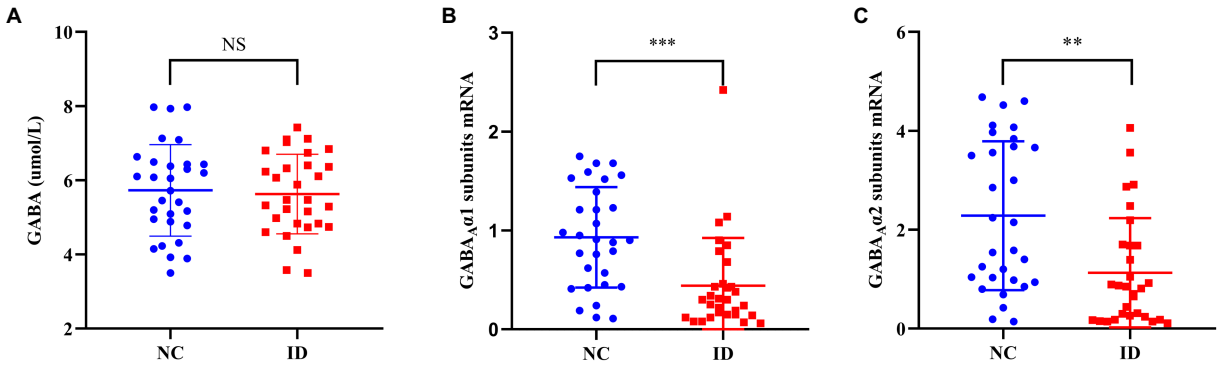

FIGURE 1
Comparison of γ-aminobutyric acid (GABA) levels and the mRNA levels of GABA$_A$ receptor α1 and α2 subunits between ID and NC. NS, no significant; ID, insomnia disorder group; NC, normal control group. **p <0.01. ***p <0.001.

TABLE 2 Analysis of related factors of serum the serum mRNA levels of GABA$_A$ receptor α1 and α2 subunits in the insomnia disorder group.

Variable	GABA$_A$ α1 subunits mRNA		GABA$_A$ α2 subunits mRNA	
	r	*p*	*r*	*p*
Age	0.462*	0.010	0.483**	0.007
Gender	0.121	0.524	0.244	0.193
Total duration of illness	0.150	0.163	0.307	0.099
Age of first onset	0.498**	0.005	0.454*	0.012
PSQI	−0.200	0.290	−0.070	0.715
Sleep quality	−0.383*	0.037	−0.325	0.080
Sleep latency	0.078	0.683	0.190	0.314
Sleep time	−0.381*	0.038	−0.147	0.440
Sleep efficiency	−0.219	0.244	−0.008	0.967
Sleep disturbance factor	0.126	0.509	0.343	0.064
Drugs	0.178	0.346	0.070	0.712
Daytime function	−0.269	0.150	−0.491**	0.006

*p < 0.05; **p < 0.01.

Correlation analysis of serum GABA levels, GABA$_A$ receptor α1 subunits mRNA and GABA$_A$ receptor α2 subunits mRNA expression levels in the insomnia disorder group

Figure 2A showed that there was a significant positive correlation between the expression levels of peripheral blood GABA$_A$ receptor α1 subunits mRNA and GABA$_A$ receptor α2 subunits mRNA in ID group ($r = 0.695$, $p < 0.001$), while no significant correlation was found between serum GABA levels and the mRNA expression levels of these two subunits (Figures 2B,C). In addition, in the NC group (Figure 3), we found statistically significant correlations between peripheral blood GABA$_A$ receptor α1 subunits mRNA and GABA$_A$ receptor α2 subunits mRNA expression, between the serum GABA levels and GABA$_A$ receptor α1 subunits mRNA expression, between the serum GABA levels and the mRNA expression levels of GABA$_A$ receptor α2 subunits.

Discussion

Our study did not find significant differences in serum GABA levels between insomnia disorder group and normal control group, but there were significant differences in the expression levels of peripheral blood GABA$_A$ receptor α1 subunits mRNA and GABA$_A$ receptor α2 subunits mRNA between the two groups. Moreover, in the ID group, the serum GABA levels did not seem to be significantly correlated with the expression of GABA$_A$ receptor α1 subunits mRNA and GABA$_A$ receptor α2 subunits mRNA, but in the NC group, there was a positive correlation between the serum GABA levels and the expression of these two subunits. In addition, the expression levels of GABA$_A$ receptor α1 subunits mRNA and GABA$_A$ receptor α2 subunits mRNA in peripheral blood were significantly positively correlated between the two groups, and the ID group was more significant.

The GABA$_A$ receptor is composed of five subunits and belongs to the ligand-gated ion channel family, which is activated after binding to the inhibitory neurotransmitter GABA to play a sleep-promoting role (26). The three generations of hypnotics used clinically are all based on the inhibition process mediated by GABA$_A$ receptors (27). There are 19 subunit types of GABA$_A$ receptors (α1-6, β1-3, γ1-3, δ, ε, θ, π, and ρ1-3) (28), and many GABA$_A$ receptors consist of two α subunits, two β subunits, and one γ subunit, α1β2γ2 type accounts for about 60% of GABA$_A$ receptors, followed by α2β3γ2 type accounting for 15–20% (29, 30). The benzodiazepine binding site is formed by one of the α1, α2, α3, and α5 subunits with the γ subunit, while non-benzodiazepines preferentially bind to α1βγ2-type GABA$_A$ receptor (31). Although the current clinically preferred non-benzodiazepines are known to bind preferentially to the α1-GABA$_A$ receptor, they can still bind to the α2-GABA$_A$ receptor and the α3-GABA$_A$ receptor. The study by Crestani et al. suggested that the sedative-hypnotic and anticonvulsant activity of zolpidem was due to its action on α1-GABA$_A$ receptors rather than α2- or α3-GABA$_A$ receptors (32). However, the study by Kopp et al. showed the opposite. Their results showed that the non-benzodiazepine drug-zolpidem seems to produce sedative-hypnotic effects after binding to α2-GABA$_A$ receptor and/or α3-GABAA receptor, but not to α1-GABAA receptor combination produced (33). In addition, Uygun et al. also suggested that the ability of zolpidem to reduce NREM sleep latency and increase sleep time may be related to α2-GABA$_A$ receptors (34). This means that GABA$_A$ receptors, especially α1-GABA$_A$ and/or α2-GABA$_A$ receptor may play an important role in the pathophysiological process

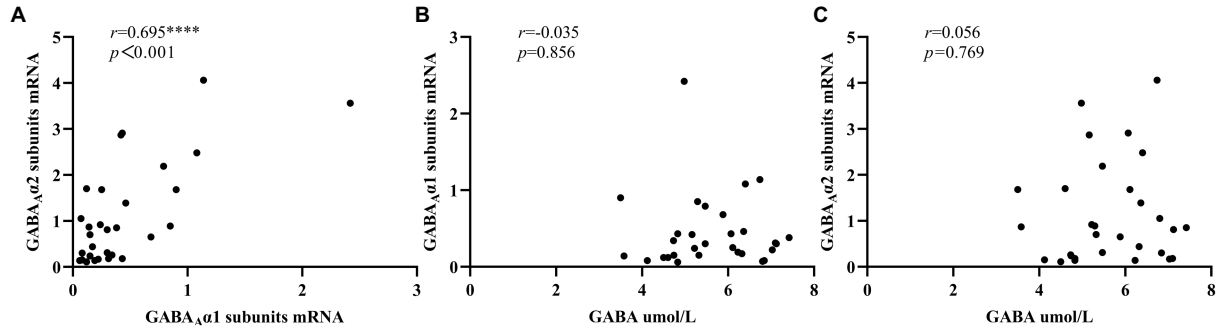

FIGURE 2
Correlation analysis of serum GABA level, $GABA_A$ receptor α1 subunits mRNA and $GABA_A$ receptor α2 subunits mRNA expression levels in the insomnia disorder group. $2^{-\Delta\Delta Ct}$ was used to calculate the relative expression of $GABA_A$ receptor α1 subunits mRNAs and $GABA_A$ receptor α2 subunits mRNAs. ****p <0.0001.

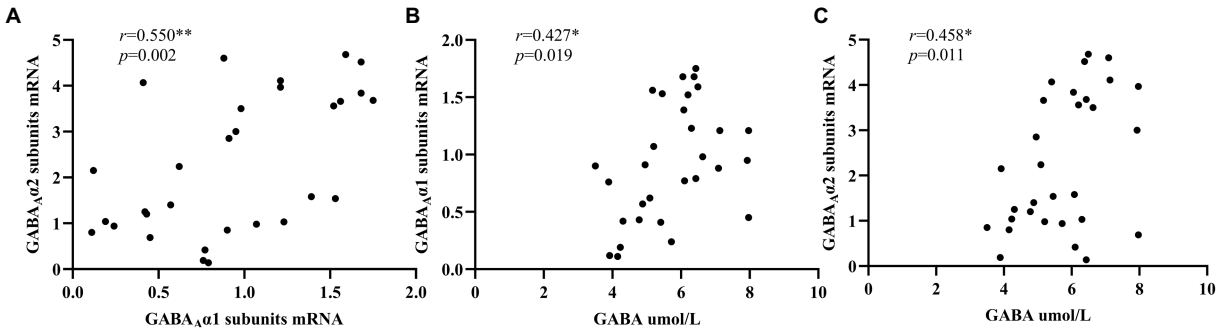

FIGURE 3
Correlation analysis of serum GABA level, $GABA_A$ receptor α1 subunits mRNA and $GABA_A$ receptor α2 subunits mRNA expression levels in the normal control group. $2^{-\Delta\Delta Ct}$ was used to calculate the relative expression of $GABA_A$ receptor α1 subunits mRNAs and $GABA_A$ receptor α2 subunits mRNAs. *p <0.05. **p <0.01.

of sleep, and the disturbance of GABAergic system may cause insomnia. Our study suggested that compared with the NC group, the expression levels of peripheral blood $GABA_A$ receptor α1 subunits mRNA and $GABA_A$ receptor α2 subunits mRNA in the ID group were significantly decreased, and $GABA_A$ receptor was activated to participate in the occurrence of sleep, and their expression decreased, which meant sleep drive and maintenance were disrupted, resulting in insomnia. α1-$GABA_A$ receptor and α2-$GABA_A$ receptor in peripheral blood may be used as biomarkers of insomnia, of course, it still needs a large number of samples to verify.

Our study also found that compared with the NC group, the GABA levels of the ID group did not observe significant changes, but the receptor expression of the latter decreased, which meant that although the GABA content in the serum of the patients remained unchanged, the number of receptors that can interact with GABA decreases, and the inhibitory effect of GABA was also affected. The expression levels of $GABA_A$ receptor α1 subunits mRNA and $GABA_A$ receptor α2 subunits mRNA in the ID group had no significant relationship with GABA, but there was a positive correlation in the NC group, which suggested that the GABAergic system of normal individuals had homeostatic self-regulation, while the peripheral blood GABA system of the ID group was damaged and could not regulate the balance of GABA levels and its receptors. Since GABA hardly crosses the blood–brain barrier (35, 36), serum GABA levels do not directly reflect GABA levels in the central nervous system. Then it could also explain the inconsistency between our results and the reduction of GABA levels in the central nervous system of patients with insomnia (18–20). However, some studies have found that some herbal medicine extracts can shorten the sleep latency and maintain sleep by increasing the level of GABA and the expression level of $GABA_A$ receptor α1 protein in mouse serum and brain tissues (37). Moreover, the combined intake of GABA and L-theanine increased the level of GABA in rat brain tissues and increased the expression of $GABA_A$ receptor, thereby promoting sleep and reversing the sleep reduction caused by caffeine in rats (38). This mechanism of improving sleep by increasing peripheral blood GABA levels may be produced through indirect pathways, such as through the enteric nervous system (ENS) (39) or the possible presence of GABA transporters in the blood–brain barrier (40).

Through correlation analysis, we found that the age of the ID group and the age of first onset were positively correlated with the expression of $GABA_A$ receptor α1 and α2 subunits mRNA. In addition, we did not find a significant correlation between the age of the NC group and the expression of these two subunits ($r = 0.268$, $p = 0.152$; $r = 0.219$, $p = 0.245$), which indicated that age might affect the expression of $GABA_A$ receptor α1 and α2 subunits mRNA in some way in the insomnia disorder patients, but there was no relevant research report so far. At the same time, our results also suggested that the patient's subjective sleep quality assessment total score (PSQI) seemed to have no significant correlation with the peripheral blood expression of these two subunits. However, by analyzing the correlation between the PSQI factor scores and the expression levels of $GABA_A$ receptor α1 and α2 subunits mRNA, we found that the worse the sleep quality and the less sleep time, the

lower the serum expression of α1-$GABA_A$ receptor. The worse the daytime function, the lower the serum level of $GABA_A$ receptor α2 subunits mRNA. Agosto et al. confirmed that $GABA_A$ receptor promotes the initiation of sleep (41), so we inferred that the activation of $GABA_A$ receptor can prolong the total sleep time by reducing the sleep latency and improve the patient's subjective sleep satisfaction. Moreover, our results were consistent with Crestani et al.'s suggestion that activation of α1-$GABA_A$ receptors may mediate sedative-hypnotic and anticonvulsant (32). Some studies have found that the expression imbalance of $GABA_A$ receptor α subunit may be related to cognitive function (42), and $GABA_A$ receptor blockade can impair social behavior and attention, but the specific subunit type needs to be further determined (43).

Our study also has certain limitations. We only measured the levels of peripheral serum GABA and $GABA_A$ receptor α1 and α2 subunits mRNA, and only used subjective assessment scales to evaluate the sleep and function of patients. In the future, while increasing the number of samples to verify the above results, we also need to measure the levels of the above indicators in the central nervous system, and combine objective evidence to explore the correlation between patients' insomnia symptoms and severity and the GABA system.

Conclusion

In summary, our research showed that the inhibition of GABA in the peripheral blood system of patients with insomnia disorder was impaired, which might be mediated by the abnormal expression of its receptor subunits. In future research, we can focus on the function of receptors in the peripheral blood system to explore the clinical characteristics of insomnia disorder.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by IRB of the First Affiliated Hospital of Jinan University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TX was responsible for research concept and design, literature research, manuscript preparation, and data analysis. JL was responsible for research concept and design, literature research, and experimental research. YiC was responsible for statistical analysis, mapping, and data collection. MF and CL were responsible for clinical research. XZ, HL, and YuC were responsible for the sleep assessment of subjects. JP was responsible for the integrity and manuscript review of the entire study. 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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Using sleep heart rate variability to investigate the sleep quality in children with obstructive sleep apnea

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Background: Obstructive sleep apnea (OSA) is associated with impaired sleep quality and autonomic dysfunction. Adenotonsillectomy significantly improves subjective and objective sleep quality in children with OSA. However, the postoperative changes in heart rate variability (HRV) indices (indicators of cardiac autonomic function) and their importance remain inconclusive in childhood OSA. This retrospective case series aimed to investigate the association of sleep HRV indices, total OSA-18 questionnaire score (a subjective indicator of sleep quality) and polysomnographic parameters (objective indicators of sleep quality), and effects of adenotonsillectomy on HRV indices, total OSA-18 questionnaire score and polysomnographic parameters in children with OSA.

Methods: Seventy-six children with OSA were included in baseline analysis, of whom 64 (84%) completed at least 3 months follow-up examinations after adenotonsillectomy and were included in outcome analysis. Associations between baseline variables, and relationships with treatment-related changes were examined.

Results: Multivariable linear regression models in the baseline analysis revealed independent relationships between tonsil size and obstructive apnea-hypopnea index (OAHI), adenoidal-nasopharyngeal ratio and very low frequency (VLF) power of HRV (an indicator of sympathetic activity), and normalized low frequency power (an indicator of sympathetic activity) and OAHI. The outcome analysis showed that adenotonsillectomy significantly improved standard deviation of all normal-to-normal intervals, and high frequency power, QoL (in terms of reduced total OSA-18 questionnaire score), OAHI and hypoxemia. Using a conceptual serial multiple mediation model, % change in OSA-18 questionnaire score and % change in VLF power serially mediated the relationships between change in tonsil size and % change in OAHI.

Conclusions: The improvement in OAHI after adenotonsillectomy was serially mediated by reductions in total OSA-18 questionnaire score and VLF power. These preliminary findings are novel and provide a direction for future research to investigate the effects of VLF power-guided interventions on childhood OSA.

KEYWORDS

adenotonsillectomy, children, heart rate variability (HRV), mediation, obstructive sleep apnea, quality of life

1. Introduction

Over 4% of children worldwide suffer from obstructive sleep apnea (OSA) (1). OSA, characterized by snoring and abnormal breathing during sleep, is a chronic disorder with many comorbidities, including cardiovascular sequelae (2) and cognitive/behavioral problems (3). OSA considerably reduces sleep quality in children (4). Furthermore, childhood OSA has been associated with hypofunction in brain autonomic control regions (5), which can influence heart rate and heart rate variability (HRV) by the interposition of cortico-subcortical pathways to the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) (6).

Unlike clinical signs and symptoms, which are often direct presentations of a disease, HRV reflects more indirect underlying pathophysiological process, either causal, mediating, or reactive, which allows measurements of the HRV to serve as a biomarker in a wide range of health conditions (7). Time domain and frequency domain HRV analysis on electrocardiograms are useful for diagnosing different clinical and functional conditions (8). For example, 24-h HRV indices are significantly associated with sleep disturbance and depression symptoms of medical students (9). In children with OSA, sleep fragmentation, arousal, and hypoxemia may increase SNS activity (10). However, sleep stage-specific HRV measurements have shown significantly downregulated PNS activity in children with sleep-disordered breathing (11). Studies on HRV in children with OSA have reported inconsistent results (12–14), and thus further investigations on cardiac autonomic function in this population are warranted.

Hypertrophy of adenoids and tonsils is the most common cause of upper airway obstruction in children (15), and adenotonsillectomy is the first-line treatment for childhood OSA (12, 16). Adenotonsillectomy significantly reduces the severity of OSA in terms of apnea-hypopnea index (AHI) and sympathetic activity (17) and sustainably improved quality of life (18). However, approximately 70% of children have residual OSA (19), which still threatens children's health. Further, changes in OSA-related HRV indices are not related to changes in AHI and hypoxemia (14). Accordingly, the aims of this study were to evaluate the reproducibility of sleep HRV analysis, the associations of sleep HRV and sleep quality, and the changes in HRV indices after adenotonsillectomy in children with OSA, and understand how these changes relate to adenoid-tonsil size and improvements in polysomnographic parameters.

2. Materials and methods

2.1. Study participants

The Institutional Review Board of Chang Gung Medical Foundation approved this retrospective case series (No. 202200882B0). The requirement for written informed consent was waived because the current study was based on a secondary analysis of existing data. This study followed the World Medical Association's Declaration of Helsinki and the Strengthening the Reporting of Cohort Studies in Surgery guidelines (20).

We included consecutive children who underwent adenotonsillectomy for OSA at Chang Gung Memorial Hospital, Linkou Main Branch (Taoyuan, Taiwan) between March 1, 2017 and September 30, 2021. The inclusion criteria were: (1) age 5–12 years, and (2) obstructive AHI (OAHI) $\geq$ 2.0 events/h or obstructive apnea index (OAI) $\geq$ 1.0 events/h (21, 22). The exclusion criteria were (1) patients with craniofacial, neuromuscular, or chronic inflammatory disorders (23, 24), or (2) patients without available polysomnographic data. All the children underwent extracapsular tonsillectomy with tonsillar pillar suturing and adenoidectomy that aimed to improve the upper airway obstruction by the principal investigator (L-AL) in a single stage under general anesthesia (25). Children with follow-up polysomnographic data were included in outcome analysis (Figure 1).

2.2. Clinical variables

Age, sex, body mass index (BMI), tonsil size, adenoidal-nasopharyngeal ratio (ANR) and evening blood pressure (BP) (2, 26), OSA-related quality of life, and polysomnographic parameters were recorded. All the clinical measurements were performed before and at least 3 months after adenotonsillectomy.

The tonsils were graded with a size scale from 1–4 (1: tonsils within the tonsillar; 2: tonsils visible outside the anterior pillars; 3: tonsils extending three-quarters of the way to the midline; 4: tonsils meeting at the midline) (27).

The ANR (distance from the point of maximal convexity of the adenoid shadow/the distance between the posterior border of the

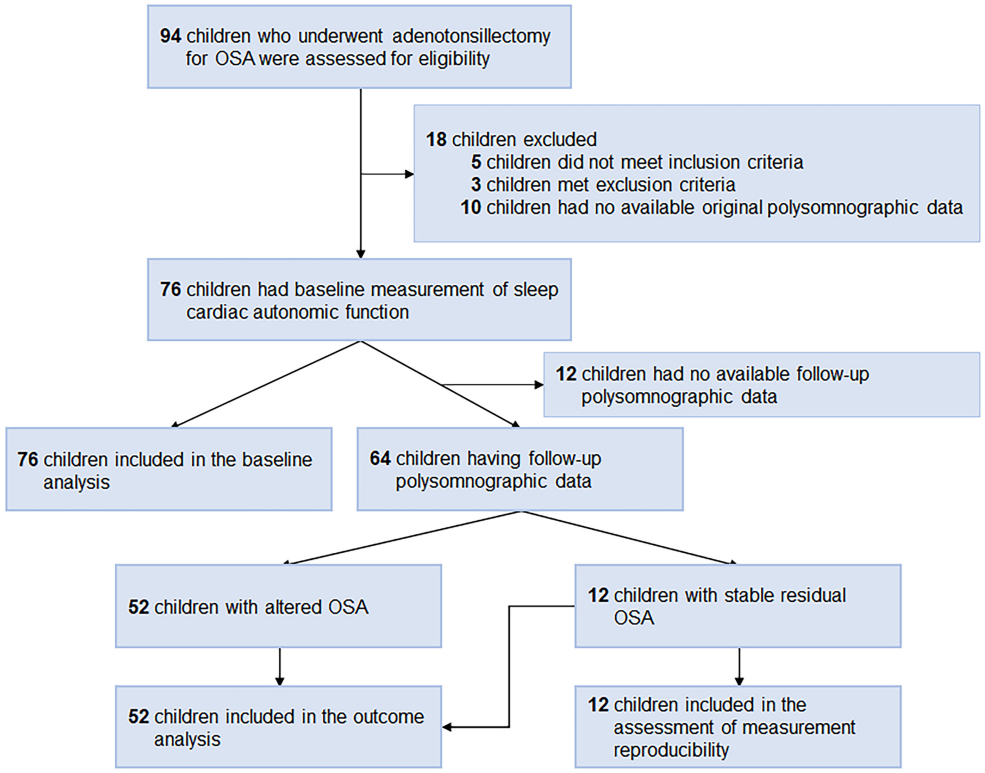

FIGURE 1
Flow diagram. OSA, obstructive sleep apnea.

hard palate and the anteroinferior edge of the sphenobasioccipital synchondrosis) was measured on neck lateral view (28).

2.3. Sleep quality

2.3.1. Subjective measurement

All parents evaluated their children's OSA-related quality of life using the Chinese version of the OSA-18 questionnaire (29), which includes 18 items grouped into 5 domains: sleep disturbance (4 items), physical suffering (4 items), emotional distress (3 items), daytime problems (3 items), and caregiver concerns (4 items). Each item was scored using a 7-point ordinal scale. The total score was calculated as the sum of the 18 items (overall range, 18–126) and has been shown to have excellent test-retest reliability (30).

2.3.2. Objective measurement

All participants underwent full-night, in-laboratory polysomnography (Nicolet Biomedical Inc., Madison, WI, USA) (23). OAHI, OAI, arousal index, mean blood oxygen saturation (SaO_2), minimal SaO_2, sleep stages and total sleep time were scored and manually verified by the study investigators (L-PC and Y-SH) using a standard approach of the American Academy of Sleep Medicine (31). For example, the AHI was calculated by dividing the sum of all apneas (defined as a $\geq$ 90% reduction in airflow for a duration of $\geq$ 2 consecutive breaths) and hypopneas (defined as a $\geq$ 30% reduction in airflow in association with electroencephalographic arousal or a $\geq$ 3% reduction in SpO_2 for a duration of $\geq$ 2 consecutive breaths) by the hours of total sleep time.

2.4. Sleep heart rate variability analysis

Electrocardiographic polysomnography signals were analyzed using HRV software (profusionSLEEP^{TM}, version 4.5, build 502, Compumedics, Abbotsford, Australia). For artifact correction, automated annotations of electrocardiographic signals, such as loose leads, motion artifacts, and broken wires (32), were manually verified by trained technicians who had been certificated by the domestic board of the Taiwan Society of Sleep Medicine and shown substantial-to-almost perfect reliabilities in the scoring of respiratory events (intraclass correlation coefficients [ICCs] ranged from 0.66 to 0.98) (33). According to standard guidelines, time-domain indices, including standard deviation of all normal-to-normal (N-N) intervals (SDNN), number of pairs of adjacent N-N intervals differing by more than 50 ms in the entire recording divided by the total number of all N-N intervals (pNN50), and square root of the mean of the sum of the squares of differences between adjacent N-N intervals (RMSSD) were recorded. In addition, frequency-domain indices, including total power (0.0033–0.4 Hz), very low frequency (VLF) power (0.0033–0.04 Hz), low frequency (LF) power (0.04–0.15 Hz), normalized

TABLE 1 Indices, units, descriptions, and meanings of heart rate variability.

Variable	Unit	Description	Meaning
Time-domain indices			
N-N	ms	Time interval between N-N heartbeats	
SDNN	ms	Standard deviation of all N-N intervals.	Total capacity of the regulation system (35)
pNN50	%	Number of pairs of adjacent N-N intervals differing by more than 50 ms divided by the total number of all N-N intervals.	Increased parasympathetic activity (35)
RMSSD	ms	The square root of the mean of the sum of the squares of di?erences between adjacent N-N intervals.	Increased parasympathetic activity (36)
Frequency-domain indices			
Total power	ms^2	The variance of N-N intervals over the approximately the temporal segment (approximately $\leq$ 0.4 Hz)	Total capacity of the regulation system (35)
VLF power	ms^2	Power in very low frequency range ($\leq$ 0.04 Hz)	Sympathetic activity (36)
LF power	ms^2	Power in low frequency range (0.04–0.15 Hz)	Baroreceptor activity (37)
LF%	%	LF power / (Total Power–VLF power) × 100	Sympathetic modulation (38)
HF power	ms^2	Power in high frequency range (0.15–0.4 Hz)	Parasympathetic modulation (39)
LF/HF ratio		Ratio LF [ms^2]/HF [ms^2]	Sympathovagal balance (34)

HF, high frequency; LF, low frequency; LF%, normalized LF power; N-N, normal-to-normal; pNN50, proportion of N-N50 divided by the total number of N-N intervals; RMSSD, square root of the mean of the sum of the squares of di?erences between adjacent N-N intervals; SDNN, standard deviation of all N-N intervals; VLF, very low frequency.

LF power (LF%), high frequency (HF) power (0.15–0.4 Hz), and LF/HF ratio were also recorded (Table 1) (34–39).

2.5. Reproducibility assessment

Reproducibility of the HRV measurements was assessed using ICCs (two-way random model; absolute agreement type) from data quantified from separate sleep HRV measurements performed at least 3 months apart in a sample of 12 children with stable residual OSA [defined as postoperative OAHI within (preoperative OAHI−5.6 events/h) to (preoperative OAHI + 6.8 events/h), compatible with the upper and lower limits of agreement of OAHI measured on the first and second night in children and adolescents] (40). This sample represented children who did not undergo adenotonsillectomy. ICCs evaluated reproducibility as "poor" (< 0.001), "slight" (0.001–0.020), "fair" (0.021–0.40), "moderate" (0.41–0.60), "substantial" (0.61–0.80), and almost perfect (0.81–1.00) (41).

2.6. Statistical analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9.0 for Windows (Graph Pad Software Inc., San Diego, CA, USA). Changes in scores were calculated as postoperative minus preoperative values. Percentage change [(change in score/preoperative value) × 100] was calculated for variables of interest. Because all the children underwent extracapsular tonsillectomy, the change in tonsil size was equal to the negative value of tonsil size and used for further statistical analysis.

Using the Shapiro-Wilk test to examine normality, descriptive statistics were expressed as mean (standard deviation) for normally distributed continuous variables, median (interquartile range [IQR]) for skewed variables, and number (proportion) for categorical variables.

For continuous variables, the independent-samples *t*-test or Mann-Whitney *U* test was used to assess between-group changes; the paired-samples *t*-test or Wilcoxon signed-rank test was used to assess within-group changes as appropriate. Differences in categorical variables between two subgroups were analyzed using Fisher's exact test.

To facilitate comparisons with previous studies, linear regression models, or mediation and moderation analysis, non-normally distributed data of reference studies were transformed to normal after estimation from the sample size (n), median (m), and the first (q_1) and third (q_3) quartiles (42, 43). The sample standard deviation was estimated to be $[(q_3 - q_1) / \eta]$ where $\eta = \eta(n) = 2\Phi^{-1}[(0.75 \times n - 0.125) / (n + 0.25)]$ (42). In addition, non-normally distributed continuous variables were transformed to normal using a two-step approach: fractional rank and inverse-normal transformation (44). For comparisons with reference values, the one-sample *t*-test was applied.

Relationships between variables of interest were assessed using Pearson and Point-Biserial correlation tests as appropriate. Multivariable linear regression models, including all variables, with manual selection based on a probability of $F < 0.05$ were used to identify independent variables. The variance inflation factor of each predictor was calculated to adjust for intervariable relationships within the model. The regression model was repeated after removing all variables with a variance inflation factor ≥ 5 to reduce multicollinearity (45).

Conditional process analysis was performed to evaluate the mediators and moderators between changes in tonsil size/ANR

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TABLE 2 Demographics of the participants in the baseline analysis and those included and excluded from the outcome analysis.

Variable	Participants included in the baseline analysis	Participants included in the outcome analysis	Participants excluded in the outcome analysis	*P* value[a]
N	76	64	12	
Clinical variables				
Age at diagnosis (years)	7 (6–9)	6 (5–9)	7 (6–10)	0.417
Male sex, *n* (%)	59 [78]	47 [73]	12 (100)	0.058
BMI (kg/m^2)	17.4 (15.3–22.8)	17.3 (15.0–21.9)	21.1 (15.6–26.8)	0.133
Tonsil size	3 (3–4)	3 (3–4)	3 (3–4)	0.703
ANR	0.800 (0.697–0.872)	0.800 (0.710–0.864)	0.691 (0.585–0.848)	0.093
Systolic BP (mmHg)	104.2 (18.0)	103.5 (17.2)	107.9 (22.1)	0.440
Diastolic BP (mmHg)	65 (59–71)	65 (59–71)	66 (57–76)	0.825
Subjective sleep quality (assessed by the OSA-18 questionnaire)				
OSA-18 score	81.3 (15.4)	81.8 (15.7)	78.4 (14.1)	0.486
Objective sleep quality (assessed by polysomnography)				
OAHI (events/h)	5.5 (2.3–12.6)	5.8 (2.4–13.1)	6.3 (2.4–10.4)	0.943
OAI (events/h)	0.4 (0.1–1.5)	0.6 (0.2–1.7)	0.5 (0.18–1.5)	0.908
Arousal index (events/h)	9.8 (7.2–16.5)	9.9 (7.3–16.9)	9.0 (6.7–15.2)	0.397
Mean SaO_2 (%)	97 (97–98)	97 (97–98)	97 (96–98)	0.480
Minimal SaO_2 (%)	84 (90–92)	90 (84–92)	90 (83–92)	0.797
N1 sleep (%)	10 (6–15)	10 (6–16)	9 (7–14)	0.569
N2 sleep (%)	39.1 (8.6)	39.2 (9.2)	39.0 (4.8)	0.911
N3 sleep (%)	28 (22–35)	27 (22–35)	29 (23–35)	0.711
REM sleep (%)	19.3 (5.9)	19.1 (5.8)	20.2 (6.3)	0.556
TST (min)	337 (321–352)	337 (320–353)	329 (321–349)	0.437
Sleep heart rate variability indices				
Heart rate (bpm)	76 (70–82)	76 (70–85)	76 (70–82)	0.770
N-N interval (ms)	791.8 (97.3)	793.7 (95.6)	781.6 (93.3)	0.694
SDNN (ms)	96.6 (32.6)	98.3 (34.1)	87.4 (21.7)	0.163
pNN50 (%)	36.9 (19.0)	37.1 (19.2)	35.8 (5.5)	0.840
RMSSD (ms)	67 (50–105)	63 (49–114)	69 (53–80)	0.680
Total power (ms^2)	8688 (4614–14944)	9454 (4499–15430)	7560 (5233–9443)	0.298
VLF power (ms^2)	1509 (1095–2540)	1509 (1095–2727)	1479 (895–1833)	0.340
LF power (ms^2)	1236 (760–2150)	1243 (734–2507)	992 (804–1526)	0.243
LF% (%)	37 (28–47)	38 (29–48)	33 (27–42)	0.494
HF power (ms^2)	2140 (1113–4228)	1970 (1103–5155)	2183 (1248–4412)	0.669
LF/HF ratio	0.59 (0.40–0.90)	0.62 (0.40–0.92)	0.50 (0.40–0.70)	0.459

Data are expressed as mean (standard deviation), median (interquartile range), or number (%).

[a] Data were compared between participants included in the outcome analysis and those excluded using the independent-samples t-test, Mann-Whitney U test, or Fisher's exact test as appropriate. ANR, adenoidal-nasopharyngeal ratio; BMI, body mass index; BP, blood pressure; bpm, beats per min; HF, high frequency; LF, low frequency; LF%, normalized LF power; N-N, normal-to-normal; OAHI, obstructive apnea-hypopnea index; OAI, obstructive apnea index; OSA, obstructive sleep apnea; pNN50, proportion of N-N50 divided by the total number of N-N intervals; REM, rapid eye movement; RMSSD, square root of the mean of the sum of the squares of di?erences between adjacent N-N intervals; SaO_2, blood oxygen saturation; SDNN, standard deviation of all N-N intervals; TST, total sleep time; VLF, very low frequency.

TABLE 3 Sleep heart rate variability indices in normal controls and in children and adolescents with OSA.

Variable	Our study	Gasior's study (47)	Isaiah's study (14)	Muzumdar's study (17)			Nisbet's study (13)						Kirk's Study (48)
Publication year		2020	2020	2011			2013						2020
Nation	Taiwan	Poland	USA	USA			Australia						Canada
Participants	OSA	NC	OSA	M-S OSA			Mild OSA			M-S OSA			OSA/obesity
Case number	76	312	404	18			39			29			12
Age (years)	7.2 (2.1)	10.1 (2.5)	6.0 (4.5)	4.9 (2.4)			4.3 (0.1)			4.2 (0.2)			12.8 (5.1)
Male sex, *n* (%)	59 (78)	159 (51)	195 (48)	13 (72)			26 (67)			18 (62)			10 (83)
OAHI (events/h)	10.2 (12.6)	NA	4.6 (4.6)*	31.9 (24.8)*			3.1 (0.9)			15.5 (12.3)			13.8 (14.5)
Sleep stage	FN	FN	FN	N1, N2	N3	REM	N1, N2	N3	REM	N1, N2	N3	REM	FN
Heart rate (bpm)	77 (9)	NA	NA	100 (17)[a]	100 (15)[a]	107 (16)[a]	NA			NA			82 (7)
N-N interval (ms)	792 (97)	NA	NA	630 (120)[b]	620 (100)[b]	580 (110)[a]	NA			NA			732 (62)
SDNN (ms)	97 (33)	54 (30)	97 (37)	NA			NA			NA			54 (25)
pNN50 (%)	37 (19)	34 (52)	36 (24)	NA			NA			NA			NA
RMSSD (ms)	76 (38)	71 (91)	81 (45)	61 (55)[b]	43 (29)[b]	76 (57)[b]	NA			NA			NA
Total power (ms^2)	10,460 (7,238)	5,348 (9,534)	8,838 (6,990)	NA			7,632 (5,908)	6,021 (6,145)	5,287 (4,103)	9,040 (5,905)[a]	6,600 (6,144)	5,827 (4,789)[a]	NA
VLF power (ms^2)	2,032 (2,284)	171 (284)	1,712 (1,186)[a]	NA			NA			NA			NA
LF power (ms^2)	1,727 (1,457)	2,023 (3,789)	1,382 (1,186)	360 (342)	184 (148)[b]	307 (293)	1,298 (1,024)	758 (781)	909 (606)	1,959 (1,023)[a]	848 (780)	1,075 (603)[a]	NA
LF% (%)	39 (15)	NA	NA	NA			NA			NA			41 (17)
HF power (ms^2)	3,149 (3,029)	3,766 (6,993)	2,742 (3,340)	902 (1,202)[b]	483 (497)[b]	412 (449)[b]	4,418 (3,610)[a]	3,985 (3,859)	2,416 (2,186)[a]	7,382 (3,608)[a]	4,126 (3,856)	2,183 (2,186)	NA
LF/HF ratio	0.80 (0.66)	0.72 (0.82)	0.53 (0.36)	1.60 (2.7)[a]	1.20 (1.60)[a]	3.0 (5.4)[a]	0.70 (0.62)	0.40 (0.25)	1.10 (0.62)	0.70 (0.54)	0.30 (0.27)[b]	0.90 (0.54)	1.40 (1.18)

To facilitate comparisons with previous studies, data are summarized as mean (standard deviation) after estimation from the sample size, median, and interquartile range.

[a]Higher than controls, $P < 0.05$; [b]Lower than controls, $P < 0.05$.

*Only AHI was available.

AHI, apnea-hypopnea index; bpm, beats per min; FN, full night; HF, high frequency; LF, low frequency; LF%, normalized LF power; M-S, moderate-to-severe; N3, stage 3 sleep; NC, normal controls; N-N, normal-to-normal; pNN50, proportion of N-N50 divided by the total number of N-N intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent N-N intervals; SDNN, standard deviation of all N-N intervals; VLF, very low frequency.

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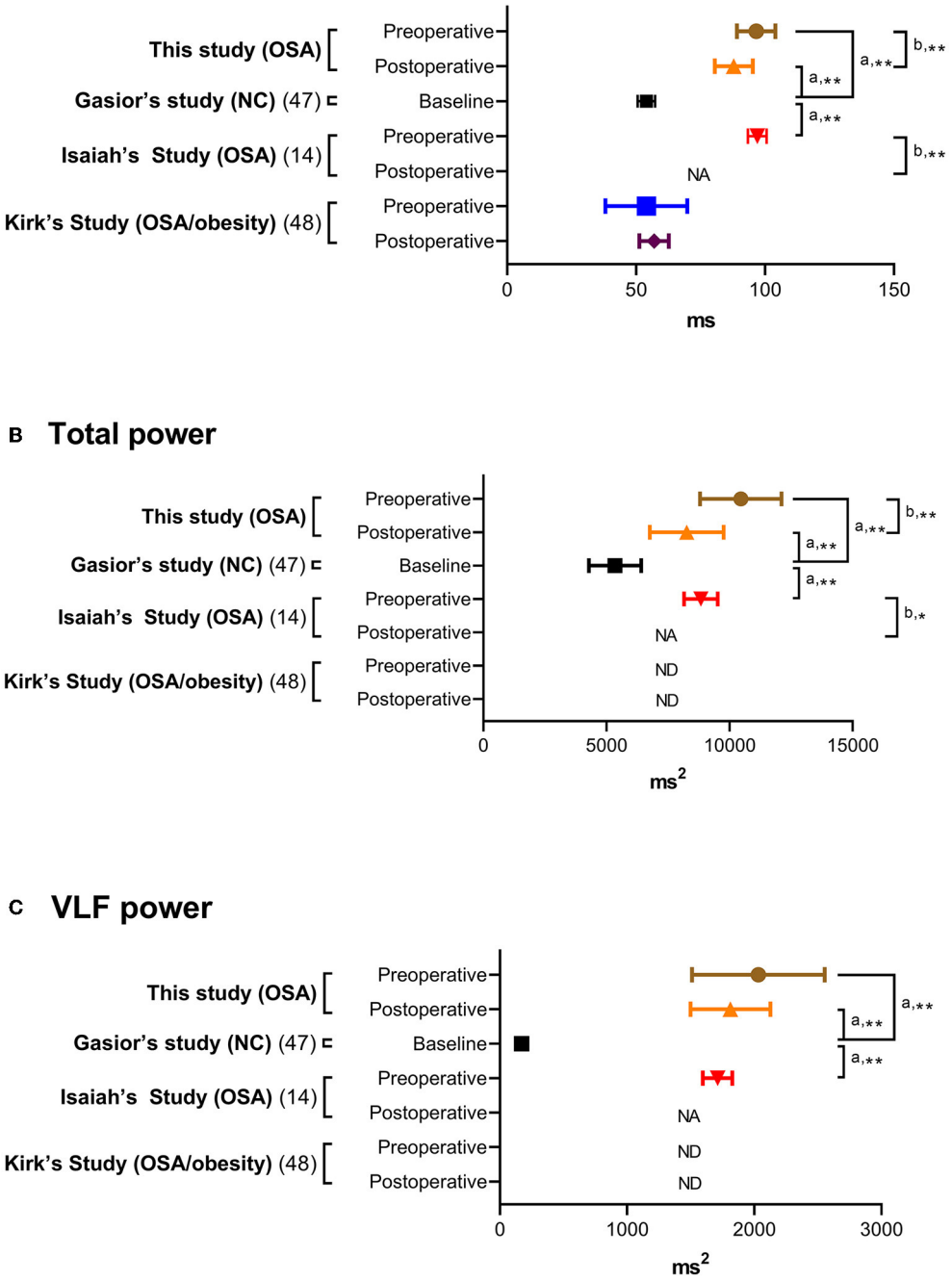

FIGURE 2
(A–C) Full-night heart rate variability indices in normal controls and children and adolescents with obstructive sleep apnea. Data are summarized as means and 95% confidence intervals. [a]The one-sample *t*-test was applied for comparisons of related samples according to the reference values of normal control (47). [b]The paired-samples *t*-test or Wilcoxon signed-rank test was used to compare related samples according to the original references (14, 48). $^{*}P < 0.05$ and ≥ 0.01; $^{**}P < 0.01$ and ≥ 0.001. NA, not available; ND, not detected; OSA, obstructive sleep apnea; SDNN, standard deviation of all normal-normal intervals; VLF, very low frequency.

and % changes in polysomnographic parameters using the SPSS PROCESS macro (version 4.1) (46). Bias-corrected 95% confidence intervals (CIs) were estimated *via* bootstrapping (5,000 runs) to verify mediation, moderated mediation, or mediated moderation. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Participants' characteristics

Seventeen (22%) girls and 59 (78%) boys with OSA (median OAHI, 5.5 [IQR, 2.3–12.6] events/h) were included in the

TABLE 4 Reproducibility of sleep HRV measurements in twelve children with stable residual OSA after adenotonsillectomy.

Variable	Preoperative	Postoperative	ICC	95% CI	*P*-value
Time-domain indices					
N-N interval (ms)	803 (685–870)	829 (728–855)	0.488	−0.123–0.823	0.053
SDNN (ms)	83 (66–102)	72 (59–111)	**0.553**	**0.011–0.846**	**0.026**
pNN50 (%)	27 (21–47)	27 (11–47)	0.256	−0.397–0.716	0.213
RMSSD (ms)	56 (44–83)	55 (33–73)	0.471	−0.136–0.815	0.060
Frequency-domain indices					
Total power (ms^2)	6,012 (3,350–13,102)	4,604 (3,222–10,158)	**0.483**	**−0.063–0.814**	**0.045**
VLF power (ms^2)	1,814 (1012–2797)	1,901 (1,006–2,393)	**0.634**	**0.290–0.833**	**0.001**
LF power (ms^2)	935 (350–1688)	645 (391–1,377)	**0.720**	**0.270–0.911**	**0.004**
LF% (%)	40 (30–50)	46 (31–59)	**0.557**	**0.034–0.846**	**0.023**
HF power (ms^2)	1,460 (677–2468)	789 (358–2,547)	0.335	−0.318–0.756	0.146
LF/HF ratio	0.67 (0.43–1.01)	1.047 (0.45–1.51)	**0.725**	**0.237–0.915**	**0.001**

Bold font indicates statistically significant differences ($P < 0.05$).
CI, confidence interval; HF, high frequency; HRV, Heart rate variability; ICC, intraclass correlation coefficient; LF, low frequency; LF%, normalized LF power; N-N, normal-to-normal; OSA, obstructive sleep apnea; pNN50, proportion of N-N50 divided by the total number of N-N intervals; RMSSD, square root of the mean of the sum of the squares of di?erences between adjacent N-N intervals; SDNN, standard deviation of all N-N intervals; VLF, very low frequency.

baseline analysis (Figure 1), of whom 64 (84%) were included in the outcome analysis and 12 (16%) were not included due to no available follow-up polysomnography. All baseline variables were comparable between these two subgroups (Table 2).

3.2. Sleep heart rate variability

Distributions of HRV indices in baseline analysis are summarized in Table 2. For comparing with previous studies, the HRV indices in this study (full-night), normal controls (full-night) (47), children with OSA (full-night) (14), children with moderate-to-severe OSA (N3 sleep) (13, 17), and children with OSA/obesity (full-night) (48) are summarized in Table 3. Comparing with three representative full-night HRV studies (14, 47, 48), SDNN, total power and VLF power in the children with OSA were significantly higher than normal values (Figure 2).

3.3. Measurement reproducibility of sleep heart rate variability

To assess measurement reproducibility, we calculated ICCs using HRV indices measured at least 3 months apart in 12 patients with stable residual OSA after adenotonsillectomy (Table 4). Their variables of interest were comparable to the patients with altered OSA (Tables 5, 6). Most HRV measurements demonstrated moderate (N-N interval, SDNN, RMSSD, total power, LF%) or substantial (VLF power, LF power, LF/HF ratio) reproducibility. Further, the reproducibility of pNN50 and HF power were fair (41).

3.4. Associations between variables of interest at baseline

Nested data structure and significant correlations were found among the polysomnographic parameters, several clinical variables and HRV indices (Figure 3). However, total OSA-18 questionnaire score was not associated with variables of interest. Using multivariable linear regression models (Table 7), male sex, OAHI and N3 sleep were independently associated with tonsil size, and systolic BP, OAHI and VLF power were independently associated with ANR. Furthermore, tonsil size, diastolic BP and LF% were independently correlated with OAHI. Table 7 summarizes the independent associations of other polysomnographic parameters with the variables of interest.

3.5. Changes in the variables of interest after adenotonsillectomy

The median follow-up period was 4 (IQR, 3–6) months. In outcome analysis, mean SaO_2, minimal SaO_2 and rapid eye movement sleep significantly increased, and OSA-18 score, OAHI, OAI, arousal index and N1 sleep significantly reduced after adenotonsillectomy (Table 5).

Regarding HRV indices, SDNN, total power and HF power significantly reduced after adenotonsillectomy (Table 6), and they were still significantly different from normal values (47) (Figure 2).

3.6. Associations of percentage changes in the variables of interest

Correlations of % changes in polysomnographic parameters and % changes in clinical variables and HRV indices also

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TABLE 5 Clinical variables, subjective quality and objective sleep quality of the study sample by altered OSA status in the outcome analysis.

Variable	All participants	Stable residual OSA	Altered OSA	*P* Value[a]
n	64	12	52	
Clinical variables				
Age at diagnosis (years)	6 (5–9)	8 (6–10)	6 (5–8)	0.132
Male sex, *n* (%)	47 (73)	10 (83)	37 (79)	0.490
BMI (kg/m^2)				
Preoperative	17.3 (15.0–21.9)	17.4 (15.3–23.0)	16.6 (14.7–21.9)	0.711
Postoperative	17.4 (15.1–22.8)	18.8 (16.4–24.5)	17.2 (15.0–22.2)	0.225
Change	4.0 (−0.4–1.4)	1.5 (−0.7–3.0)	0.4 (−0.4–1.1)	0.148
% Change	3 (−2–8)	7 (−4–16)	2 (−2–7)	0.135
Systolic BP (mmHg)				
Preoperative	103.5 (17.2)	105 (100–113)	103 (94–113)	0.558
Postoperative	105.3 (15.3)	106 (96–120)	102 (94–115)	0.642
Change	1.8 (14.9)	−1 (−9–10)	3 (−10–11)	0.783
% Change	3.2 (15.7)	−1 (−7–10)	3 (−9–11)	0.680
Diastolic BP (mmHg)				
Preoperative	65 (59–71)	61 (58–72)	65 (59–71)	0.444
Postoperative	64 (58–72)	64 (56–72)	64 (59–75)	0.530
Change	−1 (−7–7)	2 (−4–14)	−2 (−8–6)	0.136
% Change	−2 (−11–12)	4 (−6–25)	−3 (−12–9)	0.120
Objective sleep quality (assessed by the OSA-18 questionnaire)				
OSA-18 score				
Preoperative	81.8 (15.7)	89 (77–94)	82 (70–92)	0.404
Postoperative	52.0 (13.2)	54 (49–67)	50 (40–60)	0.127
Change	−26.4 (22.7)	−20 (−30–−6)	−32 (−43–−14)	0.072
% Change	−31 (24)	**−27 (−34–−3)**	**−39 (−48–−22)**	**0.037**
Subjective sleep quality (assessed by polysomnography)				
OAHI (events/h)				
Preoperative	5.8 (2.4–13.1)	5.0 (3.1–6.7)	7.7 (2.3–17.1)	0.318
Postoperative	1.4 (0.6–2.5)	**3.0 (2.4–6.4)**	**1.2 (0.5–1.8)**	**< 0.001**
Change	−3.7 (−11.2–−1.2)	**−1.8 (−3.4–0.9)**	**−5.9 (−12.6–−1.6)**	**0.006**
% Change	−75 (−92–−45)	**−32 (−46–−20)**	**−87 (−94–−64)**	**< 0.001**
OAI (events/h)				
Preoperative	0.6 (0.2–1.7)	0.4 (0.1–1.5)	0.4 (0–1.5)	0.931
Postoperative	0 (0–0.3)	**0.5 (0–0.8)**	**0 (0–0.2)**	**0.008**
Change	−0.3 (−1.0–0)	−0.2 (−0.9–0.3)	−0.3 (−1.1–0)	0.393
% Change	−79 (−100–0)	−55 (−98–95)	−85 (−100–0)	0.185
Arousal index (events/h)				
Preoperative	9.9 (7.3–16.9)	10.4 (8.0–15.5)	9.6 (7.2–17.7)	0.959
Postoperative	7.1 (6.0–9.2)	7.6 (6.0–9.0)	6.8 (6.0–9.8)	0.624
Change	−2.9 (−8.9–−3.3)	−2.2 (−7.3–−0.6)	−3.1 (−10.7–−0.3)	0.371
% Change	−33 (−53–−5)	−23 (−49–−6)	−34 (−53–−5)	0.667

(Continued)

TABLE 5 (Continued)

Variable	All participants	Stable residual OSA	Altered OSA	*P* Value[a]
n	64	12	52	
Mean SaO_2 (%)				
Preoperative	97 (97–98)	98 (97–98)	97 (97–98)	0.508
Postoperative	98 (97–98)	98 (97–98)	98 (97–98)	0.927
Change	0 (0–1)	0 (0–1)	0 (0–1)	0.731
% Change	0 (0–1)	0 (0–1)	0 (0–1)	0.589
Minimal SaO_2 (%)				
Preoperative	90 (84–92)	90 (88–92)	90 (84–92)	0.904
Postoperative	92 (89–94)	91 (89–93)	92 (89–93)	0.316
Change	2 (−1–5)	1 (−2–6)	2 (0–5)	0.329
% Change	2 (−1–6)	1 (−2–6)	2 (0–6)	0.331
N1 sleep (%)				
Preoperative	10 (6–16)	11 (6–16)	10 (7–16)	0.918
Postoperative	9 (7–12)	7 (6–10)	9 (7–13)	0.212
Change	−2 (−9–2)	−4 (−8–1)	−2 (−9–3)	0.594
% Change	−24 (−51–41)	−30 (−55–23)	−20 (−50–52)	0.439
N2 sleep (%)				
Preoperative	39.2 (9.2)	**46 (40–54)**	**39 (31–44)**	**0.012**
Postoperative	41.6 (8.8)	47 (36–52)	41 (35–46)	0.232
Change	2.4 (10.5)	1 (−11–9)	4 (−2–10)	0.225
% Change	11.3 (32.3)	2 (−21–25)	10 (−8–32)	0.203
N3 sleep (%)				
Preoperative	27 (22–35)	25 (21–28)	28 (22–37)	0.081
Postoperative	25 (21–31)	27 (20–30)	25 (21–32)	0.810
Change	−1 (−8–5)	2 (−6–8)	−4 (−9–4)	0.180
% Change	3 (−30–24)	7 (−18–32)	−12 (−31–18)	0.235
REM sleep (%)				
Preoperative	19.1 (5.8)	19 (15–22)	21 (16–23)	0.636
Postoperative	22.4 (6.3)	22 (21–26)	22 (18–27)	0.925
Change	3.3 (7.4)	6 (−1–9)	3 (−3–8)	0.564
% Change	28.4 (53.0)	27 (−7–53)	14 (−14–56)	0.667
TST (min)				
Preoperative	337 (320–353)	338 (309–354)	337 (320–353)	> 0.999
Postoperative	336 (321–350)	335 (278–352)	337 (321–350)	0.763
Change	−6 (−32–21)	−8 (−50–15)	−4 (−32–23)	0.536
% Change	−2 (−9–6)	−3 (−13–5)	−1 (−9–8)	0.547

Data are expressed as median (interquartile range) or number (%). Bold font indicates statistically significant differences ($P < 0.05$).
BMI, body mass index; BP, blood pressure; OAHI, obstructive apnea-hypopnea index; OAI, obstructive apnea index; OSA, obstructive sleep apnea; REM, rapid eye movement; SaO2, blood oxygen saturation; TST, total sleep time.

revealed significant associations with nested data structure (Figure 4). Using multivariable linear regression models (Table 8), % changes in OSA-18 score, OAHI and HF power were independently associated with change in tonsil size. Age at diagnosis, male sex and % change in arousal index were independently associated with change in ANR, and change in tonsil size was independently correlated with % change in OAHI.

TABLE 6 HRV indices of the study sample by altered OSA status in the outcome analysis.

Variable	All participants	Stable residual OSA	Altered OSA	*P* value[a]
n	64	12	52	
Time-domain indices				
N-N interval (ms)				
Preoperative	793.7 (95.6)	803 (685–870)	786 (735–849)	0.945
Postoperative	827.0 (100.5)	829 (728–855)	828 (763–915)	0.390
Change	33.3 (108.8)	−25 (−112–107)	36 (−16–96)	0.216
% Change	5.1 (13.9)	−3 (−13–15)	5 (−2–12)	0.279
SDNN (ms)				
Preoperative	98.3 (34.1)	83 (66–102)	102 (75–125)	0.194
Postoperative	87.9 (29.6)	72 (59–111)	85 (69–110)	0.282
Change	−10.4 (30.1)	−5 (−29–9)	−13 (−29–13)	0.712
% Change	−4.8 (33.8)	−5 (−28–14)	−12 (−29–10)	0.606
pNN50 (%)				
Preoperative	37.1 (19.2)	27 (21–47)	38 (25–54	0.340
Postoperative	36.6 (21.5)	27 (11–47)	40 (20–53)	0.242
Change	−0.5 (19.0)	1 (−24–15)	−1 (−12–14)	0.612
% Change	28.7 (135.5)	5 (−55–86)	−2 (−30–39)	0.843
RMSSD (ms)				
Preoperative	63 (49–114)	56 (44–83)	70 (49–116)	0.371
Postoperative	61 (38–85)	55 (33–73)	64 (41–94)	0.249
Change	−9 (−30–10)	−2 (−36–13)	−10 (−28–8)	0.891
% Change	−9 (−32–22)	−1 (−40–38)	−10 (−32–17)	0.945
Frequency-domain indices				
Total power (ms^2)				
Preoperative	9,454 (4,499–15,430)	6,012 (3,350–13,102)	9,505 (4,831–16,300)	0.169
Postoperative	6,437 (4,058–10,980)	4,605 (3,222–10,158)	6,739 (4,503–12,675)	0.180
Change	−2261 (−5568–1741)	−608 (−7189–1401)	−2,606 (−5,547–1,741)	0.904
% Change	−18 (−50–17)	−11 (−57–32)	−23 (−50–17)	0.655
VLF power (ms^2)				
Preoperative	1,509 (1,095–2,727)	1,345 (771–2,718)	1,535 (1,157–2,727)	0.399
Postoperative	1,485 (1,032–2,102)	1,456 (852–3,691)	1,485 (1,063–2,102)	0.823
Change	92 (−734–540)	193 (−387–990)	42 (−779–497)	0.318
% Change	3 (−41–38)	19 (−30–56)	0 (−41–36)	0.460
LF power (ms^2)				
Preoperative	1,243 (734–2,507)	935 (350–1,688)	1,286 (791–2,657)	0.144
Postoperative	942 (474–1,406)	645 (391–1,377)	1,022 (671–1,535)	0.279
Change	−155 (−924–231)	40 (−818–206)	−285 (−925–248)	0.439
% Change	−9 (−63–29)	9 (−56–96)	−20 (−63–19)	0.249
LF% (%)				
Preoperative	38 (29–48)	40 (30–50)	38 (28–48)	0.570
Postoperative	40 (32–50)	46 (31–59)	39 (32–49)	0.327

(Continued)

TABLE 6 (Continued)

Variable	All participants	Stable residual OSA	Altered OSA	*P* value[a]
n	64	12	52	
Change	2 (−8–13)	4 (−3–13)	2 (−10–13)	0.570
% Change	5 (−19–42)	10 (−13–33)	3 (−22–43)	0.823
HF power (ms^2)				
Preoperative	1,970 (1,103–5,155)	1,460 (677–2,468)	2,234 (1,113–5,353)	0.122
Postoperative	1,364 (636–3,360)	789 (358–2547)	1,624 (812–3,420)	0.164
Change	−531 (−1,870–301)	−284 (−1601–282)	−663 (−2229–301)	0.536
% Change	−26 (−66–21)	−15 (−70–120)	−28 (−66–15)	0.559
LF/HF ratio				
Preoperative	0.62 (0.40–0.92)	0.67 (0.43–1.01)	0.61 (0.40–0.92)	0.570
Postoperative	0.70 (0.48–1.19)	1.05 (0.45–1.51)	0.66 (0.48–1.05)	0.294
Change	0.08 (−0.08–0.40)	0.16 (−0.07–0.49)	0.07 (−0.13–0.36)	0.310
% Change	13 (−12–70)	20 (−10–69)	13 (−14–72)	0.606

Data are expressed as median (interquartile range) or number (%).
[a]Data were compared using the Mann-Whitney U test or Fisher's exact test as appropriate.
HF, high frequency; HRV, Heart rate variability; LF, low frequency; LF%, normalized LF power; N-N, normal-to-normal; OSA, obstructive sleep apnea; pNN50, proportion of N-N50 divided by the total number of N-N intervals; RMSSD, square root of the mean of the sum of the squares of di?erences between adjacent N-N intervals; SDNN, standard deviation of all N-N intervals; VLF, very low frequency.

3.7. Mediation and moderation analyses

Consistent relationships between "tonsil size and OAHI" and "change in tonsil size and % change in OAHI" were observed. Mediation and moderation analyses were performed from change in tonsil size to % change in OAHI, especially with regards to HRV indices, and only a significant conceptual serial multiple mediation model was identified: change in tonsil size (independent variable), % change in OSA-18 score (first mediator), % change in VLF power (second mediator), and % change in OAHI (dependent mediator) (Figure 5). The direct paths from change in tonsil size to % change in OAHI, change in tonsil size to % change in OSA-18 score, change in tonsil size to % change in VLF power, change in OSA-18 to % change in VLF power, and % change in VLF power to % change in OAHI were significant. In contrast, the direct paths from change in OSA-18 to % change in OAHI were not significant. The serial mediation model revealed a positive total effect ($\beta = 65.78$, standard error = 16.71, $P < 0.001$). The direct effect of change in tonsil size on % change in OAHI ($\beta = 44.47$, standard error = 18.90, $P = 0.022$) was significant. For the indirect effects, the first path from change in tonsil size to % change in OAHI through % change in OAS-18 score (effect = 12.44, 95% CI:−5.18–32.99) was not significant. The second path through % change in VLF power (effect = 13.74, 95% CI: 0.01–33.36), third path through % change in OAS-18 score and % change in VLF power (effect = −4.87, 95% CI:−13.69-−0.09), and indirect effect (effect = 21.32, 95% CI: 0.39–44.30) were significant.

4. Discussion

This study is the first to report that OSA-related quality of life and VLF power were first and second mediators of the relationship between tonsil size and improvement in AHI using a conceptual serial multiple mediation model. Beyond providing important mechanistic insights, these results suggest that VLF power could be a new target for OSA therapy in children. For example, exercise training can decrease VLF power over time (49) and reduce AHI (50) in adults.

Our results confirmed the reproducibility of sleep HRV measurements at two time points. Most measures showed moderate or substantial reproducibility, except for pNN50 and HF power. The possible reason for this relatively lower reproducibility may be related to sleep stage and arousal index. To the best of our knowledge, no comprehensive reproducibility study has reported HRV measurements in children with OSA. Accordingly, the interpretations of sleep pNN50 and HF power should be made with caution in this population.

Using full-night HRV measurements, SDNN, total power, and VLF power in the children with OSA were significantly higher than normal values (Figure 2) (14, 47, 48). SDNN and total power represent total capacity of the regulation system, whilst VLF power represents sympathetic activity (36) (Table 1). Although SNS and PNS activities both contribute to SDNN and total power, long-term recordings have revealed that SNS activity is more related to these indices (51). The transition between normal and pathological respiration can enhance SNS activity rather than PNS activity in adults with OSA (52). Additionally, the results of this and previous studies (13, 14, 53) suggest that sympathetic activity increases during sleep in children with OSA; however, SDNN in the 12 obese children with OSA in this study was comparable to normal values (47) (Table 3). This discrepancy may be explained by the patients' weight status, since childhood obesity is significantly related to low SDNN (54). Furthermore, this study and Isaiah's study (14) found that % changes in SDNN and total power were not related to %

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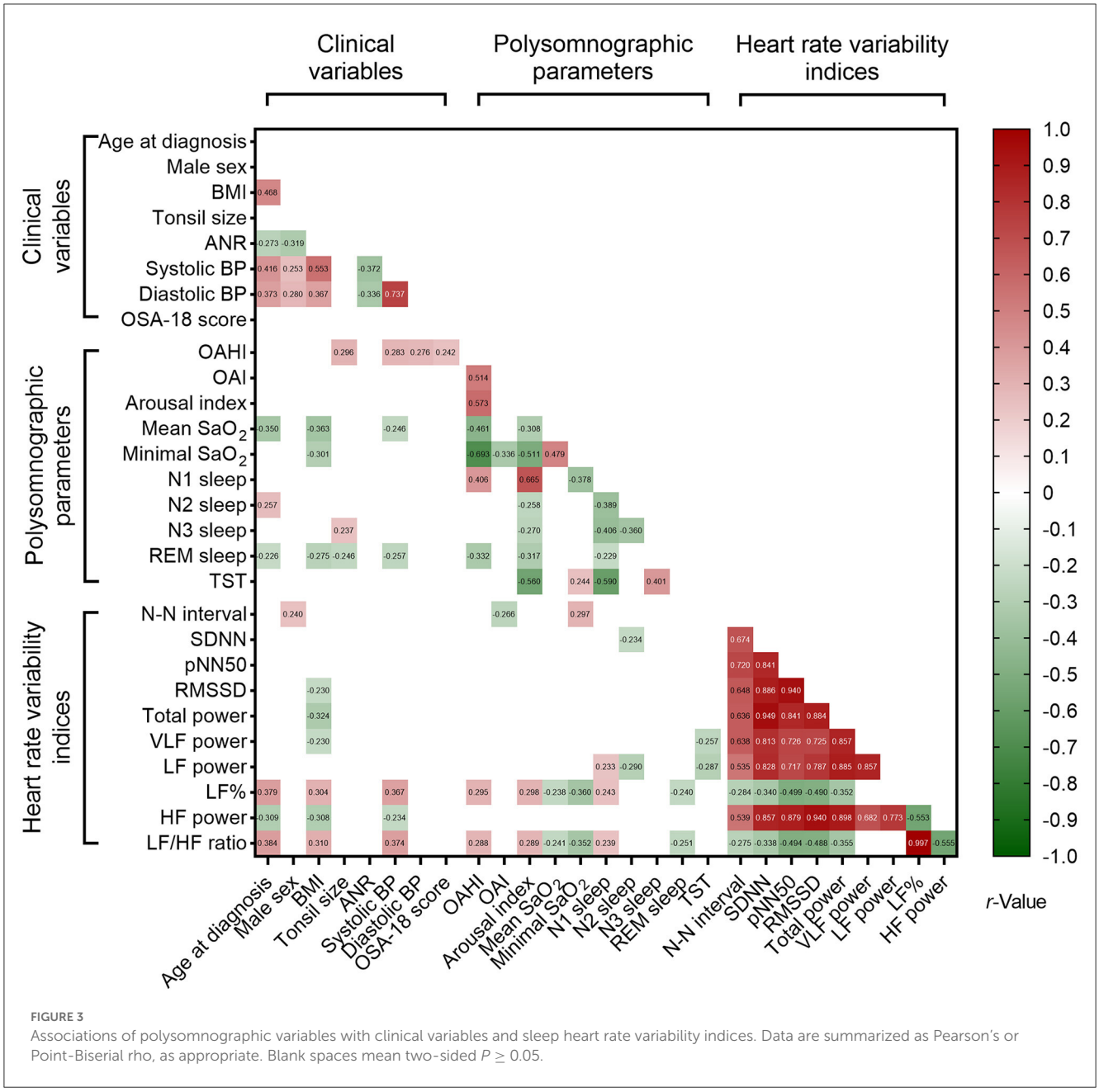

FIGURE 3
Associations of polysomnographic variables with clinical variables and sleep heart rate variability indices. Data are summarized as Pearson's or Point-Biserial rho, as appropriate. Blank spaces mean two-sided $P \geq 0.05$.

change in OAHI. Therefore, these changes could not be simply due to improvements in OAHI after adenotonsillectomy.

The baseline values and % changes in tonsil size and ANR were not consistently associated with most HRV indices. Despite increased ANR being related to decreased VLF power in children with OSA, the causal relationship between adenoid hypertrophy and reduced sympathetic activity could not be supported by the post-operative changes. Nevertheless, our findings suggested a positive relationship between change in tonsil size and % change in HF power of HRV (parasympathetic modulation). We hypothesize that tonsillectomy may directly injure or cause scar formation, thereby reducing function of the lingual branch of the hypoglossal nerve, interrupting baroreceptor signaling at the carotid sinus, influencing vagus nerve function, eventually resulting in decreased parasympathetic modulation and increased sympathetic activity of cardiac autonomic function during sleep. This condition may further interfere with the relationships between % change in SDNN or total power and % change in OAHI.

Our results demonstrated significant relationships between the change in tonsil size and % change in OAHI as well as relationships between the change in tonsil size and % change in OSA-18 score as previous studies (29, 55). Tonsil size has been significantly associated with the change in OSA-18 score after tonsillectomy in children with sleep-disordered breathing (56). Although a change in AHI has been associated with a change in OSA-18 score (23), we found that this association was not independent in this study. In simple mediation and moderation models, % change in OSA-18 score neither mediated nor moderated the relationship between the

TABLE 7 Multivariable linear regression models of independent associations of tonsil/adenoid sizes and polysomnographic parameters with other variables in the baseline analysis.

Baseline variables	Independent variables	β (95% CI)	VIF	*P* value	Adjusted R^2
Clinical variables					
Tonsil size	Male sex	−0.33 (-0.60-−0.06)	1.00	0.019	0.216
	OAHI	0.01 (0.001–0.02)	1.01	0.027	
	N3 sleep	0.02 (0.01–0.04)	1.01	0.005	
ANR	Systolic BP	−0.003 (-0.005-−0.002)	1.14	< 0.001	
	OAHI	0.003 (0.001–0.005)	1.16	0.005	
	VLF power	−0.00001 (-0.00003-−0.000003)	1.02	0.018	
Subjective sleep quality (polysomnographic parameters)					
OAHI	Tonsil size	7.96 (3.03–12.89)	1.02	0.002	0.243
	Diastolic BP	0.29 (0.02–0.56)	1.04	0.034	
	LF%	0.25 (0.07–0.44)	1.06	0.008	
OAI	OSA-18 score	0.07 (0.001–0.14)	1.00	0.049	0.119
	N-N interval	−0.01 (-0.03-−0.003)	1.00	0.015	
Arousal index	N-N interval	−0.05 (-0.08-−0.02)	1.46	0.001	0.283
	LF power	0.01 (0.003–0.01)	2.72	< 0.001	
	HF power	−0.001 (-0.003-−0.0002)	2.71	0.020	
Mean SaO_2	BMI	−0.10 (-0.15-−0.05)	1.10	< 0.001	0.228
	N-N interval	0.004 (0.001–0.01)	1.75	0.001	
	VLF power	−0.0002 (-0.0004-−0.0001)	1.84	0.007	
Minimal SaO_2	BMI	−0.50 (-0.74-−0.25)	1.09	< 0.001	0.319
	N-N interval	0.04 (0.02–0.06)	1.75	< 0.001	
	VLF power	−0.001 (-0.002-−0.001)	1.83	< 0.001	
N1 sleep	pNN50	−0.22 (-0.38-−0.06)	2.08	0.007	0.146
	LF power	0.004 (0.002–0.01)	2.08	0.001	
N2 sleep	LF power	−0.002 (-0.003-−0.0004)	1.00	0.012	0.072
N3 sleep	Tonsil size	3.59 (0.04–7.14)	1.00	0.048	0.123
	pNN50	0.15 (0.01–0.29)	2.13	0.038	
	VLF power	−0.001 (-0.003-−0.0001)	2.12	0.030	
REM sleep	Age	−0.68 (-1.30-−0.05)	1.00	0.036	0.116
	Tonsil size	−2.88 (-5.38-−0.39)	1.00	0.027	
TST	LF power	−0.01 (-0.01-−0.002)	1.00	0.013	0.070

ANR, adenoidal-nasopharyngeal ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; HF, high frequency; LF, low frequency; OAHI, obstructive apnea-hypopnea index; OAI, obstructive apnea index; OSA, obstructive sleep apnea; N-N, normal-to-normal; pNN50, proportion of N-N50 divided by the total number of N-N intervals; REM, rapid eye movement; SaO_2, blood oxygen saturation; TST, total sleep time; VIF, variance inflation factor; VLF, very low frequency.

change in tonsil size and % change in OAHI. However, in serial mediation analysis, the relationship between the change in tonsil size and % change in OAHI was mediated by % change in OSA-18 score and % change in VLF power in serial analysis, and also by % change in VLF power alone (Figure 5).

VLF rhythm is a cardiac intrinsic rhythm which is essential for health and happiness (36). Even though there is currently no agreement on the physiological mechanisms responsible for activity within the VLF band, low VLF power has been associated with adverse outcomes and all-cause mortality (57, 58). This band is generated by the stimulation of afferent sensory neurons in the heart (59). In animal models, stressful stimulation (60) and paradoxical sleep deprivation (61) have been shown to significantly reduce VLF power (60). In this study, the inverse relationship between % change in OSA-18 and % change in VLF power suggested that reduced OSA-specific stress and sleep disturbance may increase sleep VLF power.

However, VLF power is an independent predictor of AHI in humans (62). VLF power is significantly elevated during pathological respiration compared with normal respiration in OSA

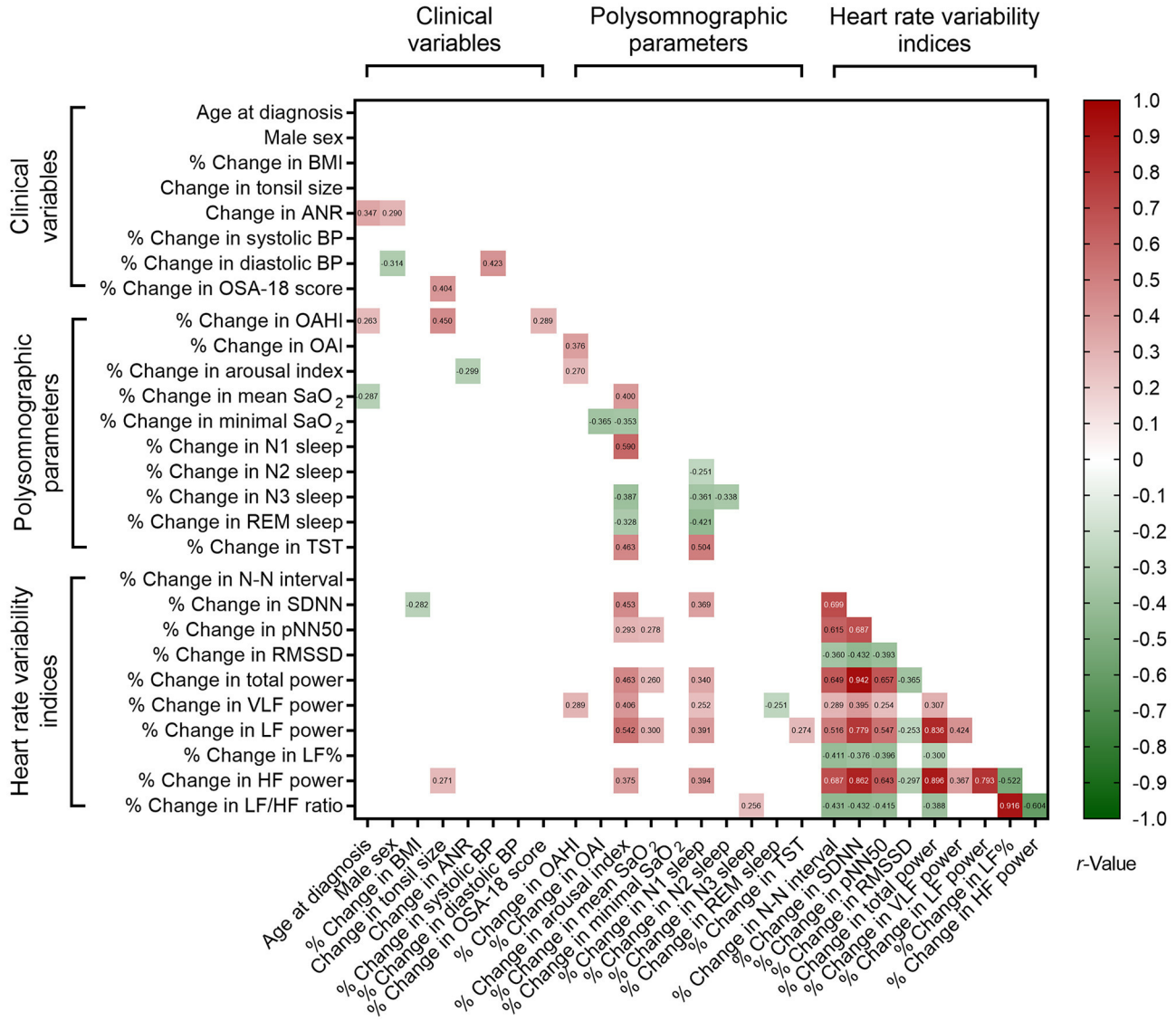

FIGURE 4
Associations of % changes in polysomnographic variables, % changes in clinical variables, and % changes in sleep heart rate variability indices. Blank spaces mean two-sided $P \geq 0.05$.

patients (52). Therefore, it is reasonable that reduced AHI may contribute to a decrease in VLF power after adenotonsillectomy. Our mediation model also highlighted the possibility that changes in VLF power may influence changes in AHI in children with OSA. Sympathetic abnormalities were shown to precede the development of mild OSA in a cohort of adults with no known diagnosis of OSA (63). Although further direct evidence is warranted, these studies suggest that a reduction in VLF power may help to alleviate the AHI in children with OSA.

Therefore, the mediation role of VLF power on the relationship between change in tonsil size and % change in AHI is of interest. Increasing exercise intensity can reduce awake VLF power (49), and morning exercise can increase sleep VLF power (64) in adults. Besides, exercise training (65) or aerobic exercise combined with resistance training can reduce AHI in adults. Therefore, VLF power is modifiable and may be a marker of therapeutic efficacy and a potential therapeutic target for OSA (66). However, in children with adenotonsillar hypertrophy, it may be unlikely that addressing the HRV independently will improve AHI unless there is a clear demonstration the neuromuscular tone is improved to the point that the tonsils do not medialize during sleep. Accordingly, future studies should focus on VLF power-lowering interventions and their effects on the severity of childhood OSA.

4.1. Strengths and limitations

Compared with previous studies (13, 14, 17, 48), the greatest strengths of this investigation were the inclusion of a sample of representative and well-characterized pediatric OSA patients. Our results provided a preliminary yet comprehensive documentation of the relationships of HRV indices with clinical

TABLE 8 Multivariable linear regression models of independent associations of changes in tonsil/adenoid size and % changes in polysomnographic parameters in the outcome analysis.

Outcome variables	Independent variables	β (95% CI)	VIF	*P* Value	Adjusted R^2
Clinical variables					
Change in tonsil size	% Change in OSA-18 score	0.01 (0.002–0.01)	1.10	0.005	0.309
	% Change in OAHI	0.002 (0.001–0.004)	1.11	0.005	
	HF power	0.001 (0.0001–0.002)	1.03	0.025	
Change in ANR	Age at diagnosis	0.01 (0.001–0.03)	1.06	0.030	0.203
	Male sex	0.06 (0.004–0.12)	1.04	0.037	
	% Change in arousal index	−0.0002 (-0.0004-−0.0003)	1.02	0.026	
Subjective sleep quality (polysomnographic parameters)					
% Change in OAHI	Change in tonsil size	65.79 (32.37–99.20)	1.00	< 0.001	0.189
% Change in OAI	None				
% Change in arousal index	Change in ANR	−317.27 (-593.74-−40.794)	1.02	0.025	0.329
	% Change in LF power	0.84 (0.49–1.18)	1.02	< 0.001	
% Change in mean SaO_2	Age at diagnosis	−0.17 (-0.31-−0.03)	1.05	0.020	0.296
	% Change in N-N interval	−0.05 (-0.08-−0.03)	1.74	< 0.001	
	% Change in pNN50	0.004 (0.002–0.01)	1.78	0.002	
	% Change in LF power	0.004 (0.001–0.01)	1.55	0.024	
% Change in minimal SaO_2	None				
% Change in N1 sleep	% Change in LF power	0.55 (0.21–0.88)	1.00	0.002	0.138
% Change in N2 sleep	None				
% Change in N3 sleep	% Change in LF/HF ratio	0.09 (0.002–0.18)	1.00	0.045	0.050
% Change in REM sleep	% Change in VLF power	−0.17 (-0.34-−0.004)	1.00	0.045	0.048
% Change in TST	% Change in LF power	0.17 (0.02–0.32)	1.00	0.031	0.060

BMI, body mass index; CI, confidence interval; HF, high frequency; LF, low frequency; OAHI, obstructive apnea-hypopnea index; OAI, obstructive apnea index; OSA, obstructive sleep apnea; N-N, normal-to-normal; pNN50, proportion of N-N50 divided by the total number of N-N intervals; REM, rapid eye movement; SaO2, blood oxygen saturation; TST, total sleep time; VIF, variance inflation factor; VLF, very low frequency.

variables and polysomnographic parameters before and after adenotonsillectomy, which showed some novel and interesting findings. However, limitations should be addressed. First, the HRV results may have been affected by certain psychophysiological changes (e.g., anthropometrics, lifestyle factors, acute or chronic diseases) other than adenotonsillectomy. However, the use of standardized, full-night, in-laboratory protocols with moderate-to-substantial reproducibility in most HRV indices among OSA patients with stable severity reduces this concern. Second, approximately half of our subjects received both adenotonsillectomy and medical treatment, and the heterogeneity of care may have had a confounding effect. Nevertheless, these interdisciplinary treatments are closer to real-world care for OSA, and a greater variability in AHI changes may contribute to better generalizability of this study. Third, 3 months may not be long enough to show cardiovascular changes, and studies with a longer follow-up period are warranted for this young population. Finally, in this study, there was no evidence of direct mediations of HRV on the relationship between adenotonsillectomy and AHI or AHI on the relationship between adenotonsillectomy and HRV indices (14), and this may be due to difficulties in measuring HRV across various sleep stages. Among school-age children, excessive body movements and parasomnia (67) make the researchers need 2-min epochs to analyze HRV and choose sleep periods free of respiratory events and movement artifacts (17). However, frequency-domain measurements, such as VLF power and LF/HF ratio, often require recording periods of at least 5 min (34). Therefore, measuring HRV across various stages in our study population is challenging. Nevertheless, averages may not be sensitive enough to detect sleep stage-specific mediating effects. In future studies, ultra-short-term HRV measurements during different sleep stages should be conducted to accurately assess the impact of nocturnal HRV changes on the management of OSA.

5. Conclusion

In conclusion, we confirmed that analysis of electrocardiographic polysomnography signals is a reliable

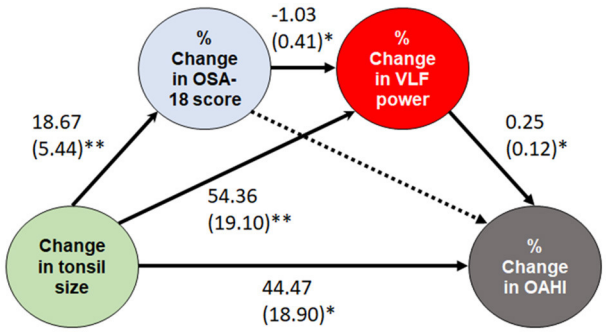

FIGURE 5
A serial multiple mediation model of the effect of change in tonsil size. Data are summarized as β and standard errors. *$P < 0.05$ and ≥ 0.01; **$P < 0.01$ and ≥ 0.001. Solid lines indicate significant paths, while a dotted line indicates a non-significant path. OAHI, obstructive apnea-hypopnea index; OSA, obstructive sleep apnea; VLF, very low frequency.

method to measure HRV over 3 months in children with OSA. Adenotonsillectomy either reduced AHI or sympathetic activity during sleep. Improved OSA-specific quality of life and reduced sleep VLF power serially mediated the relationship between the change in tonsil size and % change in AHI. These findings suggest that HRV measurement may help monitor the sleep quality status and the disease burden of childhood OSA and many other venues. Our preliminary results also support applications of wireless HRV measurements with high-fidelity psychophysiology acquisition using edge computing in the patient's natural sleeping environment to overcome the highly obtrusive effects of visiting the sleep laboratory (68). This technology can potentially be a "platinum standard" of sleep studies instead of the traditional "gold standard" of in-laboratory polysomnography.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Chang Gung Medical Foundation, Taoyuan, Taiwan. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: the current study was based on a secondary analysis of existing data. We provided a copy of the approval by the Institutional Review Board of Chang Gung Medical Foundation (No. 202200882B0), which approved the waiver of the participants' consent.

Author contributions

L-AL, H-HC, TK, and CY conceptualized and designed the research project. L-AL, H-HC, H-SH, C-YW, TK, and CY interpreted the data. L-AL, H-HC, and H-SH collected the data and wrote the initial manuscript. C-YW, L-PC, H-YL, T-JF, Y-SH, G-SL, AY, TK, and CY contributed to writing and editing the manuscript. 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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The impact of perceived social support on sleep quality in a sample of patients undergoing hemodialysis in Somalia

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Objective: The main objective of the present study is to examine the relationship between perceived social support and the quality of sleep and to determine the predictors of sleep quality in a sample of patients undergoing hemodialysis (HD) in Somalia.

Methods: A sample of 200 patients with end-stage renal disease (ESRD) who were undergoing hemodialysis treatment approximately two to three times a week were included. All participants were administered a sociodemographic data form, the Multidimensional Scale of Perceived Social Support (MSPSS), the Insomnia Severity Index (ISI), and the Pittsburgh Sleep Quality Index (PSQI). Patients undergoing HD for less than 3months prior to the study date were excluded.

Results: Of the patients undergoing hemodialysis, 200 patients aged between 18 and 68years (mean=52.29; SD=14.13) gave consent and participated in the study. Sixty-three subjects (31.5%) reported poor sleep quality, defined as having a total PSQI score>5. Forty-one subjects (20.5%) reported clinically significant (moderate-to-severe) insomnia. The majority of our patients undergoing HD reported remarkably high family support, but low friends and significant other support. Poor sleep quality significantly correlated with perceived friends' support and perceived total social support. While perceived family support significantly correlated with both family income and the duration of chronic kidney disease (CKD), perceived friends' support significantly correlated with age and family income. Hierarchical regression analyses showed that perceived family support and friends' support were significant predictors of poor sleep quality. Perceived friends' support was a significant predictor of insomnia severity. Perceived family support was a significant predictor of subjective sleep quality and sleep duration. Perceived friends' support was a significant predictor of subjective sleep quality, sleep duration, sleep latency, sleep disturbance, and daytime dysfunction. Family income was a significant predictor of sleep duration. Age and gender were significant predictors of sleep efficiency. The duration of CKD and duration of HD were significant predictors of sleep disturbance.

Conclusion: This present study has highlighted the value of family as a principal support system in Somalian culture. Understanding the impact of perceived social support on the quality of sleep in patients undergoing HD will help healthcare providers and social services to focus on and improve the social support systems of the patients as an integral part of their treatment.

KEYWORDS

end-stage renal disease, hemodialysis, social support, quality of sleep, Somalia

1. Introduction

Maintenance hemodialysis is currently the standard treatment of choice for patients with end-stage renal disease (ESRD), and more than 3 million patients with ESRD worldwide receive this treatment. Many patients undergoing hemodialysis report a poor quality of sleep, and this can potentially predict their morbidity, mortality, and overall quality of life. According to the current research, 40–85% of patients undergoing hemodialysis report sleeping problems (1–3). Insomnia, restless legs syndrome (RLS), breathing problems during sleeping, and excessive daytime sleepiness (EDS) are most commonly reported in patients with ESRD undergoing HD (24). Sleep problems in patients undergoing HD have been linked to a variety of factors, such as behavioral disturbances, biological traits, medical comorbidities, treatment-related parameters, and psychosocial circumstances (4).

Several studies have shown that sleep was disturbed in patients with ESRD undergoing hemodialysis treatment (5–7). The underlying causes of sleep disturbances were reported to be multifactorial including electrolyte imbalances, uremia, erythropoietin deficiency-related anemia, and circadian rhythm disturbances due to melatonin release. Reduced quality of life in patients undergoing hemodialysis can also be caused by sleep disturbances, which result in poor daily life functioning, inability to care for one's family needs, and inability to actively participate in social life (5–7).

Poor social support and a lack of communication with friends and family are some of the major challenges that patients with ESRD undergoing hemodialysis encounter (25). It was shown that the level of social support was crucial in a more efficient adaptation to the chronic nature of the illness, sleep problems, and potential complications encountered during the treatment (8). According to Cohen et al. (9), social support refers to the intricate network in which an individual might receive and provide assistance and have his/her emotional needs met. Social support supposedly creates a sense of physical and psychological wellbeing and has been shown to have a profound influence on the daily lives of patients undergoing HD (9, 10). Social support is often provided by family members, friends, and significant others and constitutes cognitive, emotional, and materials' support supplied to the individual (9). Although the need for examining social support has been emphasized in patients undergoing hemodialysis, to the best of our knowledge, no studies have examined this relationship and the predictive capacity of social support on the quality of sleep as a measure of overall quality of life. This is also the first study in Africa to examine this crucial relationship.

In this present study, we aimed to examine the relationship between perceived social support and the quality of sleep and to determine the predictors of sleep quality in a sample of patients undergoing hemodialysis in Somalia.

2. Methods

The study design was cross-sectional and was conducted at the hemodialysis unit of Mogadishu Somalia–Turkey Recep Tayyip Erdogan Research and Training Hospital in Mogadishu, Somalia. The participants included 200 (83 women and 117 men) patients who were undergoing hemodialysis treatment approximately two to three times a week. Patients undergoing hemodialysis for less than 3 months prior to the study date were not included in the study. The study protocol was approved by the Hospital's Ethics Review Board (MSTH/10515, Date: 05/30/2022). All participants were administered a sociodemographic data form, the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI), and the Multidimensional Scale of Perceived Social Support (MSPSS).

2.1. Psychometric scales

2.1.1. The Pittsburgh sleep quality index (PSQI)

The PSQI is a self-administered questionnaire created by Buysse et al. (11) that contains 19 self-rated questions and five questions that are rated by a bed partner or roommate. It evaluates patients' perceptions of their sleep quality over the previous 4 weeks. In total, seven component scores are created by adding the 19 self-rating questions together: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disruption, the usage of sleep drugs, and daytime dysfunction. Each component is graded on a scale of 0–3, with a score of "0″ indicating no difficulty, while a score of "3″ indicates great difficulty for each component. A total PSQI score will be generated from the seven component scores, and it will range from 0 to 21 points; higher values signify poorer sleep quality. Patients who obtain a global PSQI score of > 5 are referred to as "poor sleepers," whereas patients who obtain a score of 5 are referred to as "good sleepers." Although bed partner or roommate responses do not count in the overall PSQI total score, they can also be scored from 0 to 3 points depending on the severity of the symptom. Cronbach's alpha of the PSQI of the original study (11) was reported as 0.83. The item-total score correlations ranged from 0.19 to 0.69. In this present study, Cronbach's alpha of the PSQI for the present study sample was 0.85. The item-total score correlations ranged from 0.26 to 0.86, with an average of 0.66.

2.1.2. The insomnia severity index (ISI)

The ISI is a seven-item self-reported questionnaire, created by Morin et al. (12) to evaluate the type, intensity, and effects of insomnia. The usual recall period is the "last month," and the dimensions assessed are the severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, the interference of daytime functioning with sleep difficulties, the noticeability of sleep problems by others, and distress brought on by the lack of sleep. Each item is rated on a 5-point Likert scale (0 = no difficulty, 4 = very severe problem), which results in a total score that ranges from 0 to 28. The following categories of insomnia are used to interpret the overall score: no insomnia (0–7), sub-threshold insomnia (8–14), moderate insomnia (15–21), and severe insomnia (22–28). There are three versions available: patient, clinician, and significant other. Cronbach's alpha of the ISI of the original study was reported as 0.74. The item-total score correlations ranged from 0.36 to 0.67, with an average of 0.54. In this present study, Cronbach's alpha of the ISI for the present study sample was 0.74. The item-total score correlations ranged from 0.69 to 0.83, with an average of 0.74.

2.1.3. The multidimensional scale of perceived social support (MSPSS)

The MSPSS is a self-rated measurement tool developed by Zimet et al. (13). It consists of 12 self-reported items that are intended to assess the degree of perceived social support from three different groups: family (items 3, 4, 8, and 11), friends (items 6, 7, 9, and 12), and significant others (items 1, 2, 5, and 10). Each response is given a

Likert-type response score between 1 and 7, where 1 represents a very strong disagree and 7 represents a very strong agree. The results for each item are added together to produce a final score. The overall score ranges from 12 to 84, or it can be scored according to its subscales by combining the items in each subscale and then dividing by 4. A higher score indicates more social support than a person perceives. The subscales' and dimensions' range of possible scores is from 4 to 28. Cronbach's alpha of the MSPSS for the original study was 0.91 for the significant others subscale, 0.87 for the family subscale, 0.85 for the friends subscale, and 0.88 for the total scale (14). Cronbach's alpha of the MSPSS of the present study sample was 0.96 for the significant others subscale, 0.89 for the family subscale, 0.96 for the friends subscale, and 0.82 for the total scale. The item-total score correlations ranged from 0.36 to 0.67, with an average of 0.54. Cronbach's alpha of the MSPSS for the present study sample was 0.82. The item-total score correlations were found as 0.48 for MSPSS family, 0.89 for MSPSS friends, and 0.06 for MSPSS significant others with an average of 0.48.

2.2. Statistical analysis

All statistical analyses were performed by using SPSS (Armonk, NY, United States: IBM Corp.) version 26.0. The analysis and presentation of categorical variables in the form of frequencies and percentages were done. Mean and standard deviation were used to display the continuous variables. Since the data were non-normally distributed, Spearman's rank order test was used for correlation analyses. Hierarchical regression analyses were performed to examine the predictive relationship between social support and sleep quality parameters. A value of p of less than 0.05 and 0.01 was accepted as statistically significant.

3. Results

The average age of 200 participants in the study was 52.3 with a standard deviation of 14.13, and it ranged from 18 to 68. The sample consisted of women (41.5%) and 117 men (58.5%) undergoing hemodialysis. The majority of the participants in the study were married ($n = 139$, 69.5%) and 6% were single ($n = 12$), and the remaining participants ($n = 49$, 24.5%) were either divorced or widowed. The majority of the participants in the study were illiterate ($n = 137$, 68.5%), 84% of the participants had a duration of CKD of 1–5 years, and 88.5% had a duration of HD of 1–5 years. In 58.5% of participants, hypertension was reported as the cause of ESRD, and in 20% of the participants, diabetes mellitus was reported as the cause of ESRD (see Table 1).

Sixty-three subjects (31.5%) reported poor sleep quality defined as a total PSQI score > 5. Forty-one subjects (20.5%) reported clinically significant (moderate-to-severe) insomnia defined as with a total ISI score > 14. The mean PSQI total score was 4.39 (SD 4.73), the mean ISI total score was 5.81 (SD 7.65), the mean MSPSS family score was 6.55 (SD 0.81), the mean MSPSS friends' score was 2.72 (SD 1.87), the mean MSPSS significant others score was 1.10 (SD 0.55), and the mean MSPSS total score was 3.45 (SD 0.76; see Table 2).

The Insomnia Severity Index total was significantly correlated with MSPSS friends ($r_s = -0.195$, $p < 0.01$), MSPSS total ($r_s = -0.159$, $p < 0.05$), and PSQI total ($r_s = 0.083$, $p < 0.05$). PSQI total was negatively correlated with MSPSS friends ($r_s = -0.294$, $p < 0.01$), and MSPSS total ($r_s = -0.222$, $p < 0.01$). MSPSS total was significantly correlated with MSPSS family ($r_s = 0.481$, $p < 0.01$), MSPSS friends ($r_s = 0.892$, $p < 0.01$),

TABLE 1 Sociodemographic characteristics of the study participants (n=200).

Variable	Category	n	%
Age (years)	18–24	9	4.5
	25–34	22	11
	35–44	28	14
	45–54	45	22.5
	> 55	96	48
Gender	Female	83	41.5
	Male	117	58.5
Marital status	Single	12	6
	Married	139	69.5
	Divorced	24	12
	Widowed/Widower	25	12.5
Education status	Illiterate	137	68.5
	Intermediate	20	10
	Secondary	30	15
	University	13	6.5
Occupational status	Employed	188	94
	Unemployed	11	5.5
	Retired	1	0.5
Family income	Unknown	88	44
	1,000–1,500 dollars	22	11
	1,500–2000 dollars	45	22.5
	> 2000 dollars	45	22.5
Duration of CKD	< 1 year	40	20
	1–3 years	69	34.5
	3–5 years	59	29.5
	> 5 years	32	16
Cause of ESRD	Hypertension	117	58.5
	Diabetes mellitus	40	20
	Glomerulonephritis	5	2.5
	Others	38	19
Duration on hemodialysis	3 months	25	12.5
	1 year	46	23
	1–3 years	51	25.5
	3–5 years	55	27.1
	> 5 years	23	11.5
Number of dialysis sessions per week	Once a week	21	10.5
	Twice a week	140	70
	Thrice a week	34	17
	Four times a week	5	2.5

CKD: chronic kidney disease. ESRD: end-stage renal disease.

and family income ($r_s = 0.212$, $p < 0.01$). MSPSS family was significantly correlated with MSPSS friends ($r_s = 0.145$, $p < 0.05$), family income ($r_s = 0.231$, $p < 0.01$), and the duration of CKD ($r_s = -0.140$, $p < 0.01$). MSPSS friends was significantly correlated with age ($r_s = 0.177$, $p < 0.05$), and family income ($r_s = 0.177$, $p < 0.05$). MSPSS significant others significantly correlated with MSPSS family ($r_s = -0.132$, $p < 0.63$; see Table 3).

In hierarchical regression analyses, MSPSS friends was a significant predictor of ISI total ($\beta = -0.261$, $t = -3.545$, $p = 0.000$). MSPSS total score was a significant predictor of ISI total ($\beta = -0.167$, $t = -2.253$, $p = 0.025$). Approximately, 11.5% of variability in PSQI total scores and 8.5% increase in predictive capacity were accounted for the inclusion of MSPSS significant others, MSPSS family, and MSPSS friends subscores [$F(3, 191) = 6.110$, $p = 0.001$]. MSPSS family score was a significant predictor of PSQI total ($\beta = 0.142$, $t = 2.007$, $p = 0.046$). MSPSS friends score was a significant predictor of PSQI total ($\beta = -0.286$, $t = -3.926$, $p = 0.000$; see Table 4A). MSPSS total score was a significant predictor of PSQI total ($\beta = -0.183$, $t = -2.487$, $p = 0.014$). MSPSS family score was a significant predictor of subjective sleep quality ($\beta = 0.142$, $t = 1.988$, $p = 0.048$). MSPSS friends score was a significant predictor of subjective sleep quality ($\beta = -0.294$, $t = -3.999$, $p = 0.000$). MSPSS total score was a significant predictor of subjective sleep quality ($\beta = -0.174$, $t = -2.335$, $p = 0.021$). MSPSS friends score was a significant predictor of sleep latency ($\beta = -0.227$, $t = -3.082$, $p = 0.002$). Family income was a significant predictor of sleep duration ($\beta = 0.149$, $t = 2.107$, $p = 0.036$). MSPSS family was a significant predictor of sleep duration ($\beta = 0.156$, $t = 2.248$, $p = 0.026$). MSPSS friends' score was a significant predictor of sleep duration ($\beta = -0.250$, $t = -3.492$, $p = 0.001$). MSPSS total score was a significant predictor of sleep duration ($\beta = -0.171$, $t = -2.364$, $p = 0.019$). Age was a significant predictor of sleep efficiency ($\beta = 0.144$, $t = 2.000$, $p = 0.047$). Gender was a significant predictor of sleep efficiency ($\beta = -0.173$, $t = -2.453$, $p = 0.015$). The duration of CKD was a significant predictor of sleep disturbance ($\beta = 0.396$, $t = 3.162$, $p = 0.002$). The duration of HD was a significant predictor of sleep disturbance ($\beta = -0.306$, $t = -2.441$, $p = 0.016$). MSPSS friends score was a significant predictor of sleep disturbance ($\beta = -0.167$, $t = -2.256$, $p = 0.025$). MSPSS friends score was a significant predictor of daytime dysfunction ($\beta = -0.277$, $t = -3.748$, $p = 0.000$). MSPSS total score was a significant predictor of daytime dysfunction ($\beta = -0.195$, $t = -2.626$, $p = 0.009$; see Table 4B).

TABLE 2 Descriptive characteristics for the PSQI, ISI, and MSPSS (n=200).

Variable	Mean	Std. Deviation	Minimum	Maximum
PSQI	4.39	4.73	0	16
ISI	5.81	7.65	0	25
MSPSS				
MSPSS family	6.55	0.81	2.75	7
MSPSS friends	2.72	1.87	1	6.75
MSPSS significant others	1.1	0.55	0.75	6.25
MSPSS total	3.45	0.76	1.75	6.33

PSQI: Pittsburgh Sleep Quality Index. ISI: Insomnia Severity Index. MSPSS: Multidimensional Scale of Perceived Social Support.

4. Discussion

This study examined the relationship between social support and the quality of sleep in a sample of Somalian patients undergoing HD. A total of 32% of patients undergoing HD were poor sleepers with a total PSQI score > 5. Approximately, 30% of patients reported insomnia defined as having a total ISI score of > 7, and 21% of patients had clinically significant insomnia. While mean perceived friends' support, significant others support, and total social support scores were lower than the original scale American sample, perceived family support scores were higher than the original scale sample (13). The majority of our patients undergoing HD reported remarkably higher family support but low friends and significant others support. Poor sleep quality (measured by the PSQI Total) significantly correlated with perceived friends' support and perceived total social support. Insomnia severity (measured by the ISI Total) was significantly correlated with perceived friends' support and perceived total social support. While perceived family support significantly correlated with both family income and duration of CKD, perceived friends' support significantly correlated with age and family income. Both perceived family support and friends' support were significant predictors of poor sleep quality. Perceived friends' support was a significant predictor of insomnia severity. Perceived family support was a significant predictor of subjective sleep quality and sleep duration. Perceived friends'

TABLE 3 Correlation between perceived social support measures and demographics and scales.

	1	2	3	4	5	6
ISI total	1					
PSQI total	−0.803**	1				
MSPSS total	−0.159*	−0.222**	1			
MSPSS family	0.091	0.088	0.481**	1		
MSPSS friends	−0.195**	−0.294**	0.892**	0.145*	1	
MSPSS significant others	−0.035	−0.007	0.060	−0.132	0.044	1
Age	0.088	0.127	−0.126	0.057	−0.167*	−0.124
Duration of CKD	0.115	0.136	−0.126	−0.140*	−0.102	0.028
Family income	0.094	0.011	0.212**	0.231**	0.177*	−0.086

*$p < 0.05$; **$p < 0.01$. ISI: Insomnia Severity Index. PSQI: Pittsburgh Sleep Quality Index. MSPSS: Multidimensional Scale of Perceived Social Support. CKD: Chronic kidney disease.

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TABLE 4A A Hierarchical regression analyses of MSPSS dimensions.

Model	Independent variables	*B*	*t*	*p*	*F*	*df*	R^2	Model *p*
1	MSPSS Friends	−0.261	−3.545	0.000	5.018	3, 191	0.097	0.002
	MSPSS Total score	−0.167	−2.253	0.025				
2	MSPSS Family	0.142	2.007	0.046	6.110	3, 191	0.115	0.001
	MSPSS Friends	−0.286	−3.926	0.000				
	MSPSS Total score	−0.183	−2.487	0.014				

Model 1: Dependent variable ISI total score. Model 2: Dependent variable PSQI total score. MSPSS: Multidimensional Scale of Perceived Social Support.

TABLE 4B Hierarchical regression analyses of PSQI dimensions.

Model	Independent variables	*B*	*t*	*p*	*F*	*df*	R^2	Model *p*
1	MSPSS Family	0.142	1.988	0.048	6.302	3, 191	0.097	0.000
	MSPSS Friends	−0.294	−3.999	0.000				
	MSPSS Total score	−0.174	−2.335	0.021				
2	MSPSS Friends	−0.227	−3.082	0.002	3.640	3, 191	0.094	0.014
3	Family Income	0.149	2.107	0.036	5.755	3, 191	0.142	0.001
	MSPSS Family	0.156	2.248	0.026				
	MSPSS Friends	−0.250	−3.492	0.001				
	MSPSS Total score	−0.171	−2.364	0.019				
4	Age	0.144	2.000	0.047	1.780	3, 191	0.093	0.152
	Gender	−0.173	−2.453	0.015				
5	Duration of CKD	0.396	3.162	0.002	1.769	3, 191	0.086	0.154
	Duration of HD	−0.306	−2.441	0.016				
	MSPSS Friends	−0.167	−2.256	0.025				
6	MSPSS Friends	−0.277	−3.748	0.000	5.108	3, 191	0.087	0.002
	MSPSS Total score	−0.195	−2.626	0.009				

Model 1: Dependent variable subjective sleep quality. Model 2: Dependent variable sleep latency. Model 3: Dependent variable sleep duration. Model 4: Dependent variable sleep efficiency. Model 5: Dependent variable sleep disturbance. Model 6: Dependent variable daytime dysfunction. PSQI: Pittsburgh Sleep Quality Index. MSPSS: Multidimensional Scale of Perceived Social Support. CKD: Chronic kidney disease. HD: Hemodialysis.

support was a significant predictor of subjective sleep quality, sleep duration, sleep latency, sleep disturbance, and daytime dysfunction. Family income was a significant predictor of sleep duration. Both age and gender were significant predictors of sleep efficiency. Both the duration of CKD and the duration of HD were significant predictors of sleep disturbance.

The results of the present study showed that the prevalence of poor sleepers in patients undergoing HD was remarkably lower than in previous reports, ranging from 71 to 83.8% in other studies (15–18). Approximately 30% of patients reported insomnia, from which 21% had clinically significant insomnia. This was lower than the 55% that (19) reported earlier. The results of the present study also showed that Somalian patients undergoing hemodialysis had high perceived social support from their family and poor perceived social support from their friends. There are no established population norms on perceived social support. Norms would likely vary on the basis of culture and nationality, as well as age and gender. Overall, our findings were consistent with the traditional collective culture of the Somalian nation and validate the value of family as the principal support system in Somalian culture.

Our results showed that poor sleep quality and insomnia severity were negatively correlated with perceived friends and total social support. While perceived family support positively correlated with family income, it was negatively correlated with the duration of CKD. As the duration of CKD increased, family support levels decreased. Similarly, perceived friends' support positively correlated with family income and negatively correlated with age. As the family income increased, friends' support levels increased and the older patients had significantly worse friends' support than younger patients.

While perceived family support was a significant predictor of subjective sleep quality and sleep duration, perceived friends' support was a significant predictor of subjective sleep quality, sleep duration, sleep latency, sleep disturbance, and daytime dysfunction. Family income was a significant predictor of sleep duration. This finding was consistent with the notion that a sufficient amount of family income to afford living and treatment expenses played a crucial role equivalent to physical factors to contribute to the overall quality of life (19, 20). Both age and gender were significant predictors of sleep efficiency. Both the duration of CKD and the duration of HD were significant predictors of sleep disturbance. Our findings revealed that perceived

family and friends' support were significant predictors of overall sleep quality. These results were intuitive since the majority of our patients undergoing HD had no job or fund, and they could only afford their required hemodialysis sessions by relying on the family as their primary social and financial resource, and their access to quality care was extremely limited. Our results were consistent with previous reports and supported the notion that the higher level of perceived family and friends' support helped the patients to adapt to their chronic diseases physically and mentally and improved their coping with the chronic disease and treatments (10, 21–23). Our findings also documented further evidence that perceived social support could be an essential component of coping mechanism in a better adaptation to the burden of having end-stage renal disease and could play a fundamental role in enhancing the physical and mental health of the patients undergoing hemodialysis. A fundamental principle of social relations in Somalian society is the principle of collective responsibility. The individual is surrounded by his/her family, in the second circle matrilateral and patrilateral relatives, half-siblings, close friends, etc. Although close kin relations do not necessarily entail closer social relations, the constitution of Somalian society lies first in kinship and family, and this has been integrated into the DNA of Somalian social relations. Family provides stability and longevity to Somalian society as an agreed set of social practices and contributes to stable social relations. In contrast, friendships in the psychosocial reality of Somalian society do not follow the structure in Western societies and are entirely formal and hierarchical at the same time. Therefore, the driving force of social relations which forms Somalian communities is predominantly family-based which is so well attuned to traditional Somalian life.

This study has certain limitations. The assessment of the potential effects of biochemical laboratory parameters could have been more informative. A control group of patients including pre-dialysis stage patients with ESRD could have provided comparative data, and this can be accomplished in a follow-up study. Despite these, the findings of the present study for the first time reported the status of Somalian patients undergoing hemodialysis and might enhance our team's efforts to convince Somalian government agencies to plan better hemodialysis services in the near future.

In conclusion, the present study has highlighted for the first time the associated factors causing poor sleep and the impact of perceived social support on the quality of sleep in a sample of patients undergoing HD in Somalia. The present study contributed to the limited research knowledge that examined the relationship between social support and the quality of sleep of patients undergoing hemodialysis in Africa. Patients undergoing hemodialysis might benefit from receiving formal and informal social support such as support from family and friends. Healthcare professionals working in hemodialysis units should continuously assess patients' quality of sleep and monitor the level of social support to improve their treatment adherence. Healthcare policymakers should consider social support as a high-priority area of work and research to enhance the management of patients undergoing hemodialysis.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Mogadishu Somalia Turkey Recep Tayyip Erdogan Research and Training Hospital Ethics Review Board (MSTH/10515, Date: 05/30/2022). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SK: guarantor of integrity of the entire study. SK and NM: study concepts and designs, statistical analysis. SK, NM, YM, and AE: literature research and manuscript preparation. 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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Lower serum insulin-like growth factor 1 concentrations in patients with chronic insomnia disorder

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Objectives: Insulin-like growth factor 1 (IGF-1) is a crucial neurotrophin that is produced in the brain and periphery and may play an important role in insomnia and mood disorders. We aimed to analyze its serum concentrations in patients with chronic insomnia disorder (CID).

Methods: Patients with CID were enrolled in this study and divided into the CID group [Generalized Anxiety Disorder-7 (GAD-7) score<10] and the CID with anxiety group (GAD-7 score≥10). Age-and sex-matched healthy volunteers were recruited as controls. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and the GAD-7 and the Patient Health Questionnaire-9 to assess emotional status. All subjects were monitored via polysomnography, and the serum IGF-1 concentrations in their peripheral blood were detected via enzyme-linked immunosorbent assays.

Results: We enrolled 65 patients with CID (of whom 35 had anxiety) and 36 controls. The PSQI score and IGF-1 concentration in the CID and CID with anxiety groups were higher than those in the control group. The apparent difference in IGF-1 concentration between the CID and CID with anxiety groups was not statistically significant. The IGF-1 concentration in patients with CID was linearly correlated with the GAD-7 score, PSQI score, and stage 3 non-rapid eye movement (stage N3) time.

Conclusion: The serum IGF-1 concentration in patients with CID was lower than that of participants without CID, negatively correlated with anxiety score and sleep quality, and positively correlated with stage N3 time.

KEYWORDS

chronic insomnia disorder, anxiety, insulin-like growth factor-1, sleep quality, polysomnography

1. Introduction

Sleep is a basic physiological requirement, essential to human life. Sleep disorders are common and have detrimental effects on people's daily lives, learning, and work. Chronic insomnia is a common sleep disorder, affecting approximately 30% of the general population (1). It is characterized by persistent difficulty in falling asleep or sleep maintenance and resulting in insufficient sleep satisfaction, persisting for at least 3 months (2). Patients with chronic insomnia frequently experience a variety of nervous system symptoms, including fatigue, impaired focus, and excessive daytime sleepiness, which can increase mental disease, immunological dysfunction, and endocrine dysfunction for a long time (2–4).

Sleep is regulated by neuroendocrine signals and associated with the optimal production of hormones, including growth hormone (GH) and insulin-like growth factor 1 (IGF-1) (5, 6). Sleep deprivation and sleep restriction affect endocrine secretion; they increase cortisol concentrations in the evening and decrease concentrations of the anabolic hormone testosterone, GH, and IGF-1 (7, 8). IGF-1, a peptide hormone consisting of 70 amino acids, is a neurotrophic factor that mediates the effects of GH. IGF-1 affects metabolism, cognition, neuroprotection, regeneration, and functional plasticity (9, 10).

The IGF-1 concentration is the recommended biomarker for the diagnosis of growth-related diseases because it does not exhibit short-term variations to the same extent as GH. In mammals, adequate sleep increases the circulation of IGF-1 and insufficient sleep decreases the concentration of IGF-1 in the muscles (11–13). To the best of our knowledge, the IGF-1 concentration in patients with chronic insomnia remains unclear.

The aim of this study was to assess serum concentrations of IGF-1 in patients with chronic insomnia. We hypothesized that patients with insomnia have a decreased serum IGF-1 concentration, which may play a role in the endocrine system, providing more evidence for the evaluation and treatment of insomnia.

2. Methods

2.1. Participants

We prospectively enrolled patients diagnosed with chronic insomnia disorder (CID) according to the International Classification of Sleep Disorders—Third Edition as outpatients of the Department of Neurology, First Hospital of Jilin University, from March to July 2022. At the time of enrollment, none of the patients were using actual sleeping medication. The inclusion criteria were as follows: (1) age between 18 and 68 years, (2) sleep latency >30 min, (3) difficulty staying asleep, (4) waking up early, (5) daytime sleepiness, (6) impaired daytime function, (7) sleep difficulties and daytime function impairment lasting more than 3 days a week for more than 3 months, and (8) a Patient Health Questionnaire-9 (PHQ-9) score < 10. The exclusion criteria were as follows: (1) intracranial tumors, stroke, intracranial infection, brain trauma, and other central nervous system diseases; (2) diabetes, pituitary diseases, and other systemic diseases; and (3) taking medication that affect the secretion of growth hormones (bromocriptine, progesterone, etc.). These patients were divided into two groups according to their Generalized Anxiety Disorder-7 (GAD-7) score: the CID group (GAD-7 score < 10), and the CID with anxiety group (GAD-7 score ≥ 10). Sex-and age-matched healthy volunteers were recruited as controls. Demographic and clinical variables, including age, sex, marital status, body mass index (BMI), and insomnia duration were recorded.

This study was approved by the Ethics Committee of the First Hospital of Jilin University and followed the guidelines of the Declaration of Helsinki (1964). All the participants or their guardians provided written informed consent for participation in the study.

2.2. Questionnaires

Participants self-assessed their sleep quality using the Pittsburgh Sleep Quality Index (PSQI) questionnaire, which is one of the most widely validated and practical sleep disorder assessment scales, mainly used to provide a subjective measure of sleep quality in the last month. The questionnaire consists of 23 items grouped into seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction (14). Each component is scored from 0 (good sleep quality) to 3 (bad sleep quality), and the total PSQI score (ranging from 0 to 21) is obtained by summing the seven component scores. A total PSQI score ≤ 5 is associated with good sleep quality and > 5 with poor sleep quality. Higher sleep scores on the PSQI scale equate to poorer sleep quality (15).

Severity of anxiety was self-evaluated using the GAD-7 scale (16). The GAD-7 is a seven-item screening instrument, with each response scored from 0 (never) to 3 (almost every day). The total GAD-7 score ranges from 0 to 21, with a higher GAD-7 score indicating higher level of anxiety. A score ≥ 10 on the GAD-7 is the cutoff point for possible anxiety, with a sensitivity of 89% and specificity of 82% (17).

The PHQ-9, an effective self-rating depression scale, was used to assess depression symptoms. Participants rated depression symptoms of the past 2 weeks on a four-point scale, ranging from 0 (never) to 3 (almost every day). The total score ranges from 0 to 27, with higher scores reflecting greater levels of depression symptoms (18). A score of ≥10 on the PHQ-9 is the cutoff point for depression symptoms, with a sensitivity of 80% and a specificity of 92% (19).

2.3. Polysomnography

Before polysomnography (PSG), the participants were not permitted to consume caffeinated beverages, alcohol, or sleep medicines. PSG (Compumedics, Abbotsford, Australia) was performed in a standard, sound-attenuated sleep laboratory at our hospital, and participants were monitored for at least 8 h. These studies followed the American Academy of Sleep Medicine (AASM) standards for electroencephalography, electrooculography, chin muscle electromyography, electrocardiography, nasal pressure, finger oximetry, chest, and abdominal respiratory inductance plethysmography. Professional sleep technicians certified as PSG technologists analyzed the PSG results using the AASM version 2.3 for the Scoring of Sleep and Associated Events.

2.4. IGF-1 measurements

The IGF-1 concentration was measured in the morning under fasting conditions for all participants. Blood samples were collected at 8 a.m. Blood was centrifuged at 3,000 × *g* for 10 min, and the serum was stored at −20°C before further use. The IGF-1 concentration was measured using the Human IGF-1 Quantikine enzyme-linked immunosorbent assay, which has a measurement range of 2–1,200 ng/mL.

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, United States). The Shapiro–Wilk test was used to assess the normal distribution of continuous variables. Continuous data with a normal distribution [age, BMI, insomnia duration, GAD-7 score, PHQ-9 score, PSQI

score, IGF-1 score, total sleep time, sleep latency, sleep efficiency, rapid eye movement (REM) sleep, stage 1 non-REM (stage N1), stage 2 non-REM (stage N2), stage 3 non-REM (stage N3), stage N1 time, stage N2 time, stage N3 time, REM sleep latency, REM arousal index, arousal index, apnea-hypopnea index (AHI), periodic limb movement index (PLMI), mean SaO_2, minimum SaO_2, and end-tidal CO_2] were expressed as means and standard deviations and compared among groups by using one-way ANOVA. Categorical data (male sex and marital status) were expressed as absolute values and percentages and compared among groups by using the chi-square test. The correlations of IGF-1 concentration with the GAD-7 score, PSQI score, and stage N3 time were examined using the Pearson correlation test. Univariate and multivariate linear regression were used to assess the association between IGF-1 and clinical parameters including sex, age, BMI, insomnia duration, GAD-7 score, PHQ-9 score, PSQI score, total sleep time, sleep latency, sleep efficiency, wake after sleep onset, stage N1 time, stage N2 time, stage N3 time, REM sleep time, REM sleep latency, REM arousal index, arousal index, AHI, PLMI, mean SaO_2, minimum SaO_2, and end-tidal CO_2. In the *post hoc* analysis, the Bonferroni method was used to calculate the adjusted *p*-value. The statistical significance level was set to $p < 0.05$.

3. Results

3.1. Baseline characteristics and IGF-1 serum levels

A total of 82 patients with CID and 45 age-and sex-matched controls were enrolled in this study. Among them, 65 patients with CID (35 of whom had anxiety) and 36 controls completed PSG and IGF-1 measurements (Figure 1). Baseline characteristics and IGF-1 concentrations are summarized in Table 1 for each group. Male sex, age, marital status, BMI, and PHQ-9 score were very similar in the CID, CID with anxiety, and control groups. The PSQI score and IGF-1 concentration significantly differed among the three groups (both $p < 0.001$). The GAD-7 score in the CID with anxiety group was higher than that in the CID and control groups (both $p < 0.001$). IGF-1 serum concentrations are presented in Figure 2.

3.2. PSG parameters

A comparison of the PSG parameters between the two groups is presented in Table 2. Total sleep time, sleep latency, sleep efficiency, stage N1, stage N3, REM sleep, stage N1 time, stage N2 time, stage N3 time, REM sleep time, and arousal index significantly differed among the groups (all $p < 0.001$).

3.3. Correlation analysis for IGF-1 concentrations with GAD-7, PSQI, and PSG parameters in CID and CID with anxiety groups

Using Pearson correlation analysis, the IGF-1 concentration in patients with CID was significantly correlated with the GAD-7 score ($r = -0.289$, $p = 0.02$), PSQI score ($r = -0.318$, $p = 0.0098$), and stage N3 time ($r = 0.328$, $p = 0.008$; Figure 3).

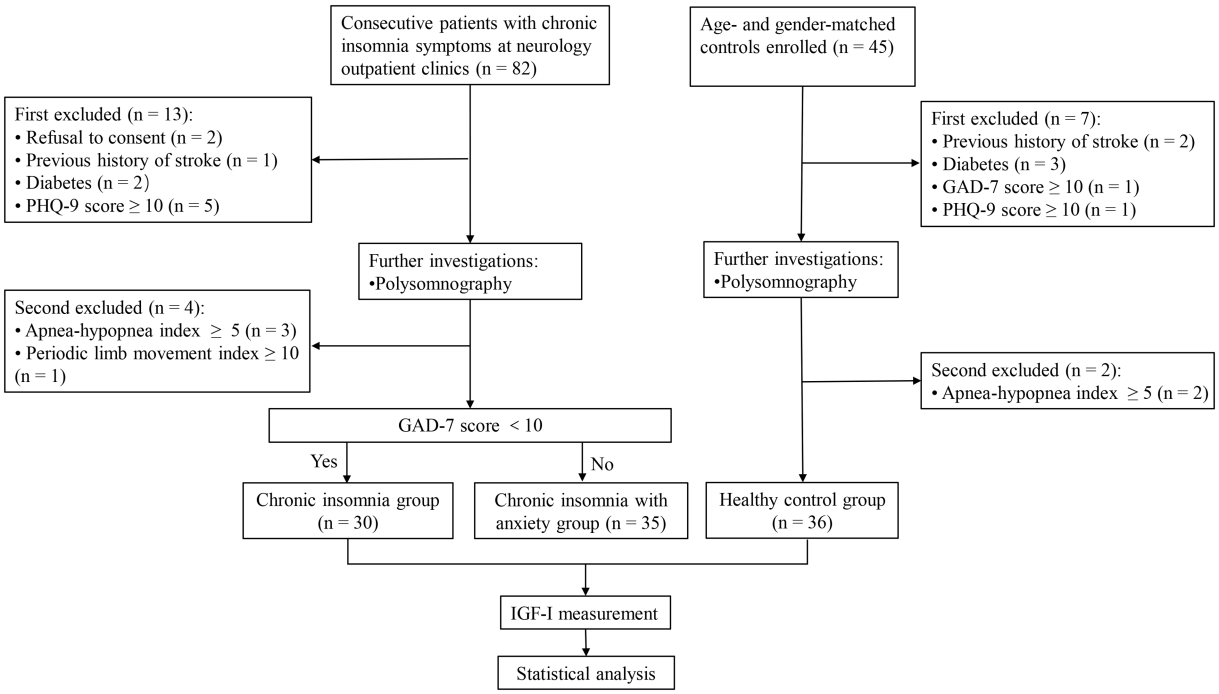

FIGURE 1
Flowchart shows the screening process for participants.

TABLE 1 Clinical characteristics and IGF-1 in the patients with CID, CID with anxiety, and HC.

	1. HC (*n*=36)	2. CID (*n*=30)	3. CID with anxiety (*n*=35)	χ^2/F	*p* value	*Post hoc* Bonferroni (*P*)		
						1 vs.2	1 vs.3	2 vs.3
Male sex	11	12	12	0.648	0.723			
Age (years)				1.346	0.969			
20 ≤ Age < 35	3	4	3					
35 ≤ Age < 45	7	5	7					
45 ≤ Age < 60	20	18	21					
≥60	6	3	4					
Marriage (yes/no)	34/2	27/3	33/2	0.624	0.732			
BMI (kg/m^2)	24.17 ± 4.03	23.74 ± 3.16	24.91 ± 3.18	0.937	0.395			
Insomnia duration (month)	-	15.3 ± 4.8	14.5 ± 5.4	-	-			
GAD-7 score	3.8 ± 1.7	4.0 ± 1.7	14.8 ± 3.2	242.773	< 0.001*	NS	< 0.001*	< 0.001*
PHQ-9 score	3.8 ± 1.1	4.3 ± 1.6	4.1 ± 1.4	1.604	0.206			
PSQI score	2.5 ± 1.2	13.5 ± 4.6	14.37 ± 3.9	126.777	< 0.001*	< 0.001*	< 0.001*	NS
IGF-1 (ng/mL)	218.537 ± 49.458	161.820 ± 35.461	146.435 ± 48.235	24.773	< 0.001*	< 0.001*	< 0.001*	NS

CID, chronic insomnia disorder; HC, healthy controls; BMI, body mass index; GAD-7, generalized anxiety disorder-7; PHQ-9, patient health questionnaire-9; PSQI, pittsburgh sleep quality index; IGF-1, insulin-like growth factor-1. NS, no significance. * *p* value < 0.05 (statistically different).

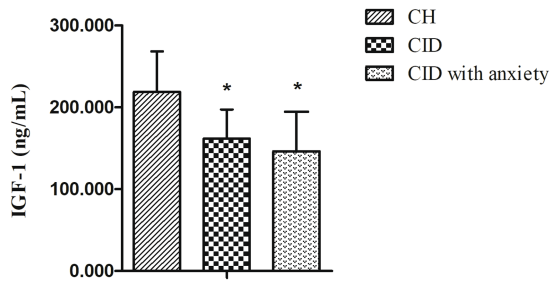

FIGURE 2
The serum levels of IGF-1 in CID, CID with anxiety patients, and HC.
* indicates statistically different (p<0.05).

3.4. Univariable and multivariable analysis actors affecting IGF-1 serum levels in CID and CID with anxiety groups

Table 3 summarizes the univariate and multivariable regression analysis of factors affecting the IGF-1 serum concentration. In the univariate model, IGF-1 concentration was associated with age (p = 0.017), GAD-7 score (p = 0.005), PSQI score (p = 0.003), and stage N3 time (p = 0.007). However, none of these or any other variables associated with IGF-1 concentration upon multivariable analysis.

4. Discussion

In this study, the IGF-1 serum concentration in patients with CID was lower than that in patients without CID. Moreover, the IGF-1 concentration was negatively correlated with participants' anxiety score and sleep quality and positively correlated with stage N3 time during PSG, which indicates that IGF-1 may play an important role in insomnia and mood disorders.

Chronic sleep deprivation reportedly reduces the total IGF-1 concentration in rats (20, 21). Chennaoui et al. also discovered that the IGF-1 system responds to sleep deprivation, with serum IGF-1 concentrations decreasing after 25 h of sleep deprivation and increasing again after a night of recovery (7). Kimura et al. reported that decreases in the symptoms of patients with circadian rhythm sleep–wake disorders were associated with increased serum concentrations of IGF-1 (22). Although the results differ among those studies, they all suggest that sleep deprivation is related to IGF-1. Disruptions during sleep, such as insomnia, can affect GH and IGF-1 concentrations, because GH is preferentially released during slow-wave sleep. In addition, a delay in sleep can result in a decrease in GH secretion (23). Our results appear to support the link between IGF-1 and insomnia and are in line with those of other studies on IGF-1. Besides, because of the small size of the age subgroups in our study, further work is needed to confirm these data.

Several potential mechanisms underlying decreased IGF-1 concentrations in patients with CID may be involved. First, as mentioned above, although GH secretion occurs in pulses throughout the day, slow-wave sleep after sleep onset is associated with particularly large bursts of GH secretion. Secretion of growth-promoting hormone cells also increases during slow-wave sleep. The relationship between nocturnal GH release and slow wave activity suggests that it can reflect the GH release hormone activity. GH-releasing hormone may promote sleep and reduce the awakening threshold of REM sleep. Symptoms of insomnia include difficulty falling asleep, decreased total sleep time, reduced slow-wave sleep time, and increased sleep fragmentation (5). These symptoms cause a decrease in GH secretion, which, in turn, causes a decrease in the IGF-1 concentration. This was supported by the correlation between IGF-1 concentration and the N3 stage in this study. Additionally, the hypothalamic–pituitary–adrenal (HPA) axis

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TABLE 2 The polysomnography parameters in CID, CID with anxiety, and HC.

	1. HC (n=36)	2. CID (n=30)	3. CID with anxiety (n=35)	F	p value	*Post hoc* Bonferroni (P)		
						1 vs.2	1 vs.3	2 vs.3
Total sleep time (min)	393.15 ± 31.93	301.98 ± 66.36	281.88 ± 43.46	53.300	< 0.001*	< 0.001*	< 0.001*	NS
Sleep latency (min)	15.73 ± 3.10	39.87 ± 7.60	41.83 ± 7.41	186.473	< 0.001*	< 0.001*	< 0.001*	NS
Sleep efficiency (%)	90.51 ± 4.02	71.72 ± 11.69	66.93 ± 11.96	57.124	< 0.001*	< 0.001*	< 0.001*	NS
Wake after sleep onset (min)	27.07 ± 20.44	58.24 ± 34.54	84.94 ± 57.75	17.956	< 0.001*	0.034	< 0.001*	NS
Stage N1 (%)	4.91 ± 1.07	19.55 ± 6.56	21.44 ± 6.40	104.963	< 0.001*	< 0.001*	< 0.001*	NS
Stage N2 (%)	49.83 ± 6.45	51.44 ± 10.03	50.01 ± 7.81	0.358	0.700			
Stage N3 (%)	20.88 ± 4.82	12.27 ± 7.37	10.14 ± 4.70	35.561	< 0.001*	< 0.001*	< 0.001*	NS
REM sleep (%)	24.39 ± 8.33	16.75 ± 8.15	18.934 ± 11.48	5.796	0.004*	0.027	NS	NS
Stage N1 time (min)	19.22 ± 4.10	58.88 ± 23.56	60.46 ± 20.83	59.319	< 0.001*	< 0.001*	< 0.001*	NS
Stage N2 time (min)	195.99 ± 31.10	155.63 ± 48.34	142.99 ± 26.78	21.050	< 0.001*	< 0.001*	< 0.001*	NS
Stage N3 time (min)	81.94 ± 19.49	37.49 ± 24.06	28.66 ± 14.30	75.892	< 0.001*	< 0.001*	< 0.001*	NS
REM sleep time (min)	96.00 ± 34.60	50.00 ± 26.72	53.82 ± 35.10	21.107	< 0.001*	< 0.001*	< 0.001*	NS
REM sleep latency	93.75 ± 24.10	117.93 ± 26.59	85.89 ± 32.05	11.449	< 0.001*	0.002	NS	< 0.001*
REM arousal index (events/h)	1.77 ± 1.36	5.07 ± 3.74	6.28 ± 4.39	16.754	< 0.001*	< 0.001*	< 0.001*	NS
Total arousal index (events/h)	5.95 ± 3.30	16.01 ± 4.86	19.50 ± 5.72	60.381	< 0.001*	< 0.001*	< 0.001*	0.039
AHI (per hour)	2.13 ± 1.60	2.31 ± 0.99	2.23 ± 1.04	0.162	0.850			
PLMI (events/h)	0.99 ± 0.84	0.82 ± 1.01	0.91 ± 0.90	0.268	0.765			
Mean SaO_2 (%)	95.83 ± 1.54	94.97 ± 1.81	95.23 ± 1.78	2.279	0.108			
Minimum SaO_2 (%)	87.86 ± 5.28	86.33 ± 6.09	86.57 ± 5.44	0.743	0.478			
End-tidal CO_2 (mmHg)	35.34 ± 2.55	35.45 ± 2.20	35.77 ± 2.53	0.298	0.743			

CID, chronic insomnia disorder; HC, healthy controls; REM, rapid eye movement; Stage N1, stage 1 non-REM; Stage N2, stage 2 non-REM; Stage N3, stage 3 non-REM; AHI, apnea-hypopnea index; PLMI, periodic limb movement index; SaO_2, arterial oxygen saturation. NS, no significance. *p value < 0.05 (statistically different).

is activated in patients with CID, which has a suppressant effect on the GH-IGF-1 axis (24). In particular, cortisol secretion is negatively correlated with GH secretion, which subsequently affects the IGF-1 concentration (25). Second, patients with CID have HPA-axis dysfunction, exhibiting an increase in the release of adrenocorticotropic hormone, increased sympathetic nervous system activity, and increased inflammatory cytokine concentration (24, 26). Experimental studies have also suggested that altered sleep may impact concentrations of inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (27). Proinflammatory cytokines may suppress the GH/IGF-1 axis and decrease both circulatory and tissue concentrations of IGF-1 (28–30).

Furthermore, IGF-1 is a neuroprotective agent, involved in brain development and survival (31). Thus, IGF-1 may play an important role in the amelioration of anxiety and memory deficits (32). A higher intraindividual IGF-1 concentration is reportedly associated with a better mood. Previous studies have revealed that IGF-1 concentrations are negatively correlated with anxiety levels (33, 34), which is consistent with our results. However, in other studies, individuals with depressive and/or anxiety disorders had higher IGF-1 concentrations than those without such disorders, which may indicate a response mechanism to counteract the impaired neurogenesis (35). Although the IGF-1 concentration was appeared lower in the CID with anxiety group than in the CID group in our study, the difference was not statistically significant. We plan to conduct further studies with larger samples to verify this result. Based on our results, we hypothesize that the HPA axis plays a role in the relationship between the GAD-7 score and the IGF-1 concentration. A dysfunctional HPA axis has been implicated in the pathogenesis of anxiety disorders. Proinflammatory cytokines, including IL-6 and TNF-α, have been implicated in the etiologies of clinical anxiety disorders, which may affect the IGF-1 concentration (36). However, anxiety may affect IGF-1 in diverse ways, and further clarity will require further investigation.

This study has several limitations. First, it was an observational study without in-depth investigation into underlying mechanisms. We are currently monitoring IGF-1 concentrations in patients with CID after treatment, in order to elucidate these mechanisms. Second, previous studies have revealed that orexin neurons are modulated by

IGF-1 (37), which may play an important role in the pathophysiology of insomnia. This aspect was not considered in the current study. Therefore, we will focus on the correlation between hypothalamic secretion and IGF-1 in the future. In addition, our study was limited by the small sample, and future studies will be conducted with larger samples to allow age stratification, which should provide a stronger evidence base for the clinical diagnosis and treatment of insomnia and mood disorders.

TABLE 3 Univariable and multivariable analysis for the IGF-1.

Factors	IGF-1, ng/mL			
	Univariable analysis		Multivariable analysis	
	β	*P*	*β*	*P*
Male sex	−0.045	0.721		
Age (years)	−0.295	0.017 [ab]	−0.167	0.154
BMI (kg/m^2)	0.204	0.104		
Insomnia duration	−0.164	0.192		
GAD-7 score	−0.346	0.005[ab]	−0.229	0.053
PHQ-9 score	0.185	0.140		
PSQI score	−0.366	0.003 [ab]	−0.227	0.062
Total sleep time (min)	0.169	0.179		
Sleep latency (min)	0.022	0.863		
Sleep efficiency (%)	0.183	0.145		
Wake after sleep onset (min)	−0.132	0.294		
Stage N1 time (min)	0.245	0.256		
Stage N2 time (min)	0.007	0.956		
Stage N3 time (min)	0.333	0.007[ab]	0.165	0.176
REM sleep time (min)	−0.042	0.742		
REM sleep latency	0.110	0.381		
REM arousal index (events/h)	0.079	0.534		
Arousal index (events/h)	−0.055	0.665		
AHI (per hour)	−0.002	0.986		
PLMI (events/h)	0.058	0.648		
Mean SaO_2 (%)	−0.086	0.494		
Minimum SaO_2 (%)	−0.070	0.579		
End-tidal CO_2 (mmHg)	0.158	0.210		

IGF-1, insulin-like growth factor-1; BMI, body mass index; GAD-7, generalized anxiety disorder-7; PHQ-9, patient health questionnaire-9; PSQI, pittsburgh sleep quality index; REM, rapid eye movement; Stage N1, stage 1 non-REM; Stage N2, stage 2 non-REM; Stage N3, stage 3 non-REM; AHI, apnea-hypopnea index; PLMI, periodic limb movement index; SaO_2, arterial oxygen saturation. [a]Nominally significant values ($p < 0.1$) included in the multivariable model; [b]p value < 0.05 (statistically different).

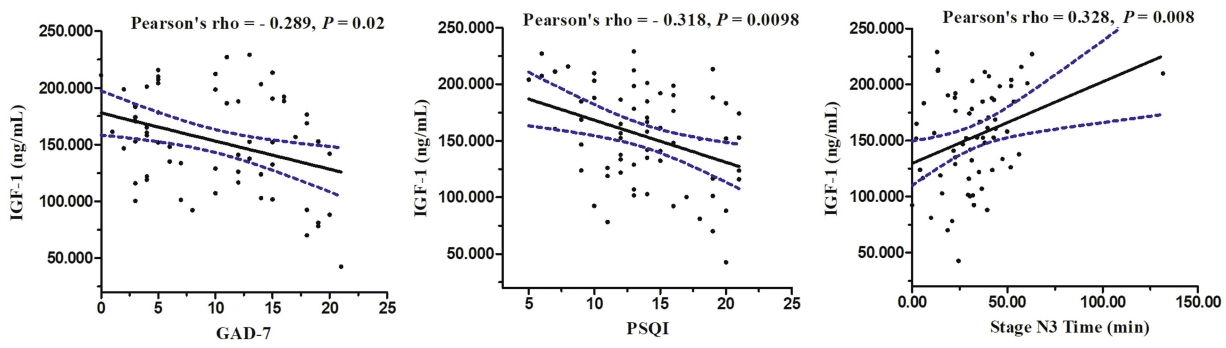

FIGURE 3
Relations between serum levels of IGF-1 and GAD-7 score, PSQI score, and stage N3 time in PSG.

5. Conclusion

In conclusion, the serum IGF-1 concentration in patients with CID was lower than that in participants without CID, negatively correlated with anxiety score and sleep quality, and positively correlated with stage N3 time during PSG. This indicates a potentially important role of IGF-1 in insomnia and emotional disorders. Further studies are needed to examine the relationship between IGF-1 and insomnia and their influence on accompanying symptoms.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Hospital of Jilin University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ wrote the manuscript. QS and HL conducted the data acquisition and data analysis. YW and DW prepared the figures. ZW managed the study and edited the final 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.

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Comparison of three measures for insomnia in ischemic stroke patients: Pittsburgh sleep quality index, insomnia severity index, and Athens insomnia scale

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Objective: This study investigated the consistency and determined the optimal threshold values of three scales in the diagnosis of insomnia of ischemic stroke (IS) patients.

Methods: Participants in this study consisted of 569 acute IS patients. All 569 patients completed the assessment of the three insomnia scales. Insomnia of IS patients were assessed by Pittsburgh sleep quality index (PSQI), Insomnia Severity Index (ISI), and Athens insomnia scale (AIS). Also, basic patient information, neurological function, and activities of daily living were assessed. General information was compared between the insomnia group and the no-insomnia group. Cronbach's α coefficients, Cohen's Kappa consistency, Receiver operating characteristic (ROC) curve and DeLong's test analysis were used to analyze the reliability and diagnostic validity of PSQI, ISI, and AIS.

Results: The PSQI and ISI showed high reliability with Cronbach's α of 0.875 and 0.858, respectively, while the AIS had an α coefficient of 0.734, demonstrating acceptable reliability. The PSQI, ISI, and AIS showed outstanding diagnostic ability with an AUC of 0.960 (95% CI: 0.946, 0.974), 0.911 (95% CI: 0.882, 0.941), and 0.876 (95% CI:0.837, 0.916). The best diagnostic cutoffs for PSQI, ISI, and AIS are ≥9, ≥15, and ≥8.

Conclusion: Each of the three questionnaires has advantages and disadvantages when assessing insomnia. In the evaluation of insomnia in IS patients, the best questionnaire selection should be made according to the purpose of clinical evaluation and considering the sensitivity and specificity.

KEYWORDS

ischemic stroke, insomnia, diagnosis, Pittsburgh sleep quality index (PSQI), insomnia severity index (ISI), Athens insomnia scale (AIS)

1. Introduction

Stroke is a leading cause of death and disability around the world (1). Ischemic stroke (IS) has high rates of morbidity, disability, recurrence and mortality (2). Insomnia is one of the common complaints of IS survivors. In contrast to other long-term sequelae of IS such as mobility and cognitive impairment, insomnia has received less attention and related research, despite being a risk factor for stroke (3). In accordance with the latest manual by the American

Association of Sleep Medicine (AASM), insomnia is defined as persistent sleep problems and daytime socio-occupational dysfunction, which may be actual or perceived despite adequate sleep opportunities (4). According to the International classification of sleep disorders-3 edition (DSM-3) and the Chinese expert consensus on the assessment and management of stroke related sleep disorders (CEC-SSD) (5), stroke-related insomnia consists of two conditions: (i) post-stroke insomnia: insomnia first appears after stroke; (ii) stroke with insomnia: insomnia existing before stroke persists or worsens after stroke and meets the diagnostic criteria for insomnia. According to reports published 30 ~ 68% of poststroke patients were burdened with insomnia (6–8). In addition, insomnia is also thought to increase the risk of psychological problems (depression and anxiety), physical function (disability), and cognitive function (dementia) in IS patients (9, 10).

Strokes are more likely to occur in people who suffer from insomnia. The results of a meta-analysis of 160,867 patients in 15 studies showed that falling/maintaining asleep difficulty, and non-restorative sleep were positively strongly associated with the risk of stroke (11). According to a prospective clinical cohort study of stroke patients, insomnia patients were more likely to be depressed, anxious, disabled, and have difficulty returning to work than stroke patients without insomnia after 1 year after stroke (12). Surveys such as that conducted by Huang et al. (13) have shown that a negatively association between insomnia and the improvement in activities of daily living was found in subacute stroke inpatients. Tang et al. (14) showed that insomnia may make stroke survivors more susceptible to suicide. Kim et al. (10) demonstrated that insomnia had a negative effect on quality of life in stroke patients at the initial phases of rehabilitation. Also, insomnia IS patients have a higher recurrence stroke rate in the first year and a higher mortality rate within 6 years compared with no-insomnia IS patients (15).

Although the prevalence of insomnia continues to rise in many countries around the world (16, 17), patients often treat insomnia as a lifestyle issue rather than a major health problem (18). Also, the importance of insomnia diagnosis has been neglected in the routine medical examination of some IS patients. Clinician assessment and judgment based on the DSM-5 and CEC-SSD remain the criteria for diagnosing insomnia in stroke patients. Polysomnography (PSG) is considered as a common objective measure for the measurement of sleep disorders. However, PSG is not easy to obtain for most clinicians' daily insomnia diagnosis routine (19), and is mostly used for the diagnosis of sleep disordered breathing (SDB). At the same time, PSG is very expensive for epidemiology and research, takes a long time and is not in line with clinical practice (19). However, multiple insomnia questionnaires have been developed including the PSQI, ISI, and AIS. All three questionnaires were used multiple times and translated into multiple languages and have been widely used in China. These questionnaires are considered to be efficient screening tools for insomnia. They are simple to perform and cost effective and do not demand additional special apparatus or facilities. The use of brief questionnaires for subjective assessment saves time and effort and ensures a high level of patient subjective willingness and compliance. Also, due to the self-explanatory nature of these tools, the need for and reliance on specialists and clinicians can be significantly reduced (20, 21). The three insomnia assessment tools used in this study, PSQI, ISI, and AIS, were not developed specifically for IS patients, and each scale validation was based on primary sleep disorders patients (22). Because of the significant role that the rating scales plays in the diagnosis of insomnia in IS patients, psychometric properties, cut-off values and diagnosis effectiveness of these tools need to be evaluated in IS patients. The purpose of this study was to the establish reliability and determine the optimal threshold values of PSQI, ISI, and AIS in the diagnosis of insomnia of IS patients.

2. Methods

2.1. Participants

This study recruited 569 IS patients on the inpatient medical care rosters of three general hospitals in Shanghai from January 2021 to September 2021. The three hospitals recruited 186, 165 and 218 IS patients, respectively. All patients received neuroradiological exam and the IS diagnosis were consistent with the "Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018 (23)." The following conditions were excluded:

① unable to respond appropriately to questionnaires (such as aphasia);
② transient ischemic attack (TIA) diagnosed by neurologists;
③ diagnosed with dementia, or another neurodegenerative or neurological condition.

The diagnosis of stroke-related insomnia (SRI) was determined by neurologist after evaluation and needed to meet both the diagnosis of stroke and insomnia. According to DSM-5 and CEC-SSD (5), the diagnosis of insomnia in this study was as follows. Patients who met all the following five conditions were insomnia IS patients, and the others were no-insomnia IS patients:

① Patients complain of disgruntlement over sleep quality or quantity. They have one or more of the following symptoms: difficulty falling or maintaining sleep; wake up early and are unable to fall back asleep.
② Patients complain that sleep disorders make them feel clinically significant distress or make it hard for them to do important things like socialize, work, behavioral, or other significant functions. They have one or more of the following symptoms: fatigue or lack of energy; decreased attention/concentration/memory; emotional instability; daytime fatigue; behavioral problems (a tendency to be hyperactive, impulsive, or aggressive); lack of energy or motivation; concerns about the quality of sleep.
③ These abnormalities cannot be accounted by inadequate sleep opportunities or inferior sleep environment.
④ Sleep disturbances and daytime symptoms ≥3 times a week.
⑤ The above symptoms are not explained by other sleep disorders.

In order to prevent the impacts of unstable neurological circumstances and environmental changes on the results, our investigation was conducted when the patient was conscious and exhibited stable vital signs after routine neurology treatment. The questionnaires of basic patient information, neurological function, three sleep assessment were applied at a mean of 5.79 days ($SD = 2.34$) after admission to the hospital. All 569 patients included in the study completed basic information collection and insomnia assessment

using three scales (PSQI, ISI, AIS). The investigators conducted face-to-face interviews with IS patients at the neurology ward using PSQI, ISI, and AIS questionnaires. All questionnaires were evaluated when patients fully understood the contents of the questionnaire items.

Ethical approval was obtained from the Ethics Approval Committee of Shanghai Tenth People's Hospital (Approval No. SHSY-IEC-KY-4.0/17–47/01). All participants agreed to participate in this study.

2.2. Measures and questionnaires

2.2.1. Basic information collection and functional assessment

The basic information of patients included age, sex, body mass index (BMI), marital status, education years, occupation, smoking, alcohol consumption, hypertension, diabetes, coronary heart disease. In this study, "smoke" was operationally defined as "current smokers" who had smoked within 30 days before the survey. "Drink" was operationally defined as consuming more than 15 g of alcohol per day within 30 days before the survey.

Each patient was assessed on the National Institute of Health stroke scale (NIHSS). The NIHSS was used to assess the severity of cerebral infarction and the degree of neurological deficit in patients. High NIHSS scores indicate more severe cerebral infarction, resulting in greater disability and functional decline. Also, each patient was assessed for activities of daily living (ADL) using Barthel index (BI). ADL competence is one of the most important indicators of the effectiveness of rehabilitation (24). The Barthel index (BI) is the most commonly used scale in the world to assess ADL competence (25). The BI consists of 10 items: feeding, bed and wheelchair transfer, personal hygiene, toileting, bathing, walking, walking up and down stairs, dressing, bowel control and urinary control. It is mainly suitable for detecting the changes of independent living activities of the elderly and patients before and after treatment.

2.2.2. PSQI

The PSQI has been extensively used in China to measure insomnia symptoms as an essential measure that is recommended globally (26). Based on DSM-5 and CEC-SSD, in clinical patients, the PSQI is the most widely used subjective measure of sleep dysfunction (27). The PSQI is a self-rating questionnaire, composed of 19 self-rated items (0 ~ 3 scale) with a total score from 0 to 21 assessing 7 domains of sleep quality and sleep disorders during the course of the past month: (i) subjective sleep quality (C1), (ii) sleep latency (C2), (iii) sleep duration (C3), (iv) normal sleep efficiency (C4), (v) sleep disturbances (C5), (vi) the application of sleep medication (C6), and (vii) daytime dysfunction (C7). The higher score indicates the worse sleep quality (28). A considerable amount of literature has been published on optimal threshold of PSQI in determining good or bad sleep quality. PSQI has not only been widely used in non-clinical populations, but has also been studied in a variety of clinical populations, including post-surgical patients (29), hemodialysis patients (30), schizophrenia (31), and anxiety (32). The cut-off values for the diagnosis of insomnia differ for different diseases. A cutoff score of 5 was suggested by Tsai et al. (33) to distinguish primary insomnia with Chinese version of PSQI among community-dwelling adults. A cross-sectional study of 327 IS patients suggested 8 as the cut-off score (34). The PSQI scale used in this study is the Chinese version translated by Liu et al. (35) in 1996. When the total PSQI score over 7, the sensitivity of distinguishing between normal and sleep-disordered populations was 98.3% and the specificity was 90.2% (35). The time to complete the PSQI assessment is approximately 5 to 10 min.

2.2.3. ISI

The ISI is a reliable instrument for population-level detection of insomnia cases and is sensitive to treatment response in clinical patients (36). The ISI is a seven-item, subjective assessment and screening tool that primarily assesses the character, gravity, and influence of insomnia over the previous 4 weeks (37). The items evaluate (i) difficulty falling asleep (initial) (I1a), (ii) difficulty maintaining sleep (middle) (I1b), (iii) early awakening (terminal) (I1c), (iv) satisfaction with current sleep situation (I2), (v) the degree of hindrance with routine function caused by sleep dilemmas (I3), (vi) the degree of impact or impairment on quality of life caused by the sleep difficulty (I4), and (vii) level of anxiety attributed to the sleep predicament (I5) (38). The time to complete the ISI assessment is approximately 5 min. The ISI uses a Likert scale of five points (0 ~ 4 scale), with a total score between 0 and 28. According to Reinsel (39), the best clinical cutoff score for identifying sleep disorders in breast cancer patients is 8. A cutoff score of 8 was suggested by Savard et al. (40) for identifying sleep difficulties in cancer patients, which produced 94.7% sensitivity and 47.4% specificity in cancer patients according to the DSM-IV criteria. At present, ISI has not established a cutoff score for the diagnosis of insomnia in many clinical patients (22).

2.2.4. AIS

The AIS was developed as a standard sleep assessment tool to quantify the degree of sleep difficulty, in accordance with the International Classification of Diseases-10 edition (ICD-10) (41). There are eight items: the first five are concerned with (i) time needed to fall asleep (A1), (ii) wakening during the night (A2), (iii) waking up earlier than desired time (A3), (iv) sleep duration (A4), and (v) sleep quality (A5); while the last three items concerned with (vi) daytime emotional state (A6), (vii) daytime functioning capacity (A7), and (viii) daytime sleepiness (A8). The AIS uses a Likert scale of 4 points (0 = no problem; 3 = serious problem), with an overall score from 0 to 24. Higher AIS scores represent higher levels of insomnia. The AIS has been translated into numerous languages and has been used by various populations worldwide, including English (41), Chinese (42), and Spanish (43). With a cut-off score of 6, AIS can be used for insomnia screening with the sensitivity of 93% and the specificity of 85% in Taiwanese cancer patients (42). A score of 6 was found to be the optimal cutoff when logistic regression analysis was performed between the total AIS score and ICD-10 insomnia diagnosis (44). Jeong et al. (45) also suggested the commonly accepted cut-off to be 6. In clinical practice and research, AIS can be utilized as a screening instrument to measure the severity of sleep-related issues as well as a tool in reliable insomnia screening. Although AIS is regarded as a useful insomnia screening tool for research prediction, it has not been tested on the IS patients.

2.3. Data analysis

EpiData 3.0 was used for data entry and aggregation for IS patients, and two researchers completed data input separately to

TABLE 1 Demographics of IS patients in the insomnia group and no-insomnia group (n = 569).

Variables	No-insomnia group (n = 480)	Insomnia group (n = 89)	$X^2/F/Z$	p
Age (years), mean ± SD	62.72 ± 10.57	66.13 ± 8.54	8.278	0.004
Sex, n (%)			26.000	<0.001
Female	174 (36.3)	58 (65.2)		
Male	306 (63.8)	31 (34.8)		
BMI (Kg/m^2), mean ± SD	24.12 ± 2.84	25.09 ± 3.21	8.485	0.004
Marital status, n (%)			0.145	0.703
Married	442 (92.1)	83 (93.3)		
Unmarried/Divorced/Widowed	38 (7.9)	6 (6.7)		
Education, n (%)			0.490	0.484
≤9 y	186 (38.8)	38 (42.7)		
>9 y	294 (61.3)	51 (57.3)		
Occupation, n (%)			3.320	0.068
Retired	340 (70.8)	72 (80.9)		
Employed	140 (29.2)	17 (19.1)		
Drink, n (%)	241 (50.2)	29 (32.6)	9.352	0.002
Smoke, n (%)	124 (25.9)	28 (31.5)	1.165	0.280
Hypertension, n (%)	353 (73.5)	62 (69.7)	0.572	0.449
Diabetes, n (%)	220 (45.8)	31 (34.8)	3.686	0.055
Coronary heart disease, n (%)	47 (9.8)	11 (12.4)	0.541	0.462
NIHSS (M, IQR)	3 (3)	3 (3)	−0.309	0.756
BI (M, IQR)	55 (25)	55 (30)	−0.004	0.997

SD, Standard deviation; n, number of patients; M, IQR, Median, Inter Quartile Range; BMI, Body mass index; NIHSS, National Institute of Health stroke scale; BI, Barthel index.

ensure data accuracy. The IBM SPSS 22.0 and MedCalc 21.0 were used to implement statistical analysis. Kolmogorov–Smirnov test was used to test the normality of the data distribution, with $p > 0.05$ considered as normal distribution. Descriptive statistics were reported as mean ± standard deviation (SD) for variables with normal distributions and as median (interquartile range, IQR) variables with for skewed distributions. If the variables in each sample were normally distributed and the overall variance was equal, ANOVA was used to compare the means between the insomnia group and the non-insomnia group, and nonparametric test of Mann–Whitney U test was used if not. Chi-square test was used to compare the rates of categorical variables between the two groups.

ROC curve analysis was used to analyze the diagnostic validity of PSQI, ISI, and AIS. The area under ROC curve (AUC) was performed to evaluate the accuracy of PSQI, ISI, and AIS for the diagnosis of insomnia in IS patients. AUC is currently accepted as a diagnostic evaluation index and a method to determine the optimal diagnostic cutoff values. The value of AUC ranges from 0.5 to 1. The diagnostic value is acceptable when the score is between 0.71 and 0.8, excellent when it is 0.81–0.9, and outstanding when it is >0.9 (46). DeLong's test (47) was performed to compare multiple ROC curves. Youden index was performed to determine the optimum cutoff diagnostic values of PSQI, ISI, and AIS (48). Cronbach's α and McDonalds Ω coefficient was used for the reliability analysis of this study. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic validity of the three scales were also analyzed. Cohen's Kappa consistency was performed between insomnia diagnosis based on PSQI, ISI, and AIS and clinician-based insomnia diagnosis.

3. Results

3.1. Characteristics of IS patients

The Demographics of IS patients in the insomnia group and no-insomnia group in this study are shown in Table 1. A total of 569 patients were separated into insomnia group (n = 89) and no-insomnia group (n = 480) in accordance with the diagnostic criteria of insomnia in IS patients. In this study, 337 (59.23%) patients were male and 232 (40.77%) were female. The average age was 63.25 (SD = 10.34) and the average BMI was 24.27 (SD = 2.92). Additionally, 157 patients (27.59%) were employed before stroke. The median (IQR) of NIHSS and ADL scores of IS patients were 3 (3) and 55 (25). 415 (72.93%) IS patients have hypertension and 251 (44.11%) IS patients have diabetes. A comparative analysis of the insomnia group and the no-insomnia group revealed significant differences in terms of age, sex, BMI, and drinking. When the insomnia group was compared with the non-insomnia group, it was found that the insomnia group was older and included more female participants. Meanwhile, patients in the insomnia group had higher BMI and more alcohol consumption.

3.2. Analysis of PSQI, ISI, and AIS scores

The number of IS patients' responses of the three questionnaires in the insomnia and no-insomnia groups is shown in Table 2. The median (IQR) of PSQI score in no-insomnia group was 3(2), and median (IQR) of PSQI score in insomnia group was 11(1). The median (IQR) of ISI score in no-insomnia group was 13(6), and median (IQR) of ISI score in insomnia group was 17(3). The median (IQR) of AIS score in no-insomnia group was 5(3), and median (IQR) of AIS score in insomnia group was 9(5). The results of the Mann–Whitney U test showed there were significant differences in scores of PSQI, ISI, and AIS between the insomnia group and the no-insomnia group ($p < 0.001$).

3.3. Reliability of the PSQI, ISI, and AIS

The PSQI and ISI showed high reliability with Cronbach's α-values of 0.875 and 0.858, while the AIS had an α coefficient of 0.734, demonstrating acceptable reliability. The factor analysis demonstrated that the ISI and AIS scale both emerged as a sole component (37, 41). The PSQI and ISI showed high reliability with McDonalds Ω values of 0.895 and 0.864, while the AIS had an α coefficient of 0.736, which is consistent with the Cronbach's alpha coefficient.

TABLE 2 The scores of PSQI, ISI, and AIS for insomnia group and no-insomnia group ($N = 569$).

Variables	No-insomnia group ($n = 480$)	Insomnia group ($n = 89$)	p
PSQI, (M, IQR)	3 (2)	11 (1)	<0.001
ISI, (M, IQR)	13 (6)	17 (3)	<0.001
AIS, (M, IQR)	5 (3)	9 (5)	<0.001

M, IQR, median, interquartile range.

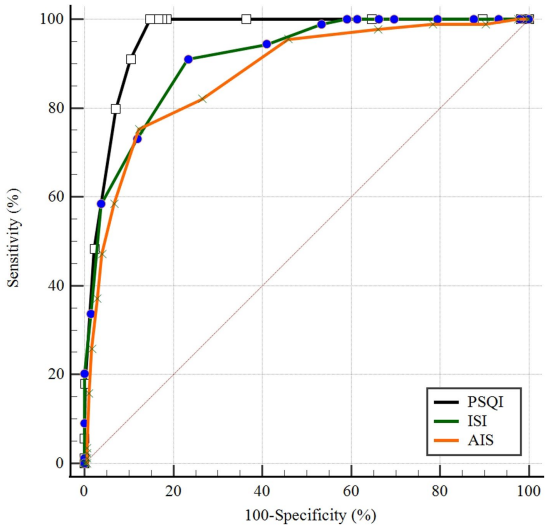

FIGURE 1
ROC curves of PSQI, ISI, and AIS in IS patients.

3.4. Diagnostic validity of PSQI, ISI, and AIS

ROC curves of PSQI, ISI, and AIS in IS patients were showed in Figure 1. The AUCs of PSQI and ISI were 0.960 (95% CI: 0.946, 0.974) and 0.911 (95% CI: 0.882, 0.941), which were greater than 0.9, showing outstanding diagnostic ability of insomnia in IS patients. The AUC of AIS was 0.876 (95% CI: 0.837, 0.916), which ranged from 0.8 to 0.9, showing excellent diagnostic ability with PSQI and ISI in IS patients. DeLong's test indicated that PSQI can be considered to have better diagnostic validity than ISI and IAS, while ISI and AIS cannot be differentiated regarding diagnostic validity (Table 3). The current study compared different PSQI, ISI, and AIS cutoff scores and the resulting sensitivity and specificity are shown in Figure 2. After determining the best cutoff values based on Youden's index, which were 9 for PSQI, 15 for ISI and 8 for AIS, other statistics were further identified, such as sensitivity, specificity, Youden index, positive and negative likelihood ratio (Table 4). When it came to distinguishing between patients with and without insomnia, the PSQI had the highest sensitivity.

Cohen's Kappa test was used to compare the consistency between clinician-based insomnia diagnosis and questionnaire-based insomnia diagnosis in Table 4. In the questionnaire-based insomnia diagnosis, PSQI ≥9, ISI ≥ 15 and AIS ≥ 8 was considered as insomnia. Comparing PSQI with the clinician-based insomnia diagnosis revealed that Cohen's kappa was 0.643 (95% CI: 0.570, 0.716). However, comparing ISI and AIS with insomnia diagnosis revealed that Cohen's kappa was 0.459 (95% CI: 0.385, 0.533) and 0.539 (95% CI: 0.451, 0.627). PSQI can be considered to have more diagnostic concordance with clinicians than ISI (no CI overlap) while AIS has the same concordance as both PSQI and ISI (CI overlap).

4. Discussion

Insomnia is a common psychiatric complaint in IS patients (9). The reported prevalence of insomnia varies widely among studies due to the different definitions and assessment tools used. Among the 569 IS patients contained in this study, 89 were diagnosed as insomnia by clinicians. The prevalence of pre-stroke insomnia in IS patients was found to be 15.64% in this study, lower than that of previously reported levels. Surveys such as that conducted by Leppävuori et al. (49) have shown that 38.6% had insomnia before the stroke and 18.1% had insomnia after the stroke. Another study found a 12% rate of new-onset insomnia after stroke when excluding patients who had insomnia before stroke (50). A study from China found that the prevalence of insomnia in stroke patients was 57.9%, of which 32.2% had insomnia before the stroke and 25.7% had new insomnia after the stroke (51). A 4-year follow-up study of 21,438 insomniacs and 64,314 non-insomniacs found that the incidence of stroke was significantly higher in insomniacs than in non-insomniacs (incidence rate ratio = 1.85; 95% CI: 0.7, 2.05) and those insomniacs had 54% higher risk of developing stroke compared with non-insomniacs (adjusted hazard ratio = 1.54; 95% CI: 1.38, 1.72) (3). There is mounting clinical evidence to support a bidirectional relationship between insomnia and stroke. Insomnia is likely to be an independent risk factor for stroke, and stroke may also be a causative factor for the development of insomnia. Insomnia should be given more attention in IS patients.

This study demonstrated high sensitivity and specificity of the PSQI, ISI, and AIS in screening for insomnia in IS patients. It was discovered that the PSQI scale was the most sensitive (identifying insomnia in 100% of the IS patients when the cutoff value is 9), while DeLong's test indicated that ISI and ASI were less but similarly sensitive, with ISI identifying insomnia in 91.01% of the IS patients when the cutoff value is 15, and AIS identifying insomnia in 75.28% of the IS patients when the cutoff value is 8. Some studies suggest that the diagnostic sensitivity to distinguish good sleep from poor sleep was 89.6% and the specificity was 86.5% when the total PSQI score > 5 (52). The Youden index of the PSQI was 0.852, with a strong ability to screen insomnia patients from non-insomnia patients. When the effect of morbidity was excluded, the positive likelihood ratio (PLR) for the PSQI was 6.761, which is a higher than ISI and AIS. Also, according to Charles, the ISI cutoff of 10 was the optimal score for identifying insomnia cases in the community people, with an 86.1% sensitivity and 87.7% specificity (36). When diagnosing insomnia on a score of ≥6, the AIS scale had a sensitivity of 93%, and a specificity of 85%, and the overall correct case identification rate is 90% (44). This confirmed the findings of these scales have excellent performance of these scales in screening for insomnia in IS patients in the literature (34, 36, 42). Our analysis showed that, identical to the widely used cutoff values for insomnia diagnosis in the general population in China, the best cutoff values in screening for insomnia in IS patients of the ISI questionnaires were "15." However, the best cutoff values in screening for insomnia in IS patients of the PSQI and AIS questionnaires were "9" and "8" respectively, higher than the widely used diagnostic cutoff values for insomnia population in China.

Cohen's kappa consistency statistic check was used to analyze the consistency of PSQI, ISI, and AIS with clinician-based insomnia diagnostic in IS patients. The kappa coefficient of PSQI, ISI, and AIS were 0.643, 0.459, and 0.539 and the asymptotic 95% confidence interval were (0.570, 0.716), (0.385, 0.533), and (0.451, 0.627). Landis and Koch (53) proposed that a kappa in the range of 0.41 ~ 0.60 be considered "moderate" agreement, kappa = 0.61 ~ 0.80 be considered "substantial" agreement, and kappa >0.81 be considered "almost perfect" agreement. This indicates that the consistency between PSQI with clinician-based insomnia diagnostic were substantial consistent. The consistency between ISI and AIS with clinician--based insomnia diagnostic was moderately consistent.

The PSQI focuses on the sleep status of patients in the past 4 weeks. Also, there are four types of responses ("not during the last month," "less than once a week," "once or twice a week," "three or more times per week") instead of using "very poor," "poor," "good," "very good" and similar language to assess sleep. Such descriptions are important to accurately measure the severity of the IS patient's sleep-related components. We believe this could help our patients better understand the PSQI question and choose the option that best matches their situation, compared to the AIS and ISI. In addition, these descriptions and response category of sleep quality severity can be translated into numerical rating ranges, so this may explain the greater sensitivity of PSQI in assessing insomnia in IS patients. PSQI is a widely used sleep quality evaluation tool to measure sleep quality and disturbances over the prior month and to discriminate between "good" and "poor" sleepers (22). Meanwhile, PSQI is often used

TABLE 3 DeLong's test on pairwise comparison of ROC curves.

Variables	PSQI and ISI	PSQI and AIS	ISI and AIS
Difference between areas	0.049	0.084	0.0348
Standard error	0.0149	0.0201	0.0234
95% *CI*	(0.019, 0.079)	(0.044, 0.123)	(−0.011, 0.081)
Z statistic	3.281	4.164	1.488
p	0.001	<0.0001	0.1368

TABLE 4 Accuracy and diagnostic validity of PSQI, ISI, and AIS in IS patients.

Variables	PSQI	ISI	AIS
AUC (*95%CI*)	0.960 (0.946, 0.974)	0.911 (0.882, 0.941)	0.876 (0.837, 0.916)
Cutoff point	≥9	≥15	≥8
Se	100%	91.01%	75.28%
Sp	85.21%	76.67%	87.71%
YI	0.852	0.677	0.630
PLR	6.761	3.900	6.125
NLR	0.000	0.117	0.282
Cohen's Kappa	0.643 (0.570, 0.716)	0.459 (0.385, 0.533)	0.539 (0.451, 0.627)

AUC, Area Under Curve; Se, Sensitivity; Sp, Specificity; YI, Youden index; PLR, Positive likelihood ratio; NLR, Negative likelihood ratio.
Cohen's Kappa = agreement with clinician-based diagnosis.

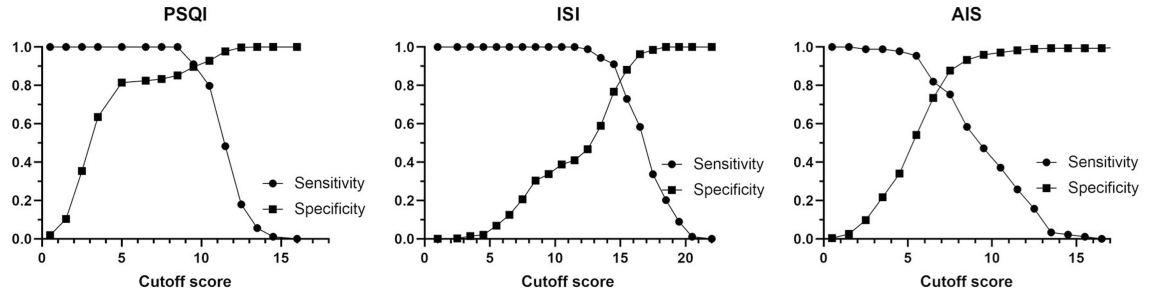

FIGURE 2
Sensitivity and specificity of PSQI, ISI, and AIS for various cutoff scores.

together with the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness, such as in medical students (54), COPD and asthma (55), or women with premenstrual syndrome (56).

Although the ROC curve was used to evaluate the diagnostic performance of the three questionnaires in insomnia, it was not the only thing to consider in choosing an assessment tool. The three questionnaires have similar content and language descriptions of sleep problems. Each of the three questionnaires has advantages and disadvantages when assessing insomnia. The PSQI cannot collect information about the patient's need of treatment options and other aspects. The PSQI scale has more questions and takes longer to assess compared to the ISI and AIS, so it performs poorly in rapidly assessing the severity of insomnia in clinical patients. It should be emphasized that PSQI is the only one of the three questionnaires that needs to calculate and transform scores. Because of the need to integrate various responses and calculate such variables as sleep efficiency, hand-calculation of scores may be somewhat burdensome (22). This undoubtedly caused additional inconvenience and time consumption for clinical evaluation.

One advantage of ISI is that there are data based on which insomnia can be classified hierarchically. In a study which set out to investigate insomnia in long-term hospitalized older adults, Aluzaite et al. (57) classified ISI scores as follows: 0 ~ 7 points represent no insomnia; 8 ~ 14 points represent sub-threshold insomnia; 15 ~ 21 points represent moderate insomnia; 22 ~ 28 points represent severe insomnia. Under this score classification, the degree of insomnia in patients can be measured. Meanwhile, for PSQI and AIS such thresholds to measure the severity of insomnia in patients have not yet been investigated. In many clinical assessments, PSQI is often used as an index to measure the overall sleep quality, and ISI is used to measure the severity of insomnia (58). ISI focuses on the subjective symptoms of insomnia, the consequences and the degree of distress, and is sensitive to detect changes in sleep conditions brought about by treatment. However, researchers need to be alert to the possibility of false positive results when patients subjectively amplify their insomnia feelings.

The AIS is designed to assessment subjective feeling of sleep difficulty that only the subjective feelings of the interviewee are considered for the rating (41). In addition, the severity of the patient's sleep difficulty as estimated by the interviewer, such as the hours of sleep or the approximate duration of sleep onset latency (41), was not considered in the AIS score since the interviewer's judgment may not be consistent with the patient's subjective assessment. Patients may exaggerate the negative feelings caused by short sleep duration, leading to bias in AIS assessment, which may also be the reason for the lower sensitivity of AIS.

There are several limitations to this study: All subjects were not tested with Polysomnography in this study. We compared the application of the three questionnaires in the diagnosis of insomnia, but did not give grade judgments for the severity of insomnia. Finally, because the information was gathered based on self-reporting, the data may be prone to information bias.

5. Conclusion

This study demonstrated high sensitivity and specificity and excellent diagnostic ability of the PSQI, ISI, and AIS questionnaires in screening for insomnia in IS patients. We found the best diagnostic cutoffs for PSQI, ISI, and AIS are ≥9, ≥15, and ≥8, respectively. Based on these cutoff values, the PSQI scale was revealed to be the most sensitive, while the ISI was the moderate sensitive and AIS was the least sensitive. Each of the three questionnaires has advantages and disadvantages when assessing insomnia. In the evaluation of insomnia in IS patients, the best questionnaire selection should be made according to the purpose of clinical evaluation (such as screening potential insomnia patients or the diagnosis of clinical insomnia) and considering the sensitivity and specificity of the questionnaire.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Boards of the Tenth People's Hospital, Tongji University (Approval No. SHSY-IEC-KY-4.0/17–47/01). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SN and YS: study conception and design, manuscript drafts and revisions. SN, SD, LCW, and LW: data collection. SN and QW: data analysis. SN, QW, SD, LCW, and YS: agree with manuscript results and conclusions. All authors approved the final manuscript and act as guarantors for the study.

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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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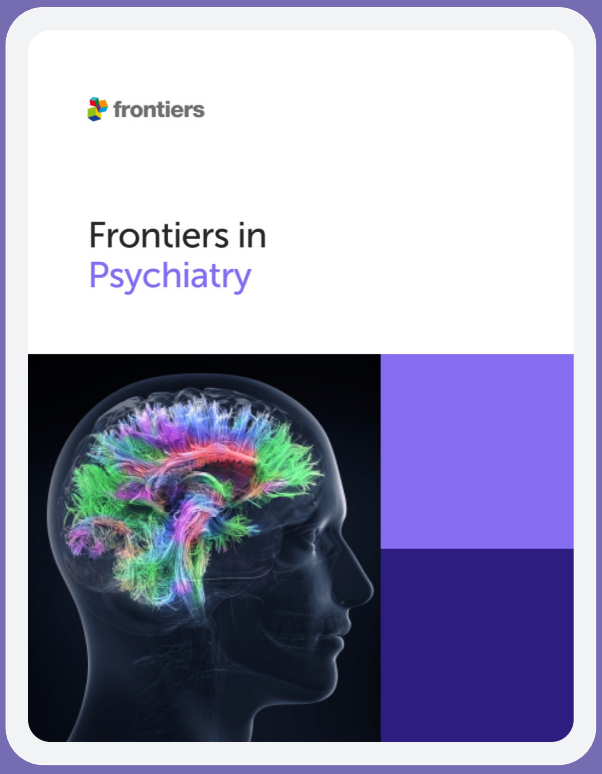

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